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Color-Tunable Fluorescent Dyes Based on Benzo[*c*]coumarin

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Hurtley condensation was shown to be a perfect tool with which to assemble a diversified library of derivatives of benzo[*c*]coumarin. Not only do simple resorcinols and *ortho*-bromobenzoic acids undergo this reaction, but also dihydroxynaphthalenes and 3-bromothiophene-2-carboxylic acid, affording the desired compounds in moderate yields. In the case of naphthalenediols, intriguing regioselectivity is observed, which holds promise for its utilization in the synthesis of previously inaccessible molecules. Further transformation made it possible to obtain benzo[*c*]coumarin bearing amino and nitro groups at various positions, which served as entry points to prepare complex hybrids of 1,4-benzoxazin-2-ones and benzo[*c*]coumarins. The hydroxyl group proved to be the synthetic handle, enabling the synthesis of strongly solvatochromic, soluble analogues. The effect of structural variation on photophysical properties was studied in detail for almost 30 compounds. The relationship between the structure and photophysical properties was thoroughly elucidated by comparison with simple analogues (coumarins, benzoxazinones). All of the obtained compounds exhibit moderate to large Stokes shifts (3300–12500 cm^{-1}). The type of π-expansion of the chromophore strongly influences the overall optical phenomena. Compounds possessing alkyl substituents on the benzo[*c*]coumarin core have much higher fluorescence quantum yields than their analogues bearing amino, fluorine, and other complex substituents. Interestingly, the product possessing a fused coumarin–thiophene skeleton exhibits over twofold higher fluorescence quantum yield than any of its coumarin–benzene analogues.

Introduction

Coumarins fused with another aromatic ring at positions 3 and 4 have been known for some time. The most typical example is the benzo[*c*]coumarin (6*H*-dibenzo[*b*,*d*]pyran-6-one) skeleton, which is prevalent in many synthetic and naturally occurring medicinal substances.[1] They display a wide spectrum of biological[2] and pharmacological activities, among which we can distinguish anticoagulant, spasmolytic, diuretic and anticancer properties.[3] Furthermore, this class of molecules can be used as valuable intermediates in the synthesis of more complex molecules such as cannabinoids, which are the active agents in pain relievers and drugs with antiemetic action.[4] Recently, new methods have been added to the growing arsenal of tools used to construct benzo[*c*]coumarin such as lactonization of hydroxy esters[5] and 2′-halobiphenylo-2-carboxylic acids,[6] oxidation of the corresponding benzo[*c*]pyrans[7] and phenanthrenes,[8] [3+3]-cyclization of the 1,3-bis(silyl enol) ethers with 1-(2-methoxyphenyl)-1-(trimethylsilyloxy)alk-1-en-3-ones followed by subsequent BBr_3-mediated lactonization[9] together with [4+2]-cyclization of 4-cyanocoumarins and 1-silyloxydienes.[10] Notably, the condensation of coumarin-derived electron-poor dienes with a range of corresponding electron-rich dienophiles (mostly enamines) to afford the corresponding benzo[*c*]coumarin through inverse electron-demand Diels–Alder reaction has been developed by Bodwell and co-workers.[11] Minuti et al. recently described a novel approach through Diels–Alder reaction under high-pressure.[11d]

Overshadowed by their presence in nature and their wide spectrum of biological activities is the fact that many benzo[*c*]coumarins emit light in the visible region.[12] Because their stability is generally higher than that of coumarins, benzo[*c*]coumarins could be a suitable fluorescent platform for bioimaging. Indeed, the design of new coumarin-based functional dyes must address the problem of the instability of simple coumarins, which is partially related to the presence of a reactive carbon–carbon double bond that can undergo [2+2] cycloaddition.[13] Within the last decade, the fusion of coumarins with pyrroles and furans has led to the creation of compounds with very advantageous luminescent properties.[14]

Whereas the influence of substitution patterns on the fluorescence of coumarins has been comprehensively studied, little is known about the relationship between structural and optical properties of benzo[*c*]coumarins. Herein, we present the synthesis of benzo[*c*]coumarin derivatives and analogues with both electron-donating and

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-withdrawing substituents in different positions through Hurtley condensation, combined with comprehensive optical investigations.

Synthesis

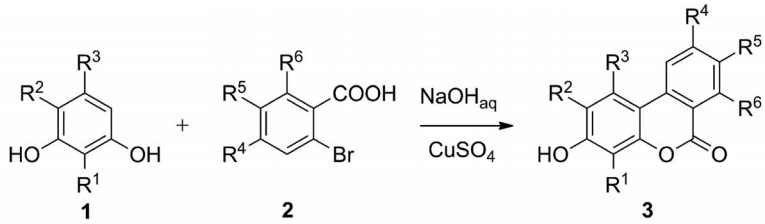
To perform a broad optical study, we sought the means to place substituents capable of modifying electron density at different positions around the molecule. In principle, the synthesis of derivatives and analogues of the benzo[*c*]coumarin skeleton can be achieved in two ways. First, the desired core may be assembled in one operation, involving such reactions as lactonization,[5,6] cyclization[7–11] or Hurtley condensation between phenols and 2-bromobenzoic acid.[15] Alternatively, the desired compounds may be realized by postfunctionalization of the parent benzo[*c*]coumarin or its easily available 3-hydroxy derivative.[16] Both strategies may potentially be efficient pathways to the desired products. We followed both approaches with a heavy focus on the former. This choice was governed by our strong interest in the study of the correlation between the chemical structure of the starting material and the Hurtley condensation output.

Almost a century ago, Hurtley reacted resorcinol and 2-bromobenzoic acid under relatively mild conditions,[15] obtaining 3-hydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-one in moderate yield. Surprisingly, this methodology has been little explored since that time because its application seemed to be limited.[17] We envisioned that this convergent and convenient protocol could be a perfect tool for the generation of benzo[*c*]coumarins possessing substituents with different electronic characteristics. We conducted a range of experiments under classical conditions and present the results in Table 1.

We directed our initial attempts at the synthesis of compounds possessing electron-withdrawing or reactive groups at suitable positions around the scaffold. For this purpose, we chose 4-fluoro, 4,5-difluoro and 6-fluoro derivatives of 2-bromobenzoic acid **2b**–**d**, as well as 2-bromo-5-nitrobenzoic acid (**2e**), 2-bromo-5-(trifluoromethyl)benzoic acid (**2f**), and 2-bromo-5-iodobenzoic acid (**2g**). Needless to say, the presence of fluorine atom(s) added no significant steric hindrance around the carboxyl group/halogen. The yields of expected products **3b**–**d** were lower in comparison to model **3a**. Product **3d** was obtained in lower yield than its regioisomer **3b**. We expected the electronic influence of a given substituent located in either the *ortho*- or *para*-position to the carboxylic group would be similar. However, Taylor and co-workers proposed that a substituent in the 6-position might prevent the formation of a planar copper chelate and would have a negative impact on the yield of the desired product.[18] Benzo[*c*]coumarins **3e**, **3j**, and **3k** bearing electron-withdrawing groups (NO_2, CF_3) in the 8-position were isolated in similar yields (35–40%). The use of phenol-substituted compounds with electron-donating groups as one of the substrates is known to promote successful Hurtley condensation reactions.[17] Bearing this idea in mind, we tested the reactivity of substituted resorcinols **1b**–**d**. The reaction with 2-bromobenzoic acid proceeded smoothly when alkyl-substituted resorcinols were used. Benzo[*c*]coumarins **3f** and **3i** were formed in yields of 43 and 51%, respectively (Table 1). In the case of product **3i**, the solubility increased appreciably in typical solvents.

Reaction with analogues of resorcinol possessing an additional hydroxyl group depended on the position of the second hydroxyl moiety. Condensation of phloroglucinol (**1d**) proceeded efficiently with both 2-bromobenzoic acid

Table 1. Synthesis of benzo[*c*]coumarin derivatives through Hurtley condensation.[a]



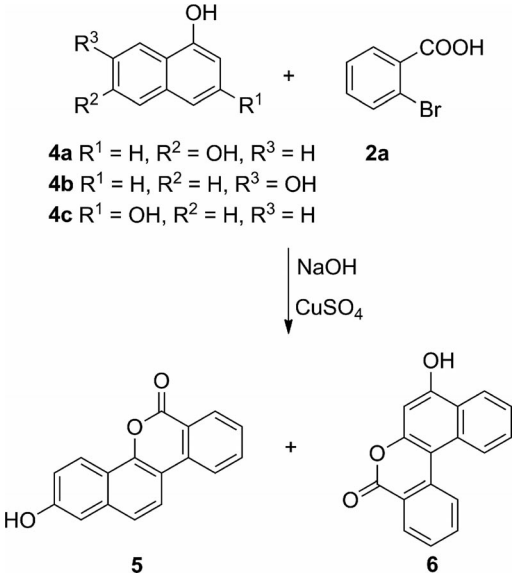
1 **2** **3**

Phenol	R^1	R^2	R^3	Acid	R^4	R^5	R^6	Benzo[*c*]coumarin	Yield[b]
1a	H	H	H	**2a**	H	H	H	**3a**	70%
1a	H	H	H	**2b**	F	H	H	**3b**	44%
1a	H	H	H	**2c**	F	F	H	**3c**	42%
1a	H	H	H	**2d**	H	H	F	**3d**	18%
1a	H	H	H	**2e**	H	NO_2	H	**3e**	40%
1b	Me	H	H	**2a**	H	H	H	**3f**	43%
1c	OH	H	H	**2a**	H	H	H	**3g**	0%
1d	H	H	OH	**2a**	H	H	H	**3h**	59%
1e	H	*n*Hex	H	**2a**	H	H	H	**3i**	51%
1d	H	H	OH	**2e**	H	NO_2	H	**3j**	35%
1e	H	*n*Hex	H	**2f**	H	CF_3	H	**3k**	36%
1a	H	H	H	**2g**	H	I	H	**3l**	39%

[a] Reaction conditions: **1** (20 mmol, 2 equiv.), **2** (10 mmol, 1 equiv.), aq. NaOH (20 mmol, 2 equiv. in 50 mL H_2O), 60 °C, 15 min; then 10% aq. $CuSO_4$, 95 °C, 3 h; then room temp. overnight. [b] Isolated yield.

(**2a**) and 2-bromo-5-nitrobenzoic acid (**2e**), leading to derivatives **3h** and **3j** in 59 and 35% yield, respectively. Pyrogallol (**1c**), on the other hand, was not reactive under these conditions, as described earlier by Leederer and Polonsky.[17b] Mass spectrometry analysis of the crude reaction mixtures revealed the presence of both unreacted 2-bromobenzoic acid and salicylic acid.[17a] Consequently, competitive reaction with hydroxide anion and limited conversion accounted for the mediocre yields of the Hurtley condensation.

Both π-expansion and replacement of benzene with a heterocyclic unit alter the physicochemical properties of aromatic fluorophores. Therefore, a series of regioisomeric dihydroxynaphthalenes and exemplary heterocyclic analogues of *o*-bromobenzoic acid were investigated in the Hurtley condensation. We questioned how these types of phenols would behave in this reaction. Three naphthalenediols, possessing various arrangements of hydroxyl groups, were selected (Scheme 1).

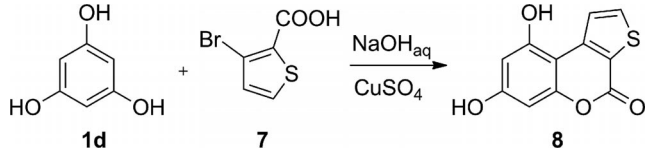


Scheme 1. Synthesis of π-extended coumarins through Hurtley condensation.

We were pleased to obtain the expected products in the case of 1,6-dihydroxynaphthalene (**4a**) and 1,3-dihydroxynaphthalene (**4c**) in 15 and 48% yields, respectively. According to the experimental results, conversion of starting material was observed in all entries; however, unwanted side reaction leading to the formation of a black tar material (probably polycondensation products) took place in each reaction to a greater or lesser extent. Reaction of 1,7-dihydroxynaphthalene (**4b**) did not afford the expected product.

It is worth noting that formation of regioisomeric products can occur (see Figure S1 in the Supporting Information). Structural identification and signal assignments were performed by the use of 2D NMR techniques. Inspection of the COSY spectra obtained for **5** revealed AMX and AB spin systems together with one showing a correlation that is characteristic of *ortho*-disubstituted benzene (ABCD) systems. This observation eliminates the possibility of formation of **5B** (see the Supporting Information). Additionally, according to the NOESY data, the correlation between the hydroxyl proton and two neighboring protons (belonging to one AMX spin system, multiplet, 7.21–7.23 ppm, 2 H) was observed. This fact let us exclude **5C** as a possible structure and to assign these protons to H^1 and H^3. Moreover, closer inspection of the AMX system in the COSY spectrum revealed an exclusive cross peak of H^3 with only one proton (doublet, δ = 8.82 ppm, 1 H), assigned to H^4, confirming the structure **5A**. The above findings were additionally confirmed by the presence of an isolated AB system that does not have a response with the –OH proton on the NOESY spectrum. The ^{1}H NMR spectrum measured for compound **6** indicated the presence of two ABCD spin systems and two signals of isolated ^{1}H atoms (singlets). One signal (broad singlet, δ = 11.24 ppm, 1 H) was assigned to the –OH group and possessed two correlation signals in NOESY: an isolated proton and a proton coming from an ABCD spin system. Only two structures, **6A** and **6C**, were expected to exhibit such cross peaks. Moreover, isolated ^{1}H atoms did not show NOESY correlation with any peak belonging to ABCD systems, satisfying only the **6C** structure. Thus, according to the spectroscopic data, we can claim the formation of regioisomerically pure **5** and **6**. Compound **5** possessed the skeleton that is present in the structure of many naturally occurring compounds in *Streptomyces* such as ravidomycin and chrysomycins.[19]

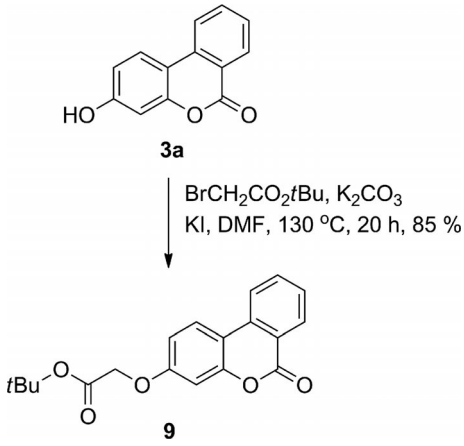
3-Bromothiophene-2-carboxylic acid (**7**) also underwent the Hurtley condensation (Scheme 2). Product **8**, which represents one of the first thieno[*c*]coumarins known, was obtained in 40% yield.[14f]



Scheme 2. Synthesis of derivative of 4*H*-thieno[2,3-*c*]chromen-4-one (**8**) through application of the Hurtley protocol.

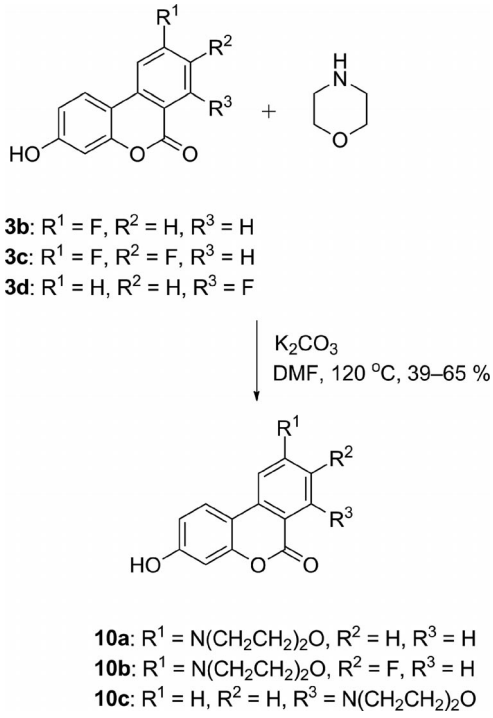
Both 7-methoxy-4-methylcoumarin[20] and 8-methoxy-4-methylbenzo[*g*]coumarin[21] displayed significantly stronger fluorescence in polar media than in nonpolar media. Ester **9** was synthesized by the Williamson method (Scheme 3) to investigate whether it also possessed such unusual optical properties. The ether, containing the *tert*-butyl ester functionality rather than a simple methyl ether, was chosen due to its prospective solubility in nonpolar solvents.

Aiming to significantly influence the photophysical parameters, we designed amine-substituted benzo[*c*]coumarins. Subjecting the previously obtained fluorobenzo[*c*]coumarins **3b**–**d** to the typical nucleophilic aromatic substitution conditions afforded the expected products **10a**–**c** in good yields (Scheme 4). Most of the previously prepared benzo[*c*]coumarins possess limited solubility in the majority of organic solvents, complicating their analysis and limiting



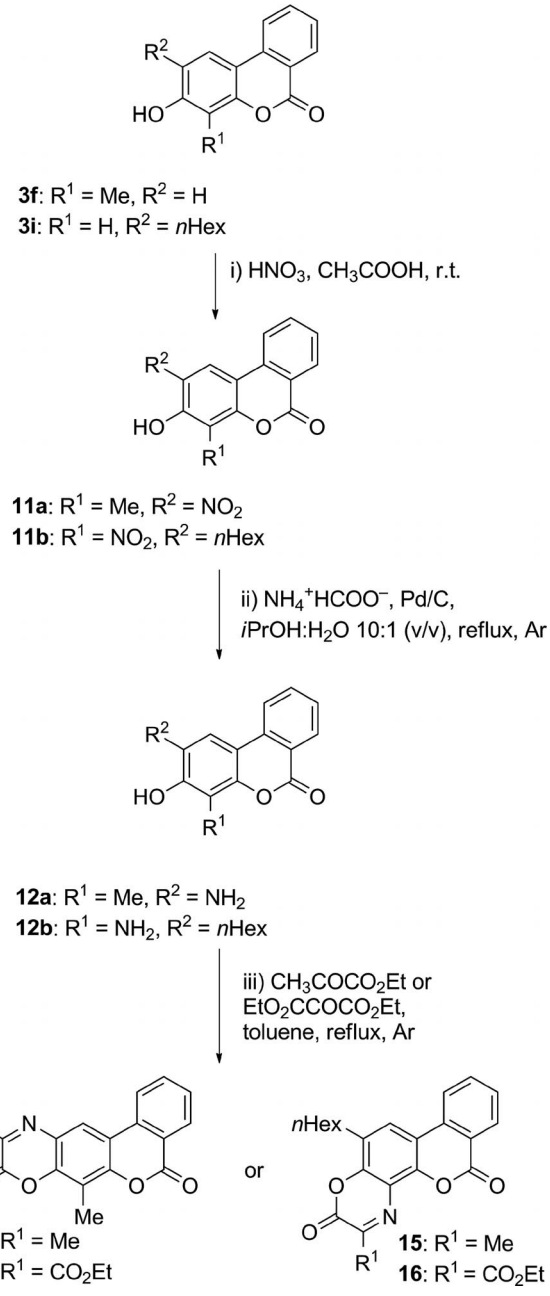
Scheme 3. Synthesis of *O*-alkylated derivative of **3a**.

further applications. Consequently, morpholine, rather than dimethylamine, was chosen as a nucleophilic partner in all of these reactions. In the case of benzo[*c*]coumarin **3c**, the process was fully regioselective and, according to experimental data, only fluorine located in the *para* position with respect to the C=O group was replaced with morpholine.



Scheme 4. Synthesis of morpholine-substituted benzo[*c*]coumarins.

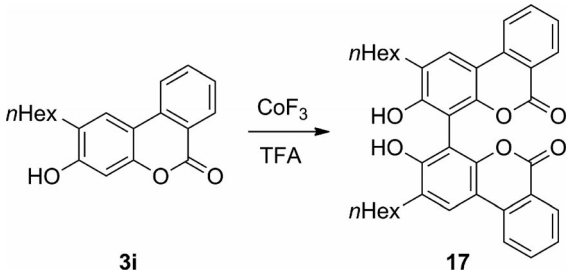
The benzo[*c*]coumarin skeleton has, in principle, various positions that can serve as entry points to further extend the π-conjugated system. In this context, we designed four different hybrids of coumarins and 1,4-benzoxazin-2-ones **13**–**16** with linear and angular junctions of the rings. Such molecules possess a π-expanded chromophore that may result in bathochromic shifts of absorption. One of the most attractive synthetic pathways leading to 1,4-benzoxazine-2-ones involves transformation of the corresponding nitro derivatives. However, nitration of unsubstituted 3-hydroxybenzocoumarin is known to lead to mixtures of two regioisomeric mono-nitro compounds and the bis-nitro derivative.[22] Consequently, we turned to a different approach involving utilization of substrates having one of the electron-rich positions blocked by alkyl substituents. This change minimizes the possibility of side reactions while simultaneously improving the solubility of the final product. Nitration of previously prepared **3f** and **3i** led cleanly to compounds **11a** and **11b**, regioselectively, in 91–93% yields (Scheme 5). The reduction of these products to the corresponding amines **12a** and **12b**, respectively, pro-



Scheme 5. Synthesis of benzoazacoumarins **13**–**16**.

ceeded smoothly.[23] The final condensation with reactive α-keto esters, such as diethyl mesoxalate and ethyl pyruvate, were performed under typical conditions (Scheme 5).[24]

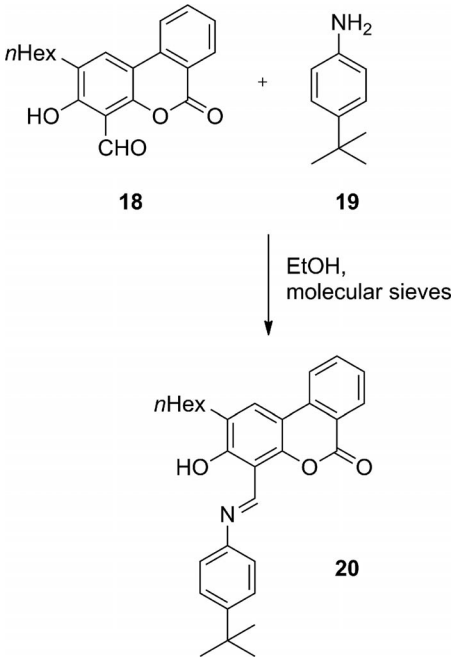
Biaryls are typical structural motifs in functional dyes because this arrangement of aromatic rings often leads to significant Stokes shifts, as a result of the difference in geometry between ground and excited states. Phenols are known to undergo oxidative aromatic coupling,[25a] leading to such architectures. In this context, we advanced the hypothesis that electron-rich benzo[*c*]coumarins will undergo dehydrogenation at positions adjacent to OH groups. Indeed, a derivative of 3-hydroxybenzo[*c*]coumarin **3i** treated with cobalt trifluoride[25b] in trifluoroacetic acid underwent oxidative coupling, and product **17** was obtained in 25% yield (Scheme 6).



3i **17**

Scheme 6. Oxidative aromatic coupling of compound **3i**.

Finally, transformation of **3i** using the optimized Duff protocol[26] led to aldehyde **18**, which, upon reaction with aromatic primary amine **19**, gave the corresponding imine **20**,[27] which possessed reasonable solubility in organic solvents (Scheme 7 and Figure 1).



Scheme 7. Synthesis of Schiff base **20**.

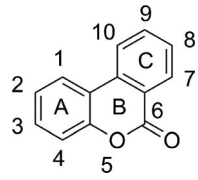


Figure 1. Position numbering.

The photophysical properties of compounds **3a**–**l**, **5**, **6**, **8**, **10a**–**c**, **11a**–**b**, **12a**–**b**, and **13**–**18** were studied in *N*,*N*-dimethylformamide (DMF), which was chosen because of its ability to dissolve all compounds and thus allow direct comparison and assessment of the effect of the architecture on the photophysical properties of the chromophore (Tables 2 and 3, Figures 2, 3, and 4). Optical properties of Schiff base **20** were measured in dichloromethane. In analogy to many coumarins, benzo[*c*]coumarins **3a**–**l**, **5**, **6**, **8** and **10a**–**c** absorbed UV radiation while emitting violet-blue light. The broad absorption band was located between 260 and 400 nm. Coumarins with amino and/or hydroxyl groups in position 7, or at both positions 7 and 6, are highly fluorescent and are known to display large Stokes shifts.[28,29] In comparison to the photophysical behavior of 7-hydroxycoumarin (umbelliferone) in DMF[30] (Table 2), 3-hydroxybenzo[*c*]coumarin (**3a**) exhibited bathochromic shifts in both absorption and emission spectra, which resulted in slightly larger Stokes shift. Because Stokes shifts in these two compounds are almost identical, one can conclude that their large values are caused by a factor that is common in both, i.e., a change in the electronic structure of the luminophore upon excitation. Umbelliferone and compound **3a** are planar, structurally rigid luminophores, the planar structure of which does not change substantially upon electronic excitation. Consequently, the large values of the Stokes shift cannot be realized in these compounds as a result of conformational processes. Notably, **3a** does possess a Φ_{fl} that is 2.5 times higher than that of umbelliferone. The fluorescence quantum yield of coumarins is strongly influenced by substituents in the 7-position, which control the relative energy ordering of the two lowest excited states; a nonemissive (n,π*) state that originates from the carbonyl-oxygen lone pair and an emissive locally excited state with (π,π*) character.[31] In addition, 7-hydroxycoumarin and its derivatives are known to undergo excited-state proton transfer (ESPT).[32] This is due to the presence of two photoactive centers (weakly acidic hydroxyl group and weakly basic carbonyl group). 7-Hydroxycoumarins undergo dramatic decreases in pK_a upon electronic excitation. As a consequence, three emitting states have been observed for these types of molecules (normal, anion, and tautomer).[33] To confirm that an analogous situation occurs for hydroxy-benzo[*c*]coumarins, fluorometric pH titration was performed for compound **3i** so that emission bands could be unambiguously assigned (see Figure S3 in the Supporting Information). It was found that the acidic form displays emission at 405 nm, whereas fluorescence of the anion appears at 450 nm. The fact that fluorescence of

the acidic form is not observed at pH values greater than pH 2 confirms that benzocoumarin **3i** is a very strong acid in the excited state. It appears that the presence of the weakly electron-withdrawing fluorine atoms (in ring C) alters the order of energetically close (nπ*) and (ππ*) states, resulting in a decrease in Φ_{fl}. Varying these substituents in ring C does not result in large shifts for these compounds and does not seem to follow a predictable pattern. On the other hand, the effect of simple alkyl substituents is rather negligible in these cases. The presence of an additional hydroxy group at position 1 of compound **3h** does not alter this delicate balance either, resulting in a moderate quantum yield of fluorescence (16%). Bisbenzo[*c*]coumarin **17** displays a larger Stokes shift than its parent compound **3i**, although the fluorescence quantum yields dropped significantly. Again, this outcome is attributed to reversal of the order of (nπ*) and (ππ*) states rather than to the presence of an additional C–C bond allowing internal conversion followed by vibrational relaxation. Both aldehyde **18** and imine **20** possess low fluorescence in solution but strong, red fluorescence in the solid state.

Table 2. Optical properties of benzo[*c*]coumarins.

Compound	λ_{abs} [nm]	λ_{em} [nm]	Φ_{fl} [%][a]	Stokes shift [cm^{-1}]
3a	334	427	21	6500
Umbelliferone	325	400	8	5800[b]
3b	370	422	8	3300
3c	339	443	3	6900
3d	351	423	16	4900
3e	368	557	0.3	9200
3f	338	427	13	6200
3h	341	438	16	6500
3i	332	434	18	7100
3j	375	452	0.1	4400
3k	339	454	5	7500
3l	375	–	–	–
5	350	451	8	6400
5′[c]	357	450	–	5800[d]
6	399	460	4	3300
8	341	425	36	5800
10a	304	408	5	8400
10b	321	426	5	7700
10c	376	453	9	4500
11a	473	–	–	–
11b	418	–	–	–
12a	351	–	–	–
12b	330	–	–	–
13	341	457	3	7400
14	323	522	2	11800
15	311	508	0.8	12500
16	321	422	0.1	7500
17	329	444	0.2	7900
18	401	542	5	6500
20	467	566	1[e]	3800

[a] Determined in DMF using quinine sulfate as standard. [b] Data in DMF.[30] [c] 8-Hydroxybenzo[*h*]coumarin. [d] Data in DMF.[34a] [e] Determined in CH_2Cl_2 using Rhodamine 6G as standard.

For amino-substituted benzo[*c*]coumarins, there is also a strong dependence of the optical properties on the position of the amino group. When compared with **3a**, the presence of a tertiary amino group at ring C typically shifts the absorption hypsochromically, although a redshift is observed in the case of derivative **10c**, which possesses a morpholine ring in direct proximity to the carbonyl group (Figure 2, Table 2). The hypsochromic shift is most probably caused by a decreased accepting ability of the ring C imparted by an amino group, which leads to a weaker intramolecular charge transfer (ICT). The presence of an additional amino group at position 6 or 8 in coumarin directly triggers a non-emissive state. In analogy, dyes **12a** and **12b**, bearing NH_2 in positions 2 or 4 (ring A), do not display any measurable fluorescence, whereas compounds bearing a tertiary amino groups at positions 7 or 9 (**10a**–**c**, ring C) have Φ_{fl} ca. 5–9%. Nevertheless, their λ_{em} (ca. 410–450 nm) is far from the value reported for analogous 7-hydroxybenzo[*c*]coumarins by Langer and co-workers[12] (ca. 480 nm), which implies excited-state intramolecular proton transfer (ESIPT) in the latter case as the most probable explanation.

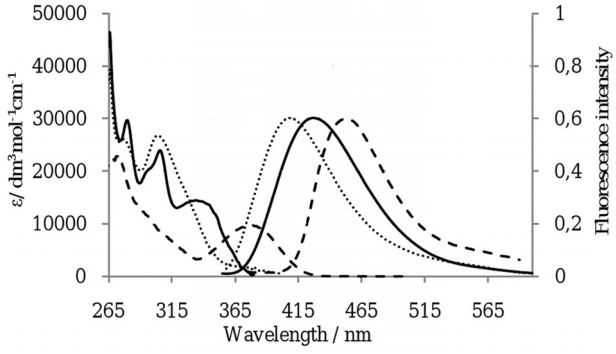


Figure 2. Absorption and emission of **3a** (solid line), **10a** (dotted line) and **10c** (dashed line) in DMF (excitation at 310 nm).

The presence of a nitro group, according to expectations, had a strong influence on both the absorption and emission properties of the studied molecules. Regardless of the location of the nitro group, its presence shifted the absorption maximum to ca. 370–480 nm in dyes **3e**, **3j**, **11a** and **11b**. The nitro group is known to quench fluorescence.[34] Nevertheless, in contrast to nonfluorescent dyes **11a** and **11b** (possessing a nitro group attached to ring A), compounds **3e** and **3j** possess low but measurable fluorescence (Table 2). These benzo[*c*]coumarins have a push-pull arrangement of substituents and, in this respect, bear analogy to fluorescent π-expanded coumarins possessing a 4-nitrophenylvinyl group at position 3, as reported previously.[35]

A variable bathochromic shift of absorption is seen when the benzo[*c*]coumarin chromophore is fused with an additional benzene ring (Scheme 1, compounds **5** and **6**). Various types of benzocoumarin have been synthesized and studied in the last decades.[36] Among them, linear benzo[*g*]-coumarins have recently attracted the widest attention due to their superb fluorescence properties.[36c–36f] Direct comparison of compound **5** and structurally related 8-hydroxybenzo[*h*]coumarin[36a] (**5′**, Table 2) enabled us to conclude that the addition of a benzene ring does not shift either absorption or fluorescence. Among the possible expansions of coumarin through fusion with the benzene ring, attachment of benzo[*c*]coumarins had a relatively small effect. Al-

though dyes **5** and **6** are regioisomers, they differed significantly in emission properties (Φ_{fl} are 8 and 4%, respectively). Vibronic coupling remains the most likely channel for nonradiative deactivation of their electronically excited states. However, intersystem crossing as a dominant process has also been observed for some coumarin derivatives.[37a] The highest fluorescence quantum yield (36%) was measured for 7,9-dihydroxy-4*H*-thieno[2,3-*c*]coumarin (**8**), which otherwise possessed analogous optical properties to benzo-analogue **3h**.

Ether **9**, according to expectations based on the weaker electron-donating properties of OCH_2CO_2tBu group versus OH, displayed hypsochromically shifted absorption and emission. In analogy to 7-methoxycoumarin, benzocoumarin **9** exhibited low fluorescence in aprotic solvents (Φ_{fl} = 4% in toluene), whereas it strongly fluoresced in protic solvents (Φ_{fl} = 25% in methanol) (Figure 3, Table 3). In contrast to 8-methoxybenzo[*g*]coumarin,[21] the bathochromic shift of emission (27 nm) was not accompanied by any shift of absorption (Table 3).

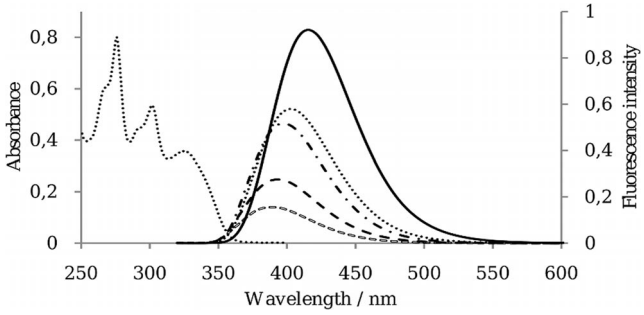


Figure 3. Absorption (dotted line) and emission spectra (excitation at 310 nm) of **9** in toluene (double dashed line), ethyl acetate (dashed line), dichloromethane (dotted/solid line), acetonitrile (dotted line) and methanol (solid line).

Table 3. Optical properties of dye **9** depending on the solvent.

Solvent	λ_{abs} [nm]	ε [$M^{-1}cm^{-1}$]	λ_{em} [nm]	Φ_{fl} [%][a]	Stokes shift [cm^{-1}]
Toluene	327	6300	389	4	4800
EtOAc	327	6600	393	6	5100
CH_2Cl_2	327	6900	398	11	5500
MeCN	327	6900	402	12	5700
MeOH	327	6500	416	25	6500

[a] Determined by using quinine sulfate as standard.

The optical characteristics are different for benzo[*c*]coumarin **3i** (possessing an OH group), which can be considered as a direct analogue of umbelliferone (Figure 4). An appreciable bathochromic shift (ca. 30 nm) of emission was observed upon moving from nonpolar solvents towards polar aprotic solvents, which can be related to the fact that, following excitation, the solvent cage undergoes relaxation, i.e., a reorganization, leading to a relaxed state of minimum free energy (the higher polarity of the solvent, the larger the redshift of the emission spectrum). On the other hand, in contrast to what was observed for compound **9**, the fluorescence quantum yield drastically decreased in MeOH [Φ_{fl} = 3% (toluene), 8% (EtOAc), 10% (CH_2Cl_2), 17% (CH_3CN), 18% (DMF), 4% (MeOH)]. Such a dramatic change can presumably be attributed to the fact that the hydrogen bond enhances excited-state proton transfer (ESPT)[31a,32,37b,37c] and intersystem crossing.[37d] In analogy to compound **9**, no solvent-dependent solvatochromism of absorption was observed.

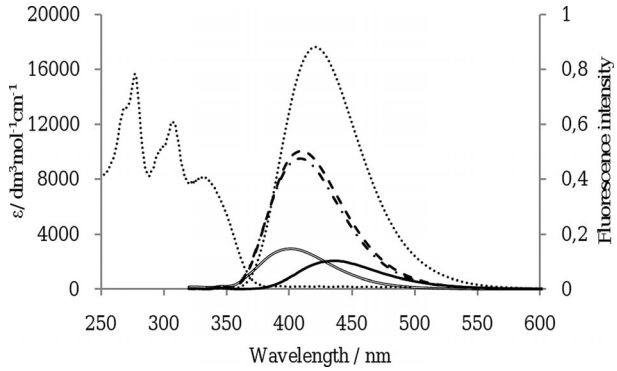


Figure 4. Absorption (dotted line) and emission spectra (excitation at 310 nm) of **3i** in toluene (double solid line), ethyl acetate (dashed line), dichloromethane (dotted/solid line), acetonitrile (dotted line), methanol (solid line).

Simple 1,4-benzoxazin-2-ones possess λ_{abs} ca. 280 nm and λ_{em} ca. 420 nm whereas the presence of a push-pull system shifts these values to 360 and 440 nm, respectively.[38] Fluorescence quantum yields are typically not high, and these compounds were studied as photogenerators of singlet oxygen.[38] Derivatives of 1,4-benzoxazin-2-one, bearing a dimethylamino group at position 7, have been utilized as a fluorescent chemodosimeter for cysteine.[39] For substituted 1,4-benzoxazin-2-one, a large increase in the dipole moment of the molecule can be expected during the excitation $S_0 \rightarrow S_1$, which will result in a large rearrangement of the surrounding solvent molecules around the excited state. Thus, the energy level of this excited state will be markedly lowered before the emission takes place, with respect to the energy level of its Franck–Condon excited state.[40] Hybrids of 1,4-benzoxazin-2-ones and benzo[*c*]coumarins **13**–**16** possess rather low Φ_{fl} but high Stokes shifts. In analogy to simpler 1,4-benzoxazinones,[38–41] the presence of an ester group causes a further decrease in Φ_{fl} (Figure 5, Table 2). Needless to say, large Stokes shifts always indicate significant changes in the electronic structure between the ground and the first excited state. Because compounds **13**–**16** have rather limited possibilities of appreciable geometry reorganization in the excited state, ICT is the only explanation.

Collecting the photophysical parameters of this large number of fluorophores enabled us to demonstrate that the introduction of many types of substituents (such as alkyls, F, tertiary amines at ring C) does not substantially decrease the fluorescence quantum yield of 3-hydroxybenzo[*c*]coumarins. On the other hand, π-expansion of that chromophore either by fusion with an additional benzene ring or by transformation into 1,4-benzoxazinones, activates various radiationless deactivation channels. It seems that the

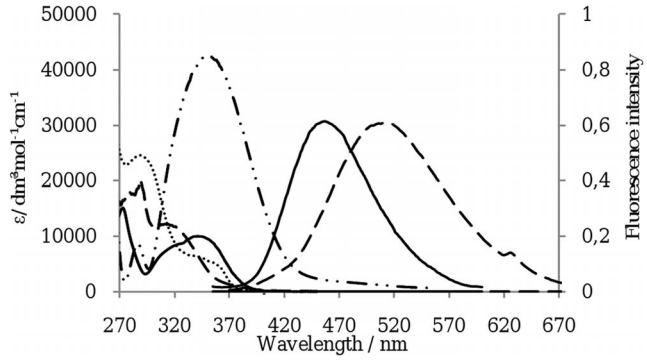


Figure 5. Absorption of compounds **12a** (solid/dotted line) and **12b** (dotted line), as well as absorption and emission of compounds **13** (solid line) and **15** (dashed line) in DMF (excitation at 310 nm).

combination of replacement of the benzene unit with various five-membered heterocycles as well as transformation of the OH into elaborated ethers is the most promising direction for further studies.

Interestingly, for complex 1,4-benzoxazinone **13**, only moderate solvatochromism was observed (Figure 6). Again, the fluorescence quantum yield decreased sharply in protic solvent [Φ_{fl} = 1.7% (toluene), 1.5% (EtOAc), 2.1% (CH_2Cl_2), 1.1% (CH_3CN), 3.0% (DMF), 0.3% (MeOH)].

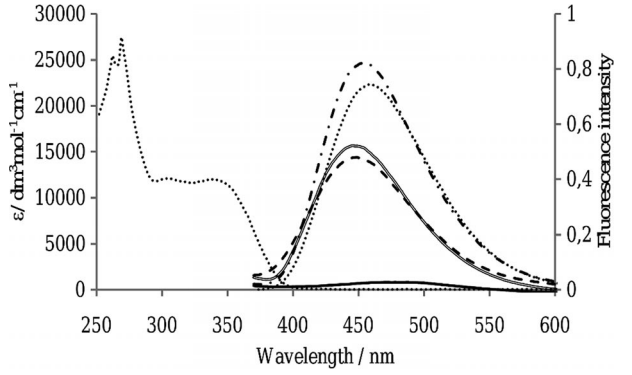


Figure 6. Absorption (dotted line) and emission spectra (excitation at 310 nm) of **13** in toluene (dashed line), ethyl acetate (double solid line), dichloromethane (dotted/solid line), acetonitrile (dotted line), methanol (solid line).

Conclusions

We have demonstrated that by arranging various substituents and/or additional extension of the chromophore it is possible to easily manipulate the emission characteristics of benzo[*c*]coumarin, with λ_{max} ranging from 420 to 560 nm. These functional dyes are easily accessible either through Hurtley condensation or by efficient transformation of its products. 3-Bromothiophene-2-carboxylic acid was also effective in this reaction.

The fusion of coumarin to a benzene ring at positions 3 and 4 leads to compounds lacking the reactive α,β-unsaturated ester moiety. Consequently, 3-hydroxybenzo[*c*]coumarins were shown to have more predictable reactivity (than 7-hydroxycoumarins) and to undergo both various electrophilic aromatic substitutions and oxidative aromatic coupling.

The replacement of the C–C double bond in 7-hydroxycoumarin with the benzene unit bathochromically shifts both absorption and emission only ca. 10–25 nm. At the same time, Φ_{fl} increases from 8 to 21% and the Stokes shifts remain almost the same. Systematic optical studies of substituted benzo[*c*]coumarins proved that most of these compounds are characterized by large Stokes shifts. Replacement of the OH group with OCH_2CO_2tBu makes it possible to obtain more soluble compounds displaying an attractive phenomenon − a strong dependence of fluorescence on solvent polarity. The most promising compound, 7,9-dihydroxy-thieno[2,3-*c*]coumarin (**8**), possesses a high fluorescence quantum yield (36%) while its calculated Stokes shift remained relatively large (5800 cm^{-1}).

The addition of the 1,4-benzoxazin-2-one ring in either linear or angular fashion to the benzo[*c*]coumarin chromophore does not shift absorption but red-shifts emission considerably. The other notable findings are as follows: (1) In most cases, π-expansion of the benzo[*c*]coumarin chromophore leads to compounds with bathochromically shifted absorption and lower Φ_{fl} when compared with the parent molecule; and (2) the presence of an auxochromic amino group shifts the absorption bathochromically or hypsochromically depending on the exact location of the amino group. These results are not only of theoretical significance in that they provide the first comprehensive study of the optical properties of derivatives and analogues of benzo[*c*]-coumarin, but they may also open the door to practical applications.

Experimental Section

General: All reagents and solvents were purchased from commercial sources and were used as received unless otherwise noted. Reagent-grade solvents (Et_2O, CH_2Cl_2, hexanes) were distilled prior to use. DMF was dried with magnesium sulfate, then distilled and stored under argon. Transformations with moisture- and oxygen-sensitive compounds were performed under a stream of argon. The reaction progress was monitored by means of thin-layer chromatography (TLC), which was performed on aluminum foil plates, covered with Silica gel 60 F_{254} (Merck) or Aluminum oxide 60 F_{254} (neutral, Merck). Product purification was achieved by means of column chromatography with Kieselgel 60 (Merck) or Aluminum oxide (Fluka). Occasionally, dry column vacuum chromatography (DCVC) for purification of products obtained by palladium-catalyzed protocol was performed by using Silica gel Type D 5F. The identity and purity of prepared compounds were established by ^1H and ^{13}C NMR spectrometry as well as by MS-spectrometry (EI-MS or ESI-MS). NMR spectra were measured with Bruker AM 500 MHz, Bruker AM 600 MHz, Varian 600 MHz, Varian 400 MHz or Varian 200 MHz instruments with TMS as internal standard. All chemical shifts are given in ppm. All melting points for crystalline products were measured with automated melting point apparatus EZ-MELT and are given without correction. 2-Bromo-5-nitrobenzoic acid was synthesized according to a previously published procedure.[42]

General Procedure for the Synthesis of Benzo[*c*]coumarins 3, 5, 6, 8:[15] A 100 mL two-necked round-bottomed flask was equipped with reflux condenser and flushed with argon. Phenol **1** (20 mmol, 2.0 equiv.), acid **2** (10 mmol, 1.0 equiv.) and an aqueous solution of sodium hydroxide (0.80 g, 20 mmol, 2.0 equiv. in 50 μL of water) were added. The resulting solution was stirred at 60 °C for 15 min. Aq. $CuSO_4$ (10%, 0.5 mL) was added dropwise to the hot reaction mixture under a positive pressure of argon. Heating was continued at 95 °C for an additional 3 h, followed by stirring overnight at room temperature. The precipitate was filtered off, washed with a significant amount of water, and dried under high vacuum. Crude products were recrystallized from acetic acid unless otherwise noted.

3-Hydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-one (3a): According to the general procedure, *o*-bromobenzoic acid (2.01 g) and resorcinol (2.20 g) were reacted, affording **3a** (1.48 g, 70%) as white crystals. R_f = 0.46 (CH_2Cl_2/acetone, 98:2); m.p. 236.5–237.5 °C (AcOH) (ref.[3c] 235–236 °C); spectral and physical properties concurred with published data.[3c] $C_{13}H_8O_3$ (212.20): calcd. C 73.58, H 3.80; found C 73.28, H 4.13.

9-Fluoro-3-hydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-one (3b): According to the general procedure, 2-bromo-4-fluorobenzoic acid (2.19 g) and resorcinol (2.20 g) were reacted, affording **3b** (1.01 g, 44%) as white crystals. R_f = 0.29 ($CHCl_3$/acetone, 98:2); m.p. 305.5–306.5 °C (AcOH). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.47 (br. s, 1 H, OH), 8.23 (dd, $^3J_1$ = 8.8, $^3J_2$ = 6.0 Hz, 1 H, C7-H), 8.16 (d, ^3J = 8.8 Hz, 1 H, C10-H), 8.11 (dd, $^3J_1$ = 10.5, $^3J_2$ = 2.4 Hz, 1 H, C8-H), 7.38 (dt, ^3J = 8.6, 2.4 Hz, 1 H, C2-H), 6.83 (dd, $^3J_1$ = 8.6, $^3J_2$ = 2.4 Hz, 1 H, C1-H), 6.74 (d, ^3J = 2.4 Hz, 1 H, C4-H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 166.0 (C9), 161.0 (C6), 160.3 (C3), 153.0 (C4a), 138.8 (C10a), 133.8 (C7), 126.0 (C1), 116.0 (C6a), 113.7 (C10), 109.4 (C10b), 108.6 (C2), 108.4 (C8), 103.3 (C4) ppm. HRMS (EI, 70 eV): calcd for $C_{13}H_7O_3F$ [M$^+$] 230.0379; found 230.0373.

8,9-Difluoro-3-hydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-one (3c): According to the general procedure, 2-bromo-4,5-difluorobenzoic acid (2.37 g) and resorcinol (2.20 g) were reacted, affording **3c** (1.04 g, 42%) as white crystals. R_f = 0.46 ($CHCl_3$/acetone, 98:2); m.p. 261–262 °C (AcOH). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.47 (br. s, 1 H, OH), 8.37 (dd, $^3J_1$ = 7.4, $^3J_2$ = 4.6 Hz, 1 H, C7-H), 8.11 (d, ^3J = 8.9 Hz, 1 H, C1-H), 8.08 (dd, $^3J_1$ = 8.2, $^3J_2$ = 2.4 Hz, 1 H, C10-H), 6.82 (dd, $^3J_1$ = 8.6, $^3J_2$ = 2.4 Hz, 1 H, C2-H), 6.72 (d, ^3J = 2.4 Hz, 1 H, C4-H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.9 (C6), 159.5 (C3), 156.1 (C9), 154.0 (C8), 152.6 (C4a), 134.6 (C10a), 125.8 (C1), 118.7 (C6a), 116.7 (C10), 113.8 (C2), 111.5 (C7), 108.8 (C10b), 103.4 (C4) ppm. HRMS (EI, 70 eV): calcd. for $C_{13}H_6O_3F_2$ [M$^+$] 248.0285; found 248.0289. $C_{13}H_6O_3F_2$ (238.03): C 62.91, H 2.44, F 15.31; found C 62.71, H 2.40, F 15.37.

7-Fluoro-3-hydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-one (3d): According to the general procedure, 2-bromo-6-fluorobenzoic acid (2.19 g) and resorcinol (2.20 g) were reacted, affording **3d** (0.41 g, 18%) as white crystals. R_f = 0.38 ($CHCl_3$/MeOH, 99:1); m.p. 261–262 °C (AcOH). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.46 (br. s, 1 H, OH), 8.14 (d, ^3J = 8.8 Hz, 1 H, C10-H), 8.07 (d, ^3J = 8.1 Hz, 1 H, C8-H), 7.88 (m, 1 H, C9-H), 7.33 (dd, $^3J_1$ = 12.0, $^3J_2$ = 8.2 Hz, 1 H, C2-H), 6.83 (dd, $^3J_1$ = 8.6, $^3J_2$ = 1.7 Hz, 1 H, C1-H), 6.71 (d, ^3J = 1.7 Hz, 1 H, C4-H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 162.0 (C7), 160.9 (C6), 156.6 (C3), 152.9 (C4a), 138.2 (C10a), 137.3 (C9), 125.9 (C1), 118.1 (C10b), 115.2 (C10), 113.7 (C6a), 109.1 (C8), 108.4 (C2), 103.2 (C4) ppm. HRMS (EI, 70 eV): calcd. for $C_{13}H_7O_3F$ [M$^+$] 230.0379; found 230.0386.

3-Hydroxy-8-nitro-6*H*-dibenzo[*b*,*d*]pyran-6-one (3e): According to the general procedure, 2-bromo-5-nitrobenzoic acid (2.46 g) and resorcinol (2.20 g) were reacted, affording **3e** (1.03 g, 40%) as yellow crystals. R_f = 0.36 ($CHCl_3$/acetone, 98:2); m.p. 218–220 °C (AcOH). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.73 (br. s, 1 H, OH), 8.77 (d, ^3J = 2.4 Hz, 1 H, C7-H), 8.56 (dd, $^3J_1$ = 9.0, $^3J_2$ = 2.5 Hz, 1 H, C9-H), 8.44 (d, ^3J = 9.0 Hz, 1 H, C10-H), 8.22 (d, ^3J = 8.9 Hz, 1 H, C1-H), 6.87 (dd, $^3J_1$ = 8.8,$^3J_2$ = 2.4 Hz, 1 H, C2-H), 6.76 (d, ^3J = 2.4 Hz, 1 H, C4-H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 162.3 (C6), 159.8 (C3), 153.7 (C4a), 146.2 (C8), 140.9 (C10a), 129.4 (C7), 126.8 (C1), 125.5 (C9), 124.0 (C10), 120.0 (C6a), 114.2 (C2), 108.8 (C10b), 103.5 (C4) ppm. HRMS (EI, 70 eV): calcd. for $C_{13}H_7NO_5$ [M$^+$] 257.0324; found 257.0313.

3-Hydroxy-4-methyl-6*H*-dibenzo[*b*,*d*]pyran-6-one (3f): According to the general procedure, 2-bromobenzoic acid (2.01 g) and 2-methylresorcinol (2.48 g) were reacted, affording **3f** (0.97 g, 43%) as beige crystals. R_f = 0.38 (CH_2Cl_2/acetone, 98:2); m.p. 250–252 °C (AcOH). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.24 (br. s, 1 H, OH), 8.23 (d, ^3J = 8.1 Hz, 1 H, C7-H), 8.18 (dd, $^3J_1$ = 8.0, $^3J_2$ = 2.5 Hz, 1 H, C10-H), 8.00 (d, ^3J = 8.8 Hz, 1 H, C1-H), 7.86 (dt, $^3J_1$ = 7.6, $^3J_2$ = 1.4 Hz, 1 H, C9-H), 7.54 (dt, $^3J_1$ = 7.6, $^3J_2$ = 1.0 Hz, 1 H, C8-H), 6.90 (d, ^3J = 8.6 Hz, 1 H, C2-H), 2.20 (s, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 161.1 (C6), 158.1 (C3), 150.6 (C4a), 136.0 (C9), 135.7 (C7), 130.1 (C1), 128.0 (C6a), 122.2 (C10), 121.7 (C8), 119.1 (C10a), 112.5 (C2), 111.8 (C10b), 109.8 (C4), 8.6 (CH_3) ppm. HRMS (EI, 70 eV): calcd. for $C_{14}H_{10}O_3$ [M$^+$] 226.0630; found 226.0620. $C_{14}H_{10}O_3$ (226.23): calcd. C 74.33, H 4.46; found C 74.03, H 4.57.

1,3-Dihydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-one (3h): According to the general procedure, 2-bromobenzoic acid (2.01 g) and phloroglucinol (2.52 g) were reacted, affording **3h** (1.35 g, 59%) as yellowish crystals. R_f = 0.43 (CH_2Cl_2/acetone, 9:1); m.p. 300–302 °C (AcOH). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.88 (br. s, 1 H, C3-OH), 10.12 (br. s, 1 H, C1-OH), 8.94 (d, ^3J = 8.0 Hz, 1 H, C7-H), 8.17 (d, ^3J = 7.4 Hz, 1 H, C10-H), 7.81 (t, ^3J = 7.1 Hz, 1 H, C9-H), 7.47 (t, ^3J = 7.1 Hz, 1 H, C8-H), 6.39 (s, 1 H, C4-H), 6.25 (s, 1 H, C2-H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.7 (C4a), 159.2 (C6), 157.7 (C3), 153.3 (C1), 135.4 (C10a), 135.0 (C9), 129.4 (C7), 126.4 (C8), 125.8 (C10), 118.4 (C6a), 99.8 (C2), 98.6 (C10b), 95.1 (C4) ppm. Spectral and physical properties concurred with published data.[31]

2-Hexyl-3-hydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-one (3i): According to the general procedure, 2-bromobenzoic acid (2.01 g) and 4-hexylresorcinol (3.88 g) were reacted, affording **3i** (1.51 g, 51%) as yellowish crystals. R_f = 0.34 (CH_2Cl_2/acetone, 98:2); m.p. 182–184 °C (AcOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.39 (dd, $^3J_1$ = 7.9, $^3J_2$ = 1.6 Hz, 1 H, C7-H), 8.06 (d, ^3J = 8.2 Hz, 1 H, C10-H), 7.82 (m, 1 H, C9-H), 7.80 (s, 1 H, C1-H), 7.52 (dt, $^3J_1$ = 7.6, $^3J_2$ = 1.2 Hz, 1 H, C8-H), 6.98 (s, 1 H, C4-H), 5.66 (br. s, 1 H, OH), 2.73 (t, ^3J = 7.5 Hz, 2 H, $ArCH_2$), 1.70 (quint, ^3J = 7.5 Hz, 2 H, $ArCH_2CH_2$), 1.44 [m, 2 H, $CH_3(CH_2)_2CH_2$], 1.36 (quint, 4 H, $CH_3CH_2CH_2$), 0.92 (t, ^3J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.0 (C6), 155.8 (C3), 150.5 (C4a), 135.5 (C10a), 134.9 (C1), 130.6 (C9), 127.6 (C7), 126.6 (C6a), 123.8 (C8), 121.1 (C10), 120.0 (C2), 111.0 (C10b), 103.8 (C4), 31.7 ($CH_3CH_2CH_2$), 29.9 ($ArCH_2CH_2$), 29.8 ($ArCH_2$), 29.2 ($ArCH_2CH_2CH_2$), 22.6 (CH_3CH_2), 14.1 (CH_3CH_2) ppm. HRMS (EI, 70 eV): calcd. for $C_{19}H_{20}O_3$ [M$^+$] 296.1412; found 296.1411. $C_{19}H_{20}O_3$ (296.37): calcd. C 77.00, H 6.74; found C 76.95, H 6.74.

1,3-Dihydroxy-8-nitro-6*H*-dibenzo[*b*,*d*]pyran-6-one (3j): According to the general procedure, 2-bromo-5-nitrobenzoic acid (2.46 g) and phloroglucinol (2.52 g) were reacted, affording **3j** (0.96 g, 35%) as

orange crystals. R_f = 0.31 (CH_2Cl_2/acetone, 1:1); m.p. 230–232 °C (AcOH). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 11.33 (br. s, 1 H, C3-OH), 10.55 (br. s, 1 H, C1-OH), 9.08 (d, ^3J = 9.1 Hz, 1 H, C7-H), 8.78 (d, ^3J = 2.4 Hz, 1 H, C10-H), 8.55 (dd, $^3J_1$ = 8.9, $^3J_2$ = 2.7 Hz, 1 H, C9-H), 6.42 (d, ^3J = 2.4 Hz, 1 H, C2-H), 6.29 (d, ^3J = 2.4 Hz, 1 H, C4-H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 162.2 (C4a), 160.3 (C3), 159.3 (C6), 155.7 (C1), 146.0 (C8), 141.7 (C10a), 129.2 (C9), 128.4 (C7), 125.6 (C10), 120.7 (C6a), 100.9 (C2), 99.7 (C10b), 97.0 (C4) ppm. HRMS (ESI): calcd. for $C_{13}H_7NO_6Na$ [M + Na]$^+$ 296.0166; found 296.0158.

2-Hexyl-3-hydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-one (3k): According to the general procedure, 2-bromo-5-(trifluoromethyl)benzoic acid (2.69 g) and 4-hexylresorcinol (3.88 g) were reacted, affording the crude product, which was purified by means of column chromatography (CH_2Cl_2/MeOH, 98:2) leading to **3k** (1.31 g, 36%) as yellowish crystals. R_f = 0.37 (CH_2Cl_2/MeOH, 98:2); m.p. 177–178 °C (CH_2Cl_2/MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.62 (s, 1 H, C7-H), 8.12 (d, ^3J = 8.4 Hz, 1 H, C10-H), 7.98 (d, ^3J = 8.2 Hz, 1 H, C9-H), 7.78 (s, 1 H, C1-H), 7.07 (s, 1 H, C4-H), 6.19 (br. s, 1 H, OH), 2.72 (t, ^3J = 7.7 Hz, 2 H, ArCH_2), 1.68 (quint, ^3J = 7.7 Hz, 2 H, ArCH_2CH_2), 1.42 [m, 2 H, $CH_3(CH_2)_2CH_2$], 1.34 (quint, 4 H, $CH_3CH_2CH_2$), 0.90 (t, ^3J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.2 (C6), 157.2 (C3), 151.0 (C4a), 138.4 (C10a), 131.1 (C9), 129.4 (q, CF_3), 128.0 (C7), 127.5 (C2), 124.3 (C1), 122.4 (C6a), 122.0 (C10), 119.8 (C8), 109.7 (C10b), 103.9 (C4), 31.9 ($CH_3CH_2CH_2$), 29.9 (ArCH_2CH_2), 29.7 (ArCH_2), 29.2 (Ar$CH_2CH_2CH_2$), 22.6 (CH_3CH_2), 14.1 (CH_3CH_2) ppm. HRMS (EI, 70 eV): calcd. for $C_{20}H_{20}O_3F_3$ [M + H$^+$] 365.1365; found 365.1360.

3-Hydroxy-8-iodo-6*H*-dibenzo[*b*,*d*]pyran-6-one (3l): According to the general procedure, 2-bromo-5-iodobenzoic acid (3.26 g) and resorcinol (2.20 g) were reacted, affording **3l** (1.31 g, 39%) as yellowish crystals. R_f = 0.48 ($CHCl_3$/acetone, 98:2); m.p. 266–268 °C (AcOH). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 11.00 (br. s, 1 H, OH), 8.38 (d, ^3J = 1.8 Hz, 1 H, C7-H), 8.13 (dd, $^3J_1$ = 8.5, $^3J_2$ = 1.8 Hz, 1 H, C10-H), 8.08 (d, ^3J = 8.8 Hz, 1 H, C9-H), 7.99 (d, ^3J = 8.5 Hz, 1 H, C1-H), 6.79 (d, ^3J = 8.6 Hz, 1 H, C2-H), 6.68 (s, 1 H, C4-H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 162.4 (C6), 159.9 (C3), 152.9 (C4a), 143.7 (C9), 137.9 (C7), 135.1 (C10a), 125.2 (C1), 124.2 (C10), 121.0 (C6a), 114.3 (C10b), 108.4 (C2), 103.6 (C4), 92.5 (C8) ppm. HRMS (EI, 70 eV): calcd. for $C_{13}H_7O_3I$ [M$^+$] 337.9440; found 337.9435.

2-Hydroxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (5): According to the general procedure, 2-bromobenzoic acid (2.01 g) and 1,6-dihydroxynaphthalene (3.20 g) were reacted, affording the crude product, which was purified by means of column chromatography (CH_2Cl_2/acetone, 98:2) leading to the desired product **5** (0.39 g, 15%) as beige crystals. R_f = 0.56 (CH_2Cl_2/acetone, 96:4); m.p. 290–292 °C. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 10.22 (br. s, 1 H), 8.40 (d, ^3J = 8.1 Hz, 1 H), 8.26 (dd, $^3J_1$ = 7.8, $^3J_2$ = 1.1 Hz, 1 H), 8.22 (m, 2 H), 7.92 (dt, $^3J_1$ = 7.3, $^3J_2$ = 1.4 Hz, 1 H), 7.66 (d, ^3J = 8.8 Hz, 1 H), 7.62 (dt, $^3J_1$ = 7.5, $^3J_2$ = 1.0 Hz, 1 H), 7.22 (m, 2 H) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 160.8, 157.7, 147.3, 136.5, 135.9, 135.7, 130.2, 128.9, 123.7, 123.4, 123.0, 120.9, 120.3, 119.9, 117.5, 110.7, 109.9 ppm. HRMS (EI, 70 eV): calcd. for $C_{17}H_{10}O_3$ [M$^+$] 262.0630; found 262.0620.

8-Hydroxy-5*H*-dibenzo[*c*,*f*]chromen-5-one (6): According to the general procedure, 2-bromobenzoic acid (2.01 g) and 1,3-dihydroxynaphthalene (3.20 g) were reacted, affording the crude product, which was purified by means of column chromatography (CH_2Cl_2/acetone, 98:2) leading to the desired product **6** (1.26 g, 48%) as beige crystals. R_f = 0.32 (CH_2Cl_2/acetone, 98:2); m.p. 290–292 °C. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 11.25 (br. s, 1 H), 8.69 (d, ^3J = 8.7 Hz, 1 H), 8.53 (d, ^3J = 8.2 Hz, 1 H), 8.26 (m, 2 H), 7.91 (dt, $^3J_1$ = 7.1, $^3J_2$ = 1.4 Hz, 1 H), 7.69 (dt, $^3J_1$ = 7.1, $^3J_2$ = 1.2 Hz, 1 H), 7.57 (t, ^3J = 7.6 Hz, 1 H), 7.53 (t, ^3J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 161.0, 156.7, 151.6, 135.7, 135.5, 130.5, 129.7, 129.0, 127.4, 125.7, 125.1, 124.9, 124.0, 123.5, 120.5, 104.3, 99.2 ppm. HRMS (EI, 70 eV): calcd. for $C_{17}H_{10}O_3$ [M$^+$] 262.0630; found 262.0624.

7,9-Dihydroxy-4*H*-thieno[2,3-*c*]chromen-4-one (8): According to the general procedure, 3-bromothiophen-2-carboxylic acid (2.07 g) and phloroglucinol (2.52 g) were reacted, affording the crude product, which was purified by means of column chromatography (CH_2Cl_2/EtOAc, 7:3) leading to **8** (0.94 g, 40%) as yellowish crystals. R_f = 0.36 (CH_2Cl_2/EtOAc, 7:3); m.p. 265 °C (dec) (CH_2Cl_2/EtOAc). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.80 (s, 1 H, C7-OH), 10.16 (s, 1 H, C9-OH), 8.24 (d, ^3J = 5.2 Hz, 1 H, C1-H), 8.02 (d, ^3J = 5.2 Hz, 1 H, C2-H), 6.37 (s, 1 H, C6-H), 6.31 (s, 1 H, C8-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 160.4 (C7), 157.6 (C5a), 156.2 (C9), 155.4 (C4), 144.9 (C9b), 138.3 (C2), 127.1 (C3a), 119.7 (C1), 100.2 (C9a), 98.6 (C8), 95.3 (C6) ppm. HRMS (EI, 70 eV): calcd. for $C_{11}H_6O_4S$ [M$^+$] 233.9987; found 233.9979.

***tert*-Butyl 2-[(6-Oxo-6*H*-benzo[*c*]chromen-3-yl)oxy]acetate (9):** A mixture of benzo[*c*]coumarin **3a** (0.53 g, 2.5 mmol, 1.0 equiv.), *tert*-butyl bromoacetate (0.50 mL, 3.4 mmol, 1.4 equiv.), potassium carbonate (0.47 g, 3.4 mmol, 1.4 equiv.), and potassium iodide (0.16 g, 1.0 mmol, 0.4 equiv.) in anhydrous DMF (5 mL) was heated at 130 °C for 20 h in a pressure tube (Aldrich, 38 mL) under an inert atmosphere. The reaction was cooled and poured into water and extracted with CH_2Cl_2 (3× 30 mL), and the combined organic phases were dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was recrystallized from ethyl acetate, affording the expected product **9** (0.69 g, 85%) as white crystals. R_f = 0.33 (CH_2Cl_2); m.p. 145–147 °C (EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.36 (dd, $^3J_1$ = 8.0, $^3J_2$ = 1.0 Hz, 1 H, C7-H), 8.01 (d, ^3J = 8.1 Hz, 1 H, C10-H), 7.97 (d, ^3J = 8.8 Hz, 1 H, C1-H), 7.79 (dt, $^3J_1$ = 7.7, $^3J_2$ = 1.5 Hz, 1 H, C9-H), 7.52 (dt, $^3J_1$ = 7.6, $^3J_2$ = 1.0 Hz, 1 H, C8-H), 6.96 (dd, $^3J_1$ = 8.8, $^3J_2$ = 2.6 Hz, 1 H, C2-H), 6.82 (d, ^3J = 2.5 Hz, 1 H, C4-H), 4.59 (s, 2 H, OCH_2), 1.51 (s, 9 H, 3× CH_3) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 167.2 (CO_2tBu), 161.3 (C6), 159.7 (C3), 152.4 (C4a), 135.0 (C9), 134.9 (C7), 130.5 (C1), 128.0 (C6a), 123.9 (C10), 121.1 (C8), 120.1 (C10a), 112.8 (C2), 111.9 (C10b), 102.4 (C4), 82.9 [$C(CH_3)_3$], 65.7 (OCH_2), 28.0 [$C(CH_3)_3$] ppm. HRMS (ESI): calcd. for $C_{19}H_{19}O_5$ [M + H]$^+$ 327.1232; found 327.1227. $C_{19}H_{18}O_5$ (326.35): calcd. C 69.93, H 5.56; found C 69.68, H 5.68.

General Procedure for the Synthesis of Compounds 10a–c:[43] A mixture of parent benzo[*c*]coumarin **3** (0.30 mmol, 1.0 equiv.), morpholine (160 μL, 1.8 mmol, 6.0 equiv.) and potassium carbonate (50 mg, 0.36 mmol, 1.2 equiv.) in anhydrous DMF (2 mL) was heated at 120 °C for 20 h in a pressure tube (Aldrich, 38 mL) under an inert atmosphere. The reaction was cooled and poured into water and extracted with ethyl acetate (3× 10 mL). The combined organic phases were dried with anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography (silica; pentane/EtOAc, 1:9) to afford the expected product **10a**–**c**.

3-Hydroxy-9-(morpholin-4-yl)-6*H*-dibenzo[*b*,*d*]pyran-6-one (10a): According to the general procedure, benzo[*c*]coumarin **3b** (69 mg) and morpholine (160 mg, 160 μL) were reacted, affording **10a** (45 mg, 50%) as white crystals. R_f = 0.33 (CH_2Cl_2/acetone, 96:4); m.p. 266–268 °C (DMA/hexanes). ^{1}H NMR (500 MHz, [D$_6$]-DMSO): δ = 10.33 (br. s, 1 H, OH), 8.21 (dd, $^3J_1$ = 9.0, $^3J_2$ =

3.2 Hz, 1 H, C7-H), 8.00 (dd, $^3J_1$ = 22.5, $^3J_2$ = 9.2 Hz, 1 H, C1-H), 7.21 (m, 2 H, C8-H and C10-H), 6.79 (dt, $^3J_1$ = 8.6, $^3J_2$ = 2.6 Hz, 1 H, C2-H), 6.72 (dd, $^3J_1$ = 25.0, $^3J_2$ = 2.5 Hz, 1 H, C4-H), 3.78 (m, 4 H, OCH_2), 3.49 (m, 4 H, NCH_2) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 159.5 (C6), 155.2 (C3), 154.4 (C4a), 152.5 (C9), 136.4 (C10a), 131.3 (C7), 125.0 (C1), 114.0 (C10), 112.6 (C6a), 109.8 (C2), 108.6 (C8), 106.3 (C10b), 103.4 (C4), 65.8 (2) (OCH_2), 46.6 (2) (NCH_2) ppm. HRMS (EI, 70 eV): calcd. for $C_{17}H_{15}NO_4$ [M$^+$] 297.1001; found 297.1010. $C_{17}H_{15}NO_4$ (297.31): calcd. C 68.68, H 5.09, N 4.71; found C 68.40, N 5.07, N 4.95.

8-Fluoro-3-hydroxy-9-(morpholin-4-yl)-6*H*-dibenzo[*b*,*d*]pyran-6-one (10b): According to the general procedure, benzo[*c*]coumarin **3c** (74 mg) and morpholine (160 mg, 160 μL) were reacted, affording **10b** (61 mg, 65%) as white crystals. R_f = 0.34 (CH_2Cl_2/acetone, 96:4); m.p. 274–276 °C (DMA/heaxanes). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.30 (br. s, 1 H, OH), 8.20 (d, ^3J = 8.5 Hz, 1 H, C7-H), 7.77 (d, ^3J = 13.6 Hz, 1 H, C1-H), 7.61 (d, ^3J = 8.2 Hz, 1 H, C10-H), 6.82 (dd, $^3J_1$ = 8.8, $^3J_2$ = 2.4 Hz, 1 H, C2-H), 6.73 (d, ^3J = 2.4 Hz, 1 H, C4-H), 3.79 (t, ^3J = 4.6 Hz, 4 H, OCH_2), 3.32 (t, ^3J = 4.6 Hz, 4 H, NCH_2) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.2 (C8), 154.7 (C6), 152.8 (C4a), 152.6 (C3), 146.5 (C9), 133.7 (C10a), 125.6 (C1), 116.4 (C7), 113.4 (C10), 112.1 (C6a), 110.6 (C10b), 109.5 (C2), 103.3 (C4), 66.4 (2× O*C*H$_2$), 50.3 (2× N*C*H$_2$) ppm. HRMS (EI, 70 eV): calcd. for $C_{17}H_{14}NO_4F$ [M$^+$] 315.0907; found 315.0912.

3-Hydroxy-7-(morpholin-4-yl)-6*H*-dibenzo[*b*,*d*]pyran-6-one (10c): According to the general procedure, benzo[*c*]coumarin **3d** (69 mg) and morpholine (160 mg, 160 μL) were reacted, affording **10c** (35 mg, 39%) as yellow crystals. R_f = 0.53 (CH_2Cl_2/acetone, 9:1); m.p. 238–241 °C (DMA/hexanes). ^{1}H NMR (500 MHz, [D$_6$]-DMSO): δ = 10.26 (br. s, 1 H, OH), 8.06 (d, ^3J = 8.8 Hz, 1 H, C10-H), 7.77 (dd, $^3J_1$ = 8.1, $^3J_2$ = 1.1 Hz, 1 H, C1-H), 7.71 (t, $^3J_1$ = 8.0 Hz, 1 H, C9-H), 7.08 (dd, $^3J_1$ = 8.1, $^3J_2$ = 1.1 Hz, 1 H, C8-H), 6.79 (dd, $^3J_1$ = 8.8, $^3J_2$ = 2.4 Hz, 1 H, C2-H), 6.66 (d, ^3J = 2.4 Hz, 1 H, C4-H), 3.79 (m, 4 H, OCH_2), 3.07 (m, 4 H, NCH_2) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.2 (C6), 157.9 (C3), 155.6 (C4a), 152.6 (C7), 138.4 (C10a), 135.9 (C9), 125.7 (C1), 117.3 (C6a), 114.6 (C8), 113.3 (C10), 110.2 (C2), 110.1 (C10b), 102.5 (C4), 66.7 (2× O*C*H$_2$), 53.0 (2× N-*C*H$_2$) ppm. HRMS (ESI): calcd. for $C_{17}H_{15}NO_4Na$ [M + Na]$^+$ 320.0893; found 320.0900. $C_{17}H_{15}NO_4$ (297.31): calcd. C 68.68, H 5.09, N 4.71; found C 68.52, N 5.02, N 4.56.

General Procedure for Nitration of Parent Benzo[*c*]coumarin Derivative:[22] Concentrated HNO_3 (0.40 mL, 6.0 mmol, 1.5 equiv.) was added to a stirred suspension of benzo[*c*]coumarin derivative (4.0 mmol, 1.0 equiv.) in glacial acetic acid (10 mL) and the resulting mixture was stirred at room temperature for 3 h. Water (10 mL) was poured into the reaction mixture, and stirring was continued for an additional 15 min. The crude product was filtered off, washed with water, dried under high vacuum and recrystallized from acetic acid if not otherwise noted.

3-Hydroxy-4-methyl-2-nitro-6*H*-dibenzo[*b*,*d*]pyran-6-one (11a): According to the general procedure, benzo[*c*]coumarin **3f** (0.91 g) and nitric acid (0.40 mL) were reacted, affording **11a** (1.01 g, 93%) as yellow crystals. R_f = 0.62 (CH_2Cl_2/acetone, 98:2); m.p. 277–279 °C (AcOH). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 10.24 (br. s, 1 H, OH), 8.81 (s, 1 H, C1-H), 8.45 (d, ^3J = 8.0 Hz, 1 H, C7-H), 8.23 (dd, $^3J_1$ = 8.0, $^3J_2$ = 1.2 Hz, 1 H, C10-H), 7.93 (dt, $^3J_1$ = 7.6, $^3J_2$ = 1.4 Hz, 1 H, C9-H), 7.66 (dt, $^3J_1$ = 7.6, $^3J_2$ = 1.0 Hz, 1 H, C8-H), 2.30 (s, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 159.2 (C6), 153.0 (C4a), 151.9 (C3), 135.4 (C9), 133.4 (C2), 133.1 (C10a), 129.5 (C7), 128.9 (C8), 122.5 (C10), 119.4 (C6a), 117.7 (C1), 115.7 (C10b), 110.5 (C4), 8.5 (*C*H$_3$) ppm. HRMS (EI, 70 eV): calcd for $C_{14}H_9O_5N$ [M$^+$] 271.0481; found 271.0472.

2-Hexyl-3-hydroxy-4-nitro-6*H*-dibenzo[*b*,*d*]pyran-6-one (11b): According to the general procedure, benzo[*c*]coumarin **3i** (1.18 g) and nitric acid (0.40 mL) were reacted, affording **11b** (1.24 g, 91%) as orange crystals. R_f = 0.28 (CH_2Cl_2); m.p. 147–149 °C (AcOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.59 (br. s, 1 H, OH), 8.39 (dd, ^3J = 8.0 Hz, 1 H, C7-H), 8.05 (m, 2 H, C10-H and C1-H), 7.88 (dt, $^3J_1$ = 7.5, $^3J_2$ = 1.4 Hz, 1 H, C9-H), 7.62 (dt, $^3J_1$ = 7.5, $^3J_2$ = 1.0 Hz, 1 H, C8-H), 2.80 (t, ^3J = 7.8 Hz, 2 H, Ar-CH_2-), 1.70 (quint, ^3J = 7.6 Hz, 2 H, ArCH_2CH_2), 1.44 [m, 2 H, $CH_3(CH_2)_2CH_2$], 1.37 (m, 4 H, $CH_3CH_2CH_2$), 0.92 (t, ^3J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1 (C6), 154.2 (C3), 144.1 (C4a), 135.4 (C1), 133.8 (C6a), 130.7 (C9), 129.1 (C2), 128.9 (C4), 128.7 (C7), 125.4 (C10a), 121.4 (C8), 119.6 (C10), 110.5 (C10b), 31.6 ($CH_3CH_2CH_2$), 30.2 (ArCH_2CH_2), 29.3 (ArCH_2), 29.1 (Ar$CH_2CH_2CH_2$), 22.6 (CH_3CH_2), 14.1 (CH_3CH_2) ppm. HRMS (ESI): calcd. for $C_{19}H_{19}NO_5Na$ [M + Na]$^+$ 364.1155; found 364.1151. $C_{19}H_{19}NO_5$ (341.36): calcd. C 66.85, H 5.61, N 4.10; found C 66.61, H 5.41, N 3.98.

General Procedure for the Reduction of Nitro-Derivatives of Benzo[*c*]coumarin:[23] Pd/C (65 mg, 0.060 mmol, 2 mol-%) and 2-propanol (40 mL) were placed in a 100 mL round-bottom ace pressure flask (Aldrich). An aqueous solution of ammonium formate (1.80 g, 30 mmol, 10 equiv. in 4 mL water) and the corresponding nitro compound (3 mmol, 1 equiv.) were added and the resulting mixture was heated at 85 °C for 72 h under an inert atmosphere. When the reaction was complete (monitored by TLC), Pd/C was filtered off through a pad of Celite using hot 2-propanol as eluent. The solvent was removed under reduced pressure and reaction mixture was diluted with dichloromethane, washed twice with brine, and dried with anhydrous sodium sulfate. The crude product was purified by column chromatography (silica; CH_2Cl_2/acetone, 98:2).

2-Amino-3-hydroxy-4-methyl-6*H*-dibenzo[*b*,*d*]pyran-6-one (12a): According to the general procedure, nitrobenzo[*c*]coumarin **11a** (0.81 g) and ammonium formate (1.80 g) were reacted, affording **12a** (0.30 g, 42%) as pale-yellow crystals. R_f = 0.32 (CH_2Cl_2/acetone, 96:4); m.p. 239–241 °C (CH_2Cl_2/acetone). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.95 (br. s, 1 H, OH), 8.19 (dd, $^3J_1$ = 7.9, $^3J_2$ = 1.3 Hz, 1 H, C7-H), 8.02 (d, ^3J = 7.9 Hz, 1 H, C10-H), 7.87 (dt, $^3J_1$ = 7.9, $^3J_2$ = 1.5 Hz, 1 H, C9-H), 7.54 (dt, $^3J_1$ = 7.6, $^3J_2$ = 0.9 Hz, 1 H, C8-H), 7.32 (s, 1 H, C1-H), 2.24 (s, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 161.5 (C6), 145.3 (C4a), 142.4 (C3), 136.0 (C10a), 135.5 (C2), 130.2 (C9), 127.7 (C7), 124.6 (C6a), 121.9 (C8), 119.6 (C10), 112.6 (C10b), 109.9 (C4), 104.2 (C1), 9.6 (*C*H$_3$) ppm. HRMS (EI, 70 eV): calcd. for $C_{14}H_{11}NO_3$ [M$^+$] 241.0739; found 241.0735.

4-Amino-2-hexyl-3-hydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-one (12b): According to the general procedure, nitrobenzo[*c*]coumarin **11b** (1.02 g) and ammonium formate (1.80 g) were reacted, affording **12b** (0.70 g, 75%) as pale-yellow crystals. R_f = 0.34 (CH_2Cl_2/acetone, 96:4); m.p. 148–152 °C (CH_2Cl_2/acetone). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.25 (d, ^3J = 8.1 Hz, 1 H, C7-H), 8.20 (dd, $^3J_1$ = 8.0, $^3J_2$ = 1.1 Hz, 2 H, C10-H), 7.85 (dt, $^3J_1$ = 7.8, $^3J_2$ = 1.4 Hz, 1 H, C9-H), 7.54 (dt, $^3J_1$ = 7.5, $^3J_2$ = 1.0 Hz, 1 H, C8-H), 7.33 (s, 1 H, C4-H), 4.82 (br. s, 2 H, NH_2), 2.64 (t, ^3J = 7.6 Hz, 2 H, Ar-CH_2-), 1.58 (quint, ^3J = 7.2 Hz, 2 H, ArCH_2CH_2), 1.31 [m, 6 H, $CH_3(CH_2)_3$], 0.86 (t, ^3J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.1 (C6), 143.8 (C3), 138.1 (C4a), 136.3 (C10a), 135.5 (C9), 130.1 (C7), 127.9 (C8), 127.0 (C6a), 125.2 (C1), 122.6 (C2), 119.5 (C10), 111.1 (C4), 110.3 (C10b), 31.7 ($CH_3CH_2CH_2$), 30.4 (ArCH_2CH_2), 30.1 (ArCH_2),

29.1 ($ArCH_2CH_2CH_2$), 22.6 (CH_3CH_2), 14.5 (CH_3CH_2) ppm. HRMS (EI): calcd. for $C_{19}H_{21}NO_3$ [M^+] 311.1521; found 311.1518. $C_{19}H_{21}NO_3$ (311.38): calcd. C 73.29, H 6.80, N 4.50; found C 73.12, H 6.75, N 4.42.

General Procedure for the Synthesis of Benzoazacoumarins:[24] The corresponding α-keto ester (0.90 mmol, 1.1 equiv.) was added to a stirred suspension of the parent aminobenzo[*c*]coumarin (0.80 mmol, 1.0 equiv.) in anhydrous toluene (4 mL). The reaction mixture was stirred in a sealed ace pressure tube (Aldrich) at 115 °C for 7 h under an inert atmosphere. Subsequently, solvent was evaporated to dryness under reduced pressure and the crude product was purified by column chromatography.

7,10-Dimethylbenzo[3,4]chromeno[7,6-*b*][1,4]oxazine-5,9-dione (13): According to the general procedure, **12a** (190 mg) and ethyl puryvate (128 mg, 120 μL) were reacted, affording the crude product, which was purified by column chromatography (CH_2Cl_2/acetone, 98:2) leading to the desired product **13** (91 mg, 39%) as yellow crystals. R_f = 0.70 (CH_2Cl_2/acetone, 95:5); m.p. 275–277 °C (CH_2Cl_2/acetone). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.47 (m, 2 H, C12-H and C4-H), 8.29 (ddd, $^3J_1$ = 8.1, $^3J_2$ = 1.4, $^3J_3$ = 0.6 Hz, 1 H, C1-H), 7.97 (dt, $^3J_1$ = 7.8, $^3J_2$ = 1.4 Hz, 1 H, C2-H), 7.71 (dt, $^3J_1$ = 7.5, $^3J_2$ = 1.2 Hz, 1 H, C3-H), 2.50 (s, 3 H, $ArCH_3$), 2.44 (s, 3 H, N=CCH_3) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.0 (C5), 154.9 (C9), 152.6 (C10), 150.0 (C6a), 146.4 (C11a), 135.9 (C2), 134.4 (C7a), 130.2 (C4), 129.8 (C7), 128.4 (C12a), 123.5 (C3), 120.7 (C1), 120.5 (C12b), 115.5 (C4a), 113.7 (C12), 21.0 (N=C-CH_3), 8.1 ($ArCH_3$) ppm. HRMS (EI, 70 eV): calcd. for $C_{17}H_{11}NO_4$ [M^+] 293.0688; found 293.0694. $C_{17}H_{11}NO_4$ (293.28): calcd. C 69.62, H 3.78, N 4.51; found C 69.56, H 4.02, N 4.51.

Ethyl 7-Methyl-5,9-dioxo-5,9-dihydrobenzo[3,4]chromeno[7,6-*b*][1,4]oxazine-10-carboxylate (14): According to the general procedure, **12a** (190 mg) and diethyl mesoxalate (157 mg, 140 μL) were reacted, affording the crude product, which was purified by column chromatography (CH_2Cl_2/acetone, 98:2) leading to the desired product **14** (101 mg, 36%) as orange crystals. R_f = 0.56 (CH_2Cl_2/acetone, 98:2); m.p. 244–246 °C (CH_2Cl_2/acetone). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.71 (s, 1 H, C12-H), 8.52 (d, ^3J = 7.9 Hz, 1 H, C4-H), 8.20 (dd, $^3J_1$ = 7.9, $^3J_2$ = 1.2 Hz, 1 H, C1-H), 7.93 (dt, $^3J_1$ = 7.8, $^3J_2$ = 1.4 Hz, 1 H, C2-H), 7.68 (dt, $^3J_1$ = 7.5, $^3J_2$ = 1.1 Hz, 1 H, C3-H), 4.42 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 2.33 (s, 3 H, $ArCH_3$), 1.38 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 161.8 (CO_2Et), 159.8 (C5), 151.9 (C9), 149.5 (C6a), 146.8 (C10), 144.2 (C11a), 136.1 (C2), 133.9 (C7a), 130.1 (C4), 130.0 (C7), 127.4 (C12a), 123.8 (C3), 122.9 (C1), 120.2 (C12b), 116.0 (C4a), 113.8 (C12), 62.6 (OCH_2CH_3), 14.5 (OCH_2CH_3), 8.2 ($ArCH_3$) ppm. HRMS (EI, 70 eV): calcd. for $C_{19}H_{13}NO_6$ [M^+] 351.0743; found 351.0749.

12-Hexyl-3-methylbenzo[3,4]chromeno[7,8-*b*][1,4]oxazine-2,6-dione (15): According to the general procedure, **12b** (250 mg) and ethyl pyruvate (128 mg, 120 μL) were reacted, affording **15** (162 mg, 55%) as yellow crystals. The product was purified by column chromatography (CH_2Cl_2/acetone, 98:2); R_f = 0.69 (CH_2Cl_2/acetone, 98:2); m.p. 208–210 °C (CH_2Cl_2/acetone). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.44 (dd, $^3J_1$ = 8.0, $^3J_2$ = 0.8 Hz, 1 H, C7-H), 8.31 (m, 2 H, C11-H and C10-H), 7.98 (dt, $^3J_1$ = 7.5, $^3J_2$ = 1.5 Hz, 1 H, C9-H), 7.71 (dt, $^3J_1$ = 7.5, $^3J_2$ = 1.3 Hz, 1 H, C8-H), 2.86 (t, ^3J = 7.8 Hz, 2 H, $ArCH_2$), 2.53 (s, 3 H, N=C-CH_3), 1.75 (quint, ^3J = 7.2 Hz, 2 H, $ArCH_2CH_2$), 1.43 [m, 2 H, CH_3-$(CH_2)_2CH_2$], 1.37 (m, 4 H, $CH_3CH_2CH_2$), 0.9 (t, ^3J = 7.0 Hz, 3 H, CH_3CH_2) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 160.2 (C6), 155.5 (C2), 152.5 (C3), 146.3 (C4b), 144.8 (C12a), 135.8 (C9), 134.6 (C4a), 130.2 (C11), 129.6 (C7), 126.4 (C10b), 124.9 (C12), 123.1 (C8), 120.7 (C6a), 120.6 (C10a), 114.6 (C10), 31.4 ($CH_3CH_2CH_2$), 29.6 ($ArCH_2CH_2$), 28.8 ($ArCH_2$), 28.6 ($ArCH_2CH_2CH_2$), 22.3 (CH_3CH_2), 21.7 ($ArCH_3$), 14.1 (CH_3CH_2) ppm. HRMS (EI, 70 eV): calcd. for $C_{22}H_{21}NO_4$ [M^+] 363.1471; found 363.1467.

Ethyl 12-Hexyl-2,6-dioxo-2,6-dihydrobenzo[3,4]chromeno[7,8-*b*][1,4]oxazine-3-carboxylate (16): According to the general procedure, **12b** (250 mg) and diethyl mesoxalate (157 mg, 140 μL) were reacted, affording **16** (212 mg, 63%) as yellow crystals. The product was purified by column chromatography (CH_2Cl_2/acetone, 98:2); R_f = 0.63 (CH_2Cl_2/acetone, 95:5); m.p. 166–170 °C (CH_2Cl_2/acetone). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.54 (s, 1 H, C11-H), 8.49 (d, ^3J = 8.2 Hz, 1 H, C7-H), 8.27 (dd, $^3J_1$ = 8.0, $^3J_2$ = 1.2 Hz, 1 H, C10-H), 7.99 (dt, $^3J_1$ = 7.7, $^3J_2$ = 1.4 Hz, 1 H, C9-H), 7.72 (dt, $^3J_1$ = 7.6, $^3J_2$ = 1.1 Hz, 1 H, C8-H), 4.46 (q, ^3J = 7.2 Hz, 2 H, CH_3CH_2O), 2.79 (t, ^3J = 8.0 Hz, 2 H, $ArCH_2$), 1.67 (quint, ^3J = 7.8 Hz, 2 H, $ArCH_2CH_2$), 1.34 [m, 6 H, $CH_3(CH_2)_3$], 1.30 (t, ^3J = 7.2 Hz, 3 H, OCH_2CH_3), 0.88 (t, ^3J = 7.0 Hz, 3 H, CH_3CH_2) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 161.9 (CO_2Et), 160.1 (C6), 149.6 (C2), 147.0 (C3), 145.4 (C4b), 144.9 (C12a), 136.1 (C9), 134.0 (C4a), 130.4 (C11), 130.0 (C7), 128.4 (C10b), 126.3 (C12), 123.3 (C8), 120.4 (C6a), 119.9 (C10a), 114.7 (C10), 62.6 (OCH_2CH_3), 31.5 ($CH_3CH_2CH_2$), 29.7 ($ArCH_2CH_2$), 28.9 ($ArCH_2$), 28.7 ($ArCH_2CH_2CH_2$), 22.5 (CH_3CH_2), 14.5 (OCH_2CH_3), 14.4 (CH_3CH_2) ppm. HRMS (EI, 70 eV): calcd. for $C_{24}H_{23}NO_6$ [M^+] 421.1525; found 421.1521. $C_{24}H_{23}NO_6$ (421.45): calcd. C 68.40, H 5.50, N 3.32; found C 68.39, H 5.68, N 3.41.

2,2′-Dihexyl-3,3′-dihydroxy-6*H*,6′*H*-[4,4′-dibenzo[*c*]chromene]-6,6′-dione (17): A mixture of benzo[*c*]coumarin **3i** (0.30 g, 1.0 mmol) and cobalt trifluoride (0.12 g, 1.0 mmol) in trifluoroacetic acid (10 mL) was heated to reflux for 24 h. The reaction mixture was poured into water and extracted with chloroform (4× 15 mL). The organic layers were collected, combined, and dried with magnesium sulfate. The crude product was purified by column chromatography (CH_2Cl_2, 100%), affording **17** (0.15 g, 25%) as yellowish crystals. R_f = 0.30 (CH_2Cl_2); m.p. 101–102 °C (CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23 (d, $^3J_1$ = 8.0, $^3J_2$ = 0.8 Hz, 2 H, C7-H and C7′-H), 8.01 (d, ^3J = 8.0 Hz, 2 H, C10-H and C10′-H), 7.88 (s, 2 H, C1-H and C1′-H), 7.77 (dt, $^3J_1$ = 8.0, $^3J_2$ = 1.4 Hz, 2 H, C9-H and C9′-H), 7.48 (t, ^3J = 7.6 Hz, 2 H, C8-H and C8′-H), 5.62 (br. s, 2 H, 2× OH), 2.73 (m, 4 H, 2× $ArCH_2$), 1.70 (m, 4 H, 2× $ArCH_2CH_2$), 1.43 [m, 4 H, 2× $CH_3(CH_2)_2CH_2$], 1.34 (m, 8 H, 2× $CH_3CH_2CH_2$), 0.90 (m, 6 H, 2× CH_3CH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.1 (C6 and C6′), 153.9 (C3 and C3′), 148.5 (C4a and C4a′), 135.2 (C10a and C10a′), 134.8 (C1 and C1′), 130.5 (C9 and C9′), 127.7 (C7 and C7′), 127.3 (C6a and C6a′), 124.8 (C8 and C8′), 121.1 (C10 and C10′), 119.9 (C2 and C2′), 111.4 (C10b and C10b′), 105.2 (C4 and C4′), 31.7 (2× $CH_3CH_2CH_2$), 30.4 (2× $ArCH_2CH_2$), 29.8 (2× $ArCH_2$), 29.3 (2× $ArCH_2CH_2CH_2$), 22.6 (2× CH_3CH_2), 14.1 (2× CH_3CH_2) ppm. HRMS (EI, 70 eV): calcd. for $C_{38}H_{38}O_6$ [M^+] 590.2668; found 590.2664. $C_{38}H_{38}O_6$ (590.71): calcd. C 77.26, H 6.48; found C 77.08, H 6.51.

(*E*)-4-({[4-(*tert*-Butyl)phenyl]imino}methyl)-2-hexyl-3-hydroxy-6*H*-benzo[*c*]chromen-6-one (20): A mixture of aldehyde **18** (0.32 g, 1.0 mmol) and 4-*tert*-butylaniline (**19**; 0.15 g, 1.0 mmol) in ethanol (5 mL) was stirred at reflux under argon atmosphere in the presence of molecular sieves for 1 h. Upon completion of the reaction, the solvent was evaporated and the crude product was recrystallized from hexanes, affording **20** (0.45 g, 99%) as orange crystals. R_f = 0.8 (CH_2Cl_2); m.p. 117–118 °C (hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.39 (s, 1 H), 8.35 (d, ^3J = 8.0 Hz, 1 H), 7.99 (d, ^3J = 7.6 Hz, 1 H), 7.84 (s, 1 H), 7.79 (t, $^3J_1$ = 7.6 Hz, 1 H), 7.48 (m, 3

H), 7.36 (d, ^3J = 8.5 Hz, 2 H), 2.75 (t, ^3J = 7.8 Hz, 2 H), 1.71 (quint, ^3J = 7.6 Hz, 2 H), 1.44 (m, 2 H), 1.36 (m, 13 H), 0.92 (t, ^3J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.4, 160.8, 155.9, 150.9, 149.7, 143.7, 135.4, 135.0, 130.6, 128.9, 127.3, 126.7, 126.4, 120.9, 120.8, 119.4, 107.4, 106.7, 34.7, 31.8, 31.3, 29.9, 29.5, 29.3, 22.7, 14.1 ppm. HRMS (EI, 70 eV): calcd. for $C_{30}H_{33}NO_3$ [M$^+$] 455.2460; found 455.2468.

Optical Measurements: A Perkin–Elmer Lambda 25 UV/Vis spectrophotometer and a Hitashi F7000 spectrofluorimeter were used to acquire the absorption and emission spectra. Spectrophotometric grade solvents were used without further purification. Fluorescence quantum yields were determined in DMF by using quinine sulfate in 0.05 M H_2SO_4 as standard, and in CH_2Cl_2 by using rhodamine in ethanol as standard.

Supporting Information (see footnote on the first page of this article): Absorption and emission spectra as well as copies of the ^{1}H and ^{13}C NMR spectra of all new compounds.

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