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ARTICLE

Microwave-Assisted Synthesis and Photophysical Studies of Novel Fluorescent *N*-acylhydrazone and Semicarbazone-7-OH-Coumarin Dyes

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A microwave-assisted synthesis of novel *N*-acylhydrazone and semicacarbazone-7-hidroxy-coumarins derivatives, starting from 3-acetyl-7-hydroxy-2*H*-chromen-2-one, is described. This optimized protocol led to higher yields and considerable reduction in reaction times of ~23 hours. Aqueous solutions of these compounds showed bright blue to cyan emission and maximum quantum yields of 0.244. The stereoelectronic effects of the attached groups led to modulation of the spectral characteristics by favoring *syn* or *anti* amide conformers. The synthesized compounds showed pH dependent luminescence and a strong batochromic shift up to 65 nm in a less polar medium (methanol) due to a better stabilization of *syn*-conformer promoting this redshifted emission. These characteristics can be exploited for designing new luminescent probes for pH as well as polar microenvironments.

Introduction

Coumarins are widely described organic heterocycles, with numerous methodologies in synthesis,[1-5] that find applications in science and technology,[6-7] such as optical brighteners,[6] biological and polymeric matrix probes,[6-8] fluorescent sensors,[7] both in water and in micellar systems,[7-9] mainly due to their interesting emissive characteristics that are often responsive to the environment.

The emergence of new fluorescent labeling led to new strategies for visualization of biochemical systems and complex mixtures, with an increasing interest in making variations in the molecular structure for specific medical applications such as diagnostics, therapeutics and biomaterials.[10-12] In biological systems, water is the main solvent and pH can be addressed to some pathologies[13-15] or organelle characteristics. Synthetic polar and pH-dependent fluorescent probes with simple structures[15,16] can be employed in cellular experiments, both *in vitro* and *in vivo,*[17] encouraging the development of highly selective molecules for specific cells with certain pathologies.[17-19]

In this work, new *N*-acylhydrazone- and semicarbazone-7-OH-coumarins were designed by molecular hybridization[20] of a fluorescent 7-OH-coumarin nucleus (blue, Figure 1) with *N*-acylhydrazone and/or semicarbazone moieties (green and red, Figure 1), which are known as privileged structures[21] capable of interacting with a variety of biological systems. Different groups were selected as substituents in "R" aiming to change the carbonyl electron density, which in turn is directly attached to the hydrazone moiety that can exert a π-conjugation extension with the fluorescent coumarin nucleus. Therefore, the influence of the "R" group on the photophysical characteristics of the synthesized compounds was evaluated.

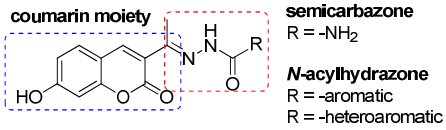

Figure 1. Designed fluorescent *N*-acylhydrazone- and semicarbazone-7-OH-coumarins.

Results and discussion

Synthesis of coumarins

Coumarin dyes (**3a-h**) were synthesized by a three-step protocol. As shown in Scheme 1, the first step was the synthesis of 3-acetyl-7-hydroxy-2*H*-chromen-2-one (**1**) by means of a Knoevenagel condensation between 4-hydroxysalicylaldehyde (**4**) and ethyl acetoacetate (**5**), refluxing in ethanol for 24h using piperidine (0.15eq) as

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† Electronic supplementary information (ESI) available: NMR and mass spectra, HPLC analyses, additional figures as mentioned in the text. See DOI: 10.1039/x0xx00000x

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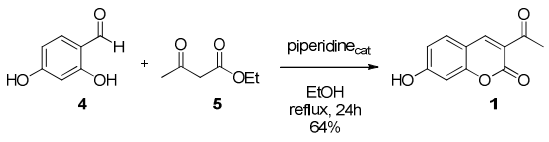
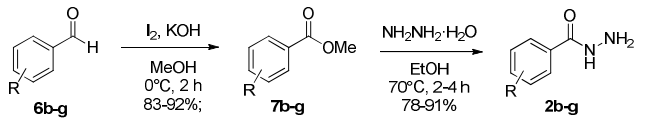
catalyst, Scheme 1. The ketone (**1**) was obtained after precipitation (64% yield).

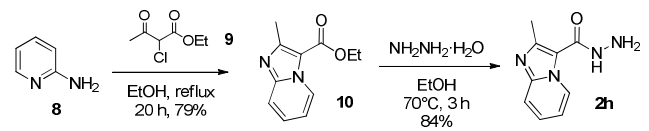


Scheme 1. Synthesis of 3-acetyl-7-hydroxy-2H-chromen-2-one (**1**).

The second step was the synthesis of hydrazides (**2b-h**), Scheme 2, as previously described.[22] Aromatic aldehydes (**6b-g**) were converted to their correspondent esters (**7b-g**) by means of a Yamada oxidation[23] and subsequently reacted with hydrazine hydrate leading to substituted benzohydrazides (**2b-g**) (78 to 91% yield). 2-methylimidazo[1,2-a]pyridinyl hydrazide (**2h**) was synthesized (84% yield) by hydrazinolysis of the 2-methylimidazo[1,2-a]pyridinyl derivative (**10**) precursor, which in turn was obtained by the regioselective cyclocondensation of 2-aminopyridine (**8**) with ethyl 2-chloro-acetoacetate (**9**) in absolute ethanol at reflux.[22]

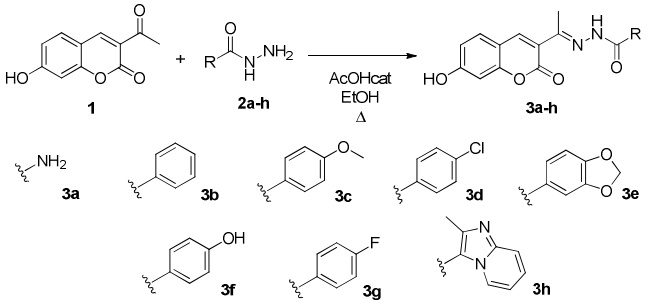


b - R = H; **c** - R = 4-OCH$_3$; **d** - R = 4-Cl; **e** - R = 3,4-OCH$_2$O-; **f** - R = 4-OH; **g** - R = 4-F



Scheme 2. Synthesis of hydrazides **2b-h**.

Finally, in the third step, coumarin dyes (**3a-h**) were obtained by the condensation reaction between 3-acetyl-7-hydroxy-2*H*-chromen-2-one (**1**) (1eq) and semicarbazide hydrochloride (**2a**) or hydrazides (**2b-h**) (1.05eq) in ethanol, using acetic acid as catalyst, Scheme 3. The optimization studies of this step are described in the next paragraphs.



Scheme 3. Synthesis of semicarbazone- (**3a**) and *N*-acylhydrazone-7-OH-coumarins (**3b-h**).

In a first attempt, the synthesis of the desired compounds **3a-h** was carried out around 80 °C by using a sealed borosilicate apparatus to avoid evaporation. Although yields of the desired products were good (70-88%), the total consumption of the ketone (**1**), monitored by thin layer chromatography, was observed only after 24 h.

Aiming to decrease reaction times for **3a-h**, microwave reaction conditions were evaluated, Table 1. In fact, the microwave assisted synthesis has already been proven suitable in obtaining different *N*-acylhydrazones from common aromatic ketones but never from coumarin ketones.[24-25]

At first, the microwave synthesis was carried out using similar conditions to the reflux method – i.e. one drop of acetic acid in ethanol at 80 °C – leading to a decrease in the reaction time of compound **3a** to 45 min. This compound was obtained with 93% yield with no traces of starting reactant (**1**), yet the *N*-acylhydrazone (**3b-h**) reactions still presented a certain amount of the ketone precursor (**1**). Reactions at higher temperatures were also attempted in sealed tubes, however no differences were observed by increasing the temperature to 100 °C, and the further increase to 150 °C led to degradations (monitored by thin layer chromatography).

Therefore, a new condition was evaluated using three drops of acetic acid instead of using only one, with the reaction under 80 °C for 1 hour. This set of conditions was the most effective in decreasing the reaction times for *N*-acylhydrazone compounds (**3b-h**) with higher yields when compared to the synthesis under conventional heating, Table 1.

Table 1. Optimization of 7-OH-coumarin (**3a-h**) synthesis.

Prod.	Conventional Heating			Microwave		
	Time	Temp °C	%Yield	Time	Temp °C	%Yield
3a	20 h	80	88[a]	45 min	80	93[a]
3b	24 h	80	69[a]	1 h	80 / 100	Nd[a,b]
3b	-	-	-	1 h	150	Nd[a,c]
3b	-	-	-	1 h	80	89[d]
3b	24 h	80	71[d]	-	-	-
3c	24 h	80	78[a]	1 h	80	95[d]
3d	24 h	80	87[a]	1 h	80	98[d]
3e	24 h	80	82[a]	1 h	80	93[d]
3f	24 h	80	70[a]	1 h	80	97[d]
3g	24 h	80	83[a]	1 h	80	74[d]
3g	-	-	-	1.5 h	80	85[d]
3h	24 h	80	72[a]	1 h	80	82[d]

[a] one drop of AcOH; [b] not determined due to the presence of starting reactants; [c] not determined due to degradations; [d] three drops of AcOH.

Structural Elucidation

The desired coumarin derivatives (**3a-h**) were confirmed by ^{1}H and ^{13}C NMR analyses and obtained as a single isomer with *E* configuration, as confirmed by NOESY experiment (SI for 3c). All data in the spectra were in good accordance with the structures, as demonstrated for **3c** and **3h** (Figure 2). Signal duplications in **3h** were ascribed to the high conversion barrier energy between *anti* and *syn*-periplanar conformers of the CO-

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NH bond (proportion of 4:1, respectively), arising from the stereo-electronic effects of imidazopyridine group.[26]

We could postulate that the ^{1}H and ^{13}C NMR signal duplication for **3h** belongs to the presence of *E*/*Z* isomers (SI). However, HPLC analysis showed the presence of only one peak, as expected for compounds with conformer populations and not for *E*/*Z* isomers. Furthermore, a dynamic ^{1}H NMR assay carried out in DMSO-d_6 at 60 °C demonstrated a partial coalescence of some signals, specially the CO-NH one. This is typical for solutions with interconversion between *syn* and *anti* conformers, and is facilitated at the higher temperature (SI).

As proposed in Figure 3, the interconversion between *syn* and *anti*-conformers can be achieved through a transition state (TS) where the nitrogen loses its conjugation with carbonyl, resulting in a pyramidal N atom with two resonance forms (**A** and **B**). For **3a-g**, π electrons of R moiety can coplanarize to the C^{+}-O^{-} p orbital that stabilize the resonance form **B1,** with a decrease in the TS energy.[26] This lower energy barrier leads to a thermal equilibrium between both *syn*- and *anti*-conformers in solution, with the observation of only single NMR signals. On the other hand, for **3h**, the *ortho*-methyl-induced loss of coplanarization and the strong electron withdrawing effect of the imidazopyridine radical destabilize the resonance form **B2**, increasing the rotational barrier energy.[26]

This fact decreases the interconversion rate and inhibits the dynamic equilibrium, favouring the observation of duplicate NMR signals.

Photophysical properties

Considering their different stereo-electronic effects, five representative compounds **3a**-**d** and **3h** were selected to determine the general photophysical characteristics of these 7-OH coumarins in water; compounds **3e-f** and **3g** show similar electronic effects to **3c** and **3d**, respectively, hence their photophysical properties were not investigated.

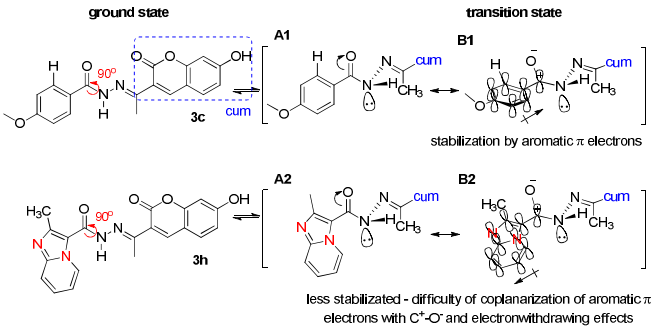

Figure 3. Structural features of NAH-coumarins **3c** and **3h** in the stabilization of the transition state of the amide bond rotamers.

UV-vis spectra of **3a-d** and **3h** in water at 298 K (Figure 4) exhibit a characteristic band at 350 - 357 nm (ε ~ 2.5 × 10^4 L mol^{-1} cm^{-1}) from a π_{coum} to π^{*}_{coum} transition localized at the 7-OH-coumarin nucleus (i.e. locally excited state, $^{1}LE_{coum}$). The insertion of an aromatic or heteroaromatic group to the "R" of the carbonyl moiety leads to higher molar extinction coefficients and redshifted bands (λ_{max} = 357 nm) when compared to **3a** (λ_{max} = 350 nm).

Compound **3h** exhibits two bands at 357 and 425 nm due to the presence of *anti* and *syn* conformers with a higher concentration of the *anti*-conformer in solution as ascertained by ^{1}H NMR (Figure 2). The minor lower energy band can be ascribed to the *syn*-conformer based on previous conformational studies of aromatic amides and similar *N*-acylhydrazones.[27-29]

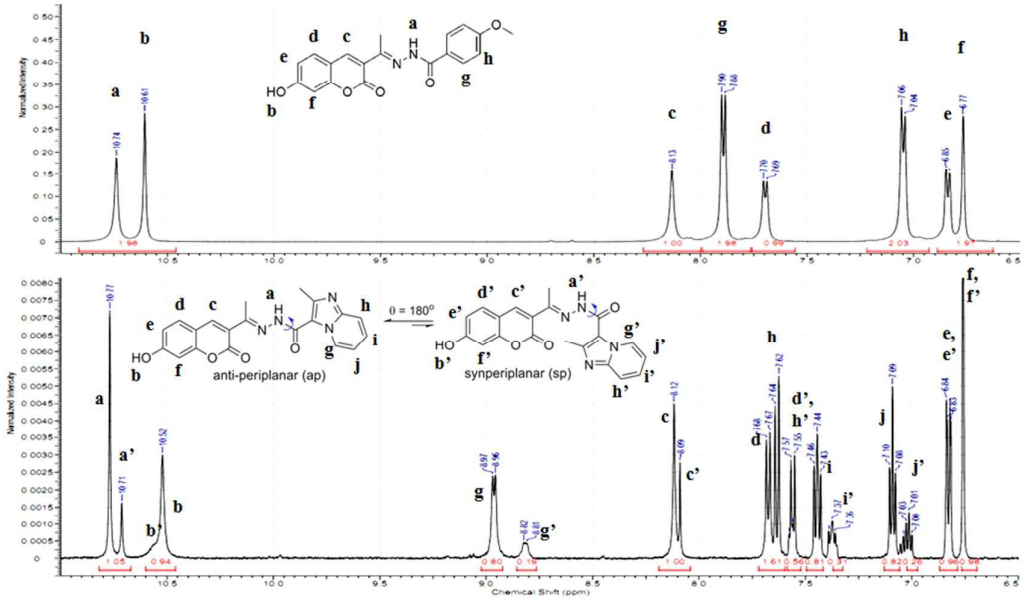

Figure 2. ^{1}H NMR spectra for compounds **3c** (A) and **3h** (B) in DMSO-d_6 at 298 K.

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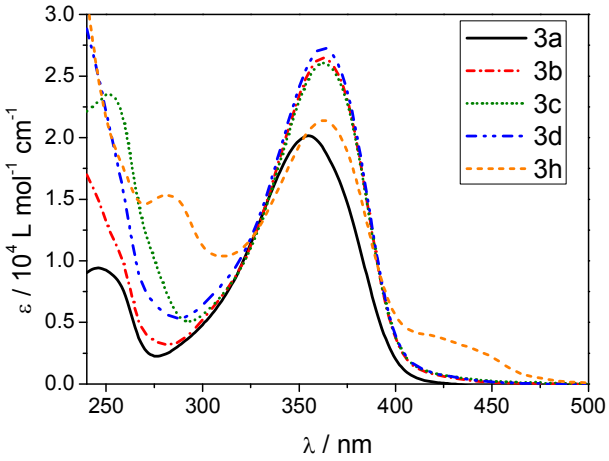

Figure 4. Absorption spectra in water (pH 4.9) at 298 K.

The excitation from 250 to 410 nm of **3a-d** and **3h** in water at pH 4.9 (298 K) leads to an intense emission (λ_{max} = 456 nm), with a narrow, vibronically-resolved spectrum profile that resembles the mirror shape of the excitation (Figure 5), typical of ππ* ^{1}LE fluorescence. The Stoke's shift between the excitation and emission maxima is relatively large ($\Delta\lambda$ = 99 nm), as has also been observed for other similar compounds.[30] Moreover, "R" groups have negligible influence on emission and absorption energies in this solvent.

Their emission quantum yields (ϕ_F) range from 0.130 for semicarbazone **3a** to 0.244 for *N*-acylhydrazones **3b-d** and **3h** (Table 2). The presence of the methyl group in the imine moiety creates a conformational restriction in bond twisting, decreasing its isomerisation that usually causes a quench in luminescence.[31] Their relatively high ϕ_F, especially for *N*-acylhydrazones, allied to a reduced inner-filter effect due to their large Stoke's shift, make these compounds promising candidates for laser dyes.[32]

Worth of note, the water pH (4.9) was carefully controlled with addition of an acetate buffer solution since the imine group and the lactone moieties in the coumarin compounds can be protonated at lower pHs,[33-36] which can lead to a considerable decrease in their k_r constants, hence to lower emission quantum yields (ϕ_F < 0.065, SI). On the other hand, at pHs higher than 5.0, the phenol group can deprotonate (pK_a = 6.7, as experimentally obtained for **3b**, SI), resulting in spectral changes in the absorption and emission (SI).[33-36]

The coumarin emissions are short-lived (few nanoseconds) as typically observed for similar fluorescent compounds.[37] The emission quantum yield and lifetime are related to the rate constants for radiative (k_r) and nonradiative (k_{nr}) excited-state decays as shown in Equations 1a and 1b.

$$\phi = \frac{k_r}{k_r + k_{nr}} \quad (1a)$$

$$\tau = \frac{1}{k_r + k_{nr}} \quad (1b)$$

For excited states with similar character, k_r varies as the square of the transition dipole moment and to the cube of the average emission energy.[38-40] By considering the same emission energy for compounds **3b-d** and **3h** (λ_{max} = 456 nm), their higher radiative rate constants indicate a more effective transient displacement of charges between the ground and the excited states. In other words, these results indicate that their emissive ^{1}LEcoum excited state possess a small extent of charge transfer character. These facts lead to a π_{coum} electron density restricted at the coumarin nucleus while its π^*_{coum} is more delocalized through the entire molecule, extending to the semicarbazone and *N*-acylhydrazone moieties.

Spectral variations are observed in the absorption spectra of substituted compounds by changing the medium polarity from water, ε= 80.1, to methanol, ε= 32.7.

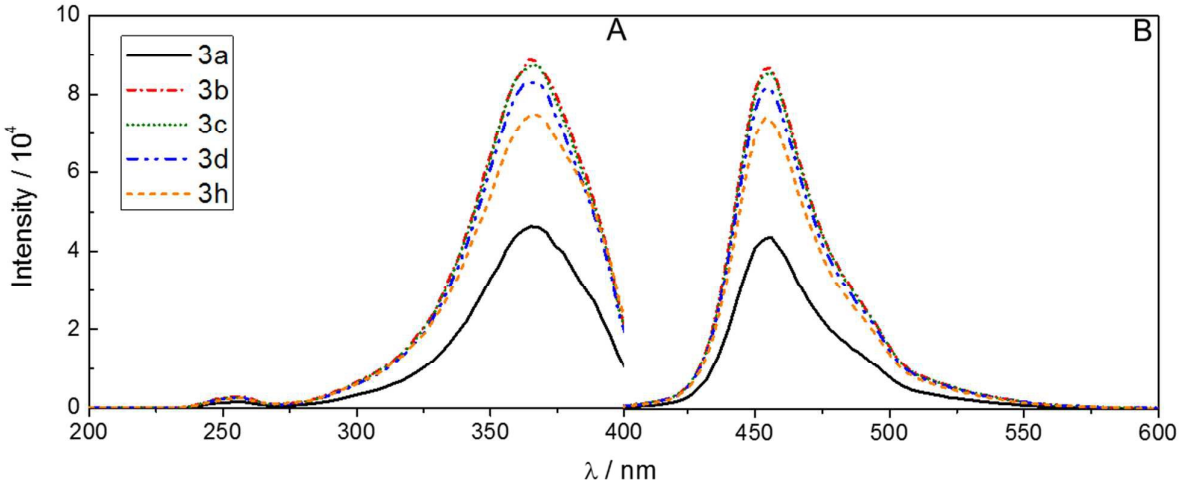

Figure 5. Excitation (λ_{em} = 455 nm) (A) and emission (λ_{ex} = 365 nm) (B) spectra in water at pH 4.9 (298 K; $\Delta\lambda$ = 2nm).

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Table 2. Photophysical parameters in water at 298 K.

Compound	ϕ_F[a]	τ/ ns[a]	k_r / 10^7 s^{-1}	k_{nr} / 10^7 s-1
3a	0.130 (± 0.001)	2.1 (± 0.3)	6.2	41
3b	0.244 (± 0.001)	2.3 (± 0.4)	10	32
3c	0.235 (± 0.001)	2.5 (± 0.3)	9.4	31
3d	0.234 (± 0.001)	2.4 (± 0.4)	9.8	32
3h	0.205 (± 0.001)	2.3 (± 0.4)	8.9	35
ethyl-7-OH-coumarin-3-carboxylate	0.83 [36]	4.8 (this work) or 5.4 [36]	---	---

[a] Values are given as: average (± standard deviation).

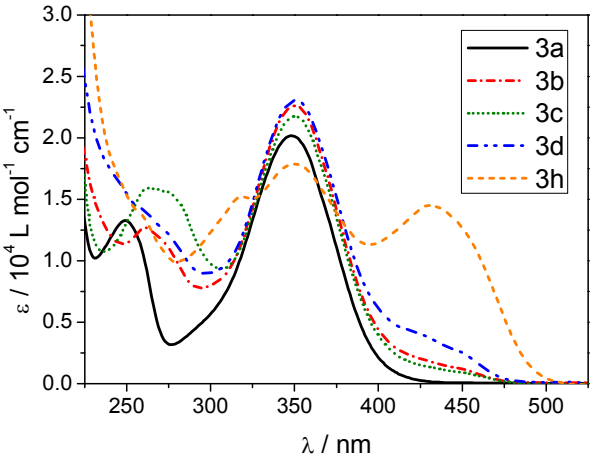

Figure 6. Absorption spectra in methanol at 298 K.

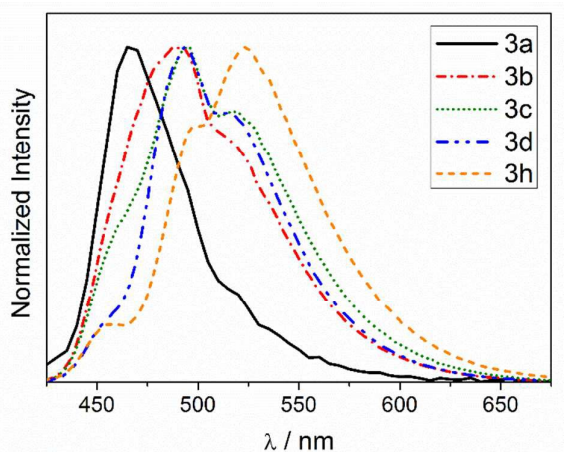

Figure 7. Emission spectra in methanol at 298 K (λ_{exc} = 410 nm).

In methanol (Figure 6), a increase in lower-lying shoulder related to the *syn*-conformer is observed around 420 nm, while the LE band at 357 nm exhibits lower extinction coefficients than in water. These facts are ascribed to an increase of the more-stabilized *syn*-conformer in less-polar solvents, as supported by other reports in the literature.[26,43]

The excitation of N-acylhydrazone compounds in methanol at 298 K leads to the *syn*-conformer emission at the cyan-green region, and in broader vibronically-resolved spectra, as exemplified in Figure 7 for compounds **3b-3d** and **3h**. The syn-emission energy clearly responds to the electron withdrawing strength of the semicarbazone nucleus, with a distinctly larger redshift for compound **3h** due to the presence of the stronger electronwithdrawing 2-methylimidazo[1,2-a]pyridinyl group. Their emission spectra also exhibit a small shoulder around 455 nm ascribed to the emission of the anti-conformer, present in the solution in a much smaller concentration. For comparison, the emission of **3a**, non-substituted, in methanol (Figura 7) is ascribed solely to the coumarin emission, with a slightly smaller energy (λ_{max} = 465 nm) and a similar spectral profile to its emission in water.

In terms of perceived color, the human vision responds to trichromatic stimuli on the virtual cortex,[39,40] quantified by the Commission Internationale de L'Eclairage (CIE) in three matching functions or spectral sensitivity curves, $x(\lambda)$, $\bar{y}(\lambda)$ and $\bar{z}(\lambda)$, available as free-access tables.[46]

The *x* and *y* CI coordinates for the emission of compounds **3a-3d** and **3h** in water and in methanol, Figure 8, were calculated by Equations 2a and 2b from their X, Y and Z tristimulus integrals, Equations 3a-3c.

$$x = \frac{X}{X+Y+Z} \qquad (2a)$$

$$y = \frac{Y}{X+Y+Z} \qquad (2b)$$

$$X = \int_{380}^{780} I(\lambda)\bar{x}(\lambda)\mathrm{d}\lambda \qquad (3a)$$

$$Y = \int_{380}^{780} I(\lambda)\bar{y}(\lambda)\mathrm{d}\lambda \qquad (3b)$$

$$Z = \int_{380}^{780} I(\lambda)\bar{z}(\lambda)\mathrm{d}\lambda \qquad (3c)$$

The CIE coordinates are very useful for an absolute and quantitative comparison of emission colors. As evidenced by Figure 8, changes in the CIE coordinates are more significant than a routine comparison of the λ_{max} of different compounds, because they also implicitly respond to spectral changes in band-shape. The *syn*-emission tuning is even more highlighted, clearly responding to the electron withdrawing strength of the

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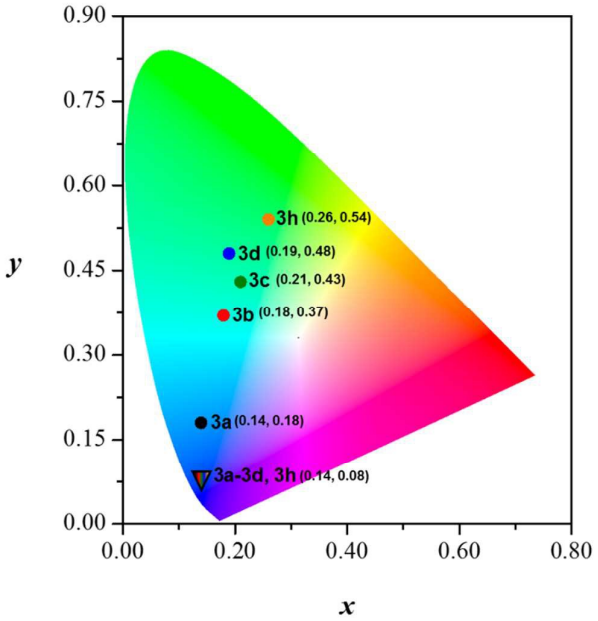

Figure 8. Color space chromaticity diagram with CIE coordinates for the photoluminescence of compounds **3a-3d** and **3h** in water (▼) or in methanol (●).

semicarbazone nucleus. These results are inspiring for a deep comprehension of emission-tuning strategies and the molecular engineering of new molecules with desired properties.

Conclusion

Herein we addressed the synthesis of novel 7-OH coumarin derivate dyads using two synthetic approaches, for which the microwave irradiation led to higher yields and a considerable reduction in the reaction times from 24 hours to about 1 hour.
Five compounds were selected for their photophysical characterization demonstrating an LE emission with relatively high quantum yields in water compared to other iminocoumarins[31], making them potential candidates to be applied as biological probes.
Finally, the modulation of the electron withdrawing effect at the "R" position can lead to a variable stabilization of *syn* conformer in methanol (lower polarity than water), resulting in considerable bathocromic shifts in their emission. These results are inspiring for more detailed photophysical characterizations in different media with different polarities, which are our ongoing efforts to be addressed in forthcoming works.

Experimental section

Materials and instruments

All chemicals were purchased from commercial suppliers and used without further purification. 4-hydroxysalicylaldehyde and semicarbazide were obtained from Sigma-Aldrich. Other chemicals were purchased from Vetec. ^{1}H and ^{13}C NMR spectra were recorded using a 400 MHz or 500 MHz Brucker Avance spectrometer (AC-400 or AC-500), using DMSO-d_6 or $CDCl_3$ and TMS as internal standard. IR spectra were obtained using a Perkin-Elmer Spectrometer model 1600. Mass spectrometry was obtained by negative ionization using an Esquire 6000-ESI Ion Trap MSn Bruker Daltonics and data were analyzed using a Compass 1.3.SR2 software. The melting points recorded are uncorrected. Elemental analyzes were carried out using a Thermo Scientific Flash EA 1112 Series CHN-Analyzer. UV-visible spectra were recorded using an Agilent 8453 diode array spectrophotometeror or a Jasco J-815 spectropolarimeter using 1.000 cm optical path quartz cuvettes. Steady-state emission spectra were recorded using a PC1 photon-counting spectrofluorimeter (ISS) with a photomultiplier based, photon-counting detector with detector sensitivity correction or using a Jasco J-815 spectropolarimeter, using 1.000 cm optical path quartz cuvettes with four polished faces. Emission decays were recorded using a ISS Chronos time-resolved fluorometer using a diode laser (λ_{ex} = 378 nm, frequency = 10 kHz) as an excitation light source. Biotage Initiator 2 Reactor was used for microwave reactions using an internal IR temperature probe.

Synthesis of 3-acetyl-7-hydroxy-2*H*-chromen-2-one (1)

A mixture of 4-hydroxysalicylaldehyde (**4**) (2.00 g, 14.48 mmol), ethyl acetoacetate (**8**) (1.85 mL, 14.48 mmol) and piperidine (215 µL, 2.17 mmol) in ethanol (40 mL) was refluxed at 90°C for 24h. Most of the solvent was evaporated and the beige solid was filtered off after refrigeration, consisting of pure product (**1**) as indicated by TLC analysis (1,887g, 64%). Mp 238°C. IR (KBr): 3488 (O-H), 2985, 2927, 1716 (C=O), 1602, 1452 (C=C) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.54 (s, 3H), 6.73 (s, 1H), 6.83-6.84 (d, J= 8.51Hz, 1H), 7.76-7.77 (d, J= 8.51Hz, 1H), 8.57 (s, 1H). ^{13}C NMR (500 MHz, DMSO-d_6): 30.6, 102.2, 111.1, 114.8, 119.4, 133.2, 148.4, 157.8, 159.6, 165.0, 195.1 ; MS (ESI-) m/z 204.0.

Synthesis of hydrazides (2b-h)

Hydrazine hydrate 100% (1.94 mL, 40 mmol) was added to the corresponding ester (**7b-g** or **10**) (4 mmol) – obtained as previously described[22] – dissolved in 10 mL of ethanol. The resulting solution was heated at 70 °C for for 2 to 4 hours for the total consumption of the ester. The solvent was almost completely evaporated in a rotary evaporator and the residue was poured into an ice/water mixture. Some hydrazides (**2d**, **2e** and **2h**) precipitated and they were just filtered off and washed with cold water, while others were extracted from aqueous media using AcOEt.

Benzohydrazide (2b)

82% yield. Mp: 121°C. IR (KBr): 3299 (NH_2), 3186 (NH), 1616 (C=O), 1349 (C-O) cm^{-1}.^{1}H NMR (200 MHz, DMSO-d_6): δ 4.51 (s, NH-N<u>H</u>$_2$), 7.54-7.39 (m, 3H, H_3, H_4), 7.83 (d, H_2, J= 7.6Hz), 9.78 (s, CO-N<u>H</u>). ^{13}C NMR (50 MHz, DMSO-d_6): δ 126.9, 128.3, 131.0, 133.3, 165.9 (C=O).

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4-methoxybenzohydrazide (2c)

88% yield. Mp: 136°C. IR (KBr): 3316 (NH_2), 3183 (NH), 1623 (C=O), 1307-1256 (C-O) cm^{-1}.^{1}H NMR (200MHz, DMSO-d_6): δ 3.79 (s, 3H, O-CH_3), 4.43 (s, NH-NH_2), 6.67 (d, 2H, H_3, J= 8.8Hz), 7.82 (d, 2H, H_2, J= 8.8Hz), 9.62 (s, CO-NH). ^{13}C NMR (50MHz, DMSO-d_6): δ 113.5, 125.5, 128.7, 161.4, 165.6 (C=O).

4-Chlorobenzohydrazide (2d)

84% yield. Mp: 131°C. IR (KBr): 3309 (NH_2), 3208 (NH), 1618 (C=O), 1348 (C-O) cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ 4.52 (s, NH-NH_2), 7.52 (d, 2H, H_3, J= 8,0Hz), 7.84 (d, 2H, H_2, J=8,0Hz), 9.85 (s, CO-NH). ^{13}C NMR (50 MHz, DMSO-d_6): δ 128.9, 129.1, 132.6, 136.4, 165.4 (C=O).

benzo[d][1,3]dioxole-5-carbohydrazide (2e)

91% yield. MP: 170°C. IR (KBr): 3316 (NH_2), 3184 (NH), 1605 (C=O), 1265-1248 (C-O) cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ 4.43 (s, NH-NH_2), 6.08 (s, O-CH_2-O), 6.96 (d, H_5, J= 8,1Hz), 7.41 (d, H_6, J= 8,1Hz), 7.45 (s, H_2), 9.62 (s, CO-NH). ^{13}C NMR (50 MHz, DMSO-d_6): δ 101.7 (O-CH_2O), 107.0, 107.9, 121.9, 127.2, 147.3, 149.6, 165.3 (C=O).

4-hydroxybenzohydrazide (2f)

80% yield. MP: 250°C. IR (KBr): 3428 (-OH); 3319, 3199 (N-H); 1622 (C=O); 1280 (C-O) cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ 4.42 (s, NH-NH_2), 7.32 (d, 2H, H_3, J= 8,0Hz), 7.95 (d, 2H, H_2, J= 8,0Hz), 9.50 (s, CO-NH), 9.96 (s, OH). ^{13}C NMR (400 MHz, DMSO-d_6): δ 110.0, 125.5, 129.4, 160.5, 165.5 (C=O).

4-fluorobenzohydrazide (2g)

78% yield. Mp: 123°C. IR (KBr): 3302, 3218 (N-H), 3019, 1661 (C=O), 1618, 1564 (N=C), 1507 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.51 (s, NH_2), 7.28-7.32 (t, 2H), 7.89-7.92 (m, 2H), 9.82 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 115.6, 130.1, 130.2, 163.0, 165.4.

2-methylimidazo[1,2-a]pyridine-3-carbohydrazide (2h)

84% yield. Mp: 180°C. IR (KBr): 3290, 3218 (N-H); 1626 (C=O); 744 (N=C) cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.53 (s, 3H, -CH_3), 4.56 (s, NH-NH_2), 7.00 (t, H_6, J= 8,0Hz), 7.36 (t, H_5, J= 8,0Hz), 7.55 (d, H_4, J= 8,0Hz), 8.94 (d, H_7, J= 6,0Hz), 9.18 (s, CO-NH). ^{13}C NMR (50 MHz, DMSO-d_6): δ 16.0, 113.33, 115.4, 116.7, 126.9, 127.4, 145.5, 145.6, 161.9.

Synthesis of *N*-acylhydrazone- (3b-h) and semicarbazone-7-OH-coumarins (3a)

Synthesis by conventional heating (CH).

3-acetyl-7-hydroxy-2H-chromen-2-one (**1**) (100 mg, 0.48 mmol) and the corresponding hydrazide **2a-h** (0.50 mmol) were added into a borosilicate sealable tube and dissolved in 2 mL of ethanol, then 1 or 3 drops of acetic acid were added. The reaction was heated at 80 °C for 24 h, then poured into ice. The precipitate was filtered off and dried at room temperature. The solid was washed with small portions of cold ethyl acetate.

Microwave-assisted synthesis (MAOS)

3-acetyl-7-hydroxy-2H-chromen-2-one (**1**) (200mg, 0.97 mmol) and the corresponding hydrazide **2a-h** (1.02 mmol) were added into a sealable microwave tube and dissolved in 4 mL of ethanol, then 3 drops of acetic acid were added. The reactions were irradiated for 45 minutes (for **2a**) or 1 hour (for **2b-h**) at 80°C and the solution was poured into ice and the precipitate was filtered off and dried at room temperature. The solid was washed with small portions of cold ethyl acetate.

(E)-2-(1-(7-hydroxy-2-oxo-2H-chromen-3yl)ethylidene)hydrazinecarboxamide (3a)

88% (CH) or 93% (MAOS) yields. Mp: 225°C. IR (KBr): 3513 (O-H), 3403 (N-H), 2922, 2852, 1691 (C=O), 1623 (C=N), 1566 (C=C) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.12 (s, 3H), 6.53 (s, 2H), 6.73 (s, 1H), 6.81- 6.83 (d, J= 8.5Hz, 1H), 7.58-7.60 (d, J= 8.5Hz, 1H), 8.24 (s, 1H), 9.46 (s, 1H), 10.70 (s, 1H). ^{13}C NMR (500 MHz, DMSO-d_6): δ 15.9, 102.2, 112.0, 114.0, 122.2, 130.8, 142.1, 143.1, 155.8, 157.7, 160.2, 162.0. MS (ESI-): m/z 260.1. elemental analysis calcd (%) for $C_{12}H_{11}N_3O_4$: C 55.17, H 4.24, N 16.09; found: C 54.84, H 4.47, N 15.92.

(E)-N'-(1-(7-hydroxy-2-oxo-2H-chromen-3-yl)ethylidene)benzohydrazide (3b)

69% (CH) or 89% (MAOS) yields. Mp: 225°C. IR (KBr): 3435 (O-H), 3058 (N-H), 2923, 2852, 1690 (C=O), 1602 (C=N), 1527 (C=C), 1456 (C=C) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.30 (s, 3H), 6.77 (s, 1H), 6.83-6.85 (d, J= 8.4Hz, 1H), 7.51-7.54 (m, J= 6.7Hz, 2H), 7.58-7.60 (d, J= 5.7Hz, 1H), 7.71-7.70 (d, J=6.1Hz, 1H), 7.88-7.89 (d, J= 6.3Hz, 2H), 8.17 (s, 1H), 10.79 (s, 2H). ^{13}C NMR (500 MHz, DMSO-d_6): δ 16.9, 102.3, 111.7, 114.2, 122.5, 128.4, 128.8, 131.2, 132.1, 134.4, 142.8, 156.1, 160.1, 162.4. MS (ESI-): m/z 321.1. elemental analysis calcd (%) for $C_{18}H_{14}N_2O_4$: C 67.07, H 4.38, N 8.69; found: C 67.18, H 4.50, N 8.55.

(E)-N'-(1-(7-hydroxy-2-oxo-2H-chromen-3-yl)ethylidene)-4-methoxybenzohydrazide (3c)

78% (CH) or 95% (MAOS) yields. Mp: 235°C. IR (KBr): 3431 (O-H), 2922, 2852, 1704 (C=O), 1609 (C=N), 1527 (C=C), 1423 (C=C) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.32 (s, 3H), 3.34 (s, 2H), 6.77 (s, 1H), 6.83-6.85 (d, J= 8.2Hz, 1H), 7.04-7.06 (d, J= 8.2Hz, 2H), 7.69-7.70 (d, J=8.20, 1H), 7.88-7.90 (d, J=8.20, 2H), 8.13 (s, 1H), 10.61 (s, 1H), 10.74 (s,1H). ^{13}C NMR (500 MHz, DMSO-d_6): δ 16.7, 55.9, 102.3, 111.7, 114.0, 114.1, 122.6, 126.3, 131.1, 142.6, 156.0, 160.1, 162.4. MS (ESI-): m/z 351.1. elemental analysis calcd (%) for $C_{19}H_{16}N_2O_5$: C 64.77, H 4.58, N 7.95; found: C 64.71, H 4.60, N 7.92.

(E)-4-chloro-N'-(1-(7-hydroxy-2-oxo-2H-chromen-3-yl)ethylidene)benzohydrazide (3d)

87% (CH) or 98% (MAOS) yields. Mp: 255°C. IR (KBr): 3431 (O-H), 2921, 2852, 1704 (C=O), 1616 (C=N), 1528 (C=C), 1432 (C=C) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.32 (s, 3H), 6.77 (s, 1H), 6.83-6.85 (d, J= 8.5Hz, 1H), 7.59-7.61 (d, J= 5.7Hz, 2H), 7.71 (s, 1H), 7.91 (s, 2H), 8.17 (s, 1H), 10.78 (s, 1H), 10.85 (s, 1H). ^{13}C NMR (500 MHz, DMSO-d_6): 17.0, 102.3, 111.7, 114.2,

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122.4, 128.9, 130.4, 131.2, 142.9, 160.1, 162.5. MS (ESI-): m/z 355.1. elemental analysis calcd (%) for $C_{18}H_{13}ClN_2O_4$: C 60.60, H 3.67, N 7.85; found: C 60.49, H 3.55, N 7.91.

(E)-N'-(1-(7-hydroxy-2-oxo-2H-chromen-3-yl)ethylidene)benzo[d][1,3]dioxole-5-carbohydrazide (3e)

82% (CH) or 93% (MAOS) yields. Mp: 249°C. IR (KBr): 3440 (O-H), 2921, 1704 (C=O), 1616 (C=N), 1529, 1259 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 2.31 (s, 3H), 6.13 (s, 2H), 6.77 (s, 1H), 6.83-6.85 (d, J= 8.5Hz, 1H), 7.03-7.05 (d, J= 7.9Hz, 1H), 7.45 (s, 1H), 7.49-7.51 (d, J= 8.2Hz, 1H), 7.68-7.70 (d, J= 8.5Hz, 1H), 8.13 (s, 1H), 10.58 (s, 1H), 10.74 (s, 1H). ^{13}C NMR (500 MHz, DMSO-d_6): 16.8, 102.2, 102.3, 108.4, 111.7, 114.2, 122.5, 128.1, 131.1, 142.7, 156.1, 160.1, 162.4. MS (M+H) and (M+Na^+): m/z 367.0 and 389.0. elemental analysis calcd (%) for $C_{19}H_{14}N_2O_6$: C 62.30, H 3.85, N 7.65; found: C 61.98, H 3.99, N 7.60.

(E)-4-hydroxy-N'-(1-(7-hydroxy-2-oxo-2H-chromen-3-yl)ethylidene)benzohydrazide (3f)

70% (CH) or 97% (MAOS) yields. Mp 266°C. IR (KBr): 3434 (O-H), 3167 (O-H), 3064 (N-H), 2922, 2853, 1680 (C=O), 1598 (C=N), 1524 (C=C), 1462 (C=C) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.30 (s, 3H), 6.77 (s, 1H), 6.83-6.85 (d, 2H), 6.87 (s, 1H), 7.69-7.71 (d, J= 8.5Hz, 1H), 7.78-7.79 (d, J=8.5Hz, 2H), 8.13 (s, 1H), 10.12 (s, 1H), 10.52 (s, 1H), 10.77 (s, 1H). ^{13}C NMR (500 MHz, DMSO-d_6): δ 16.7, 102.3, 111.7, 114.1, 115.3, 122.6, 124.7, 113.1, 142.6, 156.0, 160.2, 162.4. MS (ESI-): m/z 337.1. elemental analysis calcd (%) for $C_{18}H_{14}N_2O_5$: C 63.90, H 4.17, N 8.28; found: C 63.77, H 4.16, N 8.23.

(E)-4-fluoro-N'-(1-(7-hydroxy-2-oxo-2H-chromen-3-yl)ethylidene)benzohydrazide (3g)

83% (CH) or 85% (MAOS - 1.5 h) yields. Mp: 290°C. IR (KBr): 3437 (O-H), 3048, 2926, 2849, 1693 (C=O), 1601 (C=N), 1532 (C=C), 1456 (C=C), 1345 (C-F) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.32 (s, 3H), 6.77 (s, 1H), 6.83-6.85 (d, J= 8.5Hz, 1H), 7.36 (m, 2H), 7.70-7.71 (d, J= 6.6Hz, 1H), 7.97 (m, 2H), 8.16 (s, 1H), 10.81 (s, 1H). ^{13}C NMR (500 MHz, DMSO-d_6): δ 16.9, 102.3, 111.7, 114.2, 115.7, 122.4, 130.8, 131.2, 142.8, 148.4, 156.1, 160.1, 162.4. MS (ESI-): m/z 339.1. elemental analysis calcd (%) for $C_{18}H_{13}N_2O_4$: C 63.53, H 3.85, N 8.23; found: C 63.61, H 3.94, N 8.20.

(E)-N'-(1-(7-hydroxy-2-oxo-2H-chromen-3-yl)ethylidene)-2-methylimidazo[1,2-a]pyridine-3-carbohydrazide (3h)

72% (CH) or 82% (MAOS) yields. Mp: 240°C. IR (KBr): 3435 (O-H), 2922, 2853, 1698 (C=O), 1616 (C=N), 1585 (C=C), 1452 (C=C), 1232cm^{-1}. ^1H NMR (500MHz DMSO-d_6): δ 2.32 (s,3H), 2.62 (s,2H), 6.77 (s, 1H), 6.83-6.85 (d, J= 8.5Hz, 1H), 7.09-7.12 (t, J= 6.9Hz, 1H), 7.44-7.46-7.47 (t, J= 7.9Hz, 1H), 7.56-7.58 (d, J= 8.8Hz, 1H), 7.64-7.65 (d, J= 8.8Hz, 1H), 7.68-7.69 (d, J= 8.5Hz, 1H), 8.13 (s, 1H), 10.53 (s, 1H), 10.78 (s, 1H). ^{13}C NMR (500 MHz, DMSO-d_6): δ 16.2, 16.3, 16.5, 16.8, 102.3, 102.5, 111.7, 113.8, 114.2, 116.6, 116.7, 116.8, 122.4, 127.5, 127.6, 130.6, 131.2, 142.6, 143.4, 145.8, 145.9, 147.4, 156.0, 156.1, 160.1, 160.1, 162.4. MS (ESI-): m/z 375.1. elemental analysis calcd (%) for $C_{20}H_{16}N_4O_4$: C 63.82, H 4.28, N 14.89; found: C 63.66, H 4.45, N 14.78.

Emission quantum yields

The emission quantum yields in water at 298 K were calculated by Equation 1 using ethyl-7-OH-coumarin-3-carboxylate as a reference compound (ϕ = 0.83,[45] λ_{ex} = 350 nm). Usually, the imine and the hydroxyl groups of similar molecules can ionize at pHs lower than 4 and higher than 6, respectively; thus the pH was controlled to ~4.9 with addition of an acetate buffer solution to ensure their molecular identity.

$$\phi_{Ir} = \phi_{ref} \frac{P_{Ir}}{P_{ref}} \frac{A_{ref}}{A_{Ir}} \quad (3)$$

ϕ_{Ir} = Emission quantum yield for the sample;
ϕ_{ref} = Emission quantum yield for the reference in the same solvent;
A_{Ir} = Absorbance of the sample at the excitation wavelength;
A_{ref} = Absorbance of the reference at the excitation wavelength;
P_{Ir} = Integral of the sample phosphorescence spectrum;
P_{ref} = Integral of the reference phosphorescence spectrum.

General Procedure for pKa determination.

Sample analysis was prepared by dissolving the compound **3b** in 100% milli-Q water and filtering through a millipore filter. The final concentration was adjusted for a maximum absorbance of around 0.4. At the same time, a saturated solution of NaOH was prepared and 1 µL aliquots of this solution were added to the previously prepared solution of compound **3b**. UV-vis scan was performed in a range of 200 nm to 800 nm after each addition. An increase was observed in the band centred at 390nm and reduction at 335nm depending on pH. These wavelengths were used as references for pKa calculation. From these spectral variations, a graph of pH versus log ((A-A_f) / (A_0-A)) was plotted to determine the pKa of compound **3b** as 6.7 (SI).

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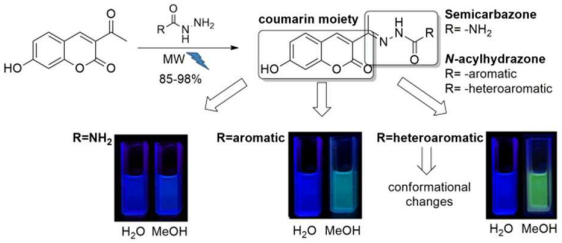

Emissive 7-OH-Coumarins were synthesized by a microwave-assisted protocol and spectral changes were induced after conformational changes in low polarity media.