Pergamon

Tetrahedron 57 (2001) 3105–3116

TETRAHEDRON

# Novel polyaminocarboxylate chelates derived from 3-aroylcoumarins

Ernesto Brunet,* María Teresa Alonso, Olga Juanes, Oscar Velasco and Juan Carlos Rodríguez-Ubis*

*Departamento de Química, Orgánica C-1, Facultad de Ciencias, Universidad Autónoma de Madrid, 28049 Madrid, Spain*

Received 24 October 2000; revised 14 December 2000; accepted 5 February 2001

**Abstract**—We have devised efficient reaction pathways to attach aminopolycarboxylate subunits to the 3-aroylcoumarin chromophore. Two series of compounds were thus prepared in which the chelating arms were directly bonded to the coumarin ring (series A) or to the 3-aroyl moiety (series B). The corresponding Eu(III) and Tb(III) chelates were easily formed and their photophysical properties measured. In all the cases, lanthanide emission lifetimes were in the range of ms. Unfortunately, quantum yields were relatively low. Measurement of $T_1$ states gave too low range of values to sensitize Tb(III). In fact, the metal emission of Tb(III) chelates of series A was not observed. However, series B was able to sensitize both metals. The absorption/energy-transfer/emission mechanisms are discussed. 

## 1. Introduction

The luminescence of lanthanide(III) compounds is widely applied in various fields, in particular time-resolved fluoroimmunoassay (TR-FIA).[1] We are currently involved in the development of $Eu^{3+}$ and $Tb^{3+}$ complexes of organic ligands bearing suitable chromophoric groups. The high efficiency of lanthanide emission sought in these complexes obliges to comply with quite stringent structural and photophysical features, namely high emission quantum yield, high kinetic stability, and good water solubility. Among the various chromophore units tried, 2,6-bis(*N*-pyrazolyl)-pyridine was one of the most successful.[2] On the other hand, the use of aminopolycarboxylate subunits appears to be an excellent choice to achieve effective isolation of the metal ion from solvent molecules,[3] which is the main cause for undesirable, nonradiative decay of the luminescent level.[4]

It has been reported in the literature excellent intersystem-crossing yields for 3-aroylcoumarins that, used as efficient triplet sensitizers,[5] may induce lanthanide emission if the chromophore is provided with adequate chelating moieties. The single example existing to our knowledge of this approach is based in a proton-ionizable 7-hydoxycoumarin derivative,[6] whose photophysical results show a low lanthanide-sensitization efficiency. In contrast, in a previous paper, we reported that crown-ether derived 3-aroylcoumarins resulted reasonably efficient triplet sensitizers of lanthanide emission,[7] even though these complexes were fluorescent, not kinetically stable and the crown ethers did not provide a perfect isolation to the lanthanide ions from the water molecules. In turn, subsequent preliminary studies showed that the replacement of crowns by iminodiacetic subunits conferred to the corresponding $Eu^{3+}$ and $Tb^{3+}$ coumarin complexes quite promising properties.[8] In this article, we give a full account of our results concerning complexation and photophysical properties of lanthanide complexes of 3-aroylcoumarins. The bis-iminodiacetic chelating units for the lanthanide metals have been attached to either ring A or B (Fig. 1; series A and B in the sequel) to check the best relative arrangement between the absorbing coumarin and the emitting metals.

## 2. Results and discussion

### 2.1. Synthesis of the ligands

The 3-aroylcoumarins described in this paper can be prepared by Claisen condensation of a salicylaldehyde with an aroylacetate. We thus envisaged the bis-ethoxycarbonylmethyl ether of 3,4-dihydroxyacetophenone, easily obtained from pyrocatechol,[9] as a common starting material for both series A and B of compounds with iminodiacetic

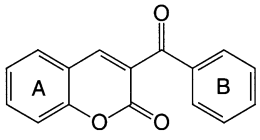
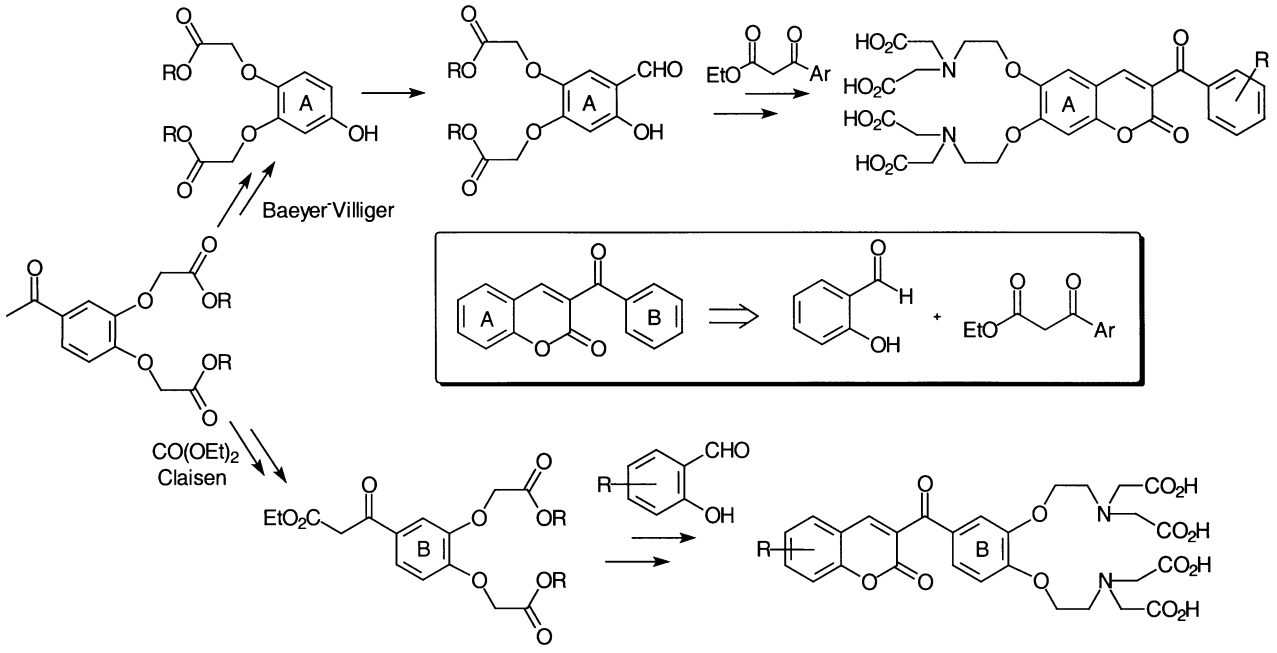



**Figure 1.** Rings A and B in coumarin moiety.

*Keywords*: polycarboxylates; lanthanide chelates; coumarins; luminescence.

* Corresponding authors. Tel.: +34-91-397-3926; fax: +34-91-397-3966; e-mail: ernesto.brunet@uam.es

0040–4020/01/$ - see front matter 
PII: S0040-4020(01)00168-5

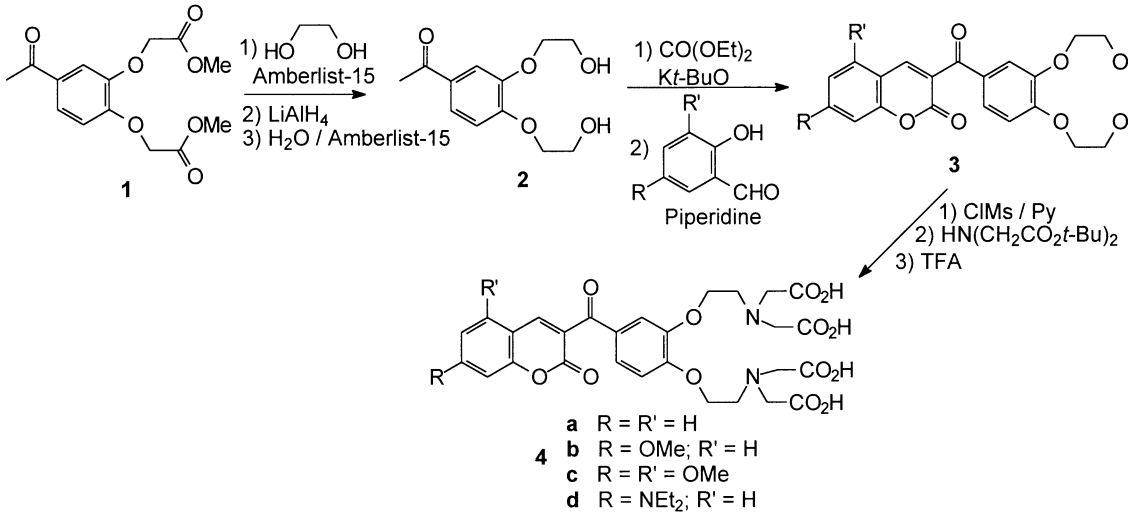



**Scheme 1.**

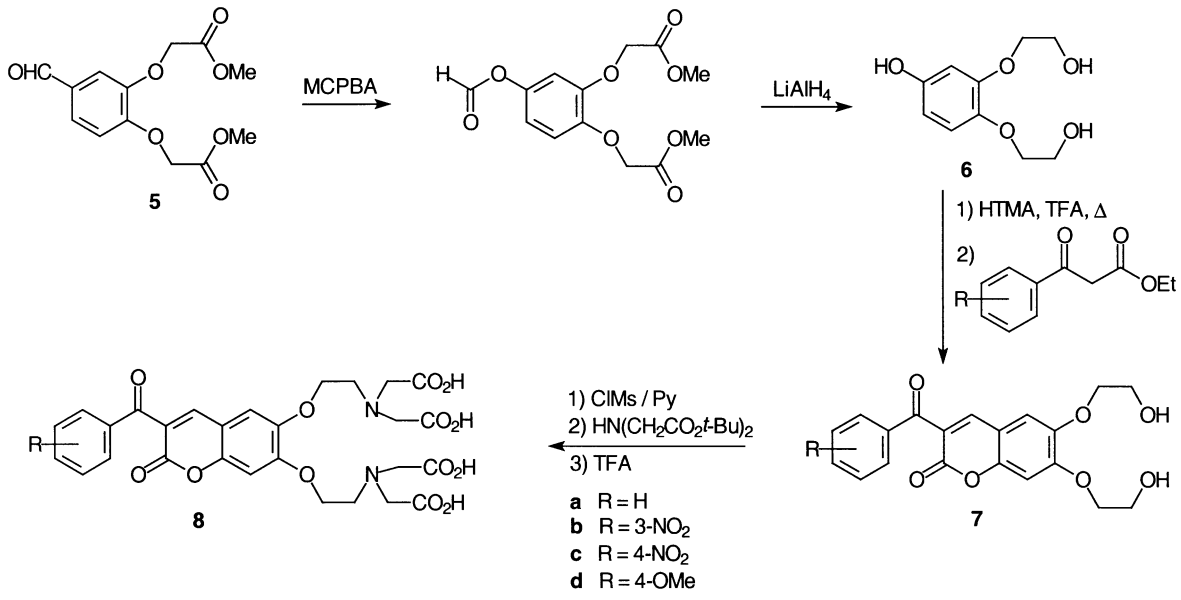
units (Scheme 1). In the case that iminodiacetates are to be bound to ring A, the acetyl group can be transformed into OH by Baeyer–Villiger oxidation and hydrolysis of the resulting acetate. Subsequent carbonylation and Claisen reaction with an aroylacetate would yield the corresponding 3-aroylcoumarin with suitable precursors of iminodiacetate groups in ring A. Series B can be prepared by Claisen reaction of the acetophenone with diethylcarbonate to give the necessary aroylacetate to be condensed with salycilaldehyde.

The synthesis of series B was accomplished (Scheme 2) as it was foreseen. Thus, 3,4-dihydroxyacetophenone was alkylated with 2 equiv. of methylbromoacetate to yield the diester **1**. Ketone protection, reduction of esters, and deprotection yielded the diol derivative **2** to which diethyl carbonate was Claisen condensed in good yield. The resulting β-ketoester reacted with substituted salicylaldehydes to form the coumarins **3**. The building of the coumarin nucleus was performed prior to the transformation of hydroxy groups in methane sulphonates to avoid undesired reactions with the β-ketoester enol form. The tetraacid ligands **4a–d** were prepared by substitution of the mesylated coumarin with di-*tert*-butyliminodiacetate. The resulting *tert*-butyl esters were easily cleaved to the corresponding acids with trifluoroacetic acid in dichloromethane.

The anticipated synthesis in Scheme 1 of coumarins of series A had to be slightly modified (Scheme 3) since the Baeyer–Villiger rearrangement occurred with low yield starting from acetophenone diester **1**. We then decided to start from the aldehyde **5**, whose one-step triple LAH




**Scheme 2.**




**Scheme 3.**

reduction led to diol **6**, which yielded coumarins by Claisen condensation and lactonization with differently substituted aroylacetates.[5] Finally, the tetra-acid ligands **8a–d** were prepared following the same methodology described as in Scheme 2.

## 2.2. Lanthanide complexes

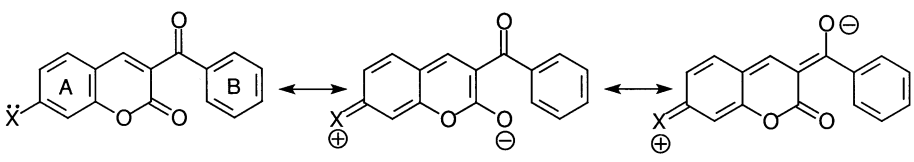
The complexes of $Eu^{3+}$ and $Tb^{3+}$ of coumarin series A and B were prepared in methanol. In all cases spectrometric titration of ligands with increasing amounts of $EuCl_3$ or $TbCl_3$ evidenced that complexes with 1:1 stoichiometry were formed. The UV–Vis spectra of complexes **8a–d** and **4a–d** (Table 1) of $Eu^{3+}$ and $Tb^{3+}$ showed similar, small shifts as compared to the free ligands but, noticeably, with a different tendency: for series A, an hypsochromic shift was observed whereas series B suffered a bathochromic shift.

The elegant measurement of the excited-state dipole moments of several 7-aminocoumarins performed very recently[10] indicates that these compounds increase their polarity when excited. However, albeit the increment was larger than 6 D in some cases, additional evidence pointed out that it was a too low change to support true internal charge-transfer (ICT) species in the excited state as it was previously proposed.[11] Therefore, the excited state of coumarins may be explained in simpler terms by a superior contribution of charge-separated resonance forms as compared to the ground state (Scheme 4).

The hypsochromic (series A) and bathochromic (series B) shifts observed upon complexation are in excellent agreement

**Table 1.** Absorption data for ligands of series A and B and their $Eu^{3+}$ and $Tb^{3+}$ complexes ($\epsilon$ l mol$^{-1}$ cm$^{-1}$)

| Coumarin Series | | Ligands | | Lanthanide complexes | | | $\Delta\lambda_{max}$ (nm) (complex-ligand) |
|---|---|---|---|---|---|---|---|
| | | $\lambda_{max}$ (nm) | $\epsilon\times10^3$ | $\lambda_{max}$ (nm) | $\epsilon\times10^3$ | | |
| | | | | | $Eu^{3+}$ | $Tb^{3+}$ | |
| A | **8a** | 363 | 9.0 | 359 | 8.0 | – | −4 |
| A | **8b** | 377 | 12.2 | 367 | 11.2 | – | −10 |
| A | **8c** | 381 | 13.4 | 367 | 12.6 | – | −14 |
| A | **8d** | 358 | 10.3 | 357 | 10.0 | – | −1 |
| B | **4a** | 317 | 13.6 | 320 | 12.8 | 12.6 | +3 |
| B | **4b** | 343 | 20.4 | 347 | 19.2 | 19.0 | +4 |
| B | **4c** | 358 | 19. 5 | 359 | 18.5 | 18.5 | +1 |
| B | **4d** | 421 | 32.8 | 427 | 30.7 | 30.6 | +6 |




**Scheme 4.**

**Table 2.** Fluorescence maxima (nm), quantum yields ($\phi$) and Stokes' shifts (nm)

| Entry | | Free ligands $\lambda_{ems}$ (nm) ($\phi$) | $Eu^{3+}/Tb^{3+}$ complexes $\lambda_{ems}$ (nm) ($\phi$) | Stokes' shifts (nm) | |
|---|---|---|---|---|---|
| | | | | Free ligands | $Eu^{3+}/Tb^{3+}$ complexes |
| 1 | **4d** | 492 (5%) | 490 (4%) | 71 | 63 |
| 2 | **8a** | 482 (3%) | 482 (2%) | 119 | 123 |
| 3 | **8b** | 481 (2%) | 479 (1%) | 104 | 112 |
| 4 | **8c** | 463 (0.2%) | 456 (0.1%) | 82 | 89 |
| 5 | **8d** | 460 (1%) | 450 (1%) | 102 | 93 |

with this assertion. Thus, the formation of the chelate close to ring B, where electronic density is likely to increase in the excited state, should stabilize it displacing the maxima bathochromically. The small effects observed (average+3.5 nm) excluded the direct interaction of lanthanides with the carbonyl groups of the 3-aroylcoumarin system[12] but, despite the remoteness of the metal, the system appears to be quite sensitive to far off electronic changes.

On the other hand, the presence of the metal cation close to ring A, where a positive charge density presumably develops when the chromophore absorbs light, should destabilize the excited state shifting the maxima hypsochromically. The observed shifts in this case were larger (average−7 nm) suggesting that the phenol oxygens, in direct conjugation with the coumarin chromophore, might play a secondary but important role in the chelation of the metal. The most sensitive compounds to the presence of the metal in series A and B were those bearing the strongest electron acceptor (**8b**, 3′-$NO_2$ and **8c**, 4′-$NO_2$) and electron donor groups (**4d**, 7-$NMe_2$), respectively, that should favour the highest internal charge displacement. This fact reinforces our assumption of stabilization (series B) or destabilization (series A) of the highly polar excited state by the lanthanide cation.

## 2.3. Fluorescence

Coumarins of series B exhibited no fluorescence in methanol at room temperature except when the strong electron-donor diethylamino group is present (**4d**). On their part, coumarins **8** (series A) resulted fluorescent (**8a** and **b**) or moderately fluorescent (**8c** and **d**; cf. Table 2). The quantum yields of fluorescence ($\phi$) in series A decreased in the order **8a**>**8b**>**8d**>**8c**.

Complexation with Eu(III) and Tb(III) changed very little fluorescence $\phi$ values. The presence of the metals, that in principle provides new pathways for energy transfer, did not affect drastically the deactivation of the ligand by fluorescence.

The variation of Stokes' shifts upon complexation deserves some comments. This is a complex phenomenon that has been largely discussed in related compounds.[13] Fortunately, the strong regularities found in our systems allowed us to venture a relatively simple explanation. Thus, we observed that compounds with donor substituents at either end of the 3-aroyl-coumarin structure suffered a diminution of their Stokes' shifts with complexation. This is the case of diethylaminocoumarin **4d** (Table 2, entry 1) and 4′-methoxy benzoyl derivative **8d** (entry 5). In contrast, the unsubstitued compound **8a** (entry 2) and those with electron-withdrawing groups (**8b** and **c**; entries 3 and 4) showed the opposite tendency, i.e. a complexation-induced increase of their Stokes' shift, which was higher for the nitro compounds. A plausible explanation is outlined in Fig. 2.

We mentioned earlier that the these compounds have a relatively high-polar excited state $S_1$ that, upon complexation, was destabilized or stabilized depending on which series A or B, respectively, one considers. Additionally, it is reasonable to assume that at room temperature in a polar, non-viscous solvent as methanol, solvation interactions are relatively fast and reach equilibrium prior to emission.[14] Therefore, after excitation, the solvent layer surrounding the fluorophore should reorganize in a process named *solvent relaxation* that stabilizes the excited state (Fig. 2). But in the cases where the $S_1$ state gains stability upon complexation (stabilized complex in Fig. 2), the role of solvation should be somewhat less important compared to the free ligand, and Stokes' shift should be lower. This is the situation of **8d** and **4d** that, upon complexation, exhibited in absorption (Table 1), a negligible hypsochromic and the highest bathochromic shifts, respectively, and a decrease of Stokes' shifts in fluorescence (Table 2). On the contrary, destabilization of $S_1$ by complexation (destabilized complex in Fig. 2) should intensify the need for solvent relaxation thus making Stokes' shift larger. This should be the case of compounds **8a**–**c** where complexation gave rise to fairly large hypsochromic shifts in absorption (Table 1) and increased Stokes' shifts in emission (Table 2).

## 2.4. Luminescence

Table 3 collects the relevant photophysical data in methanol of the studied Eu(III) and Tb(III) complexes. We measured in the corresponding Gd(III) complexes,[15] the energy of the

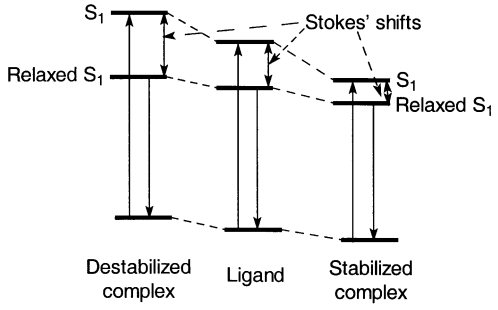



**Figure 2.** Schematic representation of the excited states of ligands and complexes.

**Table 3.** Energy of triplet-state level ($T_1$), excitation maxima ($\lambda_{exc}$), luminescence lifetimes ($\tau$), and quantum yields ($\phi$) of the lanthanide complexes of the coumarins studied in this work

| Compound | $T_1$ ($cm^{-1}$) | $\lambda_{exc}$ [$\lambda_{max}$] (nm) | $\tau$ (ms) | $\phi$ (%) |
|---|---|---|---|---|
| **4a** | 22 500 | | | |
| $Eu^{3+}$ | | 292 [320] | 0.73 | 0.6 |
| $Tb^{3+}$ | | 252 [320] | 1.45 | 2.0 |
| **4b** | 20 900 | | | |
| $Eu^{3+}$ | | 348 [347] | 0.71 | 2.0 |
| $Tb^{3+}$ | | 278 [347] | 0.98 | 0.6 |
| **4c** | 20 400 | | | |
| $Eu^{3+}$ | | 359 [359] | 0.66 | 0.9 |
| $Tb^{3+}$ | | 280 [359] | 1.15 | 0.8 |
| **4d** | 18 100 | | | |
| $Eu^{3+}$ | | 257 [427] | 0.76 | 0.4 |
| $Tb^{3+}$ | | 281 [427] | 1.71 | 1.2 |
| **8a** | 20 000 | | | |
| $Eu^{3+}$ | | 359 [359] | 0.84 | <0.1 |
| **8b** | 20 100 | | | |
| $Eu^{3+}$ | | 367 [367] | 0.90 | <0.1 |
| **8c** | 19 900 | | | |
| $Eu^{3+}$ | | 367 [367] | 1.01 | 0.7 |
| **8d** | 20 400 | | | |
| $Eu^{3+}$ | | 357 [359] | 1.45 | 0.2 |

lowest triplet state (Table 3) in order to shed additional understanding to the expected absorption/energy-transfer/emission (A–ET–E) process between the chromophore and the metal. This is of paramount importance in our current task of developing novel, efficient lanthanide chelates.

Except for the Tb(III) complexes of compounds **8a–d**, where no metal emission was observed (see below), the studied lanthanide chelates gave the typical well-structured, narrow-band emission of Eu(III) and Tb(III), centered at 621 and 525 nm, respectively.

It may be seen (Table 3) that emission lifetimes resulted in the range of ms what, in principle, makes these complexes adequate for time-resolved techniques. However, luminescence quantum yields resulted deceptively low. Other authors and we have found that polycarboxylates provide the metal with an effective shield towards solvent O–H oscillators that thermically deactivates it. Therefore, the low quantum yields should be attributed to some flaws in the A–ET–E process.

First of all, we referred above that the metal of Tb(III) complexes **8a–d** did not emit at all. This is easily understood in terms of the energy of their triplet state (19900–20400 $cm^{-1}$), which resulted clearly below the $^5D_4$ emitting level of $Tb^{3+}$ (20490 $cm^{-1}$).[16] Unfortunately, although they were above the emitting $^5D_0$ level of Eu(III) (17400 $cm^{-1}$), the emission of this metal for **8a–d** was very poor (Table 3). In previous studies,[14] we found that the best quantum yields were achieved when the triplet state of the chromophore laid closely above the $^5D_2$ state of Eu(III) (21400 $cm^{-1}$) which is not the case. Therefore, other non-radiative mechanisms of energy transfer should be preferred, namely ligand-to-metal-charge transfer (LMCT), which is specially favourable for Europium complexes due to the relative ease of $Eu^{3+}/Eu^{2+}$ reduction which drastically degrades quantum yield of metal emission. Besides, complexes **8a–d** exhibited fluorescence (see above). Our data suggests that this radiative pathway competes with the A–ET–E process because the more fluorescent the complex (**8a**>**8b**>**8d**>**8c**; cf. Table 2), the lower the metal emission (**8a**≤**8b**<**8d**<**8c**; cf. Table 3).

Another fact that is worthy of comment is that terbium complexes of ligands **4** and the europium complex of **4a** and **d** (all belonging to series B), showed excitation profiles strongly different from their absorption spectra (cf. Table 3).[17]

Besides concerning triplet states, it is remarkable that terbium complex of **4d**, whose $T_1$ level (18 100 $cm^{-1}$) is well below the $^5D_4$ emitting level of the metal, displayed a quantum yield of emission similar or even higher to those of its counterparts in the series, whose $T_1$ values were higher and therefore better placed in principle to transfer energy to the metal. These findings and the long emission lifetimes observed, specially in the case of Tb(III) complexes, suggest that, after all, there should be a viable energy-transfer mechanism from the chromophore to terbium.

The situation is similar to what we have found in other coumarin derived ligands.[18] Semiempirical calculations at the AM1 level of 3-benzoylcoumarin showed that the preferred conformation of the 3-benzoyl moiety is very far away from planarity with the coumarin nucleus, both in the ground and the excited states. Should this occur in our complexes of series B, conjugation between coumarin and aroyl parts is severed and these chromophores might be considered as independently absorbing.[19] Thus, levels $S_1$ and $T_1$, formally coumarin-centered, were too low lying and their energy could be transferred to europium but not at all to terbium. On the other hand, previous results[20] showed that 3,4-dioxaacetophenone chromophore behaved as an excellent sensitizer for terbium. Therefore, in ligands **4** there should be higher levels, formally belonging to the 3-aroyl moiety, adequately located for energy transfer to terbium. However, this process does not result very efficient, given the low quantum yields measured.

## 3. Conclusion

We have attached aminopolycarboxylate subunits to the 3-aroylcoumarin chromophore following expeditious synthesis schemes. Reaction of the prepared compounds with Eu(III) and Tb(III) salts easily led to the corresponding lanthanide chelates. Metal emission was observed in almost all cases with long lifetimes in the range of ms. However, the general poor matching between the measured $T_1$ levels of the ligands and the metal emitting levels led to low quantum yields. Various absorption/energy-transfer/emission mechanisms can be at play, in which the coumarin and 3-aroyl chromophores could be formally considered as independently absorbing. Further modification of the coumarin is in progress, in order to improve the energy transfer to the lanthanides.

## 4. Experimental

### 4.1. General

$^1$H and $^{13}$C NMR: Bruker AC-200 (Departamento de Química Orgánica, DCO) and AMX-300 (Servicio Interdepartamental de Invesigación, SIdI). M.S.: VG Autospec spectrometer (SIdI) in FAB mode (L-SIMS$^+$). Absorption spectra: Lambda 6 Perkin–Elmer spectrophotometer (DCO). Excitation and emission spectra: LS50 Perkin–Elmer spectrofluorometer (DCO). The excitation spectra were automatically corrected, and the emission spectra were corrected according to the instrument guidebook.[2] Elemental analyses: Perkin–Elmer CHN 2400 automatic analyzers (SIdI). All solvents were purified prior to their use. Lanthanide chlorides and oxides were purchased from Aldrich and used as received. IUPAC names of compounds were obtained from ChemWeb: (http://cwgen.chemweb.-com/autonom/autonomsearch.html).

**4.1.1. Synthesis of Eu(III) and Tb(III) complexes and luminescence measurements.** The complexes were formed by addition of equimolecular amounts of the corresponding lanthanide(III) chloride salt in methanol ($10^{-2}$ M) to the tetraacids solutions ($3.2\times10^{-5}$ M). Luminescence parameters were analyzed from the same spectroscopic grade solvent. The emission quantum yields were measured by a relative method using the $Eu^{3+}$ and $Tb^{3+}$ complexes of *N*,*N*,*N*′,*N*′-(6,6″-aminomethyl-4′-phenyl-2,2′:6′,2″-terpyridine) tetrakis (acetic acid) as a standard and referenced to quinine sulphate. The expected errors of this measurement are within 30%. The total luminescence intensities of complexes were determined by integrating the emissions of each lanthanide chelate. Emission lifetimes were measured as previously described and estimated errors are 10%.[2]

### 4.2. General methods

**4.2.1. Synthesis of the coumarin ring.** The corresponding salicylaldehyde (0.25 mmol) and the β-ketoester (0.25 mmol) were dissolved in 3 mL of ethanol. Piperidine (3 drops) was added, and the mixture was refluxed for 4 h. Filtration of the cooled mixture yielded the coumarin as analytically pure crystals. In selected cases, a second crop of coumarin could be obtained by total evaporation of solvent followed by column chromatography (dichoromethane/methanol 95:5). Yield 50–80%.

**4.2.2. Mesylation of coumarins.** A solution of the coumarin-diol derivative (2.08 mmol) and triethylamine (6.25 mmol) in dichloromethane (10 mL) was stirred under argon in an ice bath. Methanesulfonyl chloride (4.58 mmol) was then slowly added and the resulting mixture was stirred for 20 min. A portion (10 mL) of crushed ice was added to the reaction mixture and the organic layer was washed with 10% hydrochloric acid (3×8 mL), saturated sodium hydrogenocarbonate (3×8 mL) and brine (3×8 mL), dried over sodium sulphate, and the solvent evaporated. The residue was crushed in ether and the resulting white solid filtered off. Yield 70–95%.

**4.2.3. Reaction of mesylated derivatives with (*tert*-butoxy-carbonylmethyl-amino)-acetic acid *tert*-butyl ester.** A mixture of the dimesyl derivative (0.5 mmol), (*tert*-butoxy-carbonylmethyl-amino)-acetic acid *tert*-butyl ester, sodium iodide (1.50 mmol) and sodium carbonate (5.05 mmol) in 40 mL of acetonitrile was stirred at 120°C (autoclave) under argon for 4 days. The solvent was then removed and the resulting residue flash-chromatographed on silica-gel (dichloromethane/methanol 95:5). The fractions containing the tetraester were collected, the solvent removed and in some cases chromatographed again on silica-gel (ethyl acetate/hexane 2:1). The tetraester was obtained as yellow oil. Yield 28–43%.

**4.2.4. Hydrolysis of tetra(*tert*-butyl)esters.** A solution of tetraester (0.13 mmol) and TFA (0.18 mL) in dichloromethane (4 mL) was stirred at rt for 18 h. The solvent was then removed under vacuo, the residue crushed in acetone and the resulting white-yellow solid filtered off. Yield 96–98%.

### 4.3. Compounds series B

**4.3.1. 3-[3,4-Bis-(2-hydroxy-ethoxy)-phenyl]-3-oxo-propionic acid ethyl ester.** A suspension of potassium *tert*-butoxide (7.90 g, 66.7 mmol) in diethyl carbonate (80 mL) was stirred in an ultrasound bath for 5 min. 1-[3,4-Bis-(2-hydroxy-ethoxy)-phenyl]-ethanone[17] (**2** in Scheme 2) was added (6.00 g, 25 mmol) and the mixture was kept in the ultrasound bath for 4 h under Ar. Hexane was added (50 mL) and the orange solid was filtered and dissolved in water. HCl 10% was added until pH=2. The aqueous layer was extracted with $CH_2Cl_2$ (4×100 mL), dried over sodium sulphate and the solvent evaporated. The product was obtained as a yellow solid (6.82 g), yield 87%; mp 88–89°C. $^1$H NMR ($CDCl_3$) (corresponding to major tautomer of β-ketoester): $\delta$ 7.57 (dd, 1H, *J*=2.1 and 8.8 Hz, H-6); 7.57 (d, 1H, *J*=2.1 Hz, H-2); 6.93 (d, 1H,*J*=8.8 Hz, H-5); 4.53 (brs, 2H, $CH_2OH$); 4.21 (q, 2H, *J*=7.1 Hz, $CH_3CH_2O$); 4.18–4.14 (m, 4H, $ArOCH_2$); 4.02–3.95 (m, 4H, $CH_2OH$); 3.94 (s, 2H, $COCH_2CO$); 1.26 (t, 3H, *J*=7 Hz, $CH_3CH_2O$). $^{13}$C NMR ($CDCl_3$) (corresponding to major tautomer of β-ketoester): $\delta$ 190.9 (ArCO); 167.6 ($CO_2Et$); 153.2 (C-4); 148.1 (C-3); 129.0 (C-1); 123.7 (C-6); 112.3 (C-2); 111.4 (C-5); 70.5; 70.3 ($ArOCH_2$); 61.2 ($CH_3CH_2O$); 60.5; 60.3 ($CH_2OH$); 45.3 ($COCH_2CO$); 13.8 ($CH_3CH_2O$). Anal. calcd for $C_{15}H_{20}O_7$: C, 57.69; H, 6.41. Found: C, 57.86; H, 6.57.

**4.3.2. 3-[3,4-Bis-(2-hydroxy-ethoxy)-benzoyl]-chromen-2-one (3a).** It was obtained as a yellow solid following the general method starting from 3-[3,4-bis-(2-hydroxy-ethoxy)-phenyl]-3-oxo-propionic acid ethyl ester and salicylaldehyde. Yield 72%; mp 185–187°C. $^1$H NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 8.06 (s, 1H, H-4); 7.73–7.62 (m, 2H, H-5, H-7); 7.57 (d, 1H, *J*=2.1 Hz, H-2′); 7.47 (dd, 1H, *J*=2.1 and 8.5 Hz, H-6′); 7.45–7.36 (m, 2H, H-8, H-6); 6.93 (d, 1H, *J*=8.5 Hz, H5′); 4.20–4.15 (m, 4H, $ArOCH_2$); 3.99–3.94 (m, 4H, $CH_2OH$). $^{13}$C NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 190.7 (CO); 159.3 (C-2); 154.7 (C-9); 154.3 (C-4′); 148.9 (C-3′); 145.2 (C-4); 133.9 (C-7); 129.5 (C-1′+C-5); 127.0 (C-10); 126.2 (C-6′); 125.5 (C-6); 118.4 (C-3); 117.0 (C-8); 113.5 (C-2′); 111.8 (C-5′); 71.0; 70.8 ($ArOCH_2$); 60.6; 60.5 ($CH_2OH$). Anal. calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.86. Found: C, 64.73; H 4.69.

**4.3.3. 3-[3,4-Bis-(2-hydroxy-ethoxy)-benzoyl]-7-methoxy-chromen-2-one (3b).** It was synthesized as a dark-yellow solid following the general method starting from 3-[3,4-bis-(2-hydroxy-ethoxy)-phenyl]-3-oxo-propionic acid ethyl ester and 4-methoxysalicylaldehyde. Yield 86%; mp 195–197°C. $^1$H NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 8.05 (s, 1H, H-4); 7.53 (d, 1H, $J$=2.0 Hz, H-2′); 7.53 (d, 1H, $J$=8.5 Hz, H-5); 7.46 (dd, 1H, $J$=2.0 and 8.3 Hz, H-6′); 6.95 (dd, 1H, $J$=2.3 and 8.5 Hz, H-6); 6.93 (d, 1H, $J$=8.3 Hz, H-5′); 6.91 (d, 1H, $J$=2.3 Hz, H-8); 4.19–4.15 (m, 4H, $ArOCH_2$); 4.00–3.93 (m, 4H, C$H_2$OH); 3.94 (s, 3H, $OCH_3$). $^{13}$C NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 190.6 (CO); 164.4 (C-7); 159.1 (C-2); 156.6 (C-9); 153.4 (C-4′); 148.2 (C-3′); 145.8 (C-4); 130.2 (C-5); 129.4 (C-1′); 125.5 (C-6′); 122.5 (C-3); 113.5 (C-6); 113.3 (C-2′); 111.6 (C-10); 111.3 (C-5′); 100.4 (C-8); 70.6; 70.4 ($ArOCH_2$); 60.2; 60.0 ($CH_2OH$); 55.8 ($OCH_3$). Anal. calcd for $C_{21}H_{20}O_8$: C, 63.00; H, 5.00. Found: C, 62.80; H, 4.86.

**4.3.4. 3-[3,4-Bis-(2-hydroxy-ethoxy)-benzoyl]-5,7-dimethoxy-chromen-2-one (3c).** It was prepared as a yellow solid following the general method starting from 3-[3,4-bis-(2-hydroxy-ethoxy)-phenyl]-3-oxo-propionic acid ethyl ester and 4,6-methoxysalicylaldehyde. Yield 89%; mp 217–218°C. $^1$H NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 8.34 (s, 1H, H-4); 7.51 (d, 1H, $J$=2.0 Hz, H-2′); 7.45 (dd, 1H, $J$=2.0 and 8.5 Hz, H-6′); 6.95 (d, 1H, $J$=8.5 Hz, H-5′); 6.52 (d, 1H, $J$=2.1 Hz, H-8); 6.38 (d, 1H, $J$=2.1 Hz, H6); 4.20–4.15 (m, 4H, $ArOCH_2$); 3.99–3.93 (m, 4H, C$H_2$OH); 3.93 (s, 6H, $OCH_3$). $^{13}$C NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 190.3 (CO); 165.8 (C-7); 159.3 (C-2); 158.0 (C-5); 157.3 (C-9); 153.2 (C-4′); 148.1 (C-3′); 141.7 (C-4); 129.5 (C-1′); 125.3 (C-6′); 119.7 (C-3); 113.2 (C-2′); 111.2 (C-5′); 103.2 (C-10); 95.0 (C-6); 92.5 (C-8); 70.4; 70.2 ($ArOCH_2$); 60.1; 60.0 ($CH_2OH$); 55.7 ($OCH_3$). Anal. calcd for $C_{22}H_{22}O_9$: C, 61.39; H, 5.12. Found: C, 60.94; H, 5.24.

**4.3.5. 3-[3,4-Bis-(2-hydroxy-ethoxy)-benzoyl]-7-diethylamino-chromen-2-one (3d).** It was obtained as a yellow solid following the general method starting from 3-[3,4-bis-(2-hydroxy-ethoxy)-phenyl]-3-oxo-propionic acid ethyl ester and 4-diethylaminosalicylaldehyde. Yield 84%; mp 121–122°C. $^1$H NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 8.04 (s, 1H, H-4); 7.48 (d, 1H, $J$=2.0 Hz, H-2′); 7.47 (dd, 1H, $J$=2.0 and 8.0 Hz, H-6′); 7.38 (d, 1H, $J$=9.0 Hz, H-5); 6.92 (d, 1H, $J$=8.0 Hz, H-5′); 6.66 (dd, 1H, $J$=2.5 and 9.0 Hz, H-6); 6.53 (d, 1H, $J$=2.5 Hz, H-8); 4.19–4.14 (m, 4H, $ArOCH_2$); 3.99–3.92 (m, 4H, C$H_2$OH); 3.48 (q, 4H, $J$=7.1 Hz, $CH_3CH_2N$); 1.26 (t, 6H, $J$=7.1 Hz, $CH_3CH_2N$). $^{13}$C NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 191.3 (CO); 160.2 (C-7); 157.8 (C-2); 152.9 (C-9); 152.5 (C-4′); 147.9 (C-3′); 147.3 (C-4); 130.7 (C-5); 130.4 (C-1′); 125.0 (C-6′); 117.2 (C-3); 113.8 (C-2′); 111.4 (C-5′); 109.6 (C-6); 107.5 (C-10); 96.6 (C-8); 70.7; 70.4 ($ArOCH_2$); 60.3; 60.1 ($CH_2OH$); 44.9 ($CH_3CH_2N$); 12.1 ($CH_3CH_2N$). Anal. calcd for $C_{24}H_{27}NO_7{\cdot}0.5H_2O$: C, 64.00; H, 6.22; N, 3.11. Found: C, 63.69; H, 5.81; N, 3.16.

**4.3.6. Methanesulfonic acid 2-[2-(2-methanesulfonyloxy-ethoxy)-5-(2-oxo-2*H*-chromene-3-carbonyl)-phenoxy]-ethyl ester.** It was synthesized from **3a** as a white solid following the general method described above. Yield 84%; mp 166–168°C. $^1$H NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 8.09 (s, 1H, H-4); 7.73–7.62 (m, 2H, H-5, H-7); 7.56 (d, 1H, $J$=2.0 Hz, H-2′); 7.50 (dd, 1H, $J$=2.0 and 8.4 Hz, H-6′); 7.48–7.35 (m, 2H, H-8, H-6); 6.94 (d, 1H, $J$=8.4 Hz, H5′); 4.66–4.60 (m, 4H, $CH_2OSO_2$); 4.38–4.33 (m, 4H, $ArOCH_2$); 3.18 (s, 3H, $CH_3S$); 3.16 (s, 3H, $CH_3S$). $^{13}$C NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 191.7 (CO); 160.3 (C-2); 155.5 (C-9); 153.9 (C-4′); 148.8 (C-3′); 146.3 (C-4); 134.8 (C-7); 131.0 (C-1′); 130.2 (C-5); 127.7 (C-10); 127.0 (C-6′); 126.1 (C-6); 119.1 (C-3); 117.9 (C-8); 115.0 (C-2′); 113.2 (C-5′); 69.0; 68.7; 68.2; 67.9 ($CH_2O$); 38.6 ($CH_3S$). Anal. calcd for $C_{22}H_{22}O_{11}S_2$: C, 50.19; H, 4.18. Found: C, 49.79; H, 3.98.

**4.3.7. Methanesulfonic acid 2-[2-(2-methanesulfonyloxy-ethoxy)-5-(7-methoxy-2-oxo-2*H*-chromene-3-carbonyl)-phenoxy]-ethyl ester.** A white solid in 97% yield was obtained following the general method starting from **3b**; mp 142–143°C. $^1$H NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 8.10 (s, 1H, H-4); 7.56 (d, 1H, $J$=8.6 Hz, H-5); 7.53 (d, 1H, $J$=2.1 Hz, H-2′); 7.51 (dd, 1H, $J$=2.1 and 8.4 Hz, H-6′); 6.96 (dd, 1H, $J$=2.3 and 8.6 Hz, H-6); 6.96 (d, 1H, $J$=8.4 Hz, H-5′); 6.91 (d, 1H, $J$=2.3 Hz, H-8); 4.67–4.60 (m, 4H, $CH_2OSO_2$); 4.39–4.33 (m, 4H, $ArOCH_2$); 3.95 (s, 3H, $OCH_3$); 3.19 (s, 3H, $CH_3S$); 3.18 (s, 3H, $CH_3S$). $^{13}$C NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 190.5 (CO); 164.7 (C-7); 159.1 (C-2); 156.9 (C-9); 152.5 (C-4′); 147.6 (C-3′); 146.4 (C-4); 130.4 (C-5); 129.8 (C-1′); 125.7 (C-6′); 122.5 (C-3); 114.1 (C-6); 113.7 (C-2′); 112.1 (C-5′); 111.7 (C-10); 100.5 (C-8); 67.9; 67.7; 67.0; 66.8 ($CH_2O$); 55.9 ($OCH_3$); 37.6 ($CH_3S$). Anal. calcd for $C_{23}H_{24}O_{12}S_2$: C, 49.64; H, 4.32. Found: C, 49.41; H, 4.29.

**4.3.8. Methanesulfonic acid 2-[5-(5,7-dimethoxy-2-oxo-2*H*-chromene-3-carbonyl)-2-(2-methanesulfonyloxy-ethoxy)-phenoxy]-ethyl ester.** It was synthesized following the general method from **3c** as a white solid in 95% yield; mp 180–181°C. $^1$H NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 8.41 (s, 1H, H-4); 7.51 (d, 1H, $J$=2.0 Hz, H-2′); 7.49 (dd, 1H, $J$=2.0 and 8.4 Hz, H-6′); 6.96 (d, 1H, $J$=8.4 Hz, H-5′); 6.51 (d, 1H, $J$=2.1 Hz, H-8); 6.37 (d, 1H, $J$=2.1 Hz, H6); 4.67–4.61 (m, 4H, $CH_2OSO_2$); 4.39–4.33 (m, 4H, $ArOCH_2$); 3.93 (s, 6H, $OCH_3$); 3.19 (s, 3H, $CH_3S$); 3.18 (s, 3H, $CH_3S$). $^{13}$C NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 190.5 (CO); 165.9 (C-7); 159.1 (C-2); 158.1 (C-5); 157.5 (C-9); 152.2 (C-4′); 147.4 (C-3′); 142.2 (C-4); 130.4 (C-1′); 125.5 (C-6′); 120.5 (C-3); 114.2 (C-2′); 112.1 (C-5′); 103.8 (C-10); 95.2 (C-6); 92.8 (C-8); 67.9; 67.7; 67.1; 66.8 ($CH_2O$); 56.1 ($OCH_3$); 37.8 ($CH_3S$).

**4.3.9. Methanesulfonic acid 2-[4-(7-diethylamino-2-oxo-2*H*-chromene-3-carbonyl)-2-(2-methanesulfonyloxy-ethoxy)-phenoxy]-ethyl ester.** It was prepared from **3d** following the general method. A yellow solid was obtained in 99% yield; mp 136–138°C. $^1$H NMR ($CDCl_3$) $\delta$: 8.09 (s, 1H, H-4); 7.49 (dd, 1H, $J$=1.9 and 8.1 Hz, H-6′); 7.47 (d, 1H, $J$=1.9 Hz, H-2′); 7.38 (d, 1H, $J$=8.9 Hz, H-5); 6.90 (d, 1H, $J$=8.1 Hz, H-5′); 6.64 (dd, 1H, $J$=2.4 and 8.9 Hz, H-6); 6.51 (d, 1H, $J$=2.4 Hz, H-8); 4.64–4.58 (m, 4H, $CH_2OSO_2$); 4.35–4.31 (m, 4H, $ArOCH_2$); 3.47 (q, 4H, $J$=7.1 Hz, $CH_3CH_2N$); 3.16 (s, 3H, $CH_3S$); 3.15 (s, 3H, $CH_3S$); 1.25 (t, 6H, $J$=7.1 Hz, $CH_3CH_2N$). $^{13}$C NMR ($CDCl_3$) $\delta$: 190.8 (CO); 159.8 (C-7); 157.9 (C-2); 152.1 (C-9); 151.8 (C-4′);

147.3 (C-3′+C-4); 131.3 (C-1′); 130.9 (C-5); 125.1 (C-6′); 117.8 (C-3); 114.3 (C-2′); 112.1 (C-5′); 109.9 (C-6); 108.0 (C-10); 97.1 (C-8); 68.1; 67.9; 66.9; 66.7 ($CH_2O$); 45.2 ($CH_3CH_2N$); 37.6 ($CH_3S$); 12.3 ($CH_3CH_2N$). Anal. calcd for $C_{26}H_{31}NO_{11}S_2$ C, 52.26; H, 5.19; N, 2.34. Found: C, 52.05; H, 4.95; N, 2.23.

**4.3.10. ({2-[2-[2-(Bis-*tert*-butoxycarbonylmethyl-amino)-ethoxy]-5-(2-oxo-2*H*-chromene-3-carbonyl)-phenoxy]-ethyl}-*tert*-butoxycarbonylmethyl-amino)-acetic acid *tert*-butyl ester.** It was synthesized following the general method starting from the corresponding dimesylated derivative. Yellow oil, 33% yield. $^1$H NMR ($CDCl_3$) $\delta$: 7.96 (s, 1H, H-4); 7.65–7.57 (m, 2H, H-5, H-7); 7.50 (d, 1H, $J$=1.9 Hz, H-2′); 7.44–7.29 (m, 3H, H-6′, H-8, H-6); 6.89 (d, 1H, $J$=8.5 Hz, H-5′); 4.23–4.13 (m, 4H, $ArOCH_2$); 3.55 (s, 8H, $NCH_2CO_2$); 3.22–3.16 (m, 4H, $NCH_2$); 1.43 (s, 36H, $CCH_3$). $^{13}$C NMR ($CDCl_3$) $\delta$:189.6 (CO); 170.4 ($CO_2{}^t$Bu); 158.1 (C-2); 154.2 (C-9); 153.5 (C-4′); 148.3 (C-3′); 143.9 (C-4); 133.0 (C-7); 128.7 (C-1′+C-5); 127.0 (C-10); 125.1 (C-6′); 124.6 (C-6); 117.9 (C-3); 116.4 (C-8); 112.6 (C-2′); 111.1 (C-5′); 80.7 ($CCH_3$); 68.0 ($CH_2O$); 56.7; 56.5 ($NCH_2CO_2$); 52.9 ($CH_2CH_2N$); 27.8 ($CCH_3$). MS(L-SIMS+): 825.1 ($M+H^+$, 21%); 847.1 ($M+Na^+$, 4%); 601.3 ($M+H^+-4(C_4H_8)$, 19%); 173.0 (coumarin $CO^+$, 25%)

**4.3.11. ({2-[2-[2-(Bis-*tert*-butoxycarbonylmethyl-amino)-ethoxy]-5-(7-methoxy-2-oxo-2*H*-chromene-3-carbonyl)-phenoxy]-ethyl}-*tert*-butoxycarbonylmethyl-amino)-acetic acid *tert*-butyl ester.** It was synthesized following the general method starting from the corresponding dimesylated derivative. Yellow oil, 30% yield. $^1$H NMR ($CDCl_3$) $\delta$: 7.98 (s, 1H, H-4); 7.51 (d, 1H, $J$=8.5 Hz, H-5); 7.49 (d, 1H, $J$=1.9 Hz, H-2′); 7.43 (dd, 1H, $J$=1.9 and 8.4 Hz, H-6′); 6.90 (d, 1H, $J$=8.4 Hz, H-5′); 6.90 (dd, 1H, $J$=2.4 and 8.5 Hz, H-6); 6.84 (d, 1H, $J$=2.4 Hz, H-8); 4.25–4.15 (m, 4H, $ArOCH_2$); 3.91 (s, 3H, $OCH_3$); 3.58 (s, 8H, $NCH_2CO_2$); 3.28–3.20 (m, 4H, $NCH_2$); 1.45 (s, 36H, $CCH_3$). $^{13}$C NMR ($CDCl_3$) $\delta$: 190.0 (CO); 170.4 ($CO_2{}^t$Bu); 163.9 (C-7); 158.4 (C-2); 156.4 (C-9); 153.1 (C-4′); 148.0 (C-3′); 144.9 (C-4); 130.0 (C-5); 129.0 (C-1′); 124.8 (C-6′); 122.9 (C-3); 113.0 (C-6); 112.6 (C-2′); 111.5 (C-5′); 110.9 (C-10); 100.3 (C-8); 80.6 ($CCH_3$); 67.7 ($CH_2O$); 56.6; 56.4 ($NCH_2CO_2$); 55.6 ($OCH_3$); 52.8 ($CH_2CH_2N$); 27.8 ($CCH_3$). MS(L-SIMS+): 855.2 ($M+H^+$, 9%); 877.2 ($M+Na^+$, 6%); 631.3 ($M+H^+-4(C_4H_8)$, 10%); 203.1 (coumarin $CO^+$, 45%).

**4.3.12. ({2-[2-[2-(Bis-*tert*-butoxycarbonylmethyl-amino)-ethoxy]-5-(5,7-dimethoxy-2-oxo-2*H*-chromene-3-carbonyl)-phenoxy]-ethyl}-*tert*-butoxycarbonylmethyl-amino)-acetic acid *tert*-butyl ester.** It was synthesized following the general method starting from corresponding dimesylated derivative. Yellow oil, 28% yield. $^1$H NMR ($CDCl_3$) $\delta$: 8.31 (s, 1H, H-4); 7.8 (d, 1H, $J$=2.0 Hz, H-2′); 7.41 (dd, 1H, $J$=2.0 and 8.4 Hz, H-6′); 6.89 (d, 1H, $J$=8.4 Hz, H-5′); 6.46 (d, 1H, $J$=2.1 Hz, H-8); 6.31 (d, 1H, $J$=2.1 Hz, H6); 4.24–4.14 (m, 4H, $ArOCH_2$); 3.90 (s, 6H, $OCH_3$); 3.56 (s, 8H, $NCH_2CO_2$); 3.23–3.17 (m, 4H, $NCH_2$); 1.44 (s, 36H, $CCH_3$). $^{13}$C NMR ($CDCl_3$) $\delta$: 190.4 (CO); 170.6 ($CO_2{}^t$Bu); 165.4 (C-7); 158.9 (C-2); 158.0 (C-5); 157.5 (C-9); 153.1 (C-4′); 148.2 (C-3′); 141.0 (C-4); 129.6 (C-1′); 124.9 (C-6′); 120.8 (C-3); 113.0 (C-2′); 111.2 (C-5′); 103.4 (C-10); 94.9 (C-6); 92.6 (C-8); 80.9 ($CCH_3$); 68.5; 68.0 ($CH_2O$); 56.9; 56.6 ($NCH_2CO_2$); 55.9 ($OCH_3$); 53.1 ($CH_2CH_2N$); 28.0 ($CCH_3$). MS(L-SIMS+): 885.4 ($M+H^+$, 8%); 907.5 ($M+Na^+$, 5%); 661.3 ($M+H^+-4(C_4H_8)$, 9%); 233.1 (coumarin $CO^+$, 50%).

**4.3.13. ({2-[2-[2-(Bis-*tert*-butoxycarbonylmethyl-amino)-ethoxy]-5-(7-diethylamino-2-oxo-2*H*-chromene-3-carbonyl)-phenoxy]-ethyl}-*tert*-butoxycarbonylmethyl-amino)-acetic acid *tert*-butyl ester.** It was synthesized following the general method starting from the corresponding dimesylated derivative. Yellow oil, 35% yield. $^1$H NMR ($CDCl_3$) $\delta$: 7.96 (s, 1H, H-4); 7.45 (d, 1H, $J$=1.9 Hz, H-2′); 7.41 (dd, 1H, $J$=1.9 and 8.2 Hz, H-6′); 7.34 (d, 1H, $J$=8.9 Hz, H-5); 6.88 (d, 1H, $J$=8.2 Hz, H-5′); 6.61 (dd, 1H, $J$=2.4 and 8.9 Hz, H-6); 6.51 (d, 1H, $J$=2.4 Hz, H-8); 4.23–4.13 (m, 4H, $ArOCH_2$); 3.56 (s, 8H, $NCH_2CO_2$); 3.46 (q, 4H, $J$=7.1 Hz, $CH_3CH_2N$); 3.23–3.17 (m, 4H, $NCH_2$); 1.44 (s, 36H, $CCH_3$); 1.24 (t, 6H, $J$=7.1 Hz, $CH_3CH_2N$). $^{13}$C NMR ($CDCl_3$) $\delta$: 191.1 (ArCO); 170.7 ($CO_2{}^t$Bu); 159.7 (C-7); 157.9 (C-2); 152.8 (C-9); 152.2 (C-4′); 148.1 (C-3′); 146.7 (C-4); 130.6; 130.3 (C-1′, C-5); 124.7 (C-6′); 118.5 (C-3); 113.3 (C-2′); 111.2 (C-5′); 109.4 (C-6); 107.6 (C-10); 96.9 (C-8); 81.0; 80.9 ($CCH_3$); 67.9 ($CH_2O$); 56.8; 56.6 ($NCH_2CO_2$); 53.1 ($CH_2CH_2N$); 45.0 ($CH_3CH_2N$); 28.1 ($CCH_3$); 12.4 ($CH_3CH_2N$). MS(L-SIMS+): 896.6 ($M+H^+$, 28%); 918.6 ($M+Na^+$, 9%); 672.3 ($M+H^+-4(C_4H_8)$, 27%); 244.1 (coumarin $CO^+$, 80%).

**4.3.14. ({2-[2-[2-(Bis-carboxymethyl-amino)-ethoxy]-5-(2-oxo-2*H*-chromene-3-carbonyl)-phenoxy]-ethyl}-carboxymethyl-amino)-acetic acid (4a).** It was synthesized following the general method starting from the corresponding *tert*-butyl tetraester. Dark-yellow solid, 97% yield; mp 162–164°C. $^1$H NMR (DMSO-$d_6$) $\delta$: 8.32 (s, 1H, H-4); 7.85–7.67 (m, 2H, H-5, H-7); 7.56–7.37 (m, 4H, H-2′, H-6′, H-8, H-6); 7.05 (d, 1H, $J$=8.4 Hz, H-5′); 4.22–4.10 (m, 4H, $ArOCH_2$); 3.60; 3.58 (s, s, 8H, $NCH_2CO_2$); 3.15–3.02 (m, 4H, $NCH_2$). MS(L-SIMS+): 601.0 ($M+H^+$, 6%); 623.0 ($M+Na^+$, 2%); 543.0 ($(M+H^+)-CHCO_2H$, 1%); 173.0 (coumarin $CO^+$, 6%). Anal. calcd for $C_{28}H_{28}N_2O_{13}$: C, 56.00; H, 4.67; N, 4.67. Found: C, 56.19; H, 4.96; N, 4.86.

**4.3.15. ({2-[2-[2-(Bis-carboxymethyl-amino)-ethoxy]-5-(7-methoxy-2-oxo-2*H*-chromene-3-carbonyl)-phenoxy]-ethyl}-carboxymethyl-amino)-acetic acid (4b).** It was synthesized following the general method starting from the corresponding *tert*-butyl tetraester. Dark-yellow solid, 96% yield; mp 158–160°C. $^1$H NMR (DMSO-$d_6$) $\delta$: 8.27 (s, 1H, H-4); 7.75 (d, 1H, $J$=8.6 Hz, H-5); 7.48 (dd, 1H, $J$=1.8 and 8.3 Hz, H-6′); 7.43 (d, 1H, $J$=1.8 Hz, H-2′); 7.08 (d, 1H, $J$=2.2 Hz, H-8); 7.04 (d, 1H, $J$=8.3 Hz, H-5′); 7.01 (dd, 1H, $J$=2.2 and 8.6 Hz, H-6); 4.14–4.08 (m, 4H, $ArOCH_2$); 3.89 (s, 3H, $OCH_3$); 3.54 (s, 8H, $NCH_2CO_2$); 3.16–3.05 (m, 4H, $NCH_2$). MS(L-SIMS+): 631.0 ($M+H^+$, 15%); 653.0 ($M+Na^+$, 17%); 573.0 ($(M+H^+)-CHCO_2H$, 8%); 203.0 (coumarin $CO^+$, 31%). Anal. calcd for $C_{29}H_{30}N_2O_{14}$: C, 55.24; H, 4.76; N, 4.44. Found: C, 55.02; H, 4.52; N, 4.10.

**4.3.16. ({2-[2-[2-(Bis-carboxymethyl-amino)-ethoxy]-5-(5,7-dimethoxy-2-oxo-2*H*-chromene-3-carbonyl)-phenoxy]-ethyl}-carboxymethyl-amino)-acetic acid (4c).** It was synthesized following the general method starting

from the corresponding *tert*-butyl tetraester. Yellow solid, 98% yield; mp 139–141°C. $^1$H NMR (DMSO-$d_6$) $\delta$: 8.15 (s, 1H, H-4); 7.46–7.35 (m, 2H, H-2′, H-6′); 7.04 (d, 1H, $J$=8.3 Hz, H-5′); 6.69 (d, 1H, $J$=2.0 Hz, H-8); 6.57 (d, 1H, $J$=2.0 Hz, H-6); 4.17–4.11 (m, 4H, $ArOCH_2$); 3.90 (s, 3H, $OCH_3$); 3.88 (s, 3H, $OCH_3$); 3.61 (s, 8H, $NCH_2CO_2$); 3.16–3.05 (m, 4H, $NCH_2$). MS(L-SIMS+): 661.0 ($M+H^+$, 5%); 683.0 ($M+Na^+$, 3%); 603.0 (($M+H^+$)−$CHCO_2H$, 2%); 233.0 (coumarin $CO^+$, 22%). Anal. calcd for $C_{30}H_{32}N_2O_{15}$: C, 54.54; H, 4.85; N, 4.24. Found: C, 54.16; H, 4.57; N, 3.88.

**4.3.17. ({2-[2-[5-(Bis-carboxymethyl-amino)-ethoxy]-5-(7-diethylamino-2-oxo-2*H*-chromene-3-carbonyl)-phenoxy]-ethyl}-carboxymethyl-amino)-acetic acid (4d).** It was synthesized following the general method starting from the corresponding *tert*-butyl tetraester. Yellow solid, 97% yield; mp 154–156°C. $^1$H NMR ($CD_3OD$) $\delta$: 8.16 (s, 1H, H-4); 7.53 (d, 1H, $J$=8.9 Hz, H-5); 7.52 (dd, 1H, $J$=2.2 and 9.0 Hz, H-6′); 7.51 (d, 1H, $J$=2.2 Hz, H-2′); 7.11 (d, 1H, $J$=9.0 Hz, H-5′); 6.83 (dd, 1H, $J$=2.5 and 8.9 Hz, H-6); 6.62 (d, 1H, $J$=2.5 Hz, H-8); 4.46–4.42 (m, 4H, $ArOCH_2$); 4.16 (s, 4H, $NCH_2CO_2$); 4.11 (s, 4H, $NCH_2CO_2$); 3.75–3.70 (m, 4H, $NCH_2$); 3.57 (q, 4H, $J$=7.1 Hz, $CH_3CH_2N$); 1.27 (t, 6H, $J$=7.1 Hz, $CH_3CH_2N$). MS(L-SIMS+): 672.1 ($M+H^+$, 2%); 694.0 ($M+Na^+$, 2%); 614.1 (($M+H^+$)−$CHCO_2H$, 1%); 244.0 (coumarin $CO^+$, 7%). Anal. calcd for $C_{32}H_{37}N_3O_{13}\cdot CF_3CO_2H$: C, 51.97; H, 4.84; N, 5.35. Found: C, 51.52; H, 4.39; N, 4.98.

### 4.4. Series A

**4.4.1. (5-Formyl-2-methoxycarbonylmethoxy-phenoxy)-acetic acid methyl ester.** A mixture of 3,4-dihydroxybenzaldehyde (10 g, 72.4 mmol), ethyl bromoacetate (22.6 g, 159.3 mmol) and potassium carbonate (30 g, 217.2 mmol) in 300 mL of acetone was refluxed for 1 h. The salts were then filtered off and washed with dichloromethane. The filtrate was washed with water 3×25 mL, dried over sodium sulphate and the solvent evaporated. The product was obtained in 81% yield as yellow oil, which solidified on standing at rt; mp 55–56°C. $^1$H NMR ($CDCl_3$) $\delta$: 9.84 (s, 1H, HCO); 7.50 (dd, 1H, $J$=8.4 and 2.0 Hz, H-6), 7.40 (d, 1H, $J$=2 Hz, H-2); 6.93 (d, 1H, $J$=8.4 Hz, H-5); 4.81; 4.79 (s, 2H, $CH_2CO$); 4.70 (s, 2H, $CH_2CO$); 4.29 (q, 2H, $J$=6.6 Hz, $CH_3CH_2O$); 1.30 (t, 3H, $J$=6.6 Hz, $CH_3CH_2O$). MS(L-SIMS+): 311.1 ($M+H^+$, 100%); 136.0 ($M-C_8H_{14}O_4$, 51%).

**4.4.2. (5-Formyloxy-2-methoxycarbonylmethoxy-phenoxy)-acetic acid methyl ester.** To a stirred suspension of aldehyde **5** (18 g, 58.0 mmol) in 100 mL of dichloromethane, *m*-chloroperbenzoic acid was added in small portions (18.7 g, 87.0 mmol). The mixture was stirred overnight at rt and filtered. The filtrate was washed with 10% solution of sodium hydrogensulphite (2×25 mL), saturated solution of potassium hydrogencarbonate (3×25 mL) and brine (2×25 mL). Usual work-up of the organic layer afforded a red-brown oil which was crushed in cold hexane yielding 13.4 g (71%) of a red-orange solid; mp 62–63°C $^1$H NMR ($CDCl_3$) $\delta$: 8.28 (s, 1H, HCO); 6.95 (d, 1H, $J$=8.4 Hz, H-5); 6.77 (dd, 1H, $J$=8.4 and 2.0 Hz, H-6); 6.73 (d, 1H, $J$=2 Hz, H-2); 4.71 (s, 2H, $CH_2CO$); 4.29 (q, 2H, $J$=6.6 Hz, $CH_3CH_2O$); 1.30 (t, 3H, $J$=6.6 Hz, $CH_3CH_2O$). MS(L-SIMS+): 327.1 ($M+H^+$, 100%); 298.1 (M−CHO, 41%)

**4.4.3. 3,4-Bis-(2-hydroxy-ethoxy)-phenol.** $LiAlH_4$ (1 g, 27.6 mmol) was added in small portions to a suspension of the previous formiate (3 g, 9.2 mmol) in 70 mL of dry THF at 0°C. The mixture was stirred for 3 h and after this period it was added to 2.2 mL of 10% NaOH and heated at reflux for 4 h. The mixture was filtered and the salts washed with water (2×75 mL). The combined layers (THF and water) were acidified and extracted with ethyl acetate (3×50 mL). Work-up of the organic layer yielded 1.74 g (88%) of a brown solid; mp 123–124°C. $^1$H NMR ($D_20$) $\delta$: 6.78 (d, 1H, $J$=8.4 Hz, H-5); 6.41 (d, 1H, $J$=2.0 Hz, H-2); 6.30 (dd, 1H, $J$=8.4 and 2.0 Hz, H-6); 3.65–3.75 (m, 4H, $ArOCH_2$); 3.90–4.00 (m, 4H, $OCH_2CH_2O$). $^{13}$C NMR ($CDCl_3/CD_3OD$, 10%) $\delta$: 151.5 (C-1); 149.0 (C-3); 140.7 (C-4); 116.0 (C-2); 106.2 (C-6); 101.8 (C-5); 70.0; 69.9 ($ArOCH_2$); 60.0; 59.9 ($CH_3CO$). MS(EI+): 214.1 ($M^+$, 24%); 170.1 ($M^+-C_2H_4O$, 19%); 126.1 ($M^+-C_4H_8O_2$, 100%). Anal. calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.76; H, 6.86.

**4.4.4. 2-Hydroxy-4,5-bis-(2-hydroxy-ethoxy)-benzaldehyde.** A mixture of 3,4-bis(2-hydroxyethoxy)phenol (1 g, 4.6 mmol) and hexamethylenetetramine (0.654 g, 4.6 mmol) in TFA (11 mL) was heated at 90°C for 3 h. The mixture was cooled at rt, water (20 mL) was added and the reaction heated again for 4 h. The pH was adjusted to 7 with sat. solution of sodium hydrogencarbonate and the mixture extracted with ethyl acetate (2×50 mL). The resulting oily residue after usual work-up of the organic layer was purified by flash chromatography (dichloromethane/methanol 95:5) yielding 0.628 g (55%) of the product as a yellow solid; mp 105–106°C. $^1$H NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 9.70 (s, 1H, HCO); 7.08 (s, 1H, H-2); 6.49(s, 1H, H-6); 4.08–4.19 (m, 4H, $ArOCH_2$); 3.89–4.00 (m, 4H, $OCH_2CH_2O$). $^{13}$C NMR ($CDCl_3/CD_3OD$, 10%) $\delta$: 193.7 (CO);158.7 (C-1); 155.9 (C-3); 141.2 (C-4); 114.7 (C-6); 113.0 (C-5); 100.3 (C-2); 70.3; 69.8 ($ArOCH_2$); 59.5; 59.1 ($CH_3CO$). MS(EI+): 242.1 ($M^+$, 60%); 198.1 ($M^+-C_2H_4O$, 41%); 154.0 ($M^+-C_4H_8O_2$, 100%). Anal. calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 53.65; H, 5.91.

**4.4.5. 3-Benzoyl-6,7-bis-(2-hydroxy-ethoxy)-4a,8a-dihydro-chromen-2-one (7a).** It was synthesized following the general method starting using ethyl benzoylacetate. Yellow solid, 83% yield; mp 184–185°C. $^1$H NMR ($CDCl_3$+drop of $CD_3OD$) $\delta$: 8.10 (s, 1H, H-4); 7.90 (d, 2H, $J$=8.3 Hz, H-2′, H-6′); 7.61–7.70 (m, 2H, H-3′, H-5′); 7.49–7.59 (m, 1H, H-4′); 7.18 (s, 1H, H-5); 6.99 (s, 1H, H-8); 4.18–4.30 (m, 4H, $ArOCH_2$); 4.00–4.11 (m, 4H, $OCH_2CH_2O$). $^{13}$C NMR ($CDCl_3/CD_3OD$, 10%) $\delta$: 192.1 (CO); 159.0 (C-2); 154.5 (C-7); 151.6 (C-9); 146.4 (C-6); 146.0 (C-4); 136.4 (C-1′); 133.4 (C-4′); 129.4 (C-2′, C-6′); 128.4 (C-3′, C-5′); 122.9 (C-3); 111.3 (C-10); 110.9 (C-5); 100.7 (C-8); 71.4; 71.0 ($ArOCH_2$); 60.3; 60.0 ($CH_2OH$). MS(EI+): 370.1 ($M^+$, 69%); 326.1 ($M^+-C_2H_4O$, 15%); 282.1 ($M^+-C_4H_8O_2$, 13%); 105 (COPh, 100%).

**4.4.6. 6,7-Bis-(2-hydroxy-ethoxy)-3-(3-nitro-benzoyl)-4a,8a-dihydro-chromen-2-one (7b).** It was synthesized

following the general method using ethyl 3-nitrobenzoylacetate. Yellow solid, 95% yield; mp 206–207°C. $^1$H NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 8.54 (t, 1H, $J$=2.0 Hz, H-2′); 8.38 (dt, 1H, $J$=8.3 and 2.0 Hz, H-4′); 8.23 (s, 1H, H-4); 8.06 (dt, 2H, $J$=8.3 and 2.0 Hz, H-6′); 7.61 (t, 2H, $J$=8.3 Hz, H-5′); 7.02 (s, 1H, H-5); 6.89 (s, 1H, H-8); 4.02–4.16 (m, 4H, $ArOCH_2$); 3.87–3.98 (m, 4H, $OCH_2CH_2O$). $^{13}$C NMR ($CDCL_3$/$CD_3OD$, 10%) $\delta$: 190.2 (CO); 159.2 (C-2); 155.4 (C-7); 152.2 (C-9); 148.4 (C-4); 147.9 (C-3′); 146.3 (C-6); 138.3 (C-1′); 134.6 (C-6′); 129.4 (C-5); 127.1 (C-4′); 123.8 (C-2′); 121.1 (C-3); 111.1 (C-10); 111.0 (C-5); 100.5 (C-8); 71.2; 71.0 ($ArOCH_2$); 60.2; 50.8 ($CH_2OH$). MS(EI+): 415.1 ($M^+$, 78%); 371.1 ($M-C_2H_4O$, 14%) 353.1 ($M-NO_3$, 61%); 327.1 ($M-C_4H_8O_2$, 36%); 205.0 ($M-C_{10}H_{13}O_2$, 30%); 150.0 ($NO_2Ph^+$, 100%). Anal. calcd for $C_{20}H_{17}NO_9$: C, 57.83; H, 4.13; N, 3.37. Found: C, 57.30; H, 4.18; N, 3.34.

**4.4.7. 6,7-Bis-(2-hydroxy-ethoxy)-3-(4-nitro-benzoyl)-4a,8a-dihydro-chromen-2-one (7c).** It was synthesized following the general method using ethyl 4-nitrobenzoylacetate. Yellow solid, 94% yield; mp 181–182°C. $^1$H NMR (+1 drop of $CD_3OD$) $\delta$: 8.30 (d, 2H, $J$=8.4 Hz, H-3′, H-5′); 8.29 (s, 1H, H-4); 7.90); 7.94 (d, 2H, $J$=8.4 Hz, H-2′, H-6′); 7.05 (s, 1H, H-5); 6.90 (s, 1H, H-8); 4.09–4.20 (m, 4H, $ArOCH_2$); 3.91–4.01 (m, 4H, $OCH_2CH_2O$). $^{13}$C NMR ($CDCl_3$) $\delta$: 190.9 (CO); 159.1 (C-2); 155.5 (C-7); 152.3 (C-9); 150.0 (C-1′); 148.5 (C-4); 146.4 (C-6); 142.1 (C-4′); 129.8 (C-3′, C-5); 123.4 (C-6, C-2′); 121.0 (C-3); 111.1 (C-10); 110.9 (C-5); 100.5 (C-8); 71.0; 71.2 ($ArOCH_2$); 59.8; 60.1 ($CH_2OH$). MS(EI+): 415.2 ($M^+$, 100%); 371.1 ($M-C_2H_4O$, 22%); 353.1 ($M^+-NO_3$, 77%); 327.1 ($M-C_4H_8O_2$, 42%); 150.1 ($NO_2Ph^+$, 89%). Anal. calcd for $C_{20}H_{17}NO_9$: C, 57.83; H, 4.13; N, 3.37. Found: C, 57.95; H, 4.09; N, 3.32.

**4.4.8. 6,7-Bis-(2-hydroxy-ethoxy)-3-(4-methoxy-benzoyl)-4a,8a-dihydro-chromen-2-one (7d).** It was synthesized following the general method using ethyl 4-methoxybenzoylacetate. Yellow solid, 83% yield; mp 181–182°C. $^1$H NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 8.00 (s, 1H, H-4); 7.87 (d, 2H, $J$=8.3 Hz, H-2′, H-6′); 7.05 (s, 1H, H-5); 6.95 (d, 2H, $J$=8.3 Hz, H-3′, H-5′); 6,92 (s, 1H, H-8); 4.11–4.23 (m, 4H, $ArOCH_2$); 3.95–4.06 (m, 4H, $OCH_2CH_2O$); 3.80 (s, 3H, $OCH_3$). $^{13}$C NMR ($CDCl_3$/$CD_3OD$, 10%) $\delta$: 189.6 (CO); 162.9 (C-4′); 158.4 (C-2); 153.2 (C-7); 150.1 (C-9); 145.0 (C-6); 144.5 (C-4); 130.9 (C-2′, C-6′); 128.0 (C-1′); 122.1 (C-3); 112.6 (C-3′, C-5′); 110.0 (C-10); 109.9 (C-5); 99.5 (C-8); 70.1; 69.8 ($ArOCH_2$); 59.1; 58.8 ($CH_2OH$); 54.2 ($CH_3O$). MS(EI+): 400.2 ($M^+$, 16%); 135 ($COPhNO_2^+$, 100%). Anal. calcd for $C_{21}H_{20}O_8$: C, 62.98; H, 5.04. Found: C, 62.88; H, 5.14.

**4.4.9. Methanesulfonic acid 2-[3-benzoyl-7-(2-methanesulfonyloxy-ethoxy)-2-oxo-4a,8a-dihydro-2*H*-chromen-6-yloxy]-ethyl ester.** It was synthesized following the general method. Yellow solid, 78% yield; mp 189–190°C. $^1$H NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 8.07 (s, 1H, H-4); 7.89 (d, 2H, $J$=8.3 Hz, H-2′, H-6′); 7.69–7.78 (m, 2H, H-3′, H-5′); 7.46–7.43 (m, 1H, H-4′); 7.08 (s, 1H, H-5); 6.91 (s, 1H, H-8); 4.60–4.71 (m, 4H, $ArOCH_2$); 4.30–4.41 (m, 4H, $OCH_2CH_2O$); 3.17 (s, 6H, $SO_2CH_3$). MS(L-SIMS+): 527.0 ($M+H^+$, 34%), 307.0 ($M+H^+-2CH_2OSO_2^+$, 17%). Anal. calcd for $C_{22}H_{22}O_{11}S_2$: C, 50.19; H, 4.21; S, 12.18. Found: C, 49.92; H, 4.19; S, 12,29.

**4.4.10. Methanesulfonic acid 2-[7-(2-methanesulfonyloxy-ethoxy)-3-(3-nitro-benzoyl)-2-oxo-4a,8a-dihydro-2*H*-chromen-6-yloxy]-ethyl ester.** It was synthesized following the general method. Yellow solid, 88% yield; mp 141–142°C. $^1$H NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 8.74 (t, 1H, $J$=2.0 Hz, H-2′); 8.40 (dt, 1H, $J$=8.3 and 2.0 Hz, H-4′); 8.35 (s, 1H, H-4); 8.19 (dt, 2H, $J$=8.3 and 2.0 Hz, H-6′); 7.74 (t, 2H, $J$=8.3 Hz, H-5′); 7.22 (s, 1H, H-5); 7.02 (s, 1H, H-8); 4.62–4.73 (m, 4H, $ArOCH_2$); 4.35–4.47 (m, 4H, $OCH_2CH_2O$); 3.20 (s, 6H, $SO_2CH_3$). $^{13}$C NMR ($CDCl_3$/$CD_3OD$, 10%) $\delta$: 190.0 (CO); 158.7 (C-2); 154.3 (C-7); 152.3 (C-9); 148.0 (C-4); 147.8 (C-3′); 145.5 (C-6); 138.2 (C-1′); 134.6 (C-6′); 129.6 (C-5); 127.4 (C-4′); 124.1 (C-2′); 122.1 (C-3); 112.6 (C-10); 111.5 (C-5); 101.2 (C-8); 67.8; 67.6 ($ArOCH_2$); 67.2; 67.0 ($CH_2OS$); 37.6; 37.5 ($CH_3S$). MS(L-SIMS+): 572.1 ($M+H^+$, 42%), 307.1 ($M+H^+-2CH_2OSO_2^+$, 25%); 77.0 ($Ph^+$, 27%). Anal. calcd for $C_{22}H_{21}O_{13}NS_2$: C, 46.23; H, 3.71; N, 2.45; S, 11.20. Found: C, 46.47; H, 3.92; N, 2.25; S, 11.05.

**4.4.11. Methanesulfonic acid 2-[7-(2-methanesulfonyloxy-ethoxy)-3-(4-nitro-benzoyl)-2-oxo-4a,8a-dihydro-2*H*-chromen-6-yloxy]-ethyl ester.** It was synthesized following the general method. Yellow solid, 87% yield; mp 170–171°C. $^1$H NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 8.34 (d, 2H, $J$=8.4 Hz, H-3′, H-5′); 8.30 (s, 1H, H-4); 7.98 (d, 2H, $J$=8.4 Hz, H-2′, H-6′); 7.15 (s, 1H, H-5); 6.95 (s, 1H, H-8); 4.62–4.74 (m, 4H, $ArOCH_2$); 4.34–4.45 (m, 4H, $OCH_2CH_2O$); 3.20 (s, 6H, $SO_2CH_3$). MS(EI+): 571.1 ($M^+$, 9%); 353.1 ($M-2CH_2OSO_2$, 37%); 150.1 ($COPhNO_2^+$, 27%); 123.0 ($PhNO_2^+$, 100%). Anal. calcd for $C_{22}H_{21}O_{13}NS_2$: C, 46.23; H, 3.71; N, 2.45, S, 11.20. Found: C, 45.76; H, 3.63; N, 2.22; S, 10.95.

**4.4.12. Methanesulfonic acid 2-[7-(2-methanesulfonyloxy-ethoxy)-3-(4-methoxy-benzoyl)-2-oxo-4a,8a-dihydro-2*H*-chromen-6-yloxy]-ethyl ester.** It was synthesized following the general method. Yellow solid, 94% yield; mp 195–196°C. $^1$H NMR ($CDCl_3$+1 drop of $CD_3OD$) $\delta$: 8.02 (s, 1H, H-4); 7.89 (d, 2H, $J$=8.3 Hz, H-2′, H-6′); 7.13 (s, 1H, H-5); 7.00 (d, 2H, $J$=8.3 Hz, H-3′, H-5′); 6.99 (s, 1H, H-8); 4.60–4.72 (m, 4H, $ArOCH_2$); 4.31–4.44 (m, 4H, $OCH_2CH_2O$); 3.80 (s, 3H, $OCH_3$); 3.10 (s, 6H, $SO_2CH_3$). MS(EI+): 556.1 ($M^+$, 4%); 338.1 ($M-CH_2OSO_2CH_3$, 43%); 135 ($COPhOMe^+$, 100%). Anal. calcd for $C_{23}H_{24}O_{12}S_2$: C, 49.63; H, 4.35; S, 11.50. Found: C, 49.40; H, 4.41; S, 11.64.

**4.4.13. [(2-{3-Benzoyl-7-[2-(bis-*tert*-butoxycarbonylmethyl-amino)-ethoxy]-2-oxo-4a,8a-dihydro-2*H*-chromen-6-yloxy}-ethyl)-*tert*-butoxycarbonylmethyl-amino]-acetic acid *tert*-butyl ester.** It was synthesized following the general method. Yellow oil, 43% yield. $^1$H NMR ($CDCl_3$) $\delta$: 8.05 (s, 1H, H-4); 7.87 (d, 2H, $J$=8.3 Hz, H-2′, H-6′); 7.55–7,64 (m, 2H, H-3′, H-5′); 7.41–7.51 (m, 1H, H-4′); 7.05 (s, 1H, H-5); 6.90 (s, 1H, H-8); 4.14–4.28 (m, 4H, $ArOCH_2$); 3.57 (s, 8H, $NCH_2CO_2$); 3.14–3.28 (m, 4H, $NCH_2$); 1.44 (s, 36H, $CCH_3$). $^{13}$C NMR ($CDCl_3$) $\delta$: 192.1 (CO); 170.7 ($CO_2{}^tBu$); 159.0 (C-2); 154.6 (C-7); 151.6 (C-9); 146.5 (C-6); 146.2 (C-4); 136.8 (C-1′); 133.2

(C-4′); 129.4 (C-2′, C-6′); 128.3 (C-3′, C-5′); 122.8 (C-3); 110.8 (C-10); 110.7 (C-5); 100.4 (C-8); 81.0 ($CCH_3$), 68.9 ($CH_2O$); 57.0; 56.9 ($NCH_2CO_2$); 53.0; 52.9 ($CH_2CH_2N$); 28.0 ($CCH_3$). MS(L-SIMS+): 825.3 ($M+H^+$, 8%); 160.0 ($M+H^+-PhCO^+-O(CH_2)_2N(CH_2CO_2{}^tBu)_2-(CH_2)_2N-(CH_2CO_2{}^tBu)_2$, 100%).

**4.4.14. ({2-[7-[2-(Bis-*tert*-butoxycarbonylmethyl-amino)-ethoxy]-3-(3-nitro-benzoyl)-2-oxo-4a,8a-dihydro-2*H*-chromen-6-yloxy]-ethyl}-*tert*-butoxycarbonylmethyl-amino)-acetic acid *tert*-butyl ester.** It was synthesized following the general method. Yellow oil, 43% yield. $^1$H NMR ($CDCl_3$) $\delta$: 8.71 (t, 1H, $J$=2.0 Hz, H-2′); 8.41 (dt, 1H, $J$=8.3 and 2.0 Hz, H-4′); 8.28 (s, 1H, H-4); 8.03 (dt, 2H, $J$=8.3 and 2.0 Hz, H-6′); 7.66 (t, 2H, $J$=8.3 Hz, H-5′); 7.11 (s, 1H, H-5); 6.90 (s, 1H, H-8); 4.15–4,30 (m, 4H, $ArOCH_2$); 3.57 (s, 8H, $NCH_2CO_2$); 3.15–3.28 (m, 4H, $NCH_2$); 1.45 (s, 36H, $CCH_3$). $^{13}$C NMR ($CDCl_3$) $\delta$: 190.3 (CO); 170.7 ($CO_2{}^tBu$); 159.1 (C-2); 155.4 (C-7); 152.3 (C-9); 148.5 (C-4); 148.0 (C-3′); 146.4 (C-6); 138.6 (C-1′); 134.7 (C-6′); 129.4 (C-5); 127.1 (C-4′); 124.0 (C-2′); 121.1 (C-3); 110.9 (C-10); 110.8 (C-5); 100.4 (C-8); 81.1 ($CCH_3$); 69.0 ($CH_2O$); 57.1; 57.0 ($NCH_2CO_2$); 52.9 ($CH_2CH_2N$); 28.1 ($CCH_3$)

**4.4.15. ({2-[7-[2-(Bis-*tert*-butoxycarbonylmethyl-amino)-ethoxy]-3-(4-nitro-benzoyl)-2-oxo-4a,8a-dihydro-2*H*-chromen-6-yloxy]-ethyl}-*tert*-butoxycarbonylmethyl-amino)-acetic acid *tert*-butyl ester.** It was synthesized following the general method. Yellow oil, 36% yield. $^1$H NMR ($CDCl_3$) $\delta$: 8.32 (d, 2H, $J$=8.5 Hz, H-3′, H-5′); 8.30 (s, 1H, H-4); 7.96 (d, 2H, $J$=8.5 Hz, H-2′, H-6′); 7.11 (s, 1H, H-5); 6.92 (s, 1H, H-8); 4.16–4.30 (m, 4H, ArOCH2); 3.60 (s, 8H, $NCH_2CO_2$); 3.15–3.30 (m, 4H, $NCH_2$); 1.45 (s, 36H, $CCH_3$). $^{13}$C NMR ($CDCl_3$) $\delta$: 190.9 (CO); 170.7 ($CO_2{}^tBu$); 159.0 (C-2); 155.5 (C-7); 152.4 (C-9); 150.0 (C-1′); 148.5 (C-4); 146.4 (C-6); 142.4 (C-4′); 129.9 (C-3′, C-5); 136.4 (C-6, C-2′); 121.0 (C-3); 110.9 (C-10); 110.8 (C-5); 100.4 (C-8); 81.1 ($CCH_3$); 69.0 ($CH_2O$); 56.9; 57.0 ($NCH_2CO_2$); 52.9 ($CH_2CH_2N$); 28.1 ($CCH_3$).

**4.4.16. ({2-[7-[2-(Bis-*tert*-butoxycarbonylmethyl-amino)-ethoxy]-3-(4-methoxy-benzoyl)-2-oxo-4a,8a-dihydro-2*H*-chromen-6-yloxy]-ethyl}-*tert*-butoxycarbonylmethyl-amino)-acetic acid *tert*-butyl ester.** It was synthesized following the general method. Yellow oil, 36% yield. $^1$H NMR ($CDCl_3$) $\delta$: 8.00 (s, 1H, H-4); 7.89 (d, 2H, $J$=8.3 Hz, H-2′, H-6′); 7.05 (s, 1H, H-5); 6.96 (d, 2H, $J$=8.3 Hz, H-3′, H-5′); 6.90 (s, 1H, H-8); 4.15–4.30 (m, 4H, $ArOCH_2$); 3.90 (s, 3H, $OCH_3$); 3.59 (s, 8H, $NCH_2CO_2$); 3.15–3.30 (m, 4H, $NCH_2$); 1.45 (s, 36H, $CCH_3$). $^{13}$C NMR ($CDCl_3$) $\delta$: 190.5 (CO); 170.6 ($CO_2{}^tBu$); 163.8 (C-4′); 159.1 (C-2); 154.2 (C-7); 151.3 (C-9); 146.1 (C-6); 145.6 (C-4); 132.0 (C-2′, C-6′); 129.4 (C-1′); 123.4 (C-3); 113.6 (C-3′, C-5′); 110.8 (C-10); 110.5 (C-5); 100.4 (C-8); 81.0 ($CCH_3$); 68.9 ($CH_2O$); 57.0; 56.9 ($NCH_2CO_2$); 55.4 ($CH_3O$); 53.0; 52.9 ($CH_2CH_2N$); 28.0 ($CCH_3$). MS(L-SIMS+): 855.7 ($M+H^+$, 13%); 160.1 ($M+H^+-PhCO^+-OCH_2CH_2N(CH_2CO_2{}^tBu)_2-CH_2-CH_2N(CH_2CO_2{}^tBu)_2$, 100%).

**4.4.17. (2-{3-Benzoyl-7-[2-(bis-carboxymethyl-amino)-ethoxy]-2-oxo-4a,8a-dihydro-2*H*-chromen-6-yloxy}-ethyl)-carboxymethyl-amino]-acetic acid (8a).** It was synthesized following the general method. Yellow solid, 98% yield; $^1$H NMR (DMSO-$d_6$) $\delta$: 8.31 (s, 1H, H-4); 7.89 (d, 2H, $J$=8.3 Hz, H-2′, H-6′); 7.61–7.72 (m, 2H, H-3′, H-5′); 7.58–7.49 (m, 1H, H-4′); 7.41 (s, 1H, H-5); 7.19 (s, 1H, H-8); 4.00–4.30 (m, 4H, $ArOCH_2$); 3.5 (s, 8H, $NCH_2CO_2$); 3.00–3.20 (m, 4H, $NCH_2$). High resol. MS: $C_{28}H_{28}N_2O_{13}$: 600.1591. Found: $C_{28}H_{29}N_2O_{13}$: 601.1678.

**4.4.18. ({2-[7-[2-(Bis-carboxymethyl-amino)-ethoxy]-3-(3-nitro-benzoyl)-2-oxo-4a,8a-dihydro-2*H*-chromen-6-yloxy]-ethyl}-carboxymethyl-amino)-acetic acid (8b).** It was synthesized following the general method. Yellow solid, 97% yield. $^1$H NMR (DMSO-$d_6$) $\delta$: 8.59 (t, 1H, $J$=2.0 Hz; H-2′); 8.50 (dt, 1H, $J$=8.3 and 2.0 Hz; H-4′); 8.49 (s, 1H, H-4); 8.29 (dt, 2H, $J$=8.3 and 2.0 Hz, H-6′); 7.81 (t, 2H, $J$=8.3 Hz, H-5′); 7.48 (s, 1H, H-5); 7.20 (s, 1H, H-8); 4.15–4.30 (m, 4H, $ArOCH_2$); 3.59 (s, 8H, $NCH_2CO_2$); 3.10–3.20 (m, 4H, $NCH_2$). High resol. MS: $C_{28}H_{27}N_3O_{15}$: 645.1442. Found: $C_{28}H_{28}N_3O_{15}$: 646.1523.

**4.4.19. ({2-[7-[2-(Bis-carboxymethyl-amino)-ethoxy]-3-(4-nitro-benzoyl)-2-oxo-4a,8a-dihydro-2*H*-chromen-6-yloxy]-ethyl}-carboxymethyl-amino)-acetic acid (8c).** It was synthesized following the general method. Yellow solid, 98% yield. $^1$H NMR (DMSO-$d_6$) $\delta$: 8.50 (s, 1H, H-4); 8.31 (d, 2H, $J$=8.5 Hz, H-3′, H-5′); 8.09 (d, 2H, $J$=8.5 Hz, H-2′, H-6′); 8.49 (s, 1H, H-5); 7.20 (s, 1H, H-8); 4.05–4.30 (m, 4H, $ArOCH_2$); 3.59 (s, 8H, $NCH_2CO_2$); 3.10–3.20 (m, 4H, $NCH_2$). High resol. MS: $C_{28}H_{27}N_3O_{15}$: 645.1442. Found: $C_{28}H_{28}N_3O_{15}$: 646.1536.

**4.4.20. ({2-[7-[2-(Bis-carboxymethyl-amino)-ethoxy]-3-(4-methoxy-benzoyl)-2-oxo-4a,8a-dihydro-2*H*-chromen-6-yloxy]-ethyl}-carboxymethyl-amino)-acetic acid (8d).** It was synthesized following the general method. Yellow solid, 95% yield. $^1$H NMR (DMSO-$d_6$) $\delta$: 8.22 (brs, 1H, H-4); 7.85 (d, 2H, $J$=8.7 Hz, H-2′, H-6′); 7.36 (brs, 1H, H-5); 7.17 (brs, 1H, H-8); 7.04 (d, 2H, $J$=8.7 Hz, H-3′, H-5′); 4.35–4.00 (m, 4H, $ArOCH_2$); 3.90 (s, 3H, $OCH_3$); 3.70–3.20 (m, 8H, $NCH_2CO_2$, 4H, $NCH_2$). High resol. MS: $C_{29}H_{30}N_2O_{14}$: 630.169704. Found: $C_{29}H_{31}N_2O_{14}$: 631.176349.

## Acknowledgements

Financial support from Comisión Interministerial de Ciencia y Tecnología of Spain (CICYT; grants PB90-0176, PB93-0264, PB95-0172, PB98-0103) and indirect funding from FYSE-ERCROS S.A. are gratefully acknowledged.

## References

1. Cooper, M. E.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1695–1700. Beltyukova, S. V.; Egorova, A. V.; Teslyuk, O. I. *J. Anal. Chem.* **2000** (55), 682–685. Merio, L.; Petterson, K.; Lovgren, T. *Clin. Chem.* **1996**, *42*, 1513. Bünzli, J.-C. G. In *Lanthanide Probes in Life, Chemical and Earth Sciences*; Bünzli, J.-C. G., Chopin, G. R., Eds.; Elsevier: Amsterdam, 1989 (Chapter 7 and references cited therin).
2. Remuiñán, M. J.; Román, H.; Alonso, M. T.; Rodríguez-Ubis, J. C. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1099.

Rodríguez-Ubis, J. C.; Sedano, R.; Barroso, G.; Juanes, O.; Brunet, E. *Helv. Chim. Acta* **1997**, *80*, 86.

3. Chen, J. Y.; Selvin, P. R. *J. Photochem. Photobiol., A* **2000**, *135*, 27–32. Edder, C.; Piguet, C.; Bunzli, J. C. G.; Hopfgartner, G. *J. Chem. Soc., Dalton Trans.* **1997**, 4657. Dakubu, S.; Hale, R.; Lu, A.; Quick, J.; Solas, D.; Weinberg, J. *Clin Chem.* **1988**, *34*, 2337. Bailey, M. P.; Rocks, B. F.; Riley, C. *Analyst* **1984**, *109*, 1449.
4. Carnall, W. T. In *Handbook on the Physics and Chemistry of Rare Earths*; Gschneidner, K., Eyring, L., Eds.; North-Holland: Amsterdam, 1979; Vol. 3, pp 171. Freed, F. K. *Top. Curr. Chem.* **1976**, *15*, 23. Sinha, A. P. B. *Spectrosc. Inorg. Chem.* **1971**, *2*, 225.
5. Specht, D. P.; Martic, P. A.; Farid, S. *Tetrahedron* **1982**, *38*, 1203.
6. Toner, J. L. In *Inclusion Phenomena and Molecular Recognition*; Atwood, J., Ed.; Plenum Press: New York, 1990; pp 185–197.
7. Alonso, M. T.; Brunet, E.; Hernández, C.; Rodríguez-Ubis, J. C. *Tetrahedron Lett.* **1993**, *34*, 7465.
8. Rodríguez-Ubis, J. C.; Alonso, M. T.; Brunet, E. *Tetrahedron Lett.* **1994**, *35*, 8461.
9. *Org. Synth. Coll.*, *3*, 452. Moed, H. D.; Van Dijk, J.; Niewind, H. *Recl. Trav. Chim.* **1958**, *77*, 273.
10. Samanta, A.; Fessenden, R. W. *J. Phys. Chem. A* **2000**, *104*, 8577.
11. Párkányi, C.; Antonious, M. S.; Aaron, J.-J.; Buna, M.; Tine, A.; Cissé, L. *Spectrosc. Lett.* **1994**, *27*, 439.
12. Brunet, E.; Alonso, M. T.; Juanes, O.; Sedano, R.; Rodríguez-Ubis, J. C. *Tetrahedron Lett.* **1997**, *38*, 4459.
13. Leray, I.; HabibJiwan, J. L.; Branger, C.; Soumillion, J. P.; Valeur, B. *J. Photochem. Photobiol. A: Chem.* **2000**, *135*, 163 (and references cited therein).
14. Lakowick, J. R. In *Principles of Fluorescence Spectroscopy*; Plenum Press: New York, 1983; pp 188.
15. Latva, M.; Takalo, H.; Mukkala, V-M.; Matachescu, C.; Rodríguez-Ubis, J. C.; Kankare, J. *J. Lumin.* **1997**, *75*, 149.
16. Even in case the metal receives energy from the ligand, the proximity between the triplet state and $^5D_4$ energy levels will make the metal to easily return the energy back to the ligand. See for example Sammes, P. J.; Yahioglu, G. *Nat. Prod. Rep.* **1996**, 1. Carnall, W. T. In *Handbook on the Physics and Chemistry of Rare Earths*; Gscheider, K., Eyring, L., Eds.; North-Holland: Amsterdam, 1979; Vol. 3, pp 171.
17. Spectra are identical to those already printed in our previous communication to this work (see Ref. 8) and we do not repeat here for the sake of brevity.
18. Rodríguez-Ubis, J. C.; Alonso, M. T.; Juanes, O.; Brunet, E. *Luminescence* **2000**, *15*, 331.
19. *Modern Molecular Photochemistry*; Turro, N. J., Ed.; University Sciences Book: California, 1991.
20. Rodríguez-Ubis, J. C.; Alonso, M. T.; Juanes, O.; Sedano, R.; Brunet, E. *J. Lumin.* **1998**, *79*, 121.