RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 11064

Synthesis, characterization and spectroscopic properties of water soluble coumarins substituted with oligomeric alkoxy functions†

H. Surya Prakash Rao,* Mohan Babu and Avinash Desai

Received 15th November 2013
Accepted 8th January 2014

DOI: 10.1039/c3ra46704j

www.rsc.org/advances

Novel water soluble robust fluorescent coumarins substituted with oligomeric alkoxy functions were synthesized by incorporating the Blaise reaction in the key step. Mono-methylated oligomeric polyethylene glycols were subjected to a three step protocol, namely (i) Michael addition to acrylonitrile, (ii) Blaise reaction with ethyl bromoacetate and (iii) condensation with 4-*N*,*N*-diethylamino-2-hydroxybenzaldehyde to give fluorescent water soluble coumarins. Water solubility of the coumarins increased with the number of oxygen atoms in the side chain. However, even the most water soluble coumarin in this series can be readily extracted out of water with organic solvents like dichloromethane or ethyl acetate. Both absorption and emission spectra, recorded in four solvents, namely, hexane (non-polar), ethyl acetate (moderately polar), methanol (polar protic) and water (highly polar and protic) displayed a bathochromic shift of the absorption ($\Delta\lambda_{max} \approx 25$ nm) and emission ($\Delta\lambda_{max} \approx 57$ nm) bands with increasing solvent polarity. The $\Delta\lambda_{max}$ of emission is more pronounced than the $\Delta\lambda_{max}$ of absorption, which indicates intramolecular charge-transfer (ICT) is less in the ground state compared to the excited state. Emission spectra recorded in these four solvents showed that fluorescent intensity is maximum in ethyl acetate.

1. Introduction

Natural and synthetic coumarin derivatives represent an important group of organic compounds[1] which find use in various medicinal applications like antibiotics,[2] anti-inflammatory,[3] anti-coagulant[4] and anti-tumor agents.[5] Furthermore, materials with a coumarin ring have been used as non-linear optical materials,[6] liquid crystals,[7] fluorescent labels[8] and for fluorescent imaging.[9] Coumarins with a strong electron donating group at C7 and an electron-withdrawing group at C3 exhibit unique fluorescent properties. As an example, coumarin **1** (Fig. 1) with an electron donating diethylamino group at C7 and an electron withdrawing acetyl group at C3 is strongly fluorescent. However, such coumarins, like **1**, are practically insoluble in water, but, this property is a desirable requirement for developing lasing applications.[10] Several strategies have been employed to make the coumarins water soluble. Introduction of acidic groups like phenolic hydroxyl or carboxylic acid as found in **2** and **3** (Fig. 1) are among the most frequently used methods for making them water soluble.[11] However, while such coumarin derivatives are soluble in basic aqueous solutions they are practically insoluble under neutral or acidic conditions. Esterification of carboxylic acid in **3** with oligomeric ethylene glycol or with dendrimers incorporating multiple oxygen atoms is another method to prepare water soluble coumarins,[12] but such esters get hydrolyzed under acidic or basic conditions. So, there is a need for the synthesis of robust fluorescent coumarins which are water soluble and stable under a range of acidic to basic pH. We conceived of novel water soluble robust 7-*N*,*N*-diethylamino-3-acylcoumarins **4** having oligomeric ethylene glycol units covalently bonded to C3 acyl group (Fig. 1). In such molecules the *N*,*N*-diethylamino-3-acyl-coumarin portion would be responsible for the fluorescent property and the oligomeric ethylene glycol unit renders the molecule water soluble. In this report we describe successful synthesis, characterization and optical properties of four fluorescent coumarins **4** which are water soluble in acidic, basic and neutral conditions.

2. Results and discussion

2.1. Synthesis of fluorescent coumarins 4a–d

Water soluble robust fluorescent coumarins **4a–d** were synthesized starting from monomethyl ethers of glymes **5a–d** *via* a three step protocol by applying the Blaise reaction in the key second step (Scheme 1). The monomethyl ethers of glymes were reacted with acrylonitrile in the presence of 10% NaOH at 0 °C to furnish nitriles **6a–d** in excellent yield.[13] The nitriles **6a–d** were subjected to the Blaise reaction[14,15] by reacting with ethyl

Department of Chemistry, Pondicherry University, Pondicherry, 605 014, INDIA. E-mail: hspr.che@pondiuni.edu.in

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra46704j

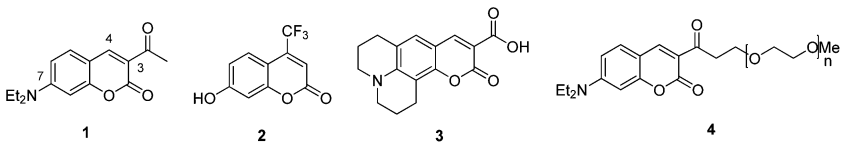
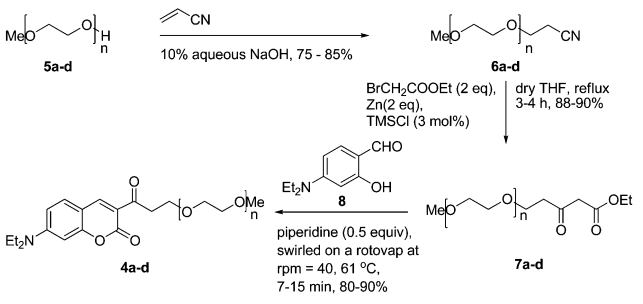


Fig. 1 Structures of selected fluorescent coumarins.

bromoacetate, Zn and a catalytic amount of TMSCl (3 mol%) in THF to yield β-keto esters **7a–d** in about 90% yield. Formation of β-keto esters **7a–d** was indicated by IR spectra, which showed characteristic bands at 1717 and 1742 cm^{-1} for the keto and the ester carbonyl groups. The ^1H NMR spectra showed a small peak at 12 ppm, which is the characteristic signal for the enolic proton. Integration of relevant signals indicated that keto and enol forms of **7a–d** were present in a ratio of about 95 : 5. Similarly, their ^{13}C NMR spectra showed two signals at 200 and 166 ppm for the aliphatic ketone and ester carbonyl groups respectively. A tiny signal located at 100 ppm was for the enolic carbon. The ratio of integration with this signal and the signal for the methylenic carbon located at 66 ppm confirmed that keto–enol forms were present in the ratio 95 : 5.

The final step in the synthesis of water soluble fluorescent coumarins is the condensation of the Blaise products **7a–d** with 4-*N*,*N*-diethylamino-2-hydroxybenzaldehyde in the presence of a base. For this effort condensation of the β-keto ester **7a** with 4-*N*,*N*-diethylamino-2-hydroxybenzaldehyde **8** was taken as a test case. Among several base catalysts like pyrrolidine, L-proline, pyridine, pyridinium acetate, piperidine, piperdinium acetate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) enlisted for the transformation, 0.5 molar equivalent of piperidine worked well in terms of yield, cleanliness and ease of conducting the reaction. Although the condensation worked in THF reflux, the yield of **4a** was poor (<30%) and the reaction was not clean. Heating the reactants, namely β-keto ester **7a**, 4-*N*,*N*-diethylamino-2-hydroxybenzaldehyde **8** and 0.5 equivalents of piperidine under neat conditions at 100 °C in a mono-mode microwave oven provided the product **4a** in 80% yield. But the reaction was not clean. After several experiments, we found that swirling the reactants **7a**, **8** and 0.5 equivalents of piperidine under solvent-free conditions on a rotovap at 40 rpm and 61 °C water bath temperature provided the product **4a** in over 90% yield.



4a (91%), **5a**, **6a**, **7a** (84%): n = 1; **4b** (87%), **5b**, **6b**, **7b** (88%): n = 2, **4c**, **5c**, **6c**, **7c** (71%): n = 3; **4d** (69%), **5d**, **6d**, **7d** (71%): n = 4.

Scheme 1 Synthesis of water soluble fluorescent coumarins (percentages in parentheses indicate the yield).

Coumarin **4a** showed one carbonyl absorption band at 1718 cm^{-1} for the lactone carbonyl in its IR spectrum. The ^1H NMR spectrum displayed a characteristic singlet at δ 8.4 ppm, assignable to the olefin hydrogen conjugated to two electron withdrawing carbonyl groups of the coumarin ring. The ^{13}C NMR spectrum displayed anticipated 17 signals, out of which 6 were quaternary. Two carbonyl carbons appeared at δ 195.8 (acyl) and 160.6 ppm (ester). The methoxy carbon appeared at δ 59 ppm. The DEPT spectrum of **4a** and analogy with signals of 3-acyl coumarin **1** were used for complete assignment of ^{13}C NMR signals. Solvent-free condensation of β-keto esters **7b–d** with 4-*N*,*N*-diethylamino-2-hydroxybenzaldehyde **8**, conducted in 5 mmol scale and in the presence of 0.5 equivalents piperidine by swirling in a rotavap at rt, provided coumarins **4b–d** in 79–91% yield (Scheme 1). While the coumarins **4a–c** are yellow colored solids, the coumarin **4d** is a viscous liquid. Among **4a–c** the melting points showed gradual decrease with increasing number of ethylene glycol units.

2.2. Absorption and emission spectra of water soluble fluorescent coumarins

The UV absorption spectra of coumarins with **4a–d** recorded in four different solvents, namely, hexane (non-polar), EA (polar aprotic), MeOH (polar protic) and water (highly polar protic) are given in Fig. 2. As anticipated, the UV spectra of the series of coumarins **4a–d** were similar with minor changes in intensity. All of them exhibited a highly intense peak in the visible region 417–442 nm. These peaks can be attributed to the π–π* transition from HOMO of the coumarins ring with extended conjugation emanating from C7 diethyl amino to C3 acyl group. In hexane medium **4a–d** exhibited a peak with fine structure with λ_{max} located at 417 nm. The fine structure could be attributed to vibronic electronic transitions which were observable in hexane. The λ_{max} located at 417 nm in hexane showed a bathochromic shift on increasing solvent polarity. In EA it is located at 424 nm, in MeOH at 432 and in water at 442 nm. This bathochromic shift (red-shift) in polar solvents indicates stabilization of partial charge transfer complex of the type **4B** (Fig. 3), which results in a large change in excited state dipole moment. Absorption characteristics of **4a–d** are gathered in Table 1. The UV-vis spectrum of **4d** in water was recorded in the range pH 1–10, there was no change in the λ_{max} or intensity of absorption indicating the robust nature of the molecule. No change in the absorption maximum even under strongly acidic conditions (pH 1) indicates that protonation of the diethylamino group is difficult.

The fluorescence spectra of **4a–d** are gathered in Fig. 4 and Table 2. For each of the coumarins **4a–d** fluorescence spectra

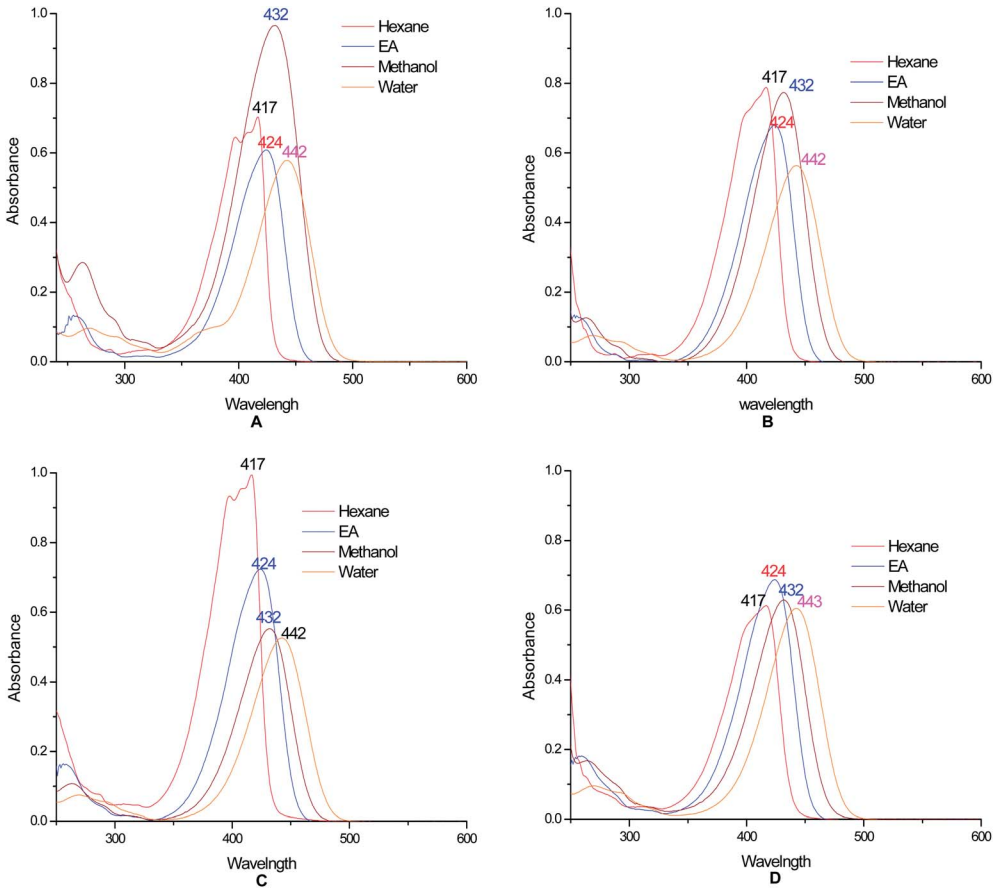


Fig. 2 Absorbance spectra of coumarins with C7-*N*,*N*-diethylamino group A: **4a** (22.0 μM); B: **4b** (at 28.1 μM); C: **4c** (at 22.2 μM); D: **4d** (at 30.2 μM); hexane (red), EA(blue), MeOH (wine), water (orange).

were recorded in four solvents namely hexane, EA, MeOH and water. Solutions of coumarins **4a–d** were strongly fluorescent and noticeable to the naked eye. The fluorescent intensity of **4a–d** was maximum in EA (1.0×10^7) with a quantum yield of about 0.41. In water, however, the intensity was low and it was around 4×10^6 with a quantum yield of 0.01 (Table 2). The fluorescence emission spectrum of **4a** exhibited a fine structure in hexane for the band with λ_{max} at 433 nm and a shoulder at 460 nm. As solvent polarity increased from hexane to water the λ_{max} located at 432 nm moved to 489 nm ($\Delta\lambda_{max}$ emission = 57 nm), which indicates that in water the excited state of the dipolar structure (**4B** over **4A** in Fig. 3) is stabilized and it is responsible for the fluorescence emission. The set of spectra given in Fig. 4 shows that the length of side chain substitution does not have a significant influence on the energy of the fluorescent Frank–Condon transition of the coumarins. Similar to absorption spectra, emission spectra of aqueous solutions of **4d** were recorded in the 1–10 pH range. There was no change in the location or intensity of the band, indicating that the chromophore remains same in pH range employed.

Normalized absorption and emission of **4d** in different solvents, namely, hexane, EA, MeOH and water are gathered in Fig. 5. In comparison with UV λ_{max} fluorescence spectra displayed a Stokes shift of about 45 nm in EA, MeOH and water, in their emission maximum, however the Stokes shift was only 15 nm in hexane medium.

2.3. Solubility of coumarins in different solvents

Coumarins **4a–d** were synthesized with the intention of making them water soluble owing to oligomeric ethylene glycol units present in the side chain, through hydrogen bonding interactions. As anticipated, water solubility among **4a–d** increased with increase in the oligomeric ethylene glycol chain length (**4a:**

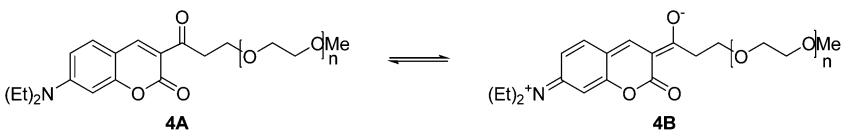


Fig. 3 Keto–enol tautomeric structures of 4A and 4B of coumarins 4a–d.

Table 1 Absorption characteristics of the compounds in hexane, EA, MeOH and water

	λ_{max} (abs)					
Compound	Hexane	EA	MeOH	Water	ε (cm^{-1} mol^{-1}) MeOH	$\Delta\lambda_{max}$
4a	417	424	432	442	86 600	25
4b	417	424	432	442	84 500	25
4c	417	424	432	443	78 820	26
4d	417	424	432	443	90 800	26

1.2 mg mL^{-1}; **4b**: 2.8 mg mL^{-1}; **4c**: 3.8; **4d**: 9.0 mg mL^{-1}). The coumarin **4d** with five oxygen atoms in the side chain is the most water soluble among its siblings.

We have selected the most water soluble coumarin **4d** in the present set to determine its partition between water and water immiscible solvents like hexane (relative polarity = 7; water = 100), *t*-butyl methyl ether (14.8) EA (20), dichloromethane (30.9), and octanol (54.3).[17] Millimolar solution of **4d** in water (1 mL) was partitioned with above solvents (1 mL). The resulting biphasic mixture was sonicated for 1 min and then centrifuged for separation of layers. UV spectra of the separated layers were recorded to determine the relative solubility in water as well as the organic solvent. Partitioning of **4d** between water and hexane resulted in yellow color remaining in the water (Fig. 6). The UV spectra recorded for hexane and water layers showed a negligible amount (less than 1%) of **4d** dissolved in hexane and over 99% remained in water. However with other solvents like *tert*-butyl methyl ether, EA, dichloromethane and octanol there was complete transfer of **4d** from the water layer into the organic layer (Fig. 6).

3. Conclusion

In conclusion we have designed and achieved a facile, high yielding synthesis of water soluble fluorescent coumarins **4a–d** by incorporating the Blaise reaction in the key step. UV absorption studies showed that each one of **4a–d** embody the typical coumarin structure with extended conjugation. Fluorescence emission spectral studies showed that **4a–d** show maximum fluorescence in EA. The coumarin **4d** is freely water

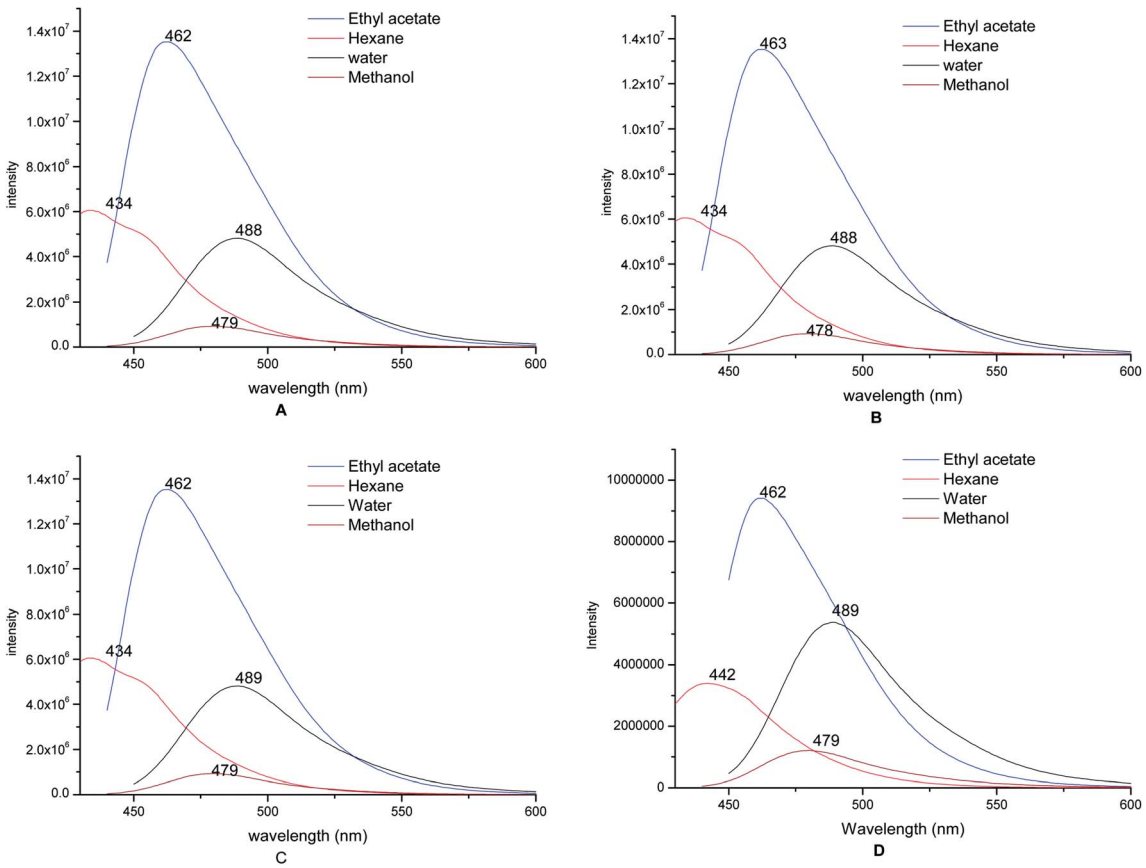


Fig. 4 Fluorescence emission spectra of **4a–d** in hexane (red), EA (blue), MeOH (wine), water (black). Set A is of **4a** (2.2 μM); set B is of **4b** (at 2.8 μM); set C is of **4c** (at 2.2 μM); set D is of **4d** (at 3.0 μM).

Table 2 Emission characteristic of the compounds in hexane, EA, MeOH and water

	λ_{max} (emission)				$\Delta\lambda_{max}$	Φ			
Coumarin	Hexane	EA	MeOH	Water	(emission)	Hexane	EA	MeOH	Water
4a	432	462	478	489	57	0.06 (6%)	0.41 (41%)	0.02 (2%)	0.007 (0.7%)
4b	433	460	479	489	56	0.05 (5%)	0.35 (35%)	0.01 (1%)	0.008 (0.8%)
4c	434	462	479	488	54	0.04 (4%)	0.32 (32%)	0.009 (0.9%)	0.009 (0.9%)
4d	442	462	478	489	47	0.03 (3%)	0.30 (30%)	0.009 (0.9%)	0.01 (1%)
1[16]	433	459	478	489	56	0.05 (5%)	0.66 (66%)	0.02 (2%)	0.006 (0.6)

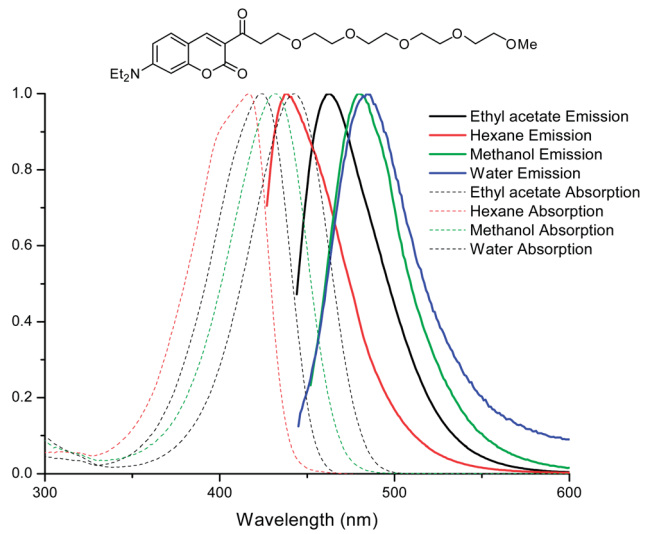
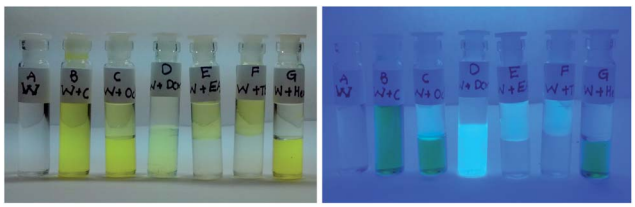


Fig. 5 Normalised absorption and emission spectra of compound **4d**.



I (Under visible light) **II** (Under UV light 364 nm)

Fig. 6 Photographs taken under visible light (I) and under UV light of 364 nm (II) of water (A), compound **4d** in water (B), water and octanol (C), water and dichloromethane (D), water and EA (E), water and *t*-butyl methyl ether (F), water and hexane (G).

soluble, but it can be extracted out from water by solvents like EA and dichloromethane.

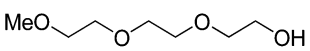
4. Experimental section

4.1. General

All reactions were carried out in dried glassware. Piperidine was distilled and stored over KOH pellets. All commercially available chemicals were used without further purification. Tetrahydrofuran (THF) was dried prior to use. Reactions were monitored by thin layer chromatography (TLC) plates of dimension 7.5 cm × 2.5 cm prepared by using an aqueous slurry of silica gel-G or silica gel-GF 254 (LOBA Chemie) having 13% $CaSO_4$ as a binder followed by drying in an oven. A mixture of ethyl acetate (EA) and hexanes (60–80 °C boiling mixtures) was used as the mobile phase. TLC spots were visualized in iodine vapour and in UV light. Column chromatography was performed on silica gel (100–200 mesh SRL Chemicals) with increasing amounts of EA in hexanes. IR spectra were recorded as KBr solid solution on a Nicolet-6700 spectrometer. Melting points were recorded using open-ended capillary tubes on VEEGO melting point apparatus. ^{1}H and ^{13}C NMR and DEPT-135 spectra were recorded on a Bruker Avance 400 spectrometer using a mixture of $CDCl_3$ and CCl_4 (1 : 1) as solvent. Chemical shift values (δ) are expressed in parts per million units, relative to the residual solvent peak (δ = 7.26 ppm for ^{1}H and δ = 77.0 ppm for ^{13}C) where possible or alternatively to $SiMe_4$ (δ = 0.00 ppm) as an internal standard. Coupling constants (J) are given in Hz and multiplicities are designated as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet) or broad (br). DEPT-135 NMR spectra were recorded for all the samples to determine the number of hydrogen atoms present on each carbon. All absorption and emission spectra were recorded in dry solvents (EA, hexanes, methanol and Millicure water). UV spectra were recorded using a Shimadzu UV-2450 double-beam spectrometer and emission spectra were recorded using a Jobin Yvou FLUOROLOG-$FL_3$11 spectrometer. Purity of the coumarins was ensured by recording UV spectra after each purification by column chromatography with spectroscopic grade solvents up to a constant molar extinction coefficient.

4.2. Representative procedure for mono-methylation of glycols

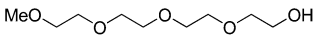
4.2.1. Synthesis of 2-(2-(2-methoxyethoxy)ethoxy)-ethanol 5c.



To triethyleneglycol (2.0 g, 13.3 mmol) taken in a 50 mL round bottomed flask, NaOH pellets (0.53 g, 13.3 mmol) were added and stirred for 10 min at 55–60 °C, by which time NaOH had completely dissolved. To this solution dimethyl sulphate (1.67 g, 13.3 mmol) was added drop-wise and stirred for 6 h while maintaining the temperature at 55–60 °C for completion of the partial methylation. The reaction mixture consisted of unreacted triethylene glycol, triethyleneglycol monomethyl ether **5c**

and triethylene glycol dimethyl ether. The reaction mixture was loaded as such on a pre-packed silica gel column (60 g, 100–200 mesh) followed by elution with increasing amounts of EA in hexanes; starting from 20% and increasing gradually to 30%. Pooled fractions which had **5c** were evaporated to provide 33% (0.72 g) of the product. IR (KBr) (ν): 3417, 2879, 1736, 1458, 1359, 1246, 1111, 934, 454 cm^{-1}; ^1H NMR (400 MHz, CCl_4 + $CDCl_3$, 1 : 1) 3.57–3.41 (m, 12H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 72.6, 71.8, 70.4, 70.3, 70.2, 61.4, 58.8 ppm.

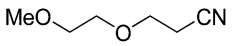
4.2.2. 2,5,8,11-Tetraoxatridecan-13-ol 5d.



Following the above described procedure mono-methylation of tetraethylene glycol (2.0 g, 10.3 mmol) and dimethyl sulfate (1.3 g, 10.3 mmol) and NaOH (0.41 g, 10.3 mmol) provided desired monomethyl ether **5d** in 35% (0.75 g) yield; IR (KBr) (ν): 3427, 2881, 1734,1647, 1459, 1246, 1106, 934, 934, 411 cm^{-1}; ^1H NMR (400 MHz, CCl_4 + $CDCl_3$, 1 : 1), 3.57–3.41 (m, 17H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 72.7, 71.9, 70.6, 70.5, 70.4, 70.2, 70.1, 61.5, 58.9 ppm.

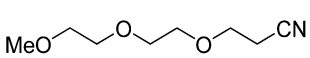
4.3. Representative procedure for conjugate addition of acrylonitrile to monomethyl ether of glycols

4.3.1. Synthesis of 3-(2-methoxyethoxy)propanenitrile 6a.



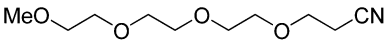
Acrylonitrile (1.14 g, 21.48 mmol) was added to a mixture of aqueous NaOH (40%, 0.8 mL) and 2-methoxyethanol (2 g, 26.28 mmol) **5a** while the temperature of the reaction mixture was maintained at 25 °C using a water bath cooled with a necessary amount of ice pieces. The reaction mixture was stirred for 6 h at this temperature. After completion of the reaction (TLC), the reaction mixture was neutralized with aqueous HCl (1 N, 10 mL) and diluted with dichloromethane (DCM, 25 mL). The organic layer was washed with 5% aqueous NaOH (15 mL) followed by brine (10 mL). The DCM solution was dried over anhydrous sodium sulphate followed by removal of solvent under reduced pressure to afford 3-(2-methoxyethoxy)propanenitrile **6a** as a colorless liquid. Yield: 92% (2.57 g); IR (KBr) (ν): 2884, 2251, 1456, 1384, 1360, 1199, 1113, 848 cm^{-1}; ^1H NMR (400 MHz, CCl_4 + $CDCl_3$, 1 : 1) 3.64 (t, J = 6.4 Hz, 2H), 3.57–3.59 (m, 2H), 3.46–3.48 (m, 2H), 3.30 (s, 3H), 2.54 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 117.4, 71.8, 70.5, 65.9, 58.9, 18.7 ppm.

4.3.2. 3-(2-(2-Methoxyethoxy)ethoxy)propanenitrile 6b.



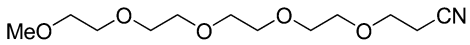
Following the above general procedure acrylonitrile (1.14 g, 21.48 mmol) was added to a mixture of aqueous NaOH (40%, 0.8 mL) and 2-(2-methoxyethoxy)ethanol (2.43 g, 20.24 mmol) **5b**, to afford **6b** as a colorless liquid. Yield: 96% (3.61 g); IR (KBr) (ν): 2881, 2250, 1461, 1357, 1112, 847 cm^{-1}; ^1H NMR (400 MHz, CCl_4 + $CDCl_3$, 1 : 1) 3.58 (td, J = 5.3 Hz, 0.8 Hz, 2H), 3.52–3.48 (m, 6H), 3.40–3.38 (m, 2H), 3.23 (s, 3H), 2.48 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 117.4, 71.6, 70.4, 70.35, 70.31, 65.7, 58.6, 18.5 ppm.

4.3.3. 2,5,8,11-Tetraoxatetradecane-14-nitrile 6c.



Following the above general procedure acrylonitrile (0.120 g, 2.26 mmol) was added to a mixture of aqueous NaOH (40%, 0.8 mL) and 2-(2-(2-methoxyethoxy)ethoxy)ethanol (0.459 g, 2.79 mmol) **5c**, to afford **6c** as a colorless liquid. Yield: 93% (569 mg); IR (KBr) (ν): 2879, 2250, 1458, 1355, 111, 849 cm^{-1}; ^1H NMR (400 MHz, CCl_4 + $CDCl_3$, 1 : 1) 3.66–3.63 (m, 2H), 3.59–3.53 (m, 10H), 3.46–3.44 (m, 2H), 3.29 (s, 3H), 2.54 (t, J = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 117.5, 71.9, 70.69, 70.63, 70.60, 70.5, 70.4, 65.9, 58.8, 18.8 ppm.

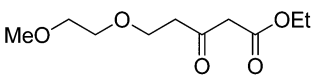
4.3.4. 2,5,8,11,14-Pentaoxaheptadecane-17-nitrile 6d.



Following the above general procedure acrylonitrile (0.250 g, 4.71 mmol) was added to a mixture of aqueous NaOH (40%, 0.8 mL) and 2,5,8,11-tetraoxatridecan-13-ol (1.17 g, 5.62 mmol) **5d**, to afford **6d** as a colorless liquid. Yield: 89% (1.327 g); IR (KBr) (ν): 2882, 2250, 1463, 1358, 1111, 847, 462 cm^{-1}; ^1H NMR (400 MHz, CCl_4 + $CDCl_3$, 1 : 1) 3.69–3.65 (m, 2H), 3.60–3.55 (m, 14H), 3.48 (t, J = 5.2 Hz, 2H), 3.31 (s, 3H), 2.61–2.55 (m, 2H); ^{13}C NMR (100 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 117.6, 71.9, 70.7, 70.68, 70.63, 70.60, 70.4, 66.04, 66.00, 58.9, 18.8 ppm.

4.4. Representative procedure for the Blaise reaction

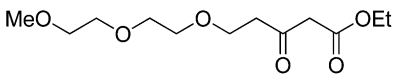
4.4.1. Synthesis of ethyl-5-(2-ethoxyethoxy)-3-oxopentanoate 7a.



To a slurry of zinc (1.26 g, 19.27 mmol) in 6 mL dry THF under an N_2 atmosphere, TMSCl (0.12 mg, 3 mol% in 1 mL THF) was added and the resulting suspension was refluxed for 25 min. To this refluxing slurry of activated zinc, 3-(2-methoxyethoxy)propanenitrile **6a** (0.51 g, 3.93 mmol) in 1 mL THF and ethyl bromoacetate (1.29 g, 7.74 mmol) in 1.0 mL THF were added simultaneously using two syringes. Soon after initial addition of the two reactants, the color of the reaction mixture changed to dark green, which turned finally to brown with progression of time. After addition of the two reactants, the reaction mixture was stirred at reflux for 6 h to completion (TLC, 20% EA in hexanes). The reaction mixture was cooled to 0 °C (ice-water) to facilitate the addition of 8 mL 3 N HCl to an ultimate pH of 2. THF was removed under reduced pressure and the resulting mixture was diluted with 10 mL dichloromethane (DCM). After separation of the DCM layer, the aqueous solution was washed with DCM (2 × 10 mL). The combined organic solutions was washed with water (2 × 5 mL) and with brine (2 × 5 mL). The resultant organic layer was dried over anhydrous sodium sulphate. The solvent was evaporated to get the crude product which was purified by column chromatography using 20% EA in

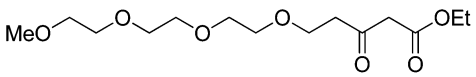
hexanes to afford ethyl-5-(2-methoxyethoxy)-3-oxopentanoate **7a**. Yield: 84% (712 mg); light yellow liquid; the ^{1}H and ^{13}C NMR spectra showed two sets of peaks in ratio 9.5 : 0.5 for keto and enols forms; spectral data for the keto form is given here by culling peaks of major isomer from the spectra of the mixture. IR (KBr) (ν): 2981, 2879, 1743, 1717, 1630, 1467, 1366, 1313, 1112, 1028, 848 cm^{-1}; ^{1}H NMR (400 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 4.10 (q, J = 7.1 Hz, 2H), 3.65 (t, J = 6.2 Hz, 2H), 3.48–3.50 (m, 2H), 3.34–3.42 (m, 2H), 3.38 (s, 2H), 3.28 (s, 3H), 2.72 (t, J = 6.2 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 200.6, 166.7, 71.8, 71.7, 61.0, 59.7, 58.8, 49.8, 42.8, 14.0 ppm.

4.4.2. Ethyl-5-butoxy-3-oxopentanoate 7b.



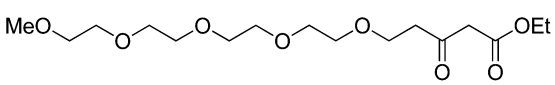
Following a representative procedure of the Blaise reaction on 3-(2-(2-methoxyethoxy)ethoxy)propanenitrile **6b** (0.58 g, 3.32 mmol) with ethyl bromoacetate (1.12 g, 6.70 mmol), zinc (1.10 g, 16.82 mmol) and catalytic amounts of TMSCl (3 mol%) afforded ethyl-5-(2-(2-methoxyethoxy)ethoxy)-3-oxopentanoate **7b** as light yellow liquid. Yield: 88% (785 mg); IR (KBr) (ν): 2879, 1740, 1464, 1312, 1110, 1029, 848, 455 cm^{-1}; ^{1}H NMR (400 MHz, CCl_4 + $CDCl_3$ 1 : 1) δ 4.14 (q, J = 7.1 Hz, 2H), 3.71 (t, J = 6.2 Hz, 2H), 3.56–3.60 (m, 6H), 3.49–3.51 (m, 2H), 3.46 (s, 2H), 3.33 (s, 3H), 2.77 (t, J = 6.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 201.5, 167.1, 71.9, 70.5 (2C), 70.4, 65.9, 61.3, 59.0, 49.7, 43.1, 14.1 ppm.

4.4.3. Ethyl-14-oxo-2,5,8,11-tetraoxahexadecan-16-oate 7c.



Following a representative procedure of the Blaise reaction on 2,5,8,11-tetraoxatetradecane-14-nitrile **6c** (0.80 g, 3.68 mmol) with ethyl bromoacetate (1.22 g, 7.35 mmol), zinc (1.20 g, 18.35 mmol) and catalytic amounts of TMSCl (3 mol%) afforded ethyl-14-oxo-2,5,8,11-tetraoxahexadecan-16-oate **7c** as a light yellow liquid. Yield: 69% (582 mg); IR (KBr) (ν): 2879, 1741, 1717, 1464, 1309, 1109, 1029, 848 cm^{-1}; ^{1}H NMR (400 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 4.22 (q, J = 6.8 Hz, 2H), 3.77 (t, J = 6.4 Hz, 2H), 3.62–3.67 (m, 10H), 3.56–3.57 (m, 2H), 3.51 (s, 2H), 3.40 (s, 3H), 2.82 (t, J = 6.4 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 201.5, 167.0, 72.0, 70.72, 70.69, 70.6 (2C), 70.5, 66.0, 61.2, 59.0, 49.7, 43.1, 14.2 ppm.

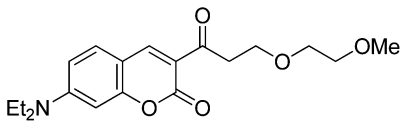
4.4.4. Ethyl-17-oxo-2,5,8,11,14-pentaoxanonadecan-19-oate 7d.



Following a representative procedure of the Blaise reaction on 2,5,8,11,14-pentaoxaheptadecane-17-nitrile **6d** (0.50 g, 1.90 mmol) with ethyl bromoacetate (0.64 g, 3.77 mmol), zinc (1.29 g, 19.73 mmol) and catalytic amounts of TMSCl (3 mol%) afforded 17-oxo-2,5,8,11,14-pentaoxanonadecan-19-oate **7d** as a light yellow color liquid. Yield: 71% (496 mg); IR (KBr) (ν): 2876, 1736, 1633, 1461, 1304, 1110, 1029, 434, cm^{-1}; ^{1}H NMR (400 MHz, CCl_4 + $CDCl_3$ 1 : 1) δ 4.18 (q, J = 14.0 Hz, 2H), 3.62–3.79 (m, 14H), 3.55–3.57 (m, 6H), 3.51 (s, 2H), 3.40 (s, 3H), 2.77 (t, J = 6.4 Hz, 2H), 1.33 (q, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 200.9, 167.8, 71.9, 70.7, 70.6, 70.55, 70.54, 70.54, 70.43, 70.42, 65.8, 61.2, 59.0, 49.7, 43.1, 14.2 ppm.

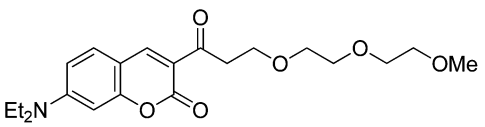
4.5. General procedure for the synthesis of 3-acylcoumarins 4a–d

4.5.1. Synthesis of 7-(diethylamino)-3-(3-(2-methoxyethoxy)-propanoyl)-2*H*-chromen-2-one 4a.



A solution of ethyl-5-(2-methoxyethoxy)-3-oxopentanoate **7a** (1.00 g, 4.58 mmol), 4-(diethylamino)-2-hydroxybenzaldehyde **8** (0.973 g, 5.04 mmol, 1.1 equiv.) and piperidine (0.19 g, 2.29 mmol, 50 mol%) taken in a 50 mL round-bottom flask was mixed thoroughly by attaching to a rotatory evaporator. The temperature of the water bath was maintained at 61 °C and the rpm was fixed at 40. TLC after 4 min indicated that the reaction was complete. The crude product obtained as a viscous liquid was directly subjected to column purification to furnish 7-(diethylamino)-3-(3-(2-methoxyethoxy)propanoyl)-2*H*-chromene-2-one **4a** as a yellow colour solid. Yield: 91% (1.44 g); mp 92 °C; UV λ_{max} (EA) 424 nm (log ε = 4.85); IR (KBr) ν: 3119, 2868, 1718, 1670, 1614, 1572, 1509, 1350, 1260, 1178, 1133, 1041, 475 cm^{-1}; ^{1}H NMR (400 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 8.38 (s, 1H), 7.35 (d, J = 9.0 Hz, 1H), 6.58 (dd, J = 9.0 Hz, 2.5 Hz, 1H), 6.42 (d, J = 2.3 Hz, 1H), 3.85 (t, J = 6.4 Hz, 2H), 3.61 (q, J = 4.4 Hz, 2H), 3.51 (q, J = 4.4 Hz, 2H), 3.37–3.45 (m, 6H), 3.33 (s, 3H), 1.21 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 195.8, 160.5, 158.6, 153.0, 147.9, 131.8, 115.9, 109.8, 108.1, 96.5, 71.8, 70.1, 66.3, 58.9, 45.1, 42.4, 12.4 ppm; HRMS (ESI-MS): (M + Na) m/z calculated 370.1630 amu, found 370.1617 amu.

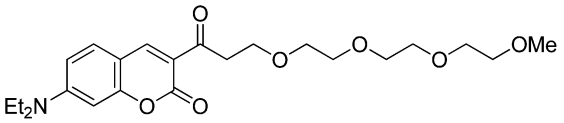
4.5.2. 7-(Diethylamino)-3-(3-(2-(2-methoxyethoxy)ethoxy)-propanoyl)-2*H*-chromen-2-one 4b.



Following the above representative procedure condensation of 4-(diethylamino)-2-hydroxybenzaldehyde **8** (0.81 g, 4.19 mmol) and ethyl-5-(2-(2-methoxyethoxy)ethoxy)-3-oxopentanoate. **7b** (1.00 g, 3.81 mmol) under piperidine catalysis (0.16 g, 1.90 mmol) resulted 7-(diethylamino)-3-(3-(2-(2-methoxyethoxy)-ethoxy)propanoyl)-2*H*-chromen-2-one **4b** as a yellow colored solid; yield: 87% (1.29 g); mp 78 °C; UV λ_{max} (EA) 424 nm (log ε = 4.83); IR (KBr) ν: 2875, 1714, 1670, 1616, 1573, 1505, 1352, 1178, 1134, 403 cm^{-1}; ^{1}H NMR (400 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 8.36 (s, 1H), 7.35 (d, J = 8.8 Hz, 1H), 6.56 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 6.42 (s, 1H), 3.83 (t, J = 6.4 Hz, 2H), 3.58–3.60 (m, 6H), 3.41–3.50 (m, 7H), 3.34 (s, 3H), 1.23 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz,

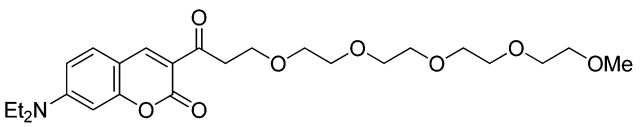
CCl_4 + $CDCl_3$, 1 : 1) δ 195.6, 160.4, 158, 152.8, 152.9, 147.9, 131.9, 116.6, 109.7, 108.4, 96.6, 72.1, 70.7, 70.6, 70.5, 66.5, 59.1, 45.2, 42.6, 12.7 ppm; HRMS (ESI-MS): (M + Na) *m*/*z* calculated 414.1892 amu, found 414.1888 amu.

4.5.3. 7-(Diethylamino)-3-(2,5,8,11-tetraoxatetradecan-14-oyl)-2*H*-chromen-2-one. 4c.



Following the above representative procedure condensation of 4-(diethylamino)-2-hydroxybenzaldehyde **8** (0.69 g, 3.59 mmol) and ethyl-14-oxo-2,5,8,11-tetraoxahexadecan-16-oate **7c** (1.00 g, 3.26 mmol) under piperidine catalysis (0.14 g, 1.63 mmol) resulted 7-(dimethylamino)-3-[3-[2-(2-methoxyethoxy)ethoxy]-propanoyl]-2H-chromen-2-one **4c** as a colored waxy solid; yield: 79%. (1.12 g); mp 62–65 °C; UV λ_{max} (EA) 424 nm (log $\varepsilon = 4.75$); IR (KBr) ν: 3047, 2923, 2872, 1723, 1669, 1617, 1575, 1507, 1351,1132, 468 cm^{-1}; ^1H NMR (400 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 8.38 (s, 1H), 7.37 (d, $J = 8.9$ Hz, 1H), 6.57 (dd, $J = 8.9$ Hz, 2.4 Hz, 1H), 6.43 (s, 1H), 3.83 (t, $J = 6.3$ Hz, 2H), 3.57–3.64 (m, 11H), 3.49–3.52 (m, 3H), 3.42–3.47 (m, 3H), 3.35 (s, 3H), 1.24 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 195.6, 160.4, 158.9, 152, 147.9, 131.9, 116.7, 109.2, 108.5, 96.9, 72.1, 70.8, 70.76, 70.71, 70.5, 66.5, 59.1, 45.3, 42.7, 12.7 ppm; HRMS (ESI-MS): (M + Na) *m*/*z* calculated 458.2154 amu, found 458.2149 amu.

4.5.4. 7-(Diethylamino)-3-(2,5,8,11,14-pentaoxaheptadecan-17-oyl)-2*H*-chromen-2-one 4d.



Following the above representative procedure condensation 4-(diethylamino)-2-hydroxybenzaldehyde **8** (0.61 g, 3.14 mmol) and ethyl-17-oxo-2,5,8,11,14-pentaoxanonadecan-19-oate **7d** (1.00 g, 2.85 mmol) under piperidine catalysis (0.12 g, 1.42 mmol) resulted 7-(diethylamino)-3-[3-[2-[2-[2-(2-methoxyethoxy) ethoxy]ethoxy]ethoxy]propanoyl]-2*H*-chromen-2-one **4d** as a yellow colored viscous liquid; yield: 76% (1.04 g); UV λ_{max} (EA) 424 nm (log $\varepsilon = 4.90$); IR (KBr) ν: 2875, 1722, 1666, 1617, 1575, 1507, 1454, 1352, 1259, 1118, 488, 423 cm^{-1}; ^1H NMR (400 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 8.42 (s, 1H), 7.42 (d, $J = 8.9$ Hz, 1H), 6.62 (dd, $J = 8.9$ Hz, 2.4 Hz, 1H), 6.48 (d, $J = 2.2$ Hz, 1H), 3.88 (t, $J = 6.6$ Hz, 2H), 3.69–3.64 (m, 10H), 3.64–3.69 (m, 6H) 3.57–3.62 (m, 6H), 3.51 (t, $J = 2.4$ Hz, 4H), 3.47–3.52 (m, 3H), 3.40 (s, 3H), 1.29 (t, $J = 7.0$ Hz, 6H); ^{13}C NMR (100 MHz, CCl_4 + $CDCl_3$, 1 : 1) δ 195.5, 160.3, 158.8, 152.9, 147.9, 131.9, 116.5, 109.7, 108.4, 96.7, 72.0, 70.86 70.81, 70.76, 70.72, 70.65, 70.62, 70.4, 66.1, 59.0, 45.2, 42.6. 12.6 ppm; HRMS (ESI-MS): (M + Na) *m*/*z* calculated 480.2 amu, found 480.2 amu.

4.6. Determination of water solubility of coumarins

To 1 mL double distilled Millipore zero conductivity water taken in a glass vial, coumarin was added at 25 °C in batches of 0.2 mg and sonicated. The addition continued till the solid did not dissolve any further. Each experiment was repeated three times and the values given are the average values. **4a:** 1.2 mg mL^{-1}; **4b:** 2.8 mg mL^{-1}; **4c:** 3.8 mg mL^{-1}; **4d:** 9.0 mg mL^{-1}.

Acknowledgements

H. S. P. R thanks UGC-SAP, CSIR and DST-FIST for financial assistance. A. D. thanks CSIR for fellowship. We thank CIF, Pondicherry University, and IISc, Bangalore for recording spectra. We thank A. K. Mishra, Professor, Department of Chemistry, IIT Madras for helpful discussions.

References

1 (*a*) J. Hepworth, *Comprehensive Heterocyclic Chemistry I*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, UK, 1984, vol. 3, pp. 737–883; (*b*) G. R. Geen, J. M. Evans and A. K. Vong, *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. Scriven, Pergamon, Oxford, UK, 2005, vol. 5, pp. 469–500; (*c*) B. W. Fravel, *Comprehensive Heterocyclic Chemistry III*, A. R. Katritzky, A. R. Christopher, F.V. Eric, E. F. Scriven and J. K. T. Richard, Pergamon, Oxford, UK, 2008, vol. 7, pp. 701–726; (*d*) R. D. H. Murry, J. Mendez and S. A. Brown, *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*, John Wiley & Sons, New York, 1982.

2 A. Maxwell, *Mol. Microbiol.*, 1993, **9**, 681–685.

3 A. A. Emmanuel, K. C. Fylaktakidou, D. J. Hadjipavlou, K. E. Litinas and D. N. Nikolaides, *J. Heterocycl. Chem.*, 2001, **38**, 717–721.

4 I. Manolov and N. D. Danchev, *Eur. J. Med. Chem.*, 1995, **30**, 531–535.

5 (*a*) T. I. Verhoef, W. K. Redekop, J. Darba, M. Geitona, D. A. Hughes, U. Siebert and A. Boer, *Pharmacogenomics*, 2010, **11**, 989–1002; (*b*) M. A. Musa, J. S. Cooperwood, M. Khan and F. Omar, *Current medicinal chemistry*, 2008, vol. 15, pp. 2664–2679; (*c*) R. M. Mohareb, D. H. Fleita and O. K. Sakka, *Molecules*, 2011, **16**, 16–27.

6 C. R. Moylan, *J. Phys. Chem.*, 1994, **98**, 13513–13516.

7 Y. Tian, E. Akiyama, Y. Nagase, A. Kanazawa, O. Tsutsumi and T. Ikeda, *Macromol. Chem. Phys.*, 2000, **201**, 1640–1652.

8 O. J. Kwon, V. Stoeva, J. Rademacher, R. Farwaha and M. A. Winnik, *J. Polym. Sci., Part A: Polym. Chem.*, 2004, **42**, 3479–3489.

9 (*a*) B. Valeur and I. Leray, *Coord. Chem. Rev.*, 2000, **205**, 3–40; (*b*) R. P. Haugland, CA, 2005, Chapter 19; (*c*) D. W. Domaille, E. L. Que and C. Chang, *Nat. Chem. Biol.*, 2008, **4**, 168–175; (*d*) K. Kikuchi, K. Komatsu and T. Nagano, *Curr. Opin. Chem. Biol.*, 2004, **8**, 182–191.

10 K. H. Drexhage, G. R. Erikson, G. H. Hawks and G. A. Reynolds, *Opt. Commun.*, 1975, **15**, 399–403.

11 T. Deligeorgiev, T. Tsvetkova and S. Stanimirov, *Color. Technol.*, 2011, **127**, 434–439.

12 W. Baoyan, G. Xiaolin, H. Yulin and S. Zhixing, *Polym. Adv. Technol.*, 2007, **18**, 529–534.

13 T. Ramakrishna and N. Jayaraman, *J. Org. Chem.*, 2003, **68**, 9694–9704.

14 H. S. P. Rao, S. Rafi and K. Padmavathy, *Tetrahedron*, 2008, **64**, 8037–8043.
15 H. S. P. Rao, S. Rafi and K. Padmavathy, *Lett. Org. Chem.*, 2008, **7**, 527–529.
16 A. Kentaro, S. Sachiko, U. Seiichi, K. Toshi, S. Tomofumi and I. Kazuhiro, *Photochem. Photobiol. Sci.*, 2003, **2**, 443–449.
17 I. M. Smallwood, *Handbook of Organic Solvent Properties*, Halsted Press, New York, 1996.