Chromenone Derivatives as Receptors for *N*-Benzoylamino Acids

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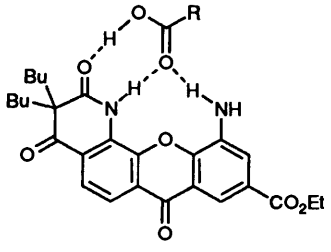
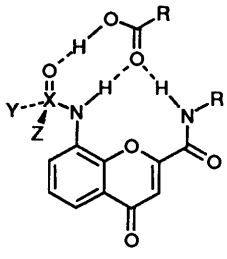
The chromenone derivative **5**, easy to synthesize from 2-hydroxyacetophenone **1**, has been used to prepare the hosts **7–10** and **12**. These combine three hydrogen bonds, π-stacking and charge-transfer interactions for the complexation of *N*-benzoylamino acids in $CDCl_3$.

In the course of our investigation on the influence of pre-organization and cavity shape on binding phenomena, we have developed several synthetic receptors. They are based on the incorporation of several hydrogen-bonding groups[1] for the complexation of acids, amides and urea groups in apolar solvents,[2] as in the case of xanthone derivatives **I**, which weakly associate with acids in deuteriochloroform.[2b] The best results were obtained when the stacking and charge-transfer interactions between the substrate and electron-deficient aromatic ring of the xanthone derivative were combined.

After these results, we designed and synthesized a simpler structure with a chromenone skeleton **II**. It bears the required alignment and binding groups to associate with carboxylic acids in the same fashion as the xanthone type receptors and it is easier to synthesize. The purpose of this research is to develop host molecules based on such structures that could bind amino acid derivatives.



I



II

X = P, Y = Z = OEt
X = S, Y = O, Z = NHC_6H_{11}

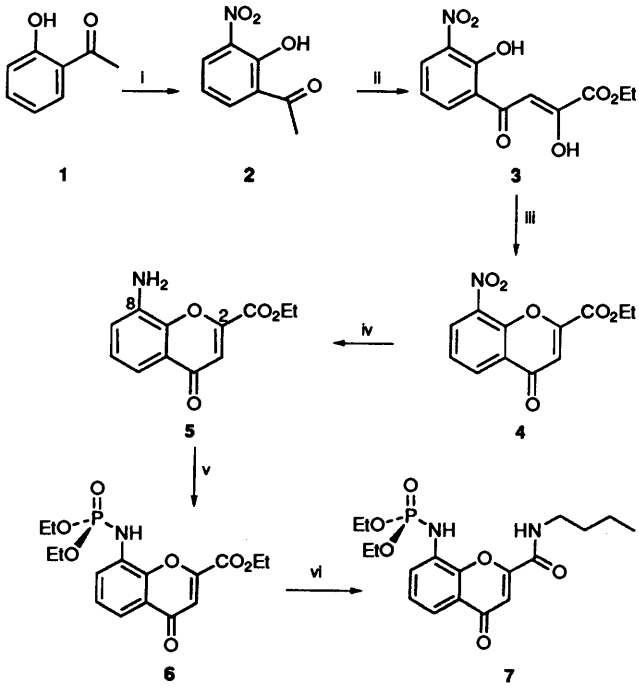
Proposed structure of the associates between a carboxylic acid and xanthone or chromenone derivatives

The association is produced by three hydrogen bonds,*[3] two of them accepted by the oxygen atom of the carboxylic group. To increase the host–guest association we combined these hydrogen bonds and a simple π-stacking surface.[4] Additional stabilization may be accomplished with a charge-transfer interaction between an electron-rich aromatic ring in the host and an electron-deficient moiety in the amino acid derivative when these two have a complementary spatial arrangement.

Results and Discussion

Examination of CPK molecular models based on these considerations suggested to us some possible receptors. They showed better stacking interactions between the aromatic ring of the *N*-benzoylamino acid derivative and a naphthyl moiety in the receptor. *N*-(3,5-Dinitrobenzoyl)isoleucine† was the guest used in our studies and the receptors had a naphthyl group bearing different electron-donor substituents.

The receptors were prepared from the nitro derivative **2**,[5] obtained by nitration of 2-hydroxyacetophenone **1**. The second ring was easily built by means of Claisen condensation with diethyl oxalate, cyclization, and selective reduction of the nitro group. This methodology allowed us to prepare the basic structure for the synthesis of chromenone derivatives (Scheme 1).



Scheme 1 *Reagents:* i, HNO_3–H_2SO_4; ii, diethyl oxalate, NaOEt; iii, H_2SO_4; iv, $SnCl_2$, HCl; v, diethyl chlorophosphate; vi, $BuNH_2$

All receptors were prepared starting from ethyl 8-amino-4-oxo-4*H*-chromene-2-carboxylate **5**.

Next, in order to build a more rigid structure, we attempted to generate a lactam fused to the benzene ring and to fix the conformation in the chain in order to cancel bond rotation in the complex, as previously done in the xanthene **I**.[2] Unfortunately, when compound **5** was treated with ethyl hydrogen dibutylmalonate monochloride, it furnished the acylated compound, but it was not possible to complete the cyclization

* The usual values of the association constants for neutral partners bound by three hydrogen bonds are 10^2–10^3 dm^3 mol^{-1} in a nonpolar organic solvent.

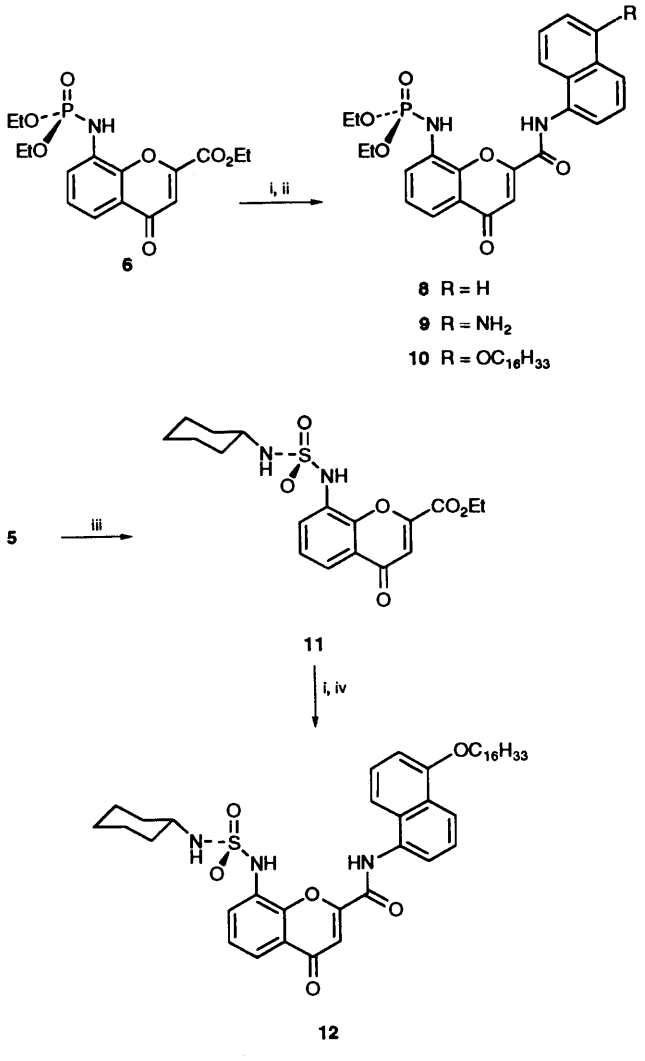
† This guest is not commercially available and was prepared by successive addition of isoleucine and 0.5 mol equiv. of 3,5-dinitrobenzoyl chloride to 1 mol equiv. of aq. sodium hydroxide. Acidification gave a solid of m.p. 176–177 °C, in quantitative yield.

Table 1 Association constants (K_s) for *N*-(3,5-dinitrobenzoyl)isoleucine with chromenone derivatives **8–10**, **12** at 20 °C in $CDCl_3$

Host	**8**	**9**	**10**	**12**
K_s (10^{-3} dm^3 mol^{-1})	1.1	4.9	5.5	9.5

because the compound decomposed under the reaction conditions.* A simple modification of the synthesis allowed us to obtain a diethoxyphosphoramide group at C-8, thus increasing the force of both donor and acceptor hydrogen bonds with respect to the amide group. Phosphoramides of types **7–10** bear a 1,3-relationship well suited for binding with the acid linkages of the guest.

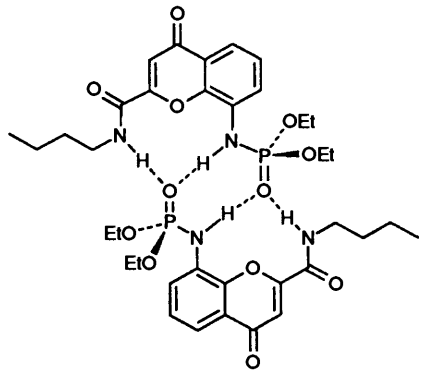
The synthesis of the receptor **7** was achieved by treatment of compound **5** with diethyl chlorophosphate to produce the phosphonamide at C-8, followed by reaction with butylamine in order to generate the amide group at C-2 (Scheme 2).



Scheme 2 *Reagents:* i, NaOH–EtOH; ii, CMC, 1-naphthylamine or 5-amino-1-naphthylamine or 5-hexadecyloxy-1-naphthylamine; iii, $C_6H_{11}NHSO_2Cl$–pyridine; iv, CMC, 5-hexadecyloxy-1-naphthylamine

* This cyclization requires the use of strong acid conditions ($MeSO_3H$–P_2O_5).

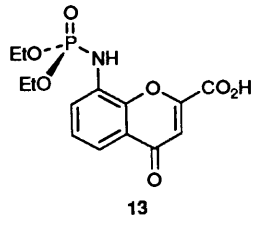
This receptor was prepared as a reference in view of the absence of a stacking effect, although it was not suitable for this purpose because it has a strong degree of self-association, since we observed a high dependence of its ^1H NMR spectral shifts with concentration. Thus, it was not possible to take any measurement of the association constant with the guest. The dimer of compound **7** can be viewed as a four-hydrogen-bond complex.



Proposed structure for the dimer of **7**

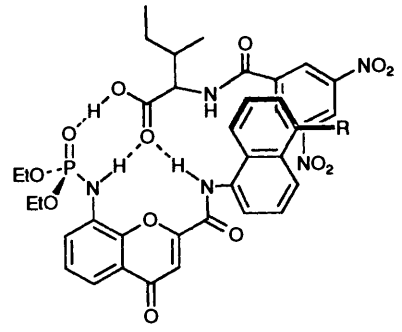
Unlike the case for species **I**, molecular models show that the dimerization of hosts **8–10** is disturbed by steric hindrance. Furthermore, these compounds introduce a favourable π-stacking interaction when a naphthyl group is present, apparently because the (smaller) benzene ring does not seem to be sufficient for the required spatial arrangement.

Hosts **8–10** were prepared from acid **13**, which was obtained by basic cleavage of the ethoxycarbonyl phosphoramide derivative **6**. The reaction of acid **13** with different naphthylamines in the presence of 1-cyclohexyl-3-(2-morpholinoethyl)-carbodiimide 'methotoluene-*p*-sulfonate' (CMC) as condensing agent gave compounds **8–10**, as shown in Scheme 2.



Binding studies were carried out by ^1H NMR titrations of the corresponding host in $CDCl_3$ at 293 K in which the addition of increasing amounts of the guest led to a progressive downfield shift of the host NH resonance. The guest chosen for study was *N*-(3,5-dinitrobenzoyl)isoleucine, although the results can be extended to other *N*-benzoylamino acids. Analysis of these data led to the determination of an association constant of 1.1×10^3 dm^3 mol^{-1} for the 1-naphthylamide derivative **8**. To increase the charge transfer, other rings carrying electron-releasing substituents were used, as in the 5-amino-1-naphthyl derivative **9**, which displayed a more efficient degree of binding (Table 1).

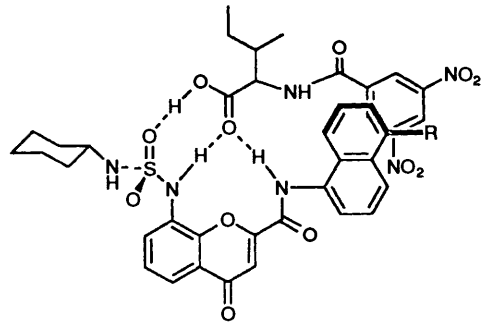
The solubility of the 5-hydroxy-1-naphthyl derivative in deuteriochloroform was insufficient for association studies by NMR spectroscopy, it being necessary to transform it into an alkoxy derivative. The ether linkage was made with the phenolate of 5-hydroxy-1-naphthylamine and hexadecyl bromide, with tetrabutylammonium chloride (TBACl) as a phase-transfer agent. This naphthylamine was treated with the acid **13** under the aforementioned conditions and gave the soluble receptor **10**. This compound showed an association constant slightly higher than that for the amine **9** (Table 1).



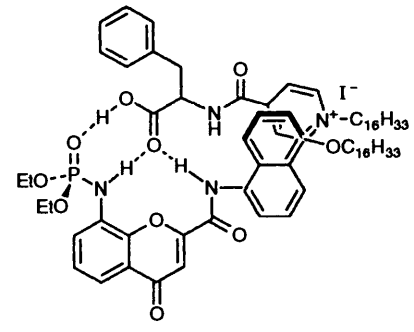
8 R = H • dinitrobenzoylisoleucine complex
9 R = NH_2 • dinitrobenzoylisoleucine complex
10 R = $OC_{16}H_{33}$ • dinitrobenzoylisoleucine complex

Association between chromenones **8–10** and 3,5-dinitrobenzoylisoleucine

(a)



(b)



Complexes between (*a*) amide **12** and dinitrobenzoylisoleucine and (*b*) amide **10** and *N*-(*N*-hexadecylpyridinium-4-ylcarbonyl)phenylalanine

The preceding results suggested a charge-transfer contribution to the complex due to the overlapping of the aromatic clouds, as can be seen above. A stronger association was obtained with the sulfurylamide derivative **12** (Scheme 2). Its synthesis was carried out from ester **5** by reaction with cyclohexylsulfamoyl chloride, followed by transformation of the product **11** into the naphthyl-substituted derivative, as in the previous synthesis of receptors **8–10**. However, the 1-naphthyl, 5-amino-1-naphthyl and 5-hydroxy-1-naphthyl derivatives were insoluble and only the 5-hexadecyloxynaphthyl derivative **12** was soluble.

The last attempt to produce a higher charge-transfer between the electron-rich naphthylamine residue and the amino acid derivative was to introduce a positive charge in the guest, as in *N*-(*N*-hexadecylpyridinium-4-ylcarbonyl)phenylalanine iodide. The association constant of this guest with the chromenone derivative **9** (K_s = 1.2 × 10^3 dm^3 mol^{-1}) was, unexpectedly, not higher. The presence of the counter-ion (iodide) could be responsible for the fact that the value of the constant did not rise. The amino acid derivative was prepared by acylation of the hydrochloride of phenylalanine methyl ester with isonicotinamoyl chloride, saponification, and treatment with hexadecyl iodide; the obtained guest was chloroform-soluble.

In summary, we have synthesized chromenone derivatives **8–10** and **12** that complex *N*-benzoylamino acid derivatives in $CDCl_3$ by three hydrogen bonds. A combination of π-stacking and charge-transfer effects increases the association constant by one order of magnitude.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. Column chromatography was performed on silica gel Merck 60, 230–400 mesh, and TLC on silica gel Merck 60, F_{254}. The ^1H and ^{13}C NMR spectra were recorded on a Bruker WP-200-SY spectrometer operating at 200 and 50.3 MHz respectively. Chemical shifts (δ) are reported in ppm with $SiMe_4$ as internal standard; *J*-values are recorded in Hz. IR spectra were determined on a Beckman 33-IR spectrophotometer. Mass spectra were measured on a VG-TS-250 spectrometer (electron-impact 70 eV). Elemental analyses were carried out using a Perkin-Elmer 240 B Analyser.

Binding Constants.—The ^1H NMR spectra were taken for a series of solutions containing the host at a fixed concentration of 1 × 10^{-3} mol dm^{-3} $CDCl_3$ and varying concentrations of the guest over the range 0–2 mol equiv., and the changes in the chemical shifts of the NH groups of the host were followed. Data were evaluated using a non-linear curve-fitting method based in the Monte Carlo program. An error of 20% is estimated. The concentrations of guest were chosen so as to allow a 70–90% range of complexation of host. $CDCl_3$ was dried over 4 Å molecular sieves.

Ethyl 8-Amino-4-oxo-4H-chromene-2-carboxylate **5**.—A solution of sodium ethoxide (10 mmol, 10 cm^3) and diethyl oxalate (1.1 g, 8 mmol) was refluxed for 10 min and 1-(2-hydroxy-3-nitrophenyl)ethanone **2** (1.5 g, 8 mmol) was added, while reflux was maintained for a further 20 min. After acidic work-up, cyclization took place in sulfuric acid. The crude reaction mixture was added to water and filtered, and the organic phase was dried to afford the condensed compound **4** in 65% total yield. Reduction of the nitro compound (0.4 g, 1.5 mmol) was carried out with tin dichloride (1.4 g, 6.5 mmol) in 2 mol dm^{-3} HCl (4 cm^3) and ethanol (4 cm^3) to total dissolution. The ethanol was evaporated off and sodium carbonate was added at basic pH. The aqueous phase was extracted with AcOEt and dried over Na_2SO_4 to yield the pure *compound* **5** (95%); m.p. 152 °C (Found: C, 61.9; H, 4.9; N, 6.0. $C_{12}H_{11}NO_4$ requires C, 61.80; H, 4.75; N, 6.01%); δ_H 1.43 (3 H, t, *J* 7.1), 4.29 (2 H, NH_2), 4.50 (2 H, q, *J* 7), 7.05 (1 H, dd, J_1 8, J_2 1.7), 7.08 (1 H, s), 7.22 (1 H, t, *J* 8) and 7.50 (1 H, dd, J_1 8, J_2 1.7); δ_C 13.9 (1 C, q), 62.8 (1 C, t), 113.2 (1 C, d), 114.1 (1 C, d), 118.3 (1 C, d), 124.6 (1 C, s), 125.9 (1 C, d), 136.9 (1 C, s), 144.4 (1 C, s), 151.2 (1 C, s), 160.3 (1 C, s) and 178.7 (1 C, s).

Ethyl 8-(Diethoxyphosphorylamino)-4-oxo-4H-chromene-2-carboxylate **6**.—The above compound **5** (1.8 g, 8 mmol) was treated with diethyl chlorophosphate (1.4 g, 8 mmol) in pyridine (5 cm^3). The mixture was stirred until a bulky yellow precipitate appeared. The solid was removed by filtration, after which the organic layer was treated with 2 mol dm^{-3} HCl and washed with water. After extraction with chloroform, the organic solution was dried (Na_2SO_4), and evaporation of the solvent gave the phosphoramide **6** (91%) (Found: C, 51.9; H, 5.5; N, 3.8. $C_{16}H_{20}NO_7P$ requires C, 52.03; H, 5.46; N, 3.79%); δ_H 1.0–1.5 (9 H, t, *J* 7.1), 3.3 (1 H, NH), 4.1–4.5 (6 H, q, *J* 7.1),

7.07 (1 H, s), 7.41 (1 H, t, *J* 8.0), 7.65 (1 H, dd, J_1 8.0, J_2 1.8) and 7.74 (1 H, dd, J_1 8.0, J_2 1.8); δ_C 13.7 (1 C, q), 15.6 (1 C, q), 15.7 (1 C, q), 62.8 (1 C, t), 63.1 (1 C, t), 63.2 (1 C, t), 114.3 (1 C, d), 117.1 (1 C, d), 120.9 (1 C, d), 124.3 (1 C, d), 125.6 (1 C, d), 129.9 (1 C, s), 144.8 (1 C, s), 151.0 (1 C, s), 159.9 (1 C, s) and 177.7 (1 C, s); *m/z* 369 (M^+, 34%), 341 (36), 313 (12), 269 (31), 241 (33), 205 (60), 161 (100), 135 (37), 99 (61) and 81 (61).

N-Butyl-8-(diethoxyphosphorylamino)-4-oxo-4H-chromene-2-carboxamide **7**.—An excess of butylamine was added to a solution of the above phosphoramide **6** (0.7 g, 2 mmol) in chloroform and the solution was stirred and refluxed for 30 min until complete dissolution. The excess of butylamine was distilled off at reduced pressure and the residue was purified by chromatography on SiO_2, with ethyl acetate as eluent. Subsequent recrystallization from ethyl acetate–hexane yielded *compound* **7** (70%) as crystals; m.p. 184 °C (Found: C, 54.4; H, 6.5; N, 6.8. $C_{18}H_{25}N_2O_6P$ requires C, 54.54; H, 6.36; N, 7.07%); δ_H 1.0 (3 H, t, *J* 7.0), 1.0–1.8 (10 H, m), 3.52 (2 H, q, *J* 7.0), 4.0–4.3 (4 H, m), 7.27 (1 H, s), 7.38 (1 H, t, *J* 8.1), 7.55 (1 H, d, *J* 8.1), 7.80 (1 H, d, NH), 7.88 (1 H, d, *J* 8.1) and 8.90 (1 H, t, NH); *m/z* 396 (M^+, 86%), 353 (100), 325 (24), 297 (23), 268 (28), 242 (18), 198 (60), 161 (40), 135 (25), 104 (46) and 81 (39).

8-(Diethoxyphosphorylamino)-4-oxo-4H-chromene-2-carboxylic Acid **13**.—Compound **6** (0.79 g, 2 mmol) was treated with a solution of sodium ethoxide (2 mmol, 2 cm^3). After 3 h the starting material had disappeared (TLC). The ethanol was then evaporated off and ethyl acetate was added to the residue; the organic solution was washed successively with 2 mol dm^{-3} HCl and water, dried (Na_2SO_4), and evaporated under reduced pressure. Subsequent crystallization led to product **13** (94%), m.p. 186 °C; δ_H 1.35 (6 H, m), 4.20 (4 H, m), 7.25 (1 H, s), 7.39 (1 H, t, *J* 8.2), 7.60 (1 H, dd, J_1 8.2, J_2 1.8), 7.71 (1 H, dd, J_1 8.2, J_2 1.8) and 7.95 (1 H, br s, NH); ν_{max}(KBr)/cm^{-1} 3600–2700, 1655, 1580, 1500, 1405, 1230, 1120 and 1050.

Preparation of Receptors **8–10**.—Naphthylamine, 5-amino-1-naphthylamine or 5-hexadecyloxy-1-naphthylamine (0.5 mmol each) and CMC (0.2 g, 0.5 mmol) were added to different suspensions of the acid **13** (0.17 g, 0.5 mmol) in 1,4-dioxane (0.5 cm^3) and the mixture was stirred vigorously for 12 h at 25 °C. The solvent was distilled off under reduced pressure and the residue was taken up in ethyl acetate, successively washed with 2 mol dm^{-3} HCl and water, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2; mixtures of ethyl acetate–hexane as eluent) to obtain compounds **8–10**.

Diethyl [2-(1-naphthylcarbamoyl)-4-oxo-4H-chromen-8-yl]-phosphoramidate **8** (80%), m.p. 245 °C (Found: C, 61.9; H, 5.1; N, 6.0. $C_{24}H_{23}N_2O_6P$ requires C, 61.80; H, 4.97; N, 6.12%); δ_H 1.21 (6 H, t, *J* 7.0), 3.41 (1 H, NH), 4.11 (4 H, q, *J* 7.0), 7.1–8.0 (11 H) and 8.55 (1 H, NH); *m/z* 466 (M^+, 10%), 368 (20), 313 (10), 285 (8), 236 (20), 224 (100), 183 (18), 143 (94) and 11 (26).

Diethyl [2-(5-amino-1-naphthylcarbamoyl)-4-oxo-4H-chromen-8-yl]phosphoramidate **9** (85%), m.p. 278 °C (Found: C, 59.75; H, 5.2; N, 8.6. $C_{24}H_{24}N_3O_6P$ requires C, 59.87; H, 5.02; N, 8.73%); δ_H 0.92 (6 H, t, *J* 7.2), 3.4 (1 H, NH), 3.51 (2 H, complex, *J* 7.2), 3.61 (2 H, q, *J* 7.2), 4.25 (2 H, NH), 6.82 (1 H, d, naphthyl), 7.20–7.60 (7 H), 7.85 (2 H, t, *J* 7.1) and 8.4 (1 H, d, NH); *m/z* 481 (M^+, 30%), 440 (9), 412 (80), 369 (51), 345 (17), 313 (21), 284 (25), 236 (28), 198 (70), 183 (52) and 158 (100).

Diethyl [2-(5-hexadecyloxy-1-naphthylcarbamoyl)-4-oxo-4H-chromen-8-yl]phosphoramidate **10** (85%), m.p. 188 °C (Found: C, 67.8; H, 7.9; N, 3.8. $C_{40}H_{55}N_2O_7P$ requires C, 67.96; H, 7.84; N, 3.96%); δ_H 0.7–1.7 (37 H), 3.50 (2 H, q, *J* 8.1), 3.80 (2 H, complex, *J* 8.2), 4.05 (2 H, t, *J* 7.0), 5.06 (1 H, NH), 6.75 (1 H, d), 7.2 (1 H, t, naphthyl), 7.20–7.50 (3 H), 7.37 (1 H, t), 7.60 (1 H, d), 7.75 (2 H, d), 8.2 (1 H, d, *J* 8) and 8.51 (1 H, d, *J* 8); *m/z* 706 (M^+, 12%), 383 (4), 263 (13), 127 (64) and 99 (100).

8-(Cyclohexylaminosulfonylamino)-N-(5-hexadecyloxy-1-naphthyl)-4-oxo-4H-chromene-2-carboxamide **12**.—A solution of compound **5** (0.5 g, 2 mmol) and cyclohexylsulfamoyl chloride (0.4 g, 2 mmol) in pyridine (5 cm^3) was stirred for 2 h at room temperature. Then, 2 mol dm^{-3} HCl and CH_2Cl_2 were added, and the organic layer was washed with water and dried over Na_2SO_4. After removal of the solvent, a solid was obtained, which after work-up and treatment with sodium hydroxide afforded an acid compound. When this acid was treated with 5-hexadecyloxynaphthalen-1-amine and CMC, *compound* **12** was obtained in 75% yield from substrate **5**, m.p. 135 °C (Found: C, 70.2; H, 8.0; N, 3.8. $C_{42}H_{56}N_2O_6S$ requires C, 70.36; H, 7.87; N, 3.90%); δ_H(*inter alia*) 0.88 (3 H, t, *J* 6.8), 1.0–1.8 (38 H), 3.1 (1 H, m), 4.0 (2 H, t, *J* 6.1), 4.6 (1 H, d, NH), 6.62 (1 H, d, *J* 7.4, naphthyl), 6.96 (1 H, s), 7.22–7.40 (4 H, m), 7.63 (1 H, t, *J* 8), 7.83 (1 H, dd, J_1 8.0, J_2 1.4), 8.05 (1 H, d, *J* 8.3) and 9.6 (1 H, s).

Acknowledgements

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References

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