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Binding properties of an abiotic receptor for complexing carboxylates of α-heterocyclic and α-keto acids

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Abstract—A receptor with high molecular recognition of carboxylates of α-heterocyclic and α-keto acids was prepared by introduction of hydroxamic function in a neutral anion binding receptor with a framework of bis-chromenylurea. The improved complexation of the host toward these guests resulted from a fifth hydrogen bond in the complexes between the OH donor of the host and the α-heteroatom acceptor of the guests.

1. Introduction

The importance of the carboxylate function in nature, where it appears in many biologically relevant molecules, is well known.[1] Such molecules are involved in both chemical and biological recognition processes and hence the design and synthesis of abiotic receptors for complexing anion carboxylates is receiving increasing attention.[2] Electroneutral anion hosts are of special relevance, among other reasons for their applications.[3]

In this sense, we have previously developed neutral anion binding receptors with urea and amide functions to bind carboxylate anions.[4] These receptors, with a bis-chromenylurea backbone (Fig. 1), bind carboxylates strongly by means of four hydrogen bonds, with $K_{ass} \geq 10^4\ M^{-1}$ in DMSO-d_6.

The strong tendency of carboxylate oxygens to form three-centred bonds[5] allows carboxylates to get commonly involved in the H-bond pattern, as depicted in Fig. 1 for receptor **1**[4a] (Scheme 1). Hydrogen bonds also permit selectivity between competing guests; the introduction of a single H-bond properly positioned in a synthetic receptor could lead to a favourable increase in binding in a similar way to enzymatic processes.[6] This feature can lead to increases in both the strength and the selective recognition of substrate binding.

Carboxylates of α-heterocyclic acids could be appropriate guests for the formation of this efficient fifth H-bond in bis-chromenylurea host–guest complexes and could permit the development of specific receptors for complexing such carboxylates.

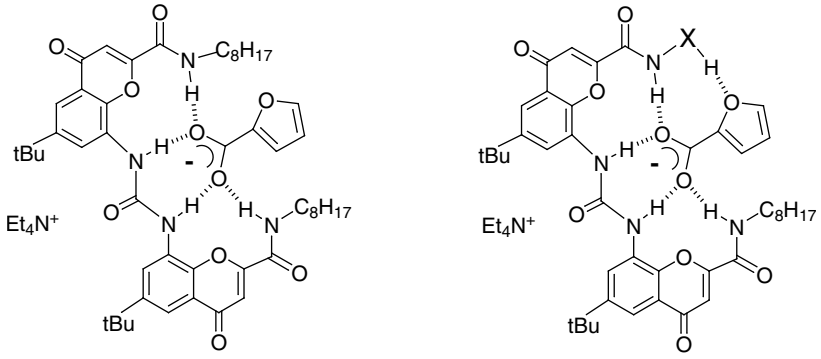

Figure 1. Proposed complexes for receptor **1** by four hydrogen bonds (left) and for new receptors **2–5** by five hydrogen bonds (right) with the tetraethylammonium salt of 2-furoic acid.

Keywords: hydrogen bonding receptor; chromenone-hydroxamic acid; carboxylates of α-heterocyclic and α-keto acids.
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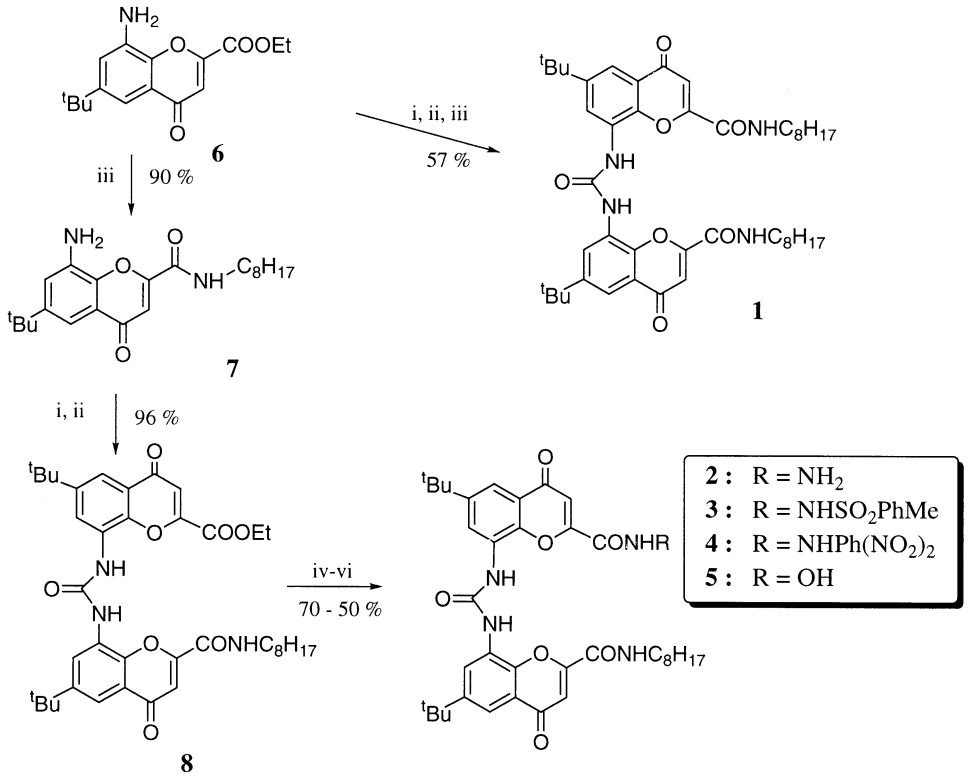


Scheme 1. *Reagents*: (i) $COCl_2$, toluene, THF; (ii) **6**: THF; (iii) (a) 2-ethylhexylamine, (b) AcOH; (iv) KOH, EtOH; (v) PCl_5, CH_2Cl_2; (vi) **2**: NH_2NH_2 (51%); **3**: NH_2NHSO_2PhMe (69%); **4**: $NH_2NHPh(NO_2)_2$ (65%); **5**: NH_3OHCl, pyridine (50%).

Our attention was initially drawn to salts of 2-furoic acid. Formation of the new hydrogen bond will fix the substrate position in the complexes, as shown in Fig. 1 for the furane ring, and this seems interesting for inducing selectivity in the complexation. Regarding this, the non-symmetrically substituted receptors **2**–**5** were designed and built by introduction of different H-bond donor moieties (R; Scheme 1).

2. Results and discussion

The synthesis of the receptors was carried out starting from ethyl amino chromenone carboxylate **6**[7] as the key building group; upon aminolysis with ethylhexylamine it yielded amide **7**. Treatment with phosgene gave the isocyanate, which reacted with amine **6** to afford urea **8**. Hydrolysis of the ethyl ester of **8** gave the corresponding monoacid, which was converted into the acyl chloride and treated with hydrazine, 4-tosylhydrazine, 2,4-dinitrophenyl hydrazine or hydroxylamine hydrochloride, leading to receptors **2**–**5** in 50–70% yields (Scheme 1).

To test the efficacy of the new binding molecules in the complexation of carboxylates with α-heteroatoms, competitive titration experiments[8] of hosts **2**–**4** were carried out, each with respect to host **1**, which lacks the possibility to form additional H-bonds. The spectra were recorded in $CDCl_3/CD_3OD$ 95:5% to assess the solubility of the receptors.

A K_{rel}=3 was obtained for receptor **2** versus receptor **1**. This low value could be explained by a more stable *cis* conformation of the acylhydrazide in solution,[9] shown in Fig. 2, where unfavourable electrostatic interactions between the

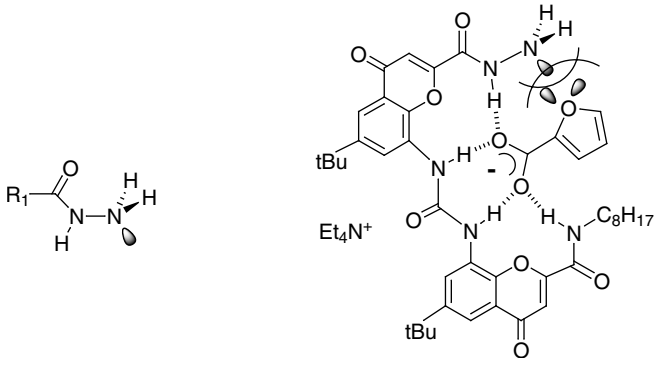


Figure 2. Most stable conformation of non-substituted acylhydrazides in solution. Unfavourable electrostatic interactions between receptor **2** and carboxylate of 2-furoic acid.

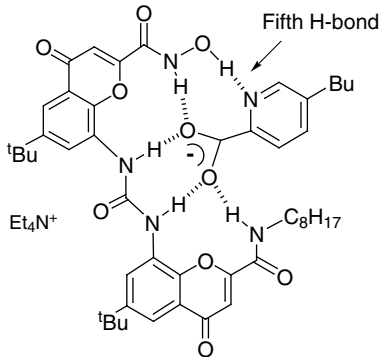


Figure 3. Proposed complex between receptor **5** and the tetraethylammonium salt of fusaric acid by five hydrogen bonds.

non-bonding electron pairs of the nitrogen of the host and the oxygen of the guest could hinder cooperation in the complex.

In order to favour the necessary conformation of this moiety and to increase the strength of the fifth H-bond, monosubstituted hydrazines[9] with higher acidity in the hydrogen atom involved in the new H-bond were used to synthesise receptors **3** and **4**, the former as a tosylhydrazide derivative[10] and the second with a 2,4-dinitrophenylhydrazide group.[11]

Higher association constants relative to **1** were expected for these new hosts, but in both cases the results obtained previously were only slightly improved to values of K_{rel}=4 and 4.7, respectively, suggesting that the binding geometry had not been properly achieved.

A good solution was found with receptor **5** (Fig. 3), bearing an hydroxamic group instead of hydrazine function.[12] Competitive titration experiments were recorded in $CDCl_3$/CD_3OD 99:1% as solvent, using the tetraethylammonium salt of 2-furoic acid as guest, and **5** and **1** as hosts. A 36-fold improvement was observed for the association constant of **5** with respect to **1**. This result suggests that an increase in the association can be promoted by the formation of the additional hydrogen bond.

A new competitive experiment with receptor **5** and both guests 2-furoate and benzoate salts, the latter without the α-heterocyclic atom, was performed; a selective binding of **5** with furoate was obtained with a K_{rel}=21.5. The same relationship was measured by conventional titration which gave $K_{ass}=1.1\times10^3$ M^{-1} for the benzoate and $K_{ass}=2.4\times10^4$ M^{-1} for the 2-furoate (Table 1).

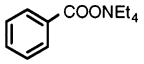
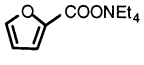
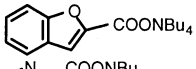
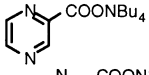
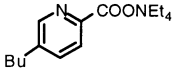
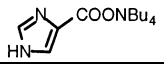
This can be explained by assuming that a new H-bond between the O*H* hydrogen of the hydroxamic function and the heterocyclic oxygen of the guest was established in the complex.

Molecular modelling[13] predicted a convergent arrangement of the binding hydrogens in the receptor around the cavity to which the guest is driven by the formation of five hydrogen bonds. The hydroxamic function has the correct geometry for establishing an effective H-bond between the NHO*H* donor and the oxygen or nitrogen acceptor atoms of the heterocyclic atom in the α-position of the carboxylates. A similar recognition pattern was obtained for the carboxylate of 5-butyl picolinic (fusaric) acid (Fig. 3).

New competitive titration experiments of host **5** with both fusaric and 2-furoic tetrabutylammonium salts revealed an 18-fold increase in complexation for the fusarate. The better complexation found for the carboxylate of fusaric acid compared with 2-furoate can be explained in terms of the greater basicity of the heterocyclic nitrogen relative to the acceptor oxygen atoms, both implicated in the additional H-bond.

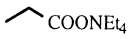
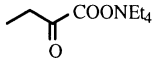
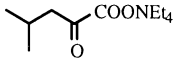
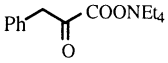
On the other hand, as mentioned above, the K_{ass} of **5** with 2-furoic carboxylate with respect to the benzoic salt was 21.5-fold improved. A high value of 392-fold,[14] $\Delta(\Delta G)$= 3.45 kcal mol^{-1}, was estimated for the association of fusaric carboxylate with respect to the benzoate, a guest which lacks the α-heterocyclic atom.

Table 1. Association constants, relative constants and free energies of complexation for the complexes of receptor **5** with different α-heterocyclic carboxylates, in $CDCl_3$/CD_3OD 99:1% at 293 K

Acid	Guest	K_{ass} (M^{-1})	K_{rel}[a]	$\Delta(\Delta G)$ (kcal/mol)
Benzoic		1.1×10^3	1	
2-Furoic		2.4×10^4	21.6[b]	1.70
Coumarilic		2.7×10^4	24.0[b]	1.82
2-Pyrazinoic		5.3×10^4	47.8[b]	2.24
Fusaric		4.3×10^5	392[c]	3.45
4-Imidazole carboxylic		4.5×10^5	414[c]	3.50

[a] Competitive titration experiments of **5** and the tetraethylammonium salts of guests relative to benzoate salt.
[b] Direct experimental data.
[c] Deduced from competitive titration of 2-furoate salt.

Table 2. Association constants, relative constants and free energies of complexation for the complexes of receptor **5** with different α-keto carboxylates, in $CDCl_3/CD_3OD$ 99:1% at 293 K

Acid	Guest	K_{ass} (M^{-1})	K_{rel}[a]	$\Delta(\Delta G)$ (kcal/mol)
Propionic		3.2×10^3	1	
Pyruvic		4.0×10^4	12.4[b]	1.45
2-Oxobutyric		4.3×10^4	13.5[b]	1.51
4-Methyl oxovaleric		6.1×10^4	19.0[b]	1.71
Phenylacetic		1.5×10^3	1	
Phenylpyruvic		1.3×10^4	8.7[c]	1.25
Phenylglyoxylic		1.4×10^4	9.3[c]	1.33

[a] Competitive titration experiments of **5** and the tetraethylammonium salts of guests.
[b] Relative to propionic salt.
[c] Relative to phenylacetic salt.

Other guests with different basicities of the H-bond acceptor heteroatom were titrated with respect to the benzoate. The overall results (Table 1) showed that, in complexes between **5** and the α-heterocyclic carboxylates explored, an additional H-bond must be established because the values obtained are in accordance with the expectations for a stronger association. The 4-imidazole and fusaric carboxylates showed complexes with higher stability, which was attributed to the similar acidity of the conjugated acid of the N of the guest and the OH hydrogen bond atom donor of the hydroxamic function in the host.[15]

Carboxylates of α-ketoacids closely resemble α-heterocyclic carboxylates in that they have a planar arrangement for complexation. We therefore considered extending these good results to that type of carboxylates. The molecular recognition of α-ketoacids and their derivatives is interesting due to the outstanding biological activity shown by some of them, such as phenylpyruvate, involved in phenylketonuria disease.[16]

Initially, the formation of a host–guest complex was checked by FABMS for **5** and the tetraethylammonium salt of 4-methyloxovaleric acid. The FAB^+ spectrum (*m*-nitrobenzyl alcohol as matrix) of a 1:1 mixture of this substrate and **5** showed a signal at *m/z* 933.7, assigned to $[host+guest+NEt_4]^+$, while the corresponding FAB^- spectrum displayed a peak at *m/z* 803.7, assigned to $[host+guest]^-$, which confirmed the formation of the complex.[17] The association constant was therefore evaluated and a $K_{ass}=3.2\times10^4\ M^{-1}$ in DMSO-d_6 was obtained.

^1H NMR titration experiments in $CDCl_3/CD_3OD$ 99:1% were carried out with receptor **5** and the carboxylates of both alkyl and aryl α-ketoacids. The pyruvic acid salt gave a complex with a $K_{ass}=4.3\times10^4\ M^{-1}$ and the phenylglyoxylic acid salt gave a complex with a $K_{ass}=1.3\times10^4\ M^{-1}$.

When association constants of receptor **5** and guests without a keto function were measured in the same solvent, a $K_{ass}=3.2\times10^3\ M^{-1}$ for the carboxylate of propionic acid and a $K_{ass}=1.8\times10^3\ M^{-1}$ for the carboxylate of phenylacetic acid were obtained. Comparison of these results with those obtained above clearly show the lower binding affinity of such carboxylates than the corresponding α-ketocarboxylates, thus confirming the establishment of the fifth H-bond.

Table 2 shows the data obtained in the titrations of the α-ketoacid tetraethylammonium salts studied. As expected, the presence of a fifth hydrogen bond produced a favourable improved binding.

In conclusion, we have synthesised a neutral bis-chromenyl urea anion receptor, which shows outstanding selectivity in the binding of some tetraethylammonium salts of α-heterocyclic acids. The structure of the complex between **5** and the guests studied is based on the formation of five hydrogen bonds. The formation of the fifth H-bond between the hydroxamic function of the host and the heterocyclic atom in the guest was demonstrated in comparative studies. Also, a better complexation was achieved with **5** and the tetraethylammonium salt of α-keto acids versus other guests without a keto function. The molecular recognition properties of this anion receptor could have applications in anion transport and in sensors for selective anion detection.

3. Experimental

3.1. General

All anhydrous reactions were carried out under an Ar atmosphere and the organic extracts were dried with anhydrous sodium sulphate. Melting points were determined on a Kofler hot-plate apparatus and are uncorrected. TLC chromatography was performed on Merck 60, F254 silica gel. Elemental analyses were carried out using a Perkin–Elmer 240 B Analyser. Infrared spectra were recorded on Bomem MB-100FT spectrophotometer liquid film or KBr disc and

reported in wave numbers (cm^{-1}). ^1H NMR spectra were recorded on a Bruker WP-200-SY apparatus. The chemical shifts δ are given in ppm with the proton signals in the deuterated solvents as internal references. Mass spectra were measured on a VG-TS-250 spectrometer at 70 eV. Fast atom bombardment (FAB) spectra were recorded on a Katros MS50, using a *meta* nitrobenzylalcohol (NOBA) as matrix and accurate mass determinations were carried out on a Katros Concept IS spectrometer.

3.2. ^1H NMR titrations

The ammonium carboxylates were prepared starting from commercially available carboxylic acids. One equivalent of a 2 M solution of Et_4NOH or Bu_4NOH in MeOH was added to the acid in MeOH. The resulting solution was evaporated under reduce pressure, and the solid salt was dried (0.01 Torr, 60°C, 12 h). Titrations were carried out at a constant 10^{-3} M host concentration in the indicated solvent. The experimental data were fitted using a Monte-Carlo non-linear curve-fitting program.

Competitive titration experiments were performed with 3×10^{-3} M hosts (or guests) solutions to which pure guest (or host) was added until saturation was reached. Proton shifts of hosts (or guests) were recorded for each experiment and plotted against each other. The data obtained were subjected to a curve fitting procedure based on the non-linear least-squares method, which provided the relative association constants.

3.2.1. Ethyl 8-amine-6-*tert*-butyl-4-oxo-(*4H*)-chromen-2-carboxylate (6) and 8-amine-6-*tert*-butyl-4-oxo-(*4H*)-chromen-2-(2-ethylhexyl) carboxamide (7). These compounds were prepared according to previously described methods.[7]

3.2.2. 1,3-bis-[6-*tert*-butyl-2-(2-ethylhexyl)-carboxamide-4-oxo-(*4H*)-chromen-8-yl]-ureide (1). A solution of 0.35 mmol of amine **6** in 20 ml of THF was slowly added to a solution of phosgene in toluene (20%) (3.2 mmol) and then refluxed for 15 min. Evaporation of the solvent gave a white solid. A solution of **6** (0.35 mmol) in THF (10 ml) was then added. The reaction was kept at room temperature for 12 h. The solvent was removed by evaporation under reduced pressure and the residue was washed with 2 M HCl and extracted with ethyl acetate. The organic layer was dried and evaporated to give a yellow solid which was then purified by crystallisation from ethyl acetate affording a diester-urea (91%); mp 192–193°C, ν_{max}: 3350, 1720, 1649, 1588, 1260, 1215 and 1123; ^1H NMR ($CDCl_3$): δ 9.20 (s, 2H, NH), 9.00 (d, J=2.4 Hz, 2H), 7.80 (d, J=2.4 Hz, 2H), 7.16 (s, 2H), 4.51 (c, J=7.5 Hz, 4H), 1.50 (t, J=7.5 Hz, 2Me), 1.42 (s, 18H); m/z 605 $[M+1]^+$.

0.17 mmol of diester-urea was disolved in 3 ml of butylamine and the solution was stirred at room temperature for 1 h. Then 2 M HCl was added to remove the excess of amine and extracted with dichloromethane. The solvent was removed under reduced pressure and 5 ml of acetic acid was added; the solution was maintained at reflux for 10 min. Then, acetic excess was eliminated at reduced pressure, and the crude product taken up in ethyl acetate–hexane for crystallisation: bis-carboxamide **1** was obtained (63%). Mp 176–178°C, ν_{max}: 3347, 1724, 1670, 1632, 1545, 1385 and 1184; ^1H NMR ($CDCl_3$): δ 8.90 (d, J=2.3 Hz, 2H), 7.77 (d, J=2.3 Hz, 2H), 7.04 (s, 2H), 3.46 (t, J=6.2 Hz, 2H), 1.8–1.2 (m, 9H), 1.41 (s, 18H), 1.0–0.8 (m, 6H); m/z 771 $[M+1]^+$. Anal. calcd for $C_{45}H_{62}N_4O_7$: C, 77.10; H, 8.11; N, 7.27. Found: C, 76.92; H, 8.29; N, 6.85%.

3.2.3. Ethyl 6-*tert*-butyl-8-{3-[6-*tert*-butyl-2-(2-ethylhexylcarbamoyl)-4-oxo-(*4H*)-chromen-8-yl]-ureide}-4-oxo-(*4H*)-chromen-2-carboxylate (8). A solution of amine **7** (1.73 mmol) in THF (40 ml) was slowly added to a solution of phosgene in toluene (20%) (10.1 mmol) and then refluxed for 15 min. Evaporation of the solvent gave a white solid. A solution of **6** (1.73 mmol) in THF (20 ml) was then added. The reaction was kept at room temperature for 48 h. The solvent was removed by evaporation under reduced pressure and a solid residue of compound **8** was obtained (96%). An analytically pure sample was obtained by recrystallisation from CH_2Cl_2–hexane: mp 158–159°C, ν_{max}: 3511, 3349, 1724, 1636, 1545, 1285 and 1184. ^1H NMR ($CDCl_3$): δ 8.99 (d, J=2.4 Hz, 1H), 8.90 (d, J=2.4 Hz, 1H), 7.79 (d, J=2.4 Hz, 2H), 7.15 (s, 1H), 6.96 (s, 1H), 4.53 (c, J=7.2 Hz, 2H), 3.45 (t, J=6.0 Hz, 2H), 1.8–1.2 (m, 9H), 1.47 (t, J=7.2 Hz, 3H), 1.42 (s, 18H), 1.0–0.8 (m, 6H); m/z 688 $[M+1]^+$. Anal. calcd for $C_{39}H_{49}N_3O_8$: C, 68.10; H, 7.18; N, 6.11. Found: C, 68.02; H, 7.29; N, 6.05%.

3.2.4. 6-*tert*-Butyl-8-{3-[6-*tert*-butyl-2-hydrazino carbonyl-4-oxo-(*4H*)-chromen-8-yl]-ureide}-4-oxo-(*4H*)-chromen-2-(2-ethylhexyl)-carboxamide (4). To 20 ml of absolute ethanol, the ester **10** (1.58 mmol) and 2 ml of dichloromethane were added, warming to complete solubilisation. Potassium hydroxide (1.58 mmol) in absolute ethanol (5 ml) was added. After 5 min, the reaction was acidified with HCl (2 M); this resulted in the formation of a yellow powder identified as the corresponding acid (99%); mp 218–220°C, ν_{max}: 3484, 3347, 3262, 3081, 1723, 1645, 1545, 1271 and 1182; ^1H NMR (DMSO-d_6): δ 8.59 (d, J=2.4 Hz, 1H), 8.37 (d, J=12.4 Hz, 1H), 7.71 (d, J=2.4 Hz, 1H), 7.46 (d, J=2.4 Hz, 1H), 6.92 (s, 1H), 6.85 (s, 1H), 3.33 (c, J=6.7 Hz, 2H), 1.1–0.9 (m, 2H), 1.34 (s, 9H), 1.33 (s, 9H), 0.9–0.7 (m, 2H), 0.84 (t, J=7.2 Hz, 3H); m/z 604 $[M+1]^+$. Anal. calcd for $C_{37}H_{45}N_3O_8$: C, 67.36; H, 6.87; N, 6.37. Found: C, 67.27; H, 6.98; N, 6.29%.

0.15 mmol of the carboxylic acid was suspended in dry dichloromethane (2 ml) and phosphorous pentachloride (0.23 mmol) was added. The mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure and the residue was treated twice with benzene, which was removed under reduced pressure. The residue was newly dissolved in 2 ml of dry dichloromethane, and dry hydrazine (0.18 mmol) was added. The solution was stirred at room temperature under an argon atmosphere for 10 min. It was then washed with water and extracted with dichloromethane. The organic layer was dried and evaporated to give a solid residue which was then purified by crystallisation from dichloromethane–hexane, affording **2** (51%); mp 188–190°C, ν_{max}: 3322, 3260, 1638, 1549, 1190 and 1123; ^1H (DMSO-d_6): δ 9.82, 9.76, 8.50 (NH), 8.52 (d, J=1.6 Hz, 1H), 8.35 (d, J=1.6 Hz, 1H), 7.64 (d, J=1.6 Hz, 1H), 7.56 (d, J=1.6 Hz, 1H), 6.83 (s,

1H), 6.61 (s, 1H), 3.20 (t, *J*=5.8 Hz, 2H), 1.2–0.7 (m, 9H), 1.34 (s, 9H), 1.31 (s, 9H); *m/z* 674 $[M+1]^+$. Anal. calcd for $C_{37}H_{47}N_5O_7$: C, 65.95; H, 7.03; N, 10.39. Found: C, 65.83; H, 7.20; N, 10.17%.

3.2.5. 6-*tert*-Butyl-8-(3-{6-*tert*-butyl-2-[*N*'-(4-toluen-sulfonyl)-hydrazinecarbonyl]-4-oxo-(*4H*)-chromen-8-yl}-ureide)-oxo-(*4H*)-chromen-2-(2-ethylhexyl)-carboxamide (3). This compound was prepared in an identical way to compound **2**, except that 4-toluen-sulfonylhydrazine (0.18 mmol) was used. The solid residue obtained was purified by crystallisation from dichloromethane–hexane to afford **3** (68%), as a pale yellow solid. Mp 186–187°C, ν_{max}: 3356, 3260, 3084, 1736, 1642, 1553, 1279, 1169, 874 and 816; ^{1}H NMR (DMSO-d_6): δ 10.2 (s, 1H, $NHSO_2$), 9.74 (sbr, 1H, NH), 9.52 (s, 2H, NHCONH), 8.83 (m, 1H, $NHCH_2$), 8.53 (d, *J*=2.6 Hz, 1H), 8.43 (d, *J*=2.6 Hz, 1H), 7.72 (d, *J*=8.0 Hz, 2H), 7.71 (d, *J*=2.6 Hz, 1H), 7.64 (d, *J*=2.6 Hz, 1H), 7.27 (d, *J*=8.0 Hz, 2H), 6.85 (s, 1H), 6.72 (s, 1H), 3.21 (t, *J*=5.8 Hz, 2H), 2.22 (s, 3H), 1.4–1.0 (m, 9H), 1.34 (s, 9H), 1.30 (s, 9H), 1.4–1.1 (m, 6H); *m/z* 828 $[M+1]^+$. Anal. calcd for $C_{44}H_{52}N_4O_9S$: C, 65.01; H, 6.45; N, 6.84. Found: C, 64.88; H, 6.32; N, 6.66%.

3.2.6. 6-*tert*-Butyl-8-(3-{6-*tert*-butyl-2-[*N'*-(2,4-dinitro phenyl)-hydrazinecarbonyl]-4-oxo-(*4H*)-chromen-8-yl}-ureide)-oxo-(*4H*)-chromen-2-(2-ethylhexyl)-carboxamide (4). This compound was prepared in a similar way to compound **2**, except that 2,4-dinitrophenylhydrazine (0.18 mmol) was used. The solid residue obtained was purified by crystallisation from dichloromethane to afford **4** (65%). Mp 209–210°C, ν_{max}: 3349, 1717, 1684, 1653, 1616, 1541, 1458, 1339 and 833; ^{1}H NMR (DMSO-d_6): δ 9.40, 9.35, 8.73 (NH), 8.87 (d, *J*=2.2 Hz, 1H), 8.61 (d, *J*=2.4 Hz, 1H), 8.50 (d, *J*=2.4 Hz, 1H), 8.23 (dd, *J*=8.0, 2.2 Hz, 1H), 7.70 (d, *J*=2.4 Hz, 1H), 7.67 (d, *J*=2.4 Hz, 1H), 7.51 (d, *J*=8.0 Hz, 1H), 7.03 (1H, s), 6.81 (s, 1H), 3.04 (m, 2H), 1.7–1.0 (m, 9H), 1.35 (s, 9H), 1.33 (s, 9H), 0.9–0.6 (m, 6H); *m/z* 840 $[M+1]^+$. Anal. calcd for $C_{43}H_{49}N_7O_{11}$: C, 61.49; H, 5.88; N, 11.67%. Found: C, 61.36; H, 5.69; N, 11.48%.

3.2.7. 6-*tert*-Butyl-8-{3-[6-*tert*-butyl-2-(2-ethylhexylcarbamoyl)-4-oxo-(*4H*)-chromen-8-yl]-ureide}-4-oxo-(*4H*)-chromen-2-hydroxamic acid (5). This compound was prepared in the same way as compound **2**, but hydroxylamine hydrochloride (0.15 mmol) and an equimolecular quantity of pyridine (0.15 mmol) were added to bis-chromenylurea acid chloride. After 12 h at room temperature, the solvent was removed under reduced pressure, and the crude product taken up in ethyl acetate and washed with 2 M HCl. Crystallisation from chloroform afforded **5** (49%). Mp 150°C, ν_{max}: 3331, 2961, 1721, 1635, 1586, 1545, 1470, 1385, 1278, 1250, 1187, 1041, 1004, 914, 873, 647, 525 and 468; ^{1}H NMR (DMSO-d_6): δ 11.7 (s, 1H, OH), 9.84 (s, 1H, NH), 9.29 (s, 2H, NHCONH), 8.70 (d, *J*=2.2 Hz, 1H), 8.64 (t, *J*=5.4 Hz, 1H, $NHCH_2$), 8.48 (d, *J*=1.6 Hz, 1H), 7.71 (d, *J*=2.2 Hz, 1H), 7.64 (d, *J*=1.6 Hz, 1H), 6.87 (s, 1H), 6.83 (s, 1H), 3.24 (t, *J*=5.9 Hz, 2H), 1.5–1.1 (m, 9H), 1.35 (s, 9H), 1.33 (s, 9H), 0.9–0.6 (m, 6H); *m/z* 675 $[M+1]^+$. Anal. calcd for $C_{37}H_{46}N_4O_8$: C, 65.86; H, 6.87; N, 8.30. Found: C, 65.73; H, 6.95; N, 8.15%.

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References

1. (a) Bianchi, A., Bowman-James, K., Garcia-España, E., Eds. *Supramolecular Chemistry of Anions*; Wiley-VCH: New York, 1997. (b) Atwood, J. L., Davies, J. E. D., Vögtle, F., Eds. *Comprehensive Supramolecular Chemistry*; Elsevier: Exeter, 1996.
2. (a) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609–1646. (b) Sebo, L.; Schweizer, B.; Diederich, F. *Helv. Chim. Acta* **2000**, *89*, 80–92. (c) Seel, C.; Galan, A.; Mendoza, J. de *Top. Curr. Chem.* **1995**, *175*, 101.
3. (a) Antonisse, M. M. G.; Reinhoudt, D. N. *Chem. Commun.* **1998**, 443–448 (and references therein). (b) Werner, F.; Schneider, H-J. *Helv. Chim. Acta* **2000**, *83*, 465–478. (c) Kubo, Y. *Synlett* **1999**, *2*, 161–174. (d) Pelizzi, N.; Casnati, A.; Friggeri, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1307–1310.
4. (a) Raposo, C.; Crego, M.; Mussons, M. L.; Caballero, M. C.; Morán, J. R. *Tetrahedron Lett.* **1994**, *35*, 3409–3411. (b) de la Torre, M. F.; González, S.; Campos, E. G.; Mussons, M. L.; Morán, J. R.; Caballero, M. C. *Tetrahedron Lett.* **1997**, *38*, 8591–8594. (c) Tejeda, A.; Oliva, A. I.; Simon, L.; Grande, M.; Caballero, M. C.; Morán, J. R. *Tetrahedron Lett.* **2000**, *41*, 4563–4566.
5. Taylor, R.; Kennard, O. *Acc. Chem. Res.* **1984**, *17*, 320–326.
6. (a) Barlett, P. A.; Marlowe, C. K. *Science* **1987**, *235*, 569–571. (b) Kirby, A. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 707–724. (c) Murakami, Y.; Kikuchi, J.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721–758.
7. Raposo, C.; Pérez, N.; Almaraz, M.; Mussons, M. L.; Caballero, M. C.; Morán, J. R. *Tetrahedron Lett.* **1995**, *36*, 3255–3258.
8. Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 3910–3915.
9. Lumbroso, H.; Barasin, J. *Bull. Soc. Chim. Fr.* **1964**, 3190–3196.
10. Fieser, L. F.; Fieser, M. In *Reagents for Organic Synthesis*, Wiley: New York, 1967; pp 441–442.
11. Cohen, S. G.; Nicholson, J. *J. Org. Chem.* **1965**, *30*, 1162–1168.
12. Bauer, L.; Exner, O. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 376–384.
13. Molecular Modeling Program: CERIUS^2 from Molecular Simulations, Force field: Dreiding 2.21.
14. Almaraz, M.; Martin, M.; Hernandez, J. V.; Caballero, M. C.; Moran, J. R. *Tetrahedron Lett.* **1998**, *39*, 1811–1814.
15. Shan, S.; Loh, S.; Herschlag, D. *Science* **1996**, *272*, 97–101.
16. Stryer, L. *Biochemistry*, 4th ed.; Freeman: New York, 1995.
17. Sawada, M.; Shizuma, M.; Takai, Y.; Yamada, H.; Kaneda, T.; Hanafusa, T. *J. Am. Chem. Soc.* **1992**, *114*, 4405–4406.