Xanthone Receptors as Oxyanion-Hole Mimics in Artificial Enzymes

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Dedicated to Professor *Rolf Huisgen* on the occasion of his 85th birthday

Different xanthone-based receptors (**2**–**10**) for lactones and lactams have been prepared, and the feasibility of these compounds to mimic the known enzymatic 'oxyanion-hole' structure is discussed. The self-association of the receptors was found to pose a serious drawback for complex formation. X-Ray crystal structures of receptor dimers allowed us to understand the reasons for their self-association and to improve the design of the catalysts. The catalytic activity of the receptors has been tested towards the nucleophilic addition of pyrrolidine to unsaturated lactones. Since the resulting complexes were very weak in organic solvents, new receptors were developed for lactams, which showed better stabilities, and their catalytic activities were studied.

Introduction. – H-Bonds play an important role in enzymatic catalysis [1]. Over the last decade, the so-called *oxyanion hole* has frequently been found as a structural motif in hydrolase-like enzymes [2]. The oxyanion hole consists of two or more H-bond donors (usually two peptide NH groups from the backbone of the enzyme) oriented towards an O-atom in the substrate (usually a C=O group), which accumulates electron density as the enzymatic reaction takes place. The increased stability of the H-bonds in the transition state reduces the energy barrier of the reaction, enhancing catalysis. In the search for organic receptors able to mimic the behavior of enzymes, it would be of great interest to design structures that could play the role of the oxyanion hole.

Enzymes such as proteases, lipases, esterases, dehalogenases, peroxidases, and epoxide hydrolases display the oxyanion-hole structure, and it has been suggested that this structural similarity may imply that these enzymes may have had a common ancestor [2]. Enoyl–CoA hydratase belongs to this family of enzymes. *Bahnson et al.* [3] described the X-ray structure of rat liver enoyl–CoA hydratase bound to 4-(*N*,*N*-dimethylamino)cinnamoyl–CoA (PDB entry 1EY3). Selected amino acids at the active site and the substrate are shown in *Fig. 1* (left). This author also discussed the important role of the oxyanion hole in catalysis in another article [4].

The structure of the xanthone receptor **1** is known from an X-ray study (*vide infra*). In *Fig. 1* (right), we have overlaid this structure with that of the enoyl–CoA hydratase active site. Besides the structural similarity, aromatic amides are expected to give stronger H-bonds than aliphatic ones, which should increase the catalytic activity. Nevertheless, synthetic availability, stability under the reaction conditions, solubility

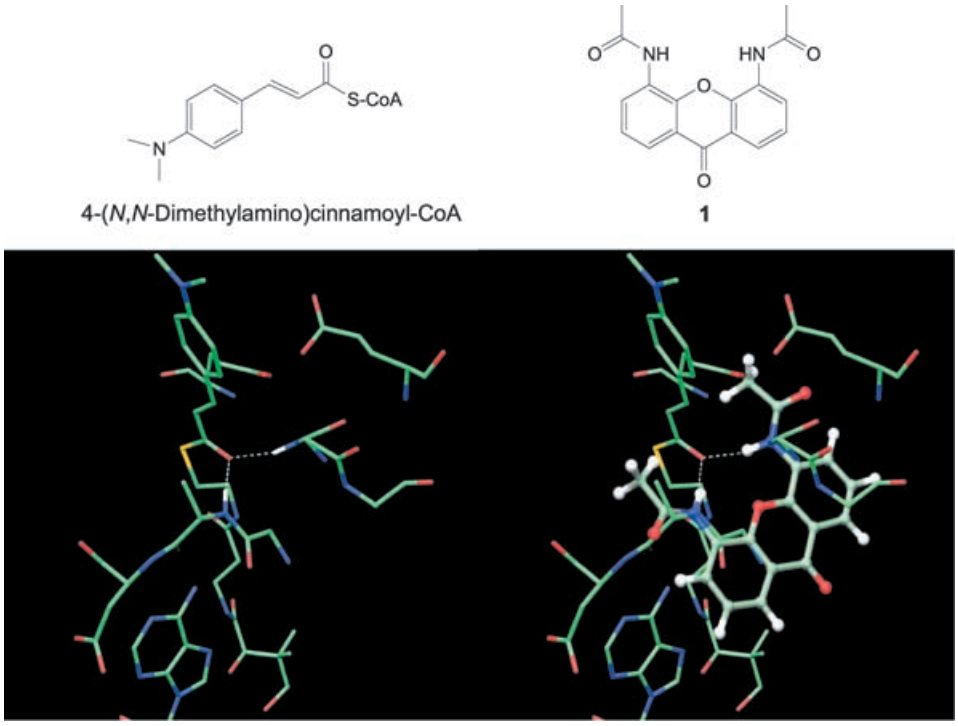


Fig. 1. *Structure of the active center of the enoyl–CoA hydratase complex*. On the right, the structure is overlaid with the xanthone-based receptor **1**.

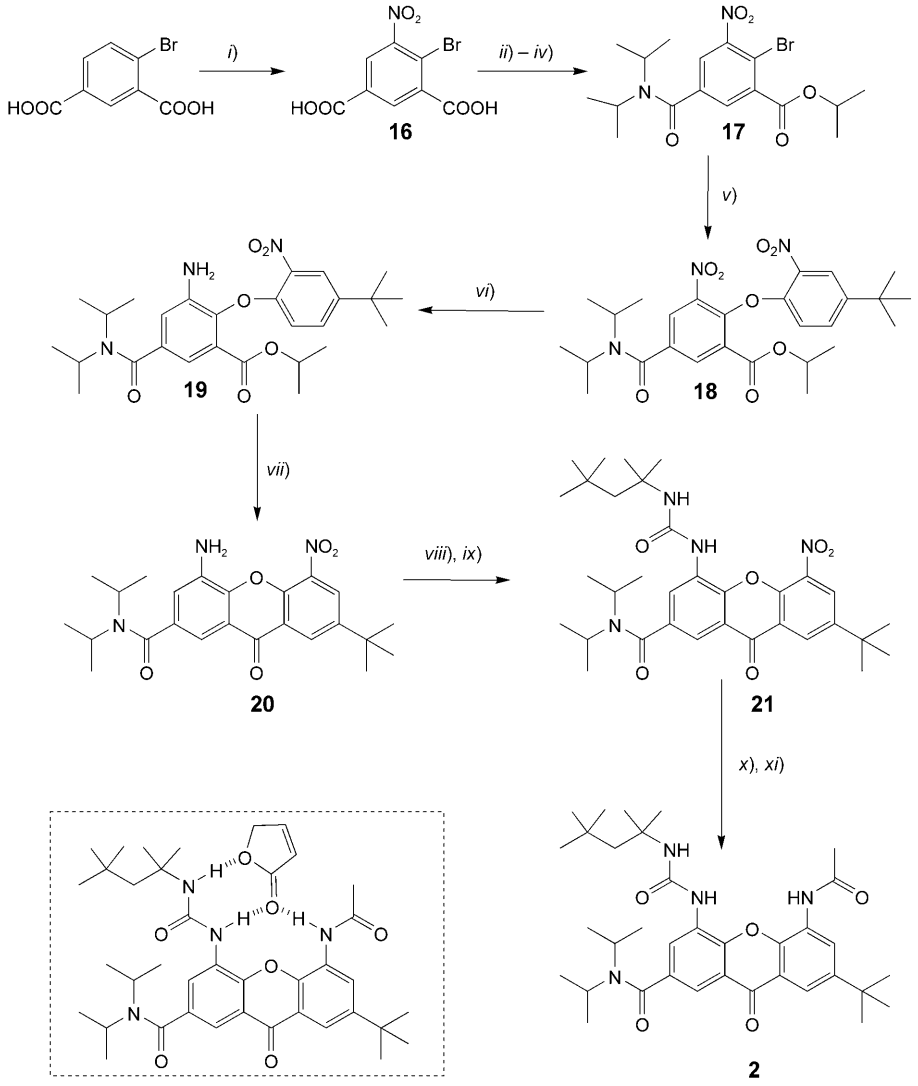
problems, and receptor self-association all need to be considered, as we attempt to do in this paper.

Results and Discussion. – 1. *Preparation and Properties of Xanthone Receptors for Lactones.* In a recent paper [5], we described the synthesis of a receptor suitable for association of amino acids. Receptor **2** is based on the same skeleton, but its synthesis (*Scheme 1*) has been modified to include a diisopropylamide group. Bulky groups in the non H-bonding region of the receptor are desirable to prevent solubility problems due to π-stacking. The urea functional group provides a third H-bond in the association of lactones.

^{1}H-NMR spectra of receptor **2** in $CDCl_3$ showed broad signals, but the addition of CD_3OD or $(D_6)DMSO$ led to sharp signals (*Fig. 2*). This effect indicates that **2** forms aggregates in $CDCl_3$ solution that are broken in the presence of more-polar solvents.

After slow evaporation of a CH_2Cl_2/undecane solution of **2**, it was possible to obtain crystals suitable for X-ray-diffraction analysis. The crystalline structure of **2** shows that this compound readily self-associates, forming dimers (*Fig. 3*). This aggregate is stabilized by two intramolecular H-bonds between the urea and the O-atom of the acetamide, and an intermolecular H-bond between the NH of the acetamide and the C=O group of the diisopropylamide. The structure is also stabilized by π-stacking and the anti-parallel orientation of the molecular dipoles.

Scheme 1. *Synthesis of Receptor* **2**, *and Its Binding Mode with Furan-2(5*H*)-one*



i) HNO_3, H_2SO_4. *ii*) PCl_5, $SOCl_2$. *iii*) $(i\text{-}Pr)_2NH$ (1 equiv.), Et_3N, CCl_4, $-30°$. *iv*) i-PrOH (excess). *v*) Potassium 4-*tert*-butyl-2-nitro-phenolate, DMF. *vi*) Fe, AcOH, MeOH. *vii*) $MeSO_3H$, P_2O_5. *viii*) $Cl_2C{=}O$ in toluene, CH_2Cl_2. *ix*) 2,4,4-Trimethylpentan-2-amine (excess), toluene. *x*) H_2, Pd/C, AcOH. *xi*) AcCl, THF.

Owing to its high value, dilution experiments did not provide an assessment of the dimerization constant of **2**. The stability of this dimer is a severe drawback for association of neutral molecules. A 25 mM solution of **2** was prepared in $CDCl_3$, and an absolute ^{1}H-NMR titration [6] with butyrolactone (=dihydrofuran-2(3*H*)-one) as guest was performed. Although some ^{1}H-NMR signals were deshielded due to complex

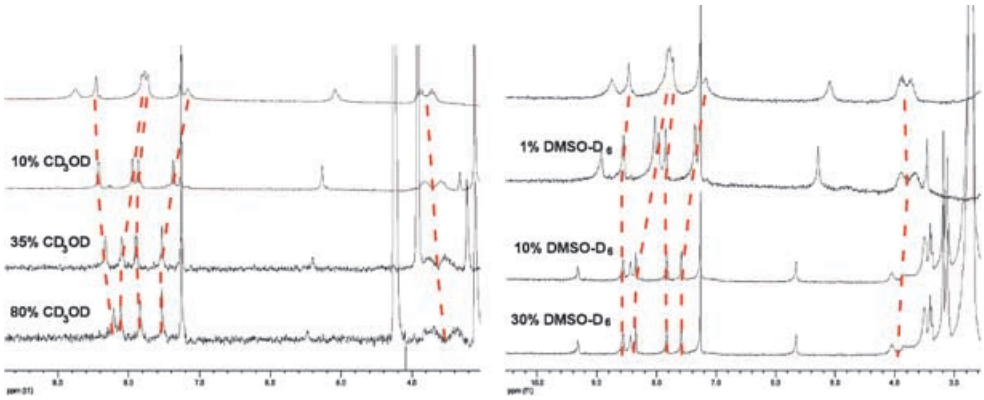


Fig. 2. *^{1}H-NMR Spectra of* **2** *in $CDCl_3$* (top), *and in mixtures of $CDCl_3$/CD_3OD* (left) vs. *$CDCl_3$/(D_6)DMSO* (right)

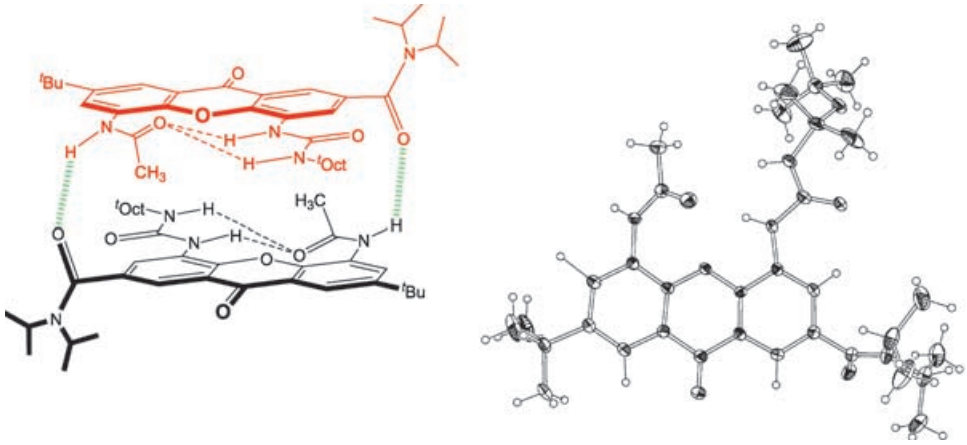
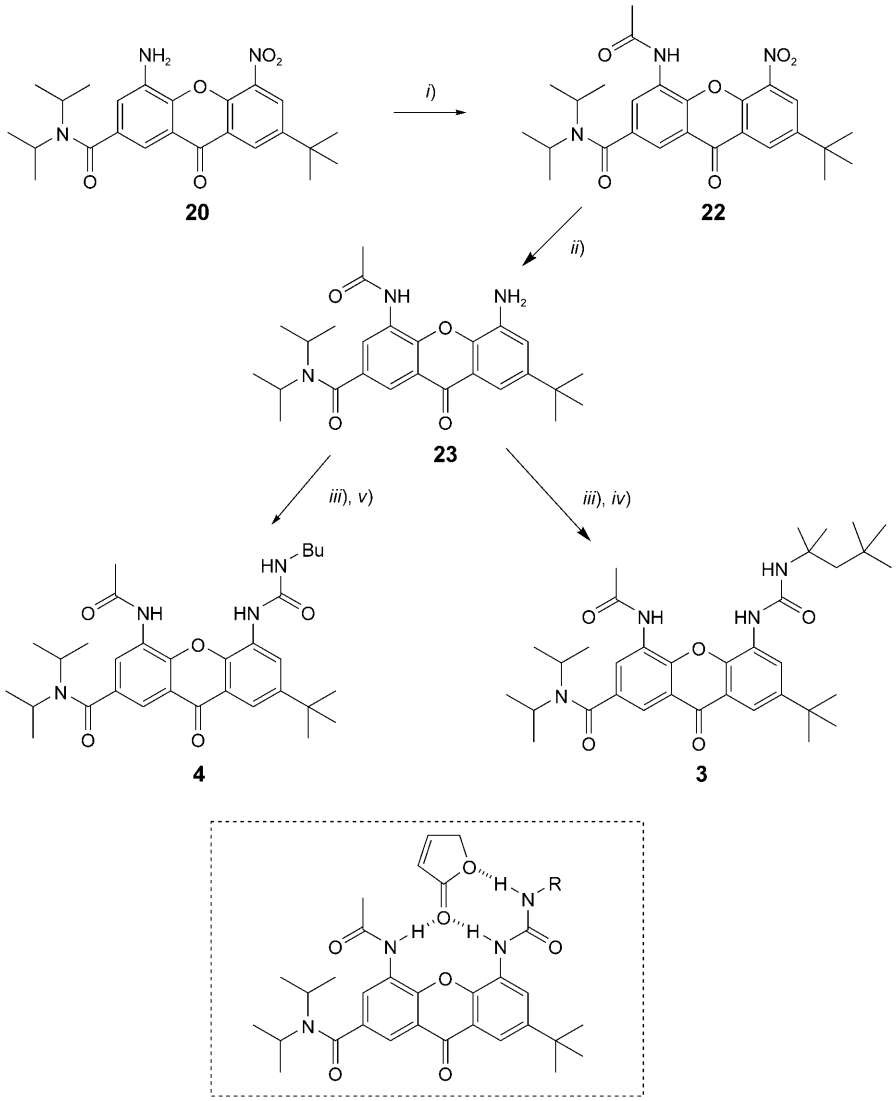


Fig. 3. *Schematic representation of the dimeric structure of* **2** *in the solid state* (left), *and X-ray crystal structure of the monomer* (thermal ellipsoids; right)

formation as the guest was added, we were unable to reproduce the conventional saturation of the ^{1}H-NMR shifts. Instead, deshielding continued after the addition of more than 35 equiv. of guest, indicating that some complex had been formed, but that the association constant was too small to be determined by this method.

A slight modification of the synthetic route yielded xanthone **3** (*Scheme 2*), in which the positions of the urea and acetamido groups are exchanged; this should prevent the formation of an aggregate similar to dimeric **2**. Nevertheless, broad ^{1}H-NMR signals were observed again, and the addition of CD_3OD or (D_6)DMSO had a effect similar to that seen for **2**. It was impossible to obtain suitable crystals of **3**, but this was possible for receptor **4** with a similar structure (*Fig. 4*).

Scheme 2. *Synthesis of Receptors* **3** *and* **4**, *and Their Binding Mode with Furan-2(5*H*)-one*



i) AcCl, THF. *ii*) H_2, Pd/C, AcOH. *iii*) $Cl_2C{=}O$ in toluene, CH_2Cl_2. *iv*) 2,4,4-trimethylpentan-2-amine (excess), toluene. *v*) $BuNH_2$ (excess), toluene.

Again, dimer formation was observed, with the C=O O-atom of the diisopropyl group of **4** fitting into the cleft of another molecule. One of every two molecules had the acetamide group twisted to establish a H-bond with the urea O-atom of a molecule belonging to a different dimer. In solution, the acetamide group is probably oriented towards the O-atom of the diisopropylamide, so that this dimer is stabilized by six H-bonds.

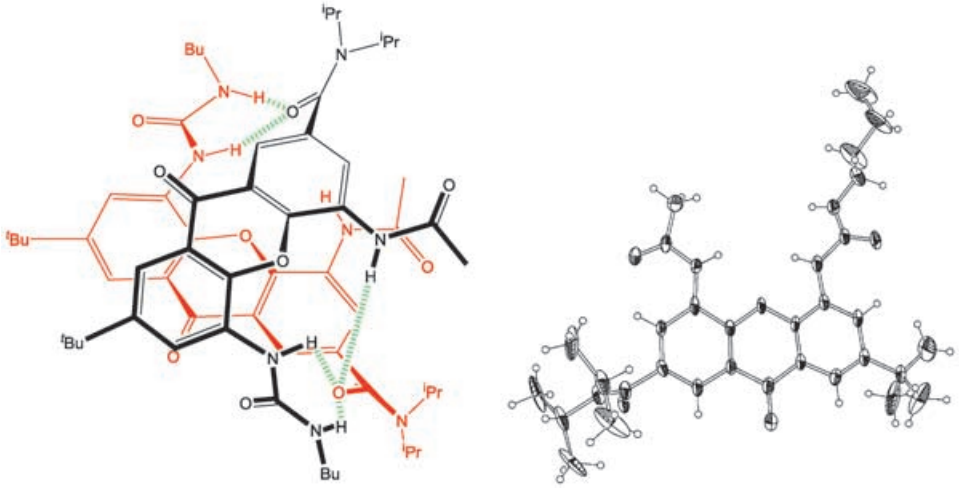


Fig. 4. *Schematic representation of the dimeric structure of* **4** *in the solid state* (left), *and X-ray crystal structure of the monomer* (thermal ellipsoids; right)

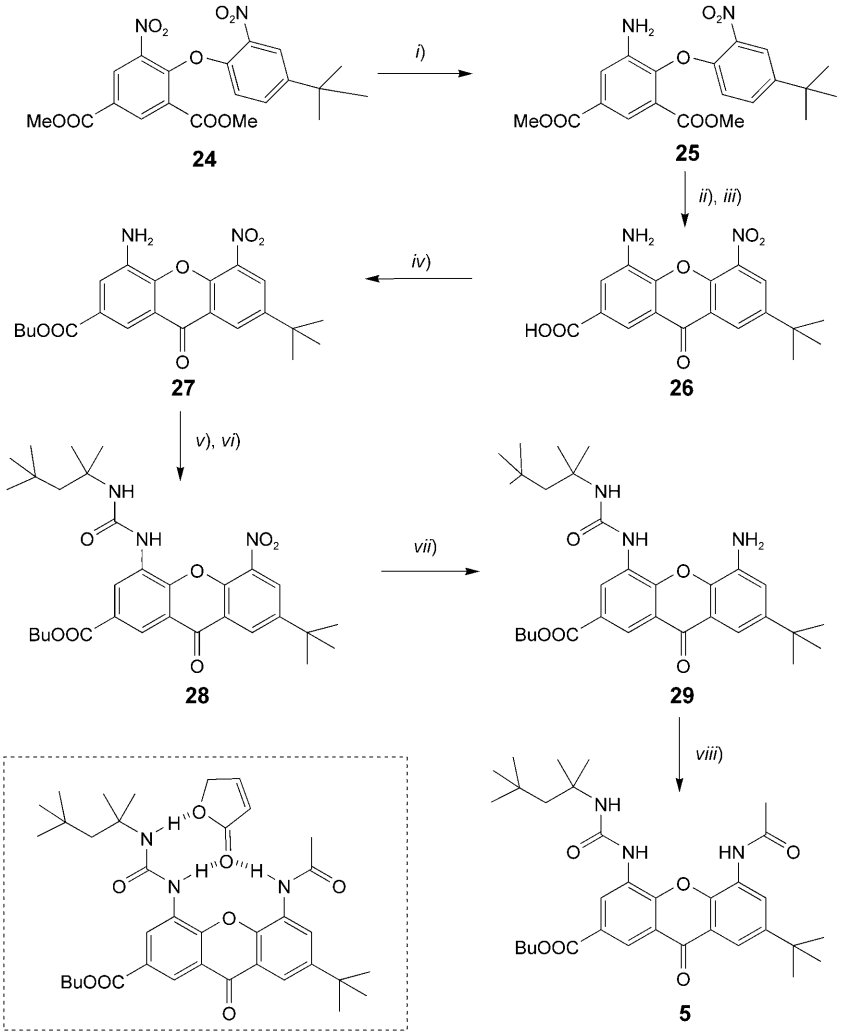
Since the diisopropylamide was involved in both dimer structures, this group was replaced with a butyl ester in receptor **5**. The planar structure of the butyl ester should prevent the establishment of intermolecular H-bonds, since, with this geometry, it should be unable to fit into the cleft of another molecule. The synthesis of this receptor is shown in *Scheme 3*.

Although xanthone **5** is considerably less soluble in chloroform than receptors **2** and **3**, ^{1}H-NMR analysis in $CDCl_3$ revealed less aggregation than for the previous receptors. Moreover, a value of 11 l/mol for the association constant with butyrolactone was calculated by means of a titration experiment.

Slow evaporation of a MeOH/benzene solution of **5** yielded crystals suitable for structural determination by X-ray diffraction (*Fig. 5*). The structure is made of chains of monomers in which the O-atoms of acetamide groups fit into the cleft of another receptor. Two independent chains are packed, and no H-bond interaction is observed between them. The urea conformation is changed from *cis* (as in **2** and **4**) to the less-stable *trans*, probably due to higher packing densities.

In an attempt to study the ability of these receptors in catalysis as oxyanion-hole mimics, we chose the *Michael* addition of pyrrolidine to an unsaturated lactone, furan-2(5*H*)-one. This reaction is expected to proceed *via* a transition state with high electron density on the C=O O-atom and could be similar to the reaction catalyzed by enoyl–CoA hydratase. The experiments were carried out at 293 K at a concentration of pyrrolidine and lactone of 0.1M each. Finally, in the catalytic experiments, 5% of receptor was added. The resulting half-lives of the reactions are summarized in *Table 1*. The best catalytic activity was obtained with receptor **5**, which is easily rationalized by means of the higher association constant. Nevertheless, in our opinion, these small association constants do not allow better results, and the solubility of **5** was still a problem.

Scheme 3. *Synthesis of Receptor* **5**, *and Its Binding Mode with Furan-2(5*H*)-one*



i) Fe, AcOH, MeOH. *ii*) HBr. *iii*) P_2O_5, $MeSO_3H$. *iv*) $SOCl_2$ (cat.), BuOH. *v*) $Cl_2C{=}O$ in toluene, CH_2Cl_2. *vi*) 2,4,4-Trimethylpentan-2-amine (excess), toluene. *vii*) H_2, Pd/C, AcOH. *viii*) AcCl, THF.

2. *Preparation and Properties of Xanthone Receptors for Lactams.* Since self-association hinders complex formation with lactones, lactams were chosen as the guests. Amide C=O groups are better H-bond acceptors [7], and should, thus, show a higher affinity for the xanthone receptors. The structure of the receptor had to be modified to accommodate the lactam NH, and, hence, structure **6** was designed (*Scheme 4*). Receptors sharing the same skeleton have already been used for the complexation of carboxylic acids [8] and diketopiperazines [9], and high association constants were

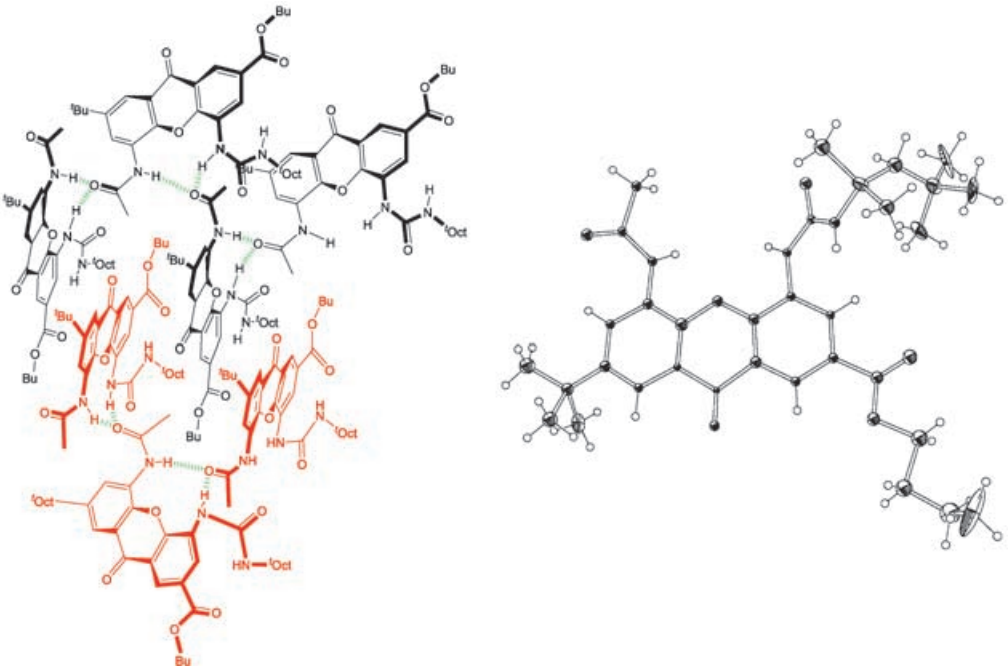


Fig. 5. *Schematic representation of the dimeric structure of* **5** *in the solid state* (left), *and X-ray crystal structure of the monomer* (thermal ellipsoids; right)

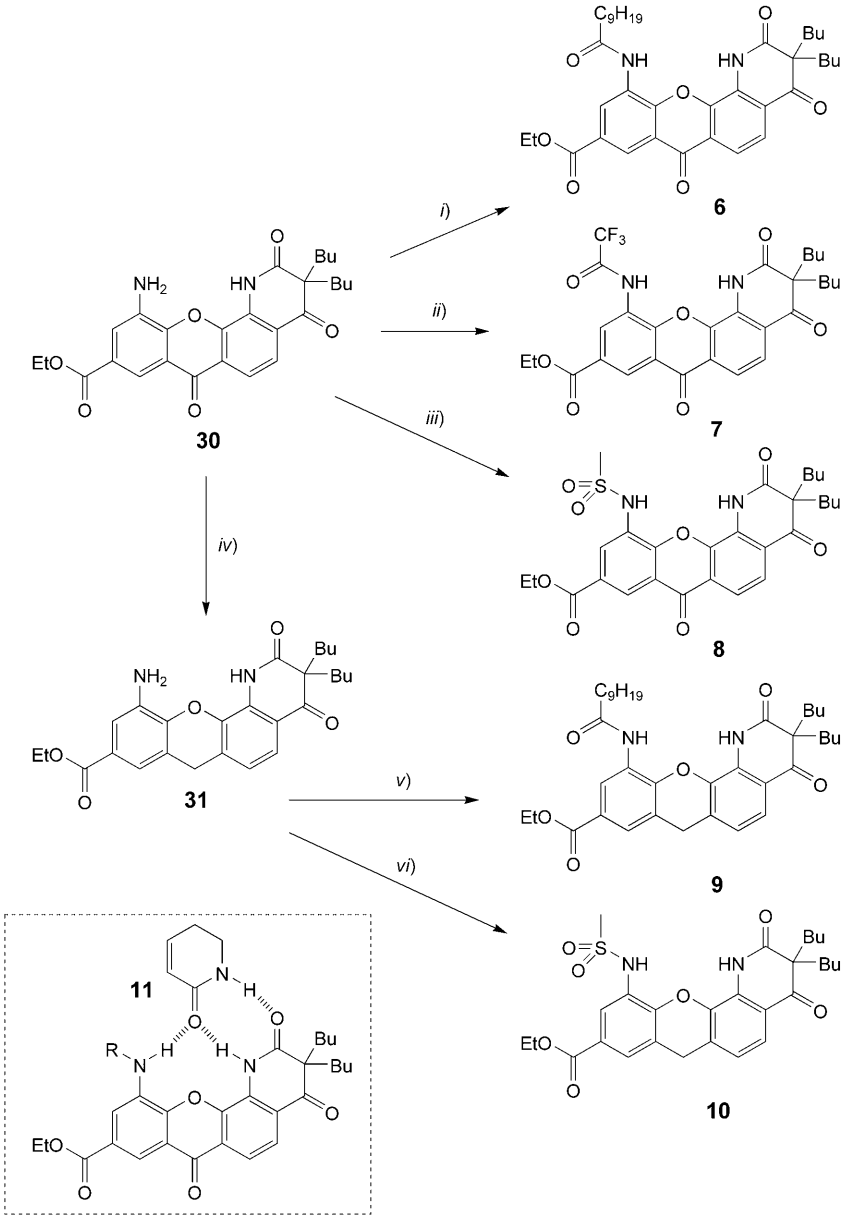
Table 1. *Half-Lives* ($t_{1/2}$) *of the* Michael *Addition Reaction between Pyrrolidine and Furan-2(5*H*)-one in the Presence of Different Receptors.* Conditions: solvent, $CDCl_3$; temperature, 298 K; receptor, 5 mol-%.

Receptor	$t_{1/2}$ [min]
None	305
2	133
3	243
5	54

obtained. Different *N*-substituents were introduced to study the effect of NH acidity on catalysis, and reduction of the C=O group would allow the preparation of xanthene receptors with less-acidic NH groups. The synthesis of these receptors (**6**–**10**) is shown in *Scheme 4*.

The lactam guest **11** (= 5,6-dihydropyridin-2(1*H*)-one) was prepared according to *Scheme 5*. *Wineman et al.* [10] have reported the synthesis of monobromide **12** by partial hydrogenation of dibromide **13**, but, instead, we used a more-suitable method with Ph_3P, followed by dithiocarbamate formation to **14** and then thermal elimination to **11**. The association constant of **6** with lactam **11** was determined in C_6D_6, monitoring

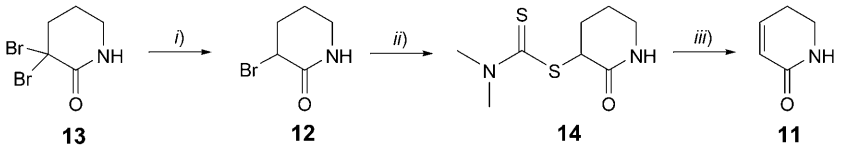
Scheme 4. *Synthesis of Receptors* **6**–**10**, *and Their Binding Mode with Lactam* **11**



i) Decanoyl chloride, THF. *ii*) Trifluoroacetyl chloride, THF. *iii*) $MeSO_2Cl$, THF. *iv*) Sn, EtOH. *v*) Decanoyl chloride, Et_3N, THF. *vi*) $MeSO_2Cl$, Et_3N, THF.

the deshielding of the H–C(10)[1]) ^{1}H-NMR signal of the host as the lactam was added. The value obtained (1.8×10^3 l/mol) was much higher than the low values obtained for the association of lactones. For receptors **7**–**10**, a competitive titration was performed to derive relative association constants with respect to **6**. The results are summarized in *Table 2*. As expected, less-acidic NH groups, and, therefore, less-stable H-bonds, correspond to lower association constants.

Scheme 5



i) Ph_3P, MeOH/H_2O 10:1. *ii*) $Me_2NC(S)S^-Me_2NH_2^+$. *iii*) 260°, 1 Torr.

Table 2. *Absolute* and *Relative* (rel) *Association Constants* K *for the Complexation of Lactam* **11** *by Different Receptors.* The *K* values of **7**–**10** were calculated from K_{rel} obtained by indirect titrations (see text). Conditions: solvent, C_6D_6; temperature, 298 K; ^{1}H-NMR titration (see text).

Receptor	*K* [l/mol]	K_{rel}
6	1800[a])	1.00
7	2700	1.5
8	9360	5.2
9	160	0.089
10	2880	1.6

[a]) Determined by direct ^{1}H-NMR titration.

The catalytic activity of the lactam receptors was also tested by *Michael* addition of pyrrolidine to the unsaturated lactam **11**. This reaction is considerably slower than the *Michael* addition of pyrrolidine to α,β-unsaturated lactones. Under the reaction conditions, pyrrolidine can be alkylated by $CHCl_3$ or CH_2Cl_2, yielding pyrrolidinium chloride, which may act as a general-acid catalyst. The presence of Cl^- may also block the receptor cleft, preventing its catalytic activity. Thus, we preferred to use C_6D_6 as solvent. To reduce the half-lives of the reaction, the pyrrolidine concentration was increased to 3.0M, and the lactam concentration was fixed at 0.80M. The temperature during the kinetic experiments was 293 K, and in the catalytic experiments, 5% of receptor was added. The half-lives obtained are summarized in *Table 3*. A plot of $t_{1/2}$ *vs.* relative association constant K_{rel} is shown in *Fig. 6*. In this plot, a clear correlation is observed between the association constants in benzene and the catalytic activity of the receptors. Nevertheless, there seems to be a saturation effect that does not allow the catalytic activities to be improved simply by increasing the association constants.

[1]) Arbitrary numbering, see *Fig. 7*. For systematic names, see *Exper. Part.*

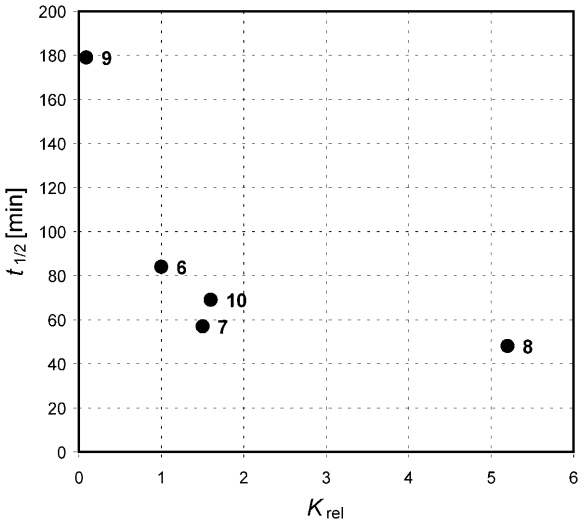


Fig. 6. *Plot of half-lives of the* Michael *addition between pyrrolidine and lactam* **11** *in the presence of different receptors* vs. *relative association constants for the corresponding 1:1 complexes between the receptors and* **11**. Conditions: solvent, C_6D_6, temperature, 293 K; 5 mol-% of receptor.

Table 3. *Half-Lives* ($t_{1/2}$) *of the Addition Reaction between Pyrrolidine and Lactam* **11** *in the Presence of Different Receptors.* Conditions: solvent, C_6D_6; temperature, 293 K; 5 mol-% receptor; ^{1}H-NMR titration (see text).

Receptor	$t_{1/2}$ [min]
None	305
6	84
7	57
8	48
9	179
10	69

This saturation effect could be rationalized by taking into account that the different association constants depend on the acidity of the NH groups. Pyrrolidine is basic and a good H-bond acceptor. In the competition between pyrrolidine and the substrate, a receptor with acidic NH groups should favor the association of pyrrolidine, since H-bonds between acceptors and donors with similar pK_a values are known to be very strong [11].

To study the influence of pyrrolidine on the association constants, a new experiment was performed. Successive portions of pyrrolidine were added to a C_6D_6 solution of the complexes of receptors **6**, **8**, and **10** with lactam **11**. The ^{1}H-NMR spectra revealed shifts in the receptor signals that could be attributed to the breakage of the lactam complexes (*Fig. 7*). It may be seen that the receptor with the most-acidic NH groups shows the greatest sensitivity to the addition of pyrrolidine. We, therefore, conclude that the receptor H-bond donor should not be too acidic.

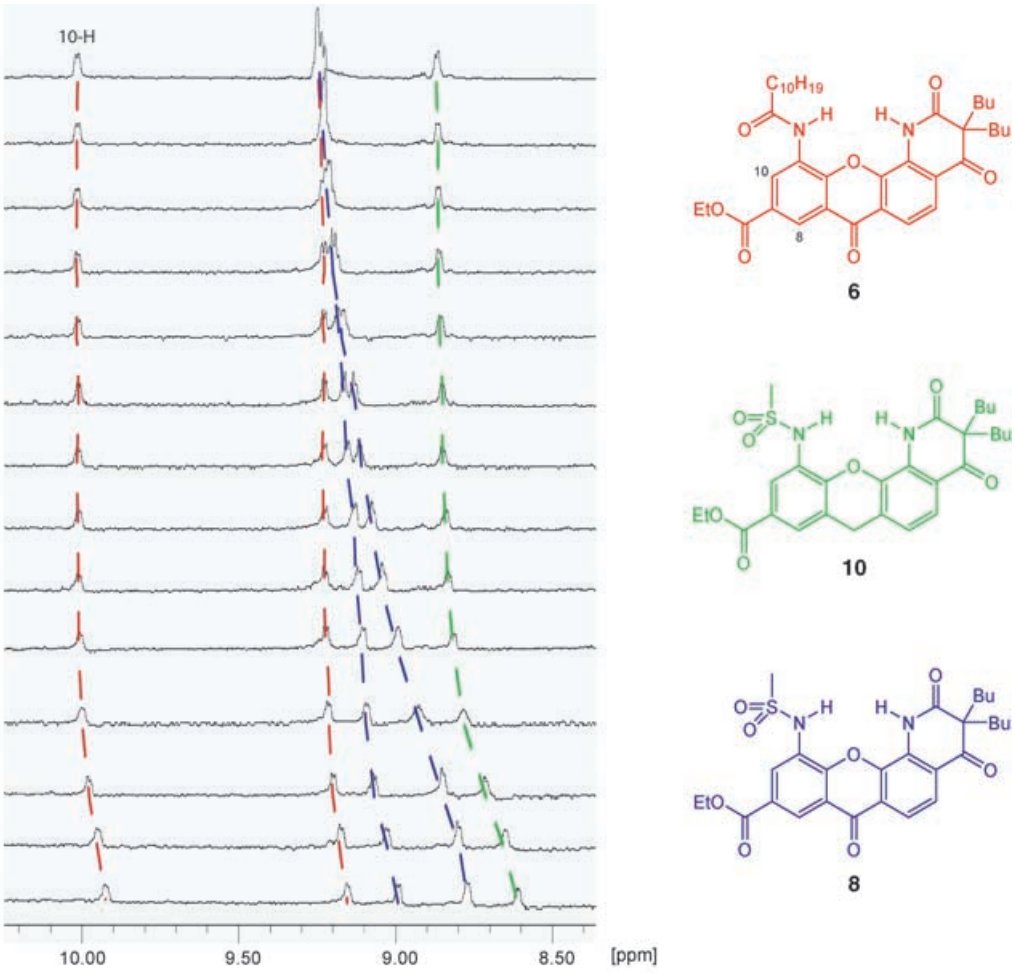


Fig. 7. *Addition of increasing amounts of complex-breaking pyrrolidine in an ^{1}H-NMR titration of the complexes* **6**, **8**, *and* **10** *with the guest* **11**. The chemical shifts of H–C(10) and H–C(8) (trivial numbering) of the receptors were followed upon addition of pyrrolidine to the complexes. Conditions: solvent, C_6D_6, temperature, 298 K.

Since it is clear that pyrrolidine competes with the lactam for receptor H-bonds, it is very important to estimate the actual association constant under the reaction conditions. An attempt to perform an ^{1}H-NMR titration in 3M pyrrolidine solution failed, because it was very difficult to follow the low degree of shielding of the receptor signals under these conditions. Since it was not possible to carry out direct measurement of the association constant, a different guest, **15**, with a similar association constant was used. The advantage of 2-[(2-ethylhexyl)oxy]naphthalene-1-carboxamide (**15**; see *Fig. 8*) is its strong shielding of the H–C(10) receptor ^{1}H-NMR signal[1]) in the complex, which makes titrations specially easy. Based on *CPK* models, this large shift probably arises since H–C(10) lies in the anisotropic shielding cone of the guest

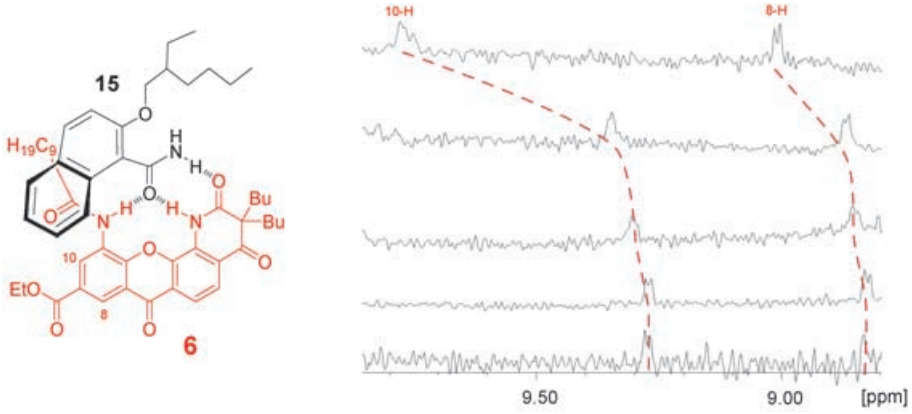


Fig. 8. *Complex between receptor* **6** *and guest* **15**, *and corresponding* ^{1}*H-NMR-titration signals upon addition of increasing amounts of guest to a* C_6D_6 *soln. of the receptor at 298 K*

naphthalene ring in the complex (*Fig. 8*). The association constant under the conditions applied was found to be 11 l/mol.

A competitive titration with receptor **6** in C_6D_6 afforded an association constant 3.85-fold higher for **11** than for **15**. Since the presence of pyrrolidine will probably reduce this ratio, we evaluated the association constant of the lactam under the reaction conditions to lies somewhere between 11 and 40 l/mol. This range ensures that most (90%) of the receptor is complexed under the reaction conditions.

The skeleton of xanthone **6** is, in our opinion, a good choice for the design of artificial enzymes mimicking an oxyanion hole. As in natural enzymes, where the oxyanion hole is only one part of the active site, our skeleton must be completed with other active groups able to collaborate in the stabilization of the transition state. In further work, we hope to include this kind of catalytic group to improve the catalytic activity of our receptors, and to obtain asymmetric induction in the addition products.

Experimental Part

1. *General.* THF was distilled from Na/benzophenone. Melting points (m.p.) were measured on a *Stuart Scientific SMP3* device. IR Spectra were recorded on a *BOMEM MB-100 FT-IR* spectrometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra were acquired on *Bruker Avance DRX-400* (400/100 MHz) or *Varian 200 Mercury VX 2000* (200/50 MHz) spectrometers; δ in ppm, J in Hz. Mass spectra were recorded on a *Waters ZQ4000* quadrupole spectrometer, with positive electrospray ionization (3.5 kV). For X-ray crystallographic data, see *Sect. 8* and *Table 4*.

2. *Synthesis of Receptor* **2**. 2.1. *4-Bromo-5-nitroisophthalic Acid* (**16**). 4-Bromoisophthalic acid (100 g, 410 mmol) was dissolved in 98% H_2SO_4 (2 l) and heated to 100°. To this soln., fuming HNO_3 (42 ml, 1.013 mol) was slowly added. After 30 min, the soln. was added to H_2O, and colorless crystals of compound **16** (100 g, 84%) were filtered off. M.p. 124–126°. IR: 3441–3256, 1732, 1640, 1597, 1537, 1262, 1192, 1165, 1140, 1098, 1038. ^{1}H-NMR ($CDCl_3$): 8.44 (*d*, J = 1.9, 1 H); 8.33 (*d*, J = 1.9, 1 H). ^{13}C-NMR ($CDCl_3$): 164.6 (C); 163.4 (C); 152.1 (C); 136.2 (C); 133.2 (C); 130.6 (C); 126.9 (CH); 117.6 (CH). ESI-MS: 312 ($[M+Na]^+$), 290 ($[M+H]^+$). Anal. calc. for $C_8H_4BrNO_6$: C 33.13, H 1.39, N 4.83; found: C 33.35, H 1.26, N 4.83.

2.2. *Isopropyl 2-Bromo-5-[(diisopropylamino)carbonyl]-3-nitrobenzoate* (**17**). Compound **16** (100 g, 346 mmol) was dissolved in CH_2Cl_2 (400 ml), and PCl_5 (144 g, 692 mmol) was added with external cooling. Once the exothermic reaction was over, the solvent was evaporated under vacuum. The intermediary acid

dichloride was then dissolved in CCl_4 (500 ml), and a soln. of (i-Pr)$_2$NH (49 ml) and Et_3N (55 ml) in CCl_4 (500 ml) was added dropwise at 0° (ice bath). When the addition was complete, i-PrOH (150 ml) was added, the solvent was evaporated under vacuum, and the residue was washed with AcOEt and 4% aq. Na_2CO_3 soln. The residue was subjected to column chromatography (CC) on SiO_2 to afford **17** (112 g, 78%). M.p. 124–126°. IR: 3000, 1732, 1640, 1597, 1537, 1454, 1373, 1339, 1285, 1262, 1192, 1165, 1140, 1098, 1038, 936. ^{1}H-NMR ($CDCl_3$): 7.73 (*d*, *J* = 2.0, 1 H); 7.69 (*d*, *J* = 2.0, 1 H); 5.36–5.24 (*m*, 1 H); 3.72–3.54 (*m*, 2 H); 1.59 (*d*, *J* = 6.0, 6 H); 1.50–1.20 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$): 166.0 (C); 151.6 (C); 140.1 (C); 138.7 (C); 136.9 (C); 129.7 (CH); 123.6 (CH); 112.4 (C); 70.6 (CH); 62.9 (CH); 21.5 (Me); 20.4 (Me). ESI-MS: 437 ($[M+Na]^+$), 415 ($[M+H]^+$). Anal. calc. for $C_{17}H_{23}BrN_2O_5$: C 49.17, H 5.58, N 6.75; found: C 49.06, H 5.65, N 6.89.

2.3. *Isopropyl 2-(4-*tert*-Butyl-2-nitrophenoxy)-5-[(diisopropylamino)carbonyl]-3-nitrobenzoate* (**18**). Compound **17** (20.2 g, 48.8 mmol) and potassium 4-*tert*-butyl-2-nitrophenolate (13.6 g, 58.3 mmol) were suspended in DMF (20 ml), and then heated to 90° for 2 h. The mixture was poured over a 2% aq. NaOH soln. cooled externally with ice. Crystals were then filtered off to yield **18** (23.1 g, 90%). M.p. 149–151°. IR: 2926, 1709, 1638, 1530, 1493, 1462, 1408, 1377, 1337, 1279, 1208, 1150, 1105, 1038, 924. ^{1}H-NMR ($CDCl_3$): 8.15 (*d*, *J* = 1.8, 1 H); 8.09 (*d*, *J* = 1.8, 1 H); 8.01 (*d*, *J* = 2.1, 1 H); 7.43 (*dd*, *J* = 8.8, 2.1, 1 H); 6.54 (*d*, *J* = 8.8, 1 H); 5.02–4.86 (*m*, 1 H); 3.86–3.18 (*m*, 2 H); 1.55–1.15 (*m*, 12 H); 1.30 (*s*, 9 H); 0.98 (*d*, *J* = 6.0, 6 H). ^{13}C-NMR ($CDCl_3$): 166.4 (C); 162.2 (C); 149.2 (C); 146.3 (C); 145.4 (C); 144.3 (C); 138.4 (C); 137.0 (C); 133.7 (CH); 131.0 (CH); 128.8 (C); 126.6 (CH); 122.7 (CH); 115.3 (CH); 70.4 (CH); 62.4 (CH); 34.4 (C); 31.0 (Me); 21.0 (Me); 20.6 (Me). ESI-MS: 552 ($[M+Na]^+$). Anal. calc. for $C_{27}H_{35}N_3O_8$: C 61.23, H 6.66, N 7.93; found: C 61.11, H 6.52, N 7.98.

2.4. *Isopropyl 3-Amino-2-(4-*tert*-butyl-2-nitrophenoxy)-5-[(diisopropylamino)carbonyl]benzoate* (**19**). Compound **18** (20 g, 38 mmol) was dissolved in a mixture of MeOH (200 ml), AcOH (45 ml), and CH_2Cl_2 (50 ml). After the addition of Fe powder (60 g, 1.07 mol) under mechanical stirring, the mixture was warmed to 35° for 30 min. The excess Fe was filtered off, and the solvent was evaporated under vacuum. The resulting residue was dissolved in MeOH (100 ml), and this soln. was slowly poured over 2M aq. HCl soln. The resulting crystals were filtered off, dried, and percolated with SiO_2 to eliminate Fe salts. Yield of **19**: 13.9 g (74%). M.p. 154–156°. IR: 3443, 3335, 2922, 1703, 1620, 1591, 1532, 1462, 1377, 1312, 1269, 1208, 1155, 1101, 1042, 1001, 903. ^{1}H-NMR ($CDCl_3$): 7.82 (*d*, *J* = 2.0, 1 H); 7.35 (*dd*, *J* = 2.0, 8.9, 1 H); 7.14 (*d*, *J* = 1.2, 1 H); 6.93 (*d*, *J* = 1.2, 1 H); 6.58 (*d*, *J* = 8.9, 1 H); 5.08–4.98 (*m*, 1 H); 3.75–3.60 (*m*, 1 H); 3.51–3.47 (*m*, 1 H); 1.40–1.35 (*m*, 12 H); 1.42–1.20 (*m*, 9 H); 0.91 (*d*, *J* = 6.2, 6 H). ^{13}C-NMR ($CDCl_3$): 175.4 (C); 169.7 (C); 147.2 (C); 146.4 (C); 143.8 (C); 137.7 (C); 136.9 (C); 129.6 (CH); 128.8 (CH); 122.9 (C); 121.1 (C); 116.8 (CH); 114.7 (CH); 111.3 (CH); 76.9 (CH); 41.0 (CH); 35.1 (C); 31.1 (Me); 21.8 (Me); 20.6 (Me). ESI-MS: 538 ($[M+K]^+$), 522 ($[M+Na]^+$), 500 ($[M+H]^+$). Anal. calc. for $C_{27}H_{37}N_3O_6$: C 64.91, H 7.46, N 8.41; found: C 64.76, H 7.58, N 8.29.

2.5. *4-Amino-7-*tert*-butyl-*N,N*-diisopropyl-5-nitro-9-oxo-9*H*-xanthene-2-carboxamide* (**20**). P_2O_5 (2.0 g, 14.1 mmol) was added to $MeSO_3H$ (20 ml), and this mixture was stirred overnight. Compound **19** (10 g, 20 mmol) was then added, and the mixture was heated to 85° for 4 h. The soln. was added to cold H_2O with strong stirring, which resulted in crystals of **20** (8.34 g, 95%). M.p. 173–175°. IR: 3360, 2926, 1672, 1630, 1532, 1462, 1377, 1312, 1287, 1206, 1157, 1123, 1044. ^{1}H-NMR ($CDCl_3$): 8.63 (*d*, *J* = 2.2, 1 H); 8.53 (*d*, *J* = 2.2, 1 H); 7.56 (*d*, *J* = 1.9, 1 H); 7.15 (*d*, *J* = 1.9, 1 H); 3.91–3.45 (*m*, 2 H); 1.44 (*s*, 9 H); 1.63–1.13 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$): 169.3 (C); 163.9 (C); 148.5 (C); 145.1 (C); 141.3 (C); 138.6 (C); 138.3 (C); 136.8 (C); 130.8 (CH); 127.1 (C); 125.7 (C); 121.9 (CH); 117.1 (CH); 115.1 (CH); 38.6 (CH); 34.2 (C); 30.9 (Me); 21.0 (Me); 20.4 (Me). ESI-MS: 462 ($[M+Na]^+$), 440 ($[M+H]^+$). Anal. calc. for $C_{24}H_{29}N_3O_5$: C 65.59, H 6.65, N 9.56; found: C 65.38, H 6.53, N 9.69.

2.6. *7-*tert*-Butyl-*N,N*-diisopropyl-5-nitro-9-oxo-4-{[[(1,1,3,3-tetramethylbutyl)amino]carbonyl}amino)-9*H*-xanthene-2-carboxamide* (**21**). Compound **20** (5 g, 11.4 mmol) was dissolved in CH_2Cl_2 (50 ml). A 0.6M phosgene soln. in toluene (3.0 ml) was added, and the mixture was refluxed for 20 min. The solvent was evaporated under vacuum, and the residue was co-evaporated with toluene (30 ml). The dry residue was dissolved in toluene (20 ml), and this soln. was added to a toluene soln. (30 ml) of 2,4,4-trimethylpentan-2-amine ('*tert*-octylamine'; 3.0 g, 23.2 mmol) with magnetic stirring at r.t. Then, the solvent was evaporated, and the residue was washed with AcOEt and 2M aq. HCl soln. The crude product from the org. layer was recrystallized from MeOH/H_2O to afford **21** (6.35 g, 94%). M.p. 215–217°. IR: 3399, 3324, 2924, 1709, 1672, 1616, 1599, 1532, 1462, 1375, 1343, 1298, 1273, 1252, 1217, 1200, 1155, 1101, 1042. ^{1}H-NMR ($CDCl_3$): 8.42 (*d*, *J* = 2.5, 1 H); 8.13 (*d*, *J* = 1.5, 1 H); 8.02 (*d*, *J* = 2.5, 1 H); 7.13 (*d*, *J* = 1.5, 1 H); 3.95–3.81 (*m*, 1 H); 3.60–3.42 (*m*, 1 H); 1.79 (*s*, 2 H); 1.60 (*d*, *J* = 6.6, 6 H); 1.45 (*s*, 15 H); 1.11 (*d*, *J* = 6.6, 6 H); 1.04 (*s*, 9 H). ^{13}C-NMR ($CDCl_3$): 173.4 (C); 169.2 (C); 153.4 (C); 147.2 (C); 145.4 (C); 144.8 (C); 138.5 (C); 137.7 (C); 134.2 (C); 128.7 (CH); 128.1 (CH); 125.3 (CH); 121.7 (C); 119.1 (C); 113.3 (CH); 54.3 (C); 51.4 (CH_2); 34.9 (C); 31.5 (CH); 31.3 (Me);

30.9 (Me); 29.8 (Me); 20.6 (Me); 20.5 (C). ESI-MS: 617 ($[M+Na]^+$), 595 ($[M+H]^+$). Anal. calc. for $C_{33}H_{46}N_4O_6$: C 66.64, H 7.80, N 9.42; found: C 66.47, H 7.93, N 9.33.

2.7. *5-(Acetylamino)-7*-tert-*butyl*-N,N-*diisopropyl-9-oxo-4-({[(1,1,3,3-tetramethylbutyl)amino]carbonyl}-amino)-9*H-*xanthene-2-carboxamide* (**2**). Compound **21** (1.0 g, 1.68 mmol) was dissolved in AcOH (10 ml), and 10% Pd/C (0.1 g) was added. The mixture was hydrogenated overnight under a pressure of 4 atm of H_2. The catalyst was filtered off, and washed several times with AcOEt. After evaporation of the solvent, the residue was dissolved in anh. THF (5.0 ml), and AcCl (1.0 ml) was added. The acylation reaction was completed within 15 min at r.t. Then, the solvent and excess AcCl were evaporated, and the remaining solid was recrystallized from MeOH/H_2O to afford crystalline **2** (0.52 g, 97%). M.p. 173–175°. IR: 3360, 2926, 1672, 1630, 1532, 1462, 1377, 1312, 1287, 1206, 1157, 1123, 1044. ^{1}H-NMR ($CDCl_3$): 8.84 (*d*, *J* = 1.6, 1 H); 8.74 (*d*, *J* = 1.6, 1 H); 8.46 (*d*, *J* = 2.0, 1 H); 8.16 (*d*, *J* = 2.0, 1 H); 4.44–4.28 (*m*, 1 H); 4.09–3.92 (*m*, 1 H); 2.72 (*s*, 3 H); 2.23 (*s*, 2 H); 1.98–1.83 (*m*, 6 H); 1.86 (*s*, 6 H); 1.81 (*s*, 9 H); 1.67–1.33 (*m*, 6 H); 1.45 (*s*, 9 H). ^{13}C-NMR ($CDCl_3$): 175.0 (C); 172.1 (C); 169.0 (C); 153.3 (C); 147.5 (C); 145.1 (C); 144.2 (C); 132.6 (C); 129.6 (C); 126.6 (CH); 126.1 (CH); 121.7 (C); 120.7 (C); 120.3 (C); 118.0 (CH); 114.1 (CH); 54.4 (C); 51.7 (CH); 51.4 (CH_2); 46.1 (CH); 34.9 (C); 31.4 (Me); 31.2 (Me); 30.0 (Me); 24.2 (Me); 20.7 (Me); 20.4 (C). ESI-MS: 629 ($[M+Na]^+$), 607 ($[M+H]^+$). Anal. calc. for $C_{35}H_{50}N_4O_5$: C 69.28, H 8.31, N 9.23; found: C 69.02, H 8.55, N 9.42.

3. *Syntheses of Receptors* **3** *and* **4**. 3.1. *4-(Acetylamino)-7*-tert-*butyl*-N,N-*diisopropyl-5-nitro-9-oxo-9*H-*xanthene-2-carboxamide* (**22**). Compound **20** (1.0 g, 2.3 mmol) was dissolved in anh. THF (5.0 ml), and AcCl (1.0 ml) was added. The mixture was maintained at r.t. for 15 min. Then, the solvent and excess reagent were evaporated, and the residue was recrystallized from MeOH/H_2O to afford **22** (1.076 g, 98%). M.p. 260–262°. IR: 3397, 2934, 1705, 1672, 1626, 1572, 1537, 1462, 1418, 1377, 1327, 1294, 1277, 1209, 1157, 1105, 1092, 1044. ^{1}H-NMR ($CDCl_3$): 8.73 (*d*, *J* = 1.7, 1 H); 8.64 (*d*, *J* = 2.2, 1 H); 8.59 (*d*, *J* = 2.2, 1 H); 7.93 (*d*, *J* = 1.7, 1 H); 3.90–3.70 (*m*, 1 H); 3.66–3.45 (*m*, 1 H); 2.35 (*s*, 3 H); 1.59–1.40 (*m*, 6 H); 1.43 (*s*, 9 H); 1.23–1.11 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$): 174.5 (C); 169.3 (C); 168.9 (C); 147.8 (C); 146.0 (C); 145.1 (C); 137.6 (C); 135.5 (C); 129.7 (CH); 129.3 (CH); 128.2 (C); 123.8 (CH); 122.7 (C); 120.8 (C); 117.4 (CH); 51.4 (CH); 46.3 (CH); 35.3 (C); 31.2 (Me); 24.7 (Me); 20.7 (Me); 20.6 (Me). ESI-MS: 504 ($[M+Na]^+$), 482 ($[M+H]^+$). Anal. calc. for $C_{26}H_{31}N_3O_6$: C 64.85, H 6.49, N 8.73; found: C 64.73, H 6.35, N 8.84.

3.2. *4-(Acetylamino)-5-amino-7*-tert-*butyl*-N,N-*diisopropyl-9-oxo-9*H-*xanthene-2-carboxamide* (**23**). Compound **22** (1.0 g, 2.1 mmol) was reduced with H_2 on Pd/C, as described for the reduction of **21**, to afford **23** (0.88 g, 94% yield). M.p. 237–239°. IR: 3381, 2924, 1701, 1663, 1603, 1541, 1464, 1377, 1333, 1294, 1250, 1204, 1157, 1103, 1042. ^{1}H-NMR ($CDCl_3$): 9.24 (*d*, *J* = 1.9, 1 H); 7.90 (*d*, *J* = 1.9, 1 H); 7.27 (*d*, *J* = 2.2, 1 H); 7.04 (*d*, *J* = 2.2, 1 H); 3.99–3.84 (*m*, 1 H); 3.68–3.55 (*m*, 1 H); 2.26 (*s*, 3 H); 2.07 (*d*, *J* = 8.2, 6 H); 1.48 (*s*, 9 H); 1.16 (*d*, *J* = 6.4, 6 H). ^{13}C-NMR ($CDCl_3$): 175.5 (C); 171.6 (C); 169.6 (C); 148.1 (C); 145.5 (C); 142.5 (C); 138.4 (C); 132.4 (C); 127.4 (C); 123.5 (CH); 121.4 (C); 120.3 (C); 116.9 (CH); 112.3 (CH); 109.3 (CH); 52.1 (CH); 46.3 (CH); 35.2 (C); 31.7 (Me); 30.8 (Me); 24.4 (Me); 20.9 (Me). ESI-MS: 474 ($[M+Na]^+$), 452 ($[M+H]^+$). Anal. calc. for $C_{26}H_{33}N_3O_4$: C 69.16, H 7.37, N 9.31; found: C 69.33, H 7.25, N 9.44.

3.3. *4-(Acetylamino)-7*-tert-*butyl*-N,N-*diisopropyl-9-oxo-5-({[(1,1,3,3-tetramethylbutyl)amino]carbonyl}-amino)-9*H-*xanthene-2-carboxamide* (**3**). Compound **23** (0.5 g, 1.11 mmol) was dissolved in CH_2Cl_2 (15 ml), and a 0.6M phosgene soln. in toluene (1.0 ml) was added. The mixture was refluxed for 20 min, the solvent was evaporated under vacuum, and the residue was co-evaporated with toluene (10 ml). The anh. residue was dissolved in toluene (15 ml), and this soln. was added to a soln. of 2,4,4-trimethylpentan-2-amine ('*tert*-octylamine'; 1 g) in toluene (15 ml) with stirring. When the addition was complete, the solvent was evaporated, and the residue was taken up in AcOEt and washed with 2M aq. HCl soln. The org. layer was dried (Na_2SO_4), and evaporated under vacuum. The residue was recrystallized from MeOH/H_2O to afford **3** (0.65 g, 96%). M.p. 186–188°. IR: 3312, 2924, 1707, 1670, 1607, 1551, 1530, 1462, 1377, 1333, 1300, 1258, 1211, 1157, 1107, 1040. ^{1}H-NMR ($CDCl_3$): 8.80 (*s*, 1 H); 8.46 (*s*, 1 H); 7.80 (*s*, 1 H); 7.78 (*s*, 1 H); 3.95–3.82 (*m*, 1 H); 3.77–3.62 (*m*, 1 H); 2.40 (*s*, 3 H); 1.77 (br. *s*, 2 H); 1.64 (*d*, *J* = 6.4 H, 6 H); 1.46 (*s*, 6 H); 1.25 (*s*, 9 H); 1.16 (*d*, *J* = 6.4, 6 H); 1.04 (*s*, 9 H). ^{13}C-NMR ($CDCl_3$): 175.0 (C); 172.4 (C); 168.8 (C); 160.7 (C); 153.2 (C); 147.9 (C); 145.1 (C); 144.1 (C); 132.5 (C); 129.8 (C); 126.6 (C); 126.1 (CH); 120.7 (CH); 120.3 (C); 118.0 (CH); 113.8 (CH); 54.5 (C); 52.0 (CH); 51.3 (CH_2); 46.1 (CH); 35.0 (C); 31.5 (Me); 31.3 (Me); 30.1 (Me); 22.6 (C); 20.9 (Me); 20.6 (Me); 14.0 (Me). ESI-MS: 629 ($[M+Na]^+$), 607 ($[M+H]^+$). Anal. calc. for $C_{35}H_{50}N_4O_5$: C 69.28, H 8.31, N 9.23; found: C 69.40, H 8.21, N 9.20.

3.4. *4-(Acetylamino)-7*-tert-*butyl-5-[[(butylamino)carbonyl]amino]*-N,N-*diisopropyl-9-oxo-9*H-*xanthene-2-carboxamide* (**4**). Compound **23** (0.4 g, 0.89 mmol) was dissolved in CH_2Cl_2 (15 ml), and a 0.6M phosgene soln. in toluene (1.0 ml) was added. The mixture was refluxed for 20 min. Then, the solvent was evaporated under vacuum, and the residue was co-evaporated with toluene (10 ml). The anh. residue was dissolved in

toluene (15 ml), and this soln. was added to a soln. of $BuNH_2$ (1 g) in toluene (15 ml) with stirring. When the addition was complete, the solvent was evaporated, and the residue was taken up in AcOEt, and extracted with 2M aq. HCl soln. The org. layer was dried (Na_2SO_4), and evaporated under vacuum to afford, after recrystallization from MeOH/H_2O, compound **4** (0.43 g, 88%). M.p. 262–264°. IR: 3383, 2926, 1697, 1655, 1607, 1534, 1458, 1418, 1375, 1325, 1294, 1250, 1208, 1157, 1103, 1042. ^{1}H-NMR ($CDCl_3$): 8.35 (*d*, *J* = 1.8, 1 H); 8.12 (*d*, *J* = 2.3, 1 H); 7.83 (*d*, *J* = 1.8, 1 H); 7.72 (*d*, *J* = 2.3, 1 H); 3.87–3.75 (*m*, 1 H); 3.59–3.41 (*m*, 1 H); 3.06 (*t*, *J* = 7.0, 2 H); 2.28 (*s*, 3 H); 1.57–1.35 (*m*, 6 H); 1.32 (*s*, 9 H); 1.15–1.02 (*m*, 10 H); 0.85 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR ($CDCl_3$): 176.1 (C); 170.2 (C); 169.5 (C); 159.6 (C); 149.5 (C); 148.8 (C); 145.7 (C); 134.7 (C); 133.2 (CH); 133.0 (C); 127.9 (C); 124.3 (CH); 122.2 (C); 122.0 (CH); 121.3 (C); 118.4 (CH); 41.4 (CH); 40.9 (CH_2); 37.5 (Me); 35.2 (C); 31.5 (Me); 29.7 (CH_2); 20.8 (Me); 20.0 (CH_2); 13.7 (Me). ESI-MS: 573 ([*M* + Na^+]), 551 ([*M* + $H]^+$). Anal. calc. for $C_{31}H_{42}N_4O_5$: C 67.61, H 7.69, N 10.17; found: C 67.53, H 7.60, N 10.22.

4. *Synthesis of Receptor* **5**. 4.1. *Dimethyl 4-(4*-tert-*Butyl-2-nitrophenoxy)-5-nitroisophthalate* (**24**). Prepared in analogy to **18**, starting from dimethyl 4-bromo-5-nitroisophthalate (120 g, 377.4 mmol). Yield: 156.1 g (96%). M.p. 112–114°. ^{1}H-NMR ($CDCl_3$): 7.97 (*d*, *J* = 2.4, 1 H); 7.90 (*d*, *J* = 2.4, 1 H); 7.67 (*d*, *J* = 2.5, 1 H); 7.40 (*dd*, *J* = 8.8, 2.5, 1 H); 6.60 (*d*, *J* = 8.8, 1 H); 3.91 (*s*, 3 H); 3.70 (*s*, 3 H); 1.30 (*s*, 9 H). ESI-MS: 455 ([*M* + $Na]^+$), 433 ([*M* + $H]^+$). Anal. calc. for $C_{20}H_{20}N_2O_9$: C 55.56, H 4.66, N 6.48; found: C 55.39, H 4.56, N 6.34.

4.2. *Dimethyl 5-Amino-4-(4*-tert-*butyl-2-nitrophenoxy)isophthalate* (**25**). Compound **24** (116 g, 269 mmol) was dissolved in a mixture of MeOH (1000 ml), AcOH (300 ml), and benzene (300 ml). Then, Fe powder (350 g, 6.25 mol) was added, and the mixture was vigorously (mechanically) stirred for 2 h, the temp. being kept at 30° with an external cooling bath. Excess Fe was filtered off, and most of the solvent was evaporated under vacuum. The residue was dissolved in AcOEt and washed with H_2O. The org. layer was dried (Na_2SO_4) and evaporated, and the resulting residue was percolated over SiO_2 to separate it from Fe salts. Yield of **25**: 90.52 g (84%). M.p. 112–114°. ^{1}H-NMR ($CDCl_3$): 7.81 (*d*, *J* = 2.2, 1 H); 7.77 (*d*, *J* = 2.2, 1 H); 7.61 (*d*, *J* = 2.5, 1 H); 7.41 (*dd*, *J* = 8.8, 2.5, 1 H); 6.54 (*d*, *J* = 8.8, 1 H); 3.98 (*s*, 3 H); 3.96 (*s*, 3 H); 1.20 (*s*, 9 H). ESI-MS: 425 ([*M* + $Na]^+$), 403 ([*M* + $H]^+$). Anal. calc. for $C_{20}H_{22}N_2O_7$: C 59.70, H 5.51, N 6.96; found: C 59.52, H 5.56, N 6.84.

4.3. *4-Amino-7*-tert-*butyl-5-nitro-9-oxo-9*H-*xanthene-2-carboxylic Acid* (**26**). Compound **25** (40.6 g, 101 mmol) was suspended in 48% HBr (400 ml). The mixture was refluxed for 3 h, whereupon a homogeneous soln. resulted. Ice was added, and crystals of the diacid were filtered from the cold suspension (35.8 g, 95.7 mmol, 95%). Once dried, the intermediary diacid was added to a suspension of P_2O_5 (10 g) in $MeSO_3H$ (100 ml), which had previously been stirred overnight. The mixture was heated to 90° for 2 h, and then added to cold H_2O to afford crystalline **26** (33.2 g, 97% (second step)). M.p. 280–282°. IR: 2924, 1696, 1618, 1535, 1476, 1287, 1196, 1055. ^{1}H-NMR ($CDCl_3$): 8.52 (*d*, *J* = 2.5, 1 H); 8.42 (*d*, *J* = 2.5, 1 H); 7.90 (*d*, *J* = 2.0, 1 H); 7.38 (*d*, *J* = 2.0, 1 H); 1.34 (*s*, 9 H). ESI-MS: 379 ([*M* + $Na]^+$), 357 ([*M* + $H]^+$). Anal. calc. for $C_{18}H_{16}N_2O_6$: C 60.67, H 4.53, N 7.86; found: C 60.53, H 4.39, N 7.94.

4.4. *Butyl 4-Amino-7*-tert-*butyl-5-nitro-9-oxo-9*H-*xanthene-2-carboxylate* (**27**). Acid **26** (15 g, 42.1 mmol) was suspended in BuOH (250 ml), and $SOCl_2$ (3.0 ml) was carefully added. The mixture was refluxed for 3 h, whereupon the starting material completely dissolved. The solvent was partially evaporated under vacuum, and hexane (300 ml) was added to induce the crystallization of **27** (16.1 g, 93%). M.p. 188–190°. IR: 3483, 3368, 2924, 1717, 1665, 1622, 1570, 1537, 1464, 1377, 1310, 1285, 1252, 1225, 1113, 1053, 1017. ^{1}H-NMR ($CDCl_3$): 8.62 (*d*, *J* = 2.3, 1 H); 8.51 (*d*, *J* = 2.3, 1 H); 8.25 (*d*, *J* = 1.6, 1 H); 7.72 (*d*, *J* = 1.6, 1 H); 4.33 (*t*, *J* = 6.6, 2 H); 1.89–1.74 (*m*, 2 H); 1.56–1.43 (*m*, 2 H); 1.44 (*s*, 9 H); 0.98 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR ($CDCl_3$): 175.2 (C); 165.5 (C); 147.6 (C); 146.0 (C); 138.3 (C); 137.7 (C); 136.6 (C); 129.6 (CH); 128.8 (CH); 127.5 (C); 122.9 (C); 121.0 (C); 119.0 (CH); 116.5 (CH); 65.3 (CH_2); 35.1 (Me); 31.0 (CH_2); 30.7 (C); 19.2 (CH_2); 13.7 (Me). ESI-MS: 435 ([*M* + $Na]^+$), 413 ([*M* + $H]^+$). Anal. calc. for $C_{22}H_{24}N_2O_6$: C 64.07, H 5.87, N 6.79; found: C 64.01, H 5.89, N 6.68.

4.5. *Butyl 7*-tert-*Butyl-5-nitro-9-oxo-4-({[(1,1,3,3-tetramethylbutyl)amino]carbonyl}amino)-9*H-*xanthene-2-carboxylate* (**28**). Prepared by reaction with a 0.6M phosgene soln. in toluene, as described for **17**. Yield of **28**: 95%. M.p. 236–238°. IR: 3445, 3403, 2924, 2855, 1724, 1672, 1618, 1574, 1534, 1464, 1377, 1344, 1317, 1285, 1248, 1198, 1107, 1061. ^{1}H-NMR ($CDCl_3$): 9.10 (*d*, *J* = 1.8, 1 H); 8.62 (*d*, *J* = 2.4, 1 H); 8.56 (*d*, *J* = 2.4, 1 H); 8.49 (*d*, *J* = 1.8, 1 H); 4.36 (*t*, *J* = 6.8, 2 H); 1.82 (*s*, 2 H); 1.90–1.73 (*m*, 2 H); 1.51 (*s*, 6 H); 1.57–1.41 (*m*, 2 H); 1.44 (*s*, 9 H); 1.07 (*s*, 9 H); 0.98 (*t*, *J* = 7.3, 3 H). ^{13}C-NMR ($CDCl_3$): 174.9 (C); 165.5 (C); 152.9 (C); 148.2 (C); 146.6 (C); 146.2 (C); 137.3 (C); 130.4 (CH); 129.9 (C); 129.4 (CH); 128.0 (C); 124.6 (CH); 123.1 (C); 120.5 (CH); 120.4 (C); 65.7 (CH_2); 55.5 (C); 52.2 (CH_2); 35.4 (C); 31.7 (Me); 31.3 (Me); 30.9 (CH_2); 29.8 (Me); 20.5 (C); 19.4 (CH_2); 14.0 (Me). ESI-MS: 590 ([*M* + $Na]^+$), 568 ([*M* + $H]^+$). Anal. calc. for $C_{31}H_{41}N_3O_7$: C 65.59, H 7.28, N 7.40; found: C 65.48, H 7.39, N 7.24.

4.6. *Butyl 5-Amino-7-*tert*-butyl-9-oxo-4-({[(1,1,3,3-tetramethylbutyl)amino]carbonyl}amino)-9*H*-xanthene-2-carboxylate* (**29**). Prepared in analogy to the synthetic path leading to **2**, but starting from **28**. Yield of **29**: 92%. M.p. 127–129°. IR: 3376, 2928, 2855, 1715, 1655, 1626, 1605, 1539, 1464, 1377, 1314, 1283, 1246, 1219, 1155, 1101, 1061, 768, 721. ^{1}H-NMR ($CDCl_3$): 8.68 (br. *s*, 1 H); 7.71 (*d*, *J* = 2.2, 1 H); 7.18 (*d*, *J* = 2.2, 1 H); 6.87 (br. *s*, 1 H); 4.36 (*t*, *J* = 6.6, 2 H); 1.79 (*s*, 2 H); 1.76–1.59 (*m*, 2 H); 1.46 (*s*, 6 H); 1.34 (*s*, 9 H); 1.41–0.96 (*m*, 14 H). ^{13}C-NMR ($CDCl_3$): 177.7 (C); 165.9 (C); 154.6 (C); 148.8 (C); 148.4 (C); 142.2 (C); 138.3 (C); 136.2 (C); 129.2 (C); 125.8 (CH); 121.7 (CH); 121.0 (C); 120.9 (C); 117.8 (CH); 110.5 (CH); 65.4 (CH_2); 54.8 (C); 51.7 (CH_2); 34.6 (C); 31.4 (Me); 31.1 (Me); 30.7 (CH_2); 29.8 (Me); 20.5 (C); 19.1 (CH_2); 13.6 (Me). ESI-MS: 560 ($[M+Na]^+$), 538 ($[M+H]^+$). Anal. calc. for $C_{31}H_{43}N_3O_5$: C 69.25, H 8.06, N 14.88; found: C 69.19, H 8.12, N 14.81.

4.7. *Butyl 5-(Acetylamino)-7-*tert*-butyl-9-oxo-4-({[(1,1,3,3-tetramethylbutyl)amino]carbonyl}amino)-9*H*-xanthene-2-carboxylate* (**5**). Prepared in analogy to the synthetic path leading to **2**, but starting from **29**. Yield of **5**: 98%. M.p. 198–200°. IR: 3343, 3293, 3187, 3063, 2926, 1723, 1705, 1642, 1605, 1539, 1466, 1375, 1300, 1277, 1242, 1221, 1105, 1072, 1024. ^{1}H-NMR ($CDCl_3$): 8.47 (br. *s*, 1 H); 8.36 (br. *s*, 1 H); 7.96 (br. *s*, 1 H); 7.31 (br. *s*, 1 H); 4.31 (*t*, *J* = 6.7, 2 H); 2.37 (*s*, 3 H); 1.75 (*s*, 2 H); 1.79–1.70 (*m*, 2 H); 1.49–1.39 (*m*, 2 H); 1.42 (*s*, 6 H); 1.34 (*s*, 9 H); 0.99 (*s*, 9 H); 0.96 (*t*, *J* = 7.4, 3 H). ^{13}C-NMR ($CDCl_3$): 176.5 (C); 169.8 (C); 165.6 (C); 154.2 (C); 147.9 (C); 144.6 (C); 138.8 (C); 129.1 (C); 126.7 (CH); 126.3 (C); 125.8 (CH); 123.1 (CH); 121.7 (CH); 120.9 (C); 120.7 (C); 118.2 (CH); 65.4 (CH_2); 54.5 (C); 51.4 (CH_2); 34.9 (C); 31.3 (Me); 31.0 (Me); 30.6 (CH_2); 29.7 (Me); 23.9 (Me); 20.7 (C); 19.1 (CH_2); 13.6 (Me). ESI-MS: 602 ($[M+Na]^+$). Anal. calc. for $C_{33}H_{45}N_3O_6$: C 68.37, H 7.82, N 7.25; found: C 68.32, H 7.89, N 7.37.

5. *Syntheses of Receptors* **6**–**8**. 5.1. *Ethyl 3,3-Dibutyl-11-(decanoylamino)-2,3,4,7-tetrahydro-2,4,7-trioxo-1*H*-[1]benzopyrano[3,2-*h*]quinoline-9-carboxylate* (**6**). Amine **30** (1.0 g, 2.09 mmol) was dissolved in anh. THF (5.0 ml), and decanoyl chloride (1.2 g, 6.3 mmol) was added. The reaction was complete after 10 min at r.t. H_2O (0.3 ml) was added, and the mixture was heated to 50° for 30 min to hydrolyze the excess decanoyl chloride. The solvent was evaporated, and the residue was subjected to CC (SiO_2) to afford **6** (1.15 g, 87%). M.p. 194–196°. IR: 3403, 3248, 2926, 1713, 1682, 1651, 1609, 1584, 1537, 1464, 1377, 1285, 1246, 1213, 1099, 1022. ^{1}H-NMR ($CDCl_3$): 9.25 (*d*, *J* = 2.1, 1 H); 8.82 (*d*, *J* = 2.1, 1 H); 8.14 (*d*, *J* = 8.4, 1 H); 7.97 (*d*, *J* = 8.4, 1 H); 4.47 (*q*, *J* = 7.1, 2 H); 2.61 (*t*, *J* = 7.3, 2 H); 2.18–2.03 (*m*, 2 H); 1.94–1.80 (*m*, 4 H); 1.46 (*t*, *J* = 7.1, 3 H); 1.42–1.38 (*m*, 12 H); 1.30–1.17 (*m*, 8 H); 0.89 (*t*, *J* = 6.6, 3 H); 0.79 (*t*, *J* = 6.4, 6 H). ^{13}C-NMR ($CDCl_3$): 196.5 (C); 178.5 (C); 175.2 (C); 172.9 (C); 165.5 (C); 149.4 (C); 143.7 (C); 130.9 (CH); 130.5 (C); 128.6 (C); 126.5 (C); 124.5 (CH); 123.3 (C); 122.6 (C); 122.3 (CH); 122.0 (C); 117.3 (CH); 62.9 (CH_2); 62.4 (C); 41.4 (CH_2); 37.6 (CH_2); 32.4 (CH_2); 30.2 (CH_2); 28.2 (CH_2); 26.0 (CH_2); 23.6 (CH_2); 23.2 (CH_2); 14.9 (Me); 14.5 (Me); 14.3 (Me); 14.0 (Me). ESI-MS: 671 ($[M+K]^+$), 655 ($[M+Na]^+$), 633 ($[M+H]^+$). Anal. calc. for $C_{37}H_{48}N_2O_7$: C 70.23, H 7.65, N 4.43; found: C 70.17, H 7.75, N 4.49.

5.2. *Ethyl 3,3-Dibutyl-2,3,4,7-tetrahydro-11-{[(trifluoromethyl)carbonyl]amino}-2,4,7-trioxo-1*H*-[1]benzopyrano[3,2-*h*]quinoline-9-carboxylate* (**7**). Compound **30** (0.4 g, 0.84 mmol) was reacted in anh. THF with an excess of trifluoroacetic anhydride (2 ml) under conditions similar to those used to prepare **6**. When the reaction was complete, and the excess of reagent was hydrolyzed, the solvent was evaporated under vacuum, and the residue was taken up in AcOEt and washed with a dilute soln. of aq. Na_2CO_3. The org. layer was dried (Na_2SO_4), the solvent was evaporated, and the residue was recrystallized from CH_2Cl_2/Et_2O to afford **7** (0.42 g, 87%). M.p. 152–154°. IR: 3248, 3067, 2926, 1738, 1699, 1657, 1605, 1584, 1555, 1501, 1462, 1377, 1283, 1244, 1215, 1155, 1067, 1024. ^{1}H-NMR ($CDCl_3$): 9.00 (*d*, *J* = 1.8, 1 H); 8.93 (*d*, *J* = 1.8, 1 H); 8.13 (*d*, *J* = 8.4, 1 H); 7.97 (*d*, *J* = 8.4, 1 H); 4.51 (*q*, *J* = 7.1, 2 H); 2.11–1.93 (*m*, 4 H); 1.49 (*t*, *J* = 7.1, 3 H); 1.01–0.78 (*m*, 8 H); 0.53–0.24 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$): 195.9 (C); 177.2 (C); 174.0 (C); 163.8 (C); 155.8 (C); 149.1 (C); 143.0 (C); 130.5 (C); 129.8 (CH); 127.1 (C); 125.8 (C); 125.5 (CH); 124.3 (C); 122.6 (C); 121.9 (C); 121.6 (CH); 120.9 (CH); 62.0 (C); 40.6 (CH_2); 27.1 (CH_2); 22.7 (CH_2); 14.1 (Me); 13.0 (Me). ESI-MS: 597 ($[M+Na]^+$), 575 ($[M+H]^+$). Anal. calc. for $C_{29}H_{29}F_3N_2O_7$: C 60.62, H 5.09, N 4.88; found: C 60.65, H 4.99, N 4.96.

5.3. *Ethyl 3,3-Dibutyl-2,3,4,7-tetrahydro-11-[(methylsulfonyl)amino]-2,4,7-trioxo-1*H*-[1]benzopyrano[3,2-*h*]quinoline-9-carboxylate* (**8**). Prepared, in analogy to **7**, from **30** (0.4 g, 0.84 mmol) and excess of methanesulfonic acid chloride (2 ml). Yield of **8**: 0.428 g (92%). M.p. 144–146°. IR: 3260, 2926, 1715, 1674, 1651, 1603, 1495, 1464, 1377, 1283, 1208, 1157, 1144, 1047, 1024. ^{1}H-NMR ($CDCl_3$): 8.86 (*d*, *J* = 2.1, 1 H); 8.77 (*d*, *J* = 2.1, 1 H); 8.12 (*d*, *J* = 8.4, 1 H); 8.01 (*d*, *J* = 8.4, 1 H); 4.46 (*q*, *J* = 7.1, 2 H); 3.30 (*s*, 3 H); 2.18–1.86 (*m*, 4 H); 1.45 (*t*, *J* = 7.1, 3 H); 1.16–0.93 (*m*, 8 H); 0.59 (*t*, *J* = 5.7, 6 H). ^{13}C-NMR ($CDCl_3$): 196.3 (C); 176.4 (C); 174.6 (C); 164.3 (C); 149.2 (C); 143.1 (C); 138.8 (C); 131.0 (C); 127.6 (CH); 126.8 (C); 125.6 (CH); 124.7 (C); 122.9 (C); 122.1 (CH); 120.4 (CH); 118.0 (C); 62.5 (C); 61.8 (CH_2); 40.5 (Me); 39.5 (CH_2); 27.1 (CH_2); 22.7

(CH_2); 14.1 (Me); 13.3 (Me). ESI-MS: 579 ($[M+Na]^+$), 557 ($[M+H]^+$). Anal. calc. for $C_{28}H_{32}N_2O_8S$: C 60.42, H 5.79, N 5.03, S 5.76; found: C 60.35, H 5.99, N 4.85, S 5.73.

6. *Syntheses of Receptors* **9** *and* **10**. 6.1. *Ethyl 11-Amino-3,3-dibutyl-2,3,4,7-tetrahydro-2,4-dioxo-1*H*-[1]benzopyrano[3,2-*h*]quinoline-9-carboxylate* (**31**). Compound **30** (2.0 g, 4.18 mmol) was dissolved in anh. EtOH (100 ml), and ground Sn (4 g, 33.7 mmol) was added. The mixture was vigorously stirred at refluxed. When TLC analysis indicated that the reaction was complete, 35% HCl soln. (60 ml) was added. The EtOH was partially evaporated at reduced pressure, and the resulting mixture was added to cold H_2O, whereupon **31** (1.8 g, 93%) crystallized. Anal. calc. for $C_{27}H_{32}N_2O_5$: C 69.81, H 6.94, N 6.03; found: C 69.72, H 6.85, N 6.15.

6.2. *Ethyl 3,3-Dibutyl-11-(decanoylamino)-2,3,4,7-tetrahydro-2,4-dioxo-1*H*-[1]benzopyrano[3,2-*h*]quinoline-9-carboxylate* (**9**). Compound **31** (1.0 g, 2.16 mmol) were dissolved in anh. THF (20 ml), and an excess of Et_3N (1 ml) and decanoyl chloride (0.41 g, 2.15 mmol) was added. The mixture was heated to 50° during 1 h, and then the solvents were evaporated under vacuum. The residue was dissolved in AcOEt, washed with 2M aq. HCl soln., and the org. layer was dried and evaporated. The resulting residue was subjected to CC (SiO_2) to afford **9** (1.10 g, 83%). M.p. 212–214°. IR: 3408, 3235, 2926, 1707, 1670, 1647, 1632, 1541, 1464, 1377, 1314, 1217, 1024. ^{1}H-NMR ($CDCl_3$): 8.83 (*d*, *J* = 1.8, 1 H); 7.71 (*d*, *J* = 1.8, 1 H); 7.70 (*d*, *J* = 8.1, 1 H); 7.03 (*d*, *J* = 8.1, 1 H); 4.40 (*q*, *J* = 7.1, 2 H); 4.14 (br. *s*, 2 H); 2.56 (*t*, *J* = 7.2, 2 H); 2.14–1.97 (*m*, 2 H); 1.87–1.74 (*m*, 4 H); 1.65–1.55 (*m*, 4 H); 1.42 (*t*, *J* = 7.1, 3 H); 1.39–1.36 (*m*, 4 H); 1.24–1.17 (*m*, 12 H); 0.89 (*t*, *J* = 6.6, 3 H); 0.79 (*t*, *J* = 6.4, 6 H). ^{13}C-NMR ($CDCl_3$): 197.1 (C); 178.3 (C); 173.2 (C); 166.4 (C); 144.6 (C); 138.8 (C); 138.7 (C); 129.7 (C); 127.3 (C); 126.5 (C); 126.3 (CH); 124.5 (CH); 123.6 (CH); 122.5 (CH); 120.3 (C); 119.4 (C); 62.2 (CH_2); 61.8 (C); 41.6 (CH_2); 37.5 (CH_2); 32.4 (CH_2); 30.2 (CH_2); 28.2 (CH_2); 23.7 (CH_2); 23.2 (CH_2); 15.0 (Me); 14.5 (Me); 14.1 (Me). ESI-MS: 641 ($[M+Na]^+$), 619 ($[M+H]^+$). Anal. calc. for $C_{37}H_{50}N_2O_6$: C 71.82, H 8.14, N 4.53; found: C 71.92, H 8.08, N 4.63.

6.3. *Ethyl 3,3-Dibutyl-2,3,4,7-tetrahydro-11-[(methylsulfonyl)amino]-2,4-dioxo-1*H*-[1]benzopyrano[3,2-*h*]quinoline-9-carboxylate* (**10**). Prepared in analogy to **9**, from **31** (1 g, 2.16 mmol) and methanesulfonic acid chloride (3 ml). The excess reagent was hydrolyzed by adding H_2O (1 ml). After evaporation of the solvent at reduced pressure, the residue was dissolved in AcOEt, and washed with 4% aq. Na_2CO_3 soln. The org. layer was evaporated to afford **10** (1.08 g, 92%). M.p. 127–129°. IR: 3217, 2926, 2855, 1707, 1647, 1605, 1466, 1377, 1341, 1290, 1213, 1192, 1157, 1076, 1024. ^{1}H-NMR ($CDCl_3$): 8.26 (*d*, *J* = 1.9, 1 H); 7.79 (*d*, *J* = 1.9, 1 H); 7.72 (*d*, *J* = 8.1, 1 H); 7.02 (*d*, *J* = 8.1, 1 H); 4.39 (*q*, *J* = 7.0, 2 H); 4.39 (br. *s*, 2 H); 3.16 (*s*, 3 H); 2.11–1.93 (*m*, 4 H); 1.78–1.62 (*m*, 4 H); 1.41 (*t*, *J* = 7.0, 3 H); 1.15–0.99 (*m*, 4 H); 0.60 (*t*, *J* = 6.0, 6 H). ^{13}C-NMR ($CDCl_3$): 196.6 (C); 176.8 (C); 165.1 (C); 145.6 (C); 138.5 (C); 137.8 (C); 129.7 (C); 127.5 (C); 127.1 (CH); 126.8 (C); 125.5 (C); 124.1 (CH); 123.1 (CH); 122.1 (CH); 119.8 (C); 61.8 (CH_2); 61.2 (C); 40.1 (Me); 39.7 (CH_2); 28.1 (CH_2); 27.1 (CH_2); 22.8 (CH_2); 14.2 (Me); 13.4 (Me). ESI-MS: 565 ($[M+Na]^+$), 543 ($[M+H]^+$). Anal. calc. for $C_{28}H_{34}N_2O_7S$: C 61.97, H 6.32, N 5.16, S 5.91; found: C 61.84, H 6.23, N 5.04, S 6.01.

7. *Synthesis of the Guest* **11**. 7.1. *3-Bromopiperidin-2-one* (**12**). Dibromide **13** (10 g, 39 mmol) was dissolved in a mixture of MeOH (45 ml) and H_2O (5.0 ml). To this soln., Ph_3P (10.2 g, 39 mmol) was slowly added, keeping the temp. below 40° with external cooling. When the phosphine was completely dissolved, *ca*. half of the solvent was evaporated under vacuum, and H_2O was slowly added to induce crystallization of $Ph_3P{=}O$, which was separated by filtration. The filtrate was extracted several times with mixtures of AcOEt and THF, the extraction being facilitated by adding salt to the aq. layer. The org. layers were evaporated to afford **12** (5.5 g, 79%). M.p. 123–125°. IR: 3256, 2926, 1655, 1462, 1377, 1165, 1113, 1090, 1049. ^{1}H-NMR ($CDCl_3$): 4.51 (*t*, *J* = 4.2, 1 H); 3.47–3.27 (*m*, 2 H); 2.34–2.20 (*m*, 2 H); 1.88–1.73 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$): 168.6 (C); 44.6 (CH); 41.7 (CH_2); 31.2 (CH_2); 18.5 (CH_2). ESI-MS: 200 ($[M+Na]^+$), 178 ($[M+H]^+$). Anal. calc. for C_5H_8BrNO: C 33.73, H 4.53, N 7.87; found: C 33.64, H 4.61, N 7.89.

7.2. *2-Oxopiperidin-3-yl Dimethyldithiocarbamate* (**14**). Compound **12** (10 g, 56 mmol) was dissolved in MeOH (100 ml), and dimethylammonium dimethyldithiocarbamate (9.30 g, 56 mmol) was added with external cooling. Most of the solvent was evaporated at reduced pressure, and H_2O was added to induce the crystallization of **14** (11.5 g, 96%). Anal. calc. for $C_8H_{14}N_2OS_2$: C 44.01, H 6.46, N 12.83, S 29.37; found: C 43.94, H 6.52, N 12.77, S 29.29.

7.3. *5,6-Dihydropyridin-2(1*H*)-one* (**11**). Compound **14** was heated to 260° at 1 Torr. Under these conditions, product **11** sublimed, but was still contaminated with small amounts of the reagent, which was removed by CC (SiO_2). Yield of **11**: 68%. Liquid at r.t. IR: 3202, 2926, 1670, 1603, 1458, 1377, 1341, 1314, 1263, 1202, 1142, 1115, 1059, 1001. ^{1}H-NMR ($CDCl_3$): 6.62 (*td*, *J* = 4.2, 9.5, 1 H); 5.87 (*dt*, *J* = 10.5, 1.8, 1 H); 3.44–3.33 (*m*, 2 H); 2.37–2.23 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$): 166.9 (C); 141.7 (CH); 125.0 (CH); 39.7 (CH_2); 24.0 (CH_2). ESI-MS: 120 ($[M+Na]^+$). Anal. calc. for C_5H_7NO: C 61.84, H 7.27, N 14.42; found: C 61.77, H 7.32, N 14.35.

8. *X-Ray Diffraction Studies*[2]). Crystallographic data were collected on a four-circle *Seifert XRD 3003 SC* diffractometer, with CuK_α radiation ($\lambda = 1.54180$ Å) and graphite monochromator at ambient temperature in the ω-2θ scan mode. A summary of the X-ray and refinement data of compounds **2**, **4**, and **5** is given in *Table 4*.

Table 4. *Crystal Data and Structure Refinement for Compounds* **2**, **4**, *and* **5**

	2	**4**	**5**
Empirical formula	$C_{35}H_{50}N_4O_5$	$C_{33}H_{45}N_3O_6$	$C_{63}H_{88}N_8O_{11}$
Formula weight	606.79	579.72	1133.41
Temperature [K]	293(2)	293(2)	293(2)
Wavelength [Å]	1.54180	1.54180	1.54180
Crystal system, space group	Trigonal, $R\bar{3}$	Orthorhombic, $P2_12_12_1$	Monoclinic, $C2/c$
Unit cell dimensions: a [Å]	27.100(4)	8.857(2)	36.912(7)
b [Å]	27.100(4)	23.073(5)	14.761(3)
c [Å]	25.133(5)	31.756(6)	26.859(5)
α [°]	90	90	90
β [°]	90	90	92.17(3)
γ [°]	120	90	90
Volume [Å^3]	15985.3(45)	6489.6(23)	14623.8(51)
Z	18	8	8
Density (calc.) [Mg/m^3]	1.135	1.187	1.030
Absorption coefficient [mm^{-1}]	0.607	0.658	0.572
F(000)	5904	2496	4880
Crystal size [mm]	0.1 × 0.08 × 0.06	0.1 × 0.09 × 0.07	0.08 × 0.06 × 0.05
Θ Range for data collection	2.58 – 59.98°	2.37 – 60.06°	2.40 – 60.03°
Limiting indexes	$-20 \le h \le 20$, $-30 \le k \le 0$, $-7 \le l \le 27$	$0 \le h \le 9$, $-1 \le k \le 23$, $-6 \le l \le 30$	$-35 \le h \le 35$, $-14 \le k \le 0$, $-26 \le l \le 0$
Reflections collect. (obs.)	4722 (1769)	5148 (685)	9958 (2526)
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data, restraints, parameters	4721, 0, 446	5144, 1, 344	9948, 7, 752
Goodness-of-fit on F^2	0.922	0.651	0.954
Final R indexes [$I > 2\sigma(I)$]	$R1 = 0.0750$, $wR2 = 0.2206$	$R1 = 0.0700$, $wR2 = 0.0934$	$R1 = 0.1494$, $wR2 = 0.3910$
R Indexes (all data)	$R1 = 0.1616$, $wR2 = 0.2550$	$R1 = 0.2902$, $wR2 = 0.1696$	$R1 = 0.2810$, $wR2 = 0.4600$
Largest diff. peak and hole [e Å^{-3}]	1.059 and −0.242	0.297 and −0.263	0.952 and −0.353

The unit-cell parameters were determined by least-squares refinement on the 2θ values of 25 strong, well-centered reflections in the range $16° < 2\theta < 40°$. Scattering factors for neutral atoms and anomalous dispersion correction for C-, N-, and O-atoms were taken from the literature [12]. The structures of **2**, **4**, and **5** were solved by direct methods. All calculations were performed with the CRYSOM software [13] for data collection, with

[2]) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication numbers CCDC-264634 (**2**), -264635 (**4**), and -264636 (**5**). These data can be obtained, free of charge, *via* the internet at http://www.ccdc.cam.ac.uk/data_request/cif.

XRAY8O [14] for data reduction, and with SHELXTL [15] to resolve and refine the structures, and to prepare the graphical material for publication.

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