DOI: 10.1002/ejoc.200700130

Anion Receptors Based on a Quinoline Backbone

Markus Albrecht,*[a] Triyanti,[a] Stefanie Schiffers,[a] Olga Osetska,[a] Gerhard Raabe,[a] Thomas Wieland,[a] Luca Russo,[b] and Kari Rissanen[b]

Keywords: Anions / Quinoline / Receptors / Ab initio calculations / Fluorescence

2-Amido-8-urea substituted quinoline derivatives are potent receptors for the binding of halide or benzoate anions in chloroform. The selectivity and affinity of the receptors for fluoride can be tuned by variation of the substituents at the receptor side chains. Computational considerations show that the cleft of the receptors provides space for effective binding of F^-, but not bigger anions.

Introduction

Anions play an important role in many biological and chemical processes.[1] For example, the disfunction of anion-channel proteins can be the reason for *cystic fibrosis*, a genetic disease.[2] Despite the importance of the specific recognition and transport of anions, the molecular principles of anion binding and recognition are not fully understood.

The shape of anions is very often overestimated in binding modes; in only a few cases does it strictly follow the lock-and-key principle.[3] Very often, anion binding occurs only as a result of electrostatic attraction and entropic driving forces; shape usually only has a minor influence.[4]

To gain some deeper understanding on processes involving anions, it is necessary to thoroughly investigate the anion binding properties of simple receptor molecules. Therefore, this field of research became an important topic of current supramolecular chemistry.

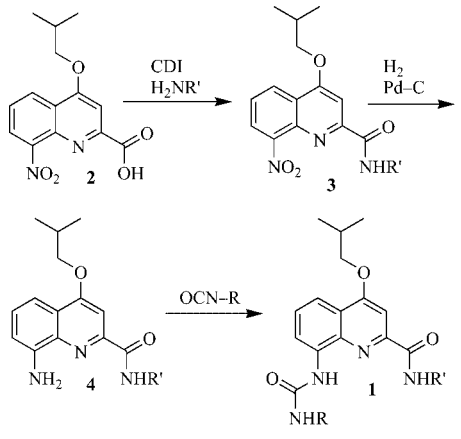
A series of cationic anion receptors were developed, which can bind simple inorganic but also sophisticated organic anions even in water.[5] Alternatively, neutral receptors can be used to investigate anion binding mechanisms, as demonstrated by the work of Sessler, Schmidtchen, Gale and many others.[6] Recently, we reported a simple quinoline derivative of type **1**, which is able to bind halide anions with moderate affinities in a 1:1 fashion; some selectivity for the smaller anions was discovered.[7] On the basis of those preliminary results, we now describe the synthesis of a series of related quinoline-type receptors **1** and the optimisation of the halide binding properties. In addition, we discuss their ability to bind simple organic (carboxylate) anions. To gain some deeper insight into the interaction between anions and receptors, supporting computational studies were performed.[8]

[a] Institut für Organische Chemie, RWTH Aachen,
Landoltweg 1, 52072 Aachen, Germany
E-mail: markus.albrecht@oc.rwth-aachen.de
[b] Nanoscience Centre, Department of Chemistry, University of Jyväskylä,
Survontie 9, 40014 Jyväskylä, Finland

Results and Discussion

Synthesis of the Receptors

Quinoline derivatives **1** were prepared following the synthetic procedure as described previously for **1a**.[9] The synthesis is depicted in Scheme 1. The reaction sequence starts with Huc's nitroquinoline carboxylic acid **2**.[10] From **2**, amides **3** (**a**: R′ = C_6H_{13}, **b**: R = Ph) were prepared by coupling with an appropriate amine, H_2N–R′, in the presence of carbonyl diimidazole (CDI) as the coupling reagent. Hydrogenative reduction of the nitro group with Pd–C as the catalyst afforded amine **4** (**a**: R′ = C_6H_{13}, **b**: R = Ph) in quantitative yield as the crude product. Even though this



Scheme 1. Synthetic pathway for the preparation of quinoline derivatives **1** (CDI = carbonyl diimidazole).

amine can be purified, it usually reacts with isocyanates without work up to form desired urea derivatives **1**.

Following this approach, differently substituted compounds **1a** (R = C_8H_{17}, R′ = C_6H_{13}), **1b** (R = C_8H_{17}, R′ = Ph), **1c** (R = C_4H_9, R′ = Ph), **1d** (R = Ph, R′ = C_6H_{13}) and **1e** (R = Ph, R′ = Ph) were prepared in moderate-to-good yields (56–85% overall yield starting from **2**). The compounds were characterised by standard spectroscopic methods (see Experimental Section) and the X-ray structure of **1c**·CH_3CN as well as **1e**·DMSO (vide infra) could be obtained.

Solid State Structures and Conformational Considerations

Figure 1 shows the result of the X-ray structure analysis of the DMSO adduct of 5,7-dibromo-8-hydroxyquinoline-2-carboxylic acid (**5**) from a weakly diffracting crystal. The representation nicely shows the orientation of the two acidic protons (phenol and carboxylic acid) towards the front of the molecule. This front position is enforced by intramolecular hydrogen bonding to the quinoline nitrogen atom,[11] and owing to this, the hydrogen atoms are ideally predisposed for the tweezer-type interaction with hydrogen-bond acceptors − in the present case DMSO. As shown earlier, only weak binding of anions can be expected by derivatives such as **5**. However, by using the intramolecular interactions such as those in **5**·DMSO as a starting point, we developed and optimised anion receptors **1**.

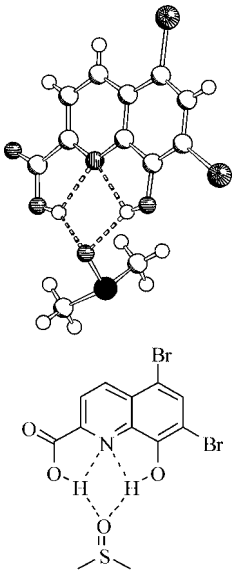


Figure 1. X-ray structure of **5**·DMSO.

Weakly diffracting crystals of **1c**·CH_3CN with only moderate X-ray quality were also obtained. They show the formation of a hydrogen-donor binding pocket, in which, for example, anionic guest species can be introduced. Similar to that observed for model **5**, intramolecular hydrogen bonds between the quinoline N atom and a urea unit and between the quinoline N atom and the amide NH are formed. These contacts fix the molecule in a tweezer-type arrangement with the hydrogen-bond donors pointing to the front of the molecule (Figure 2).

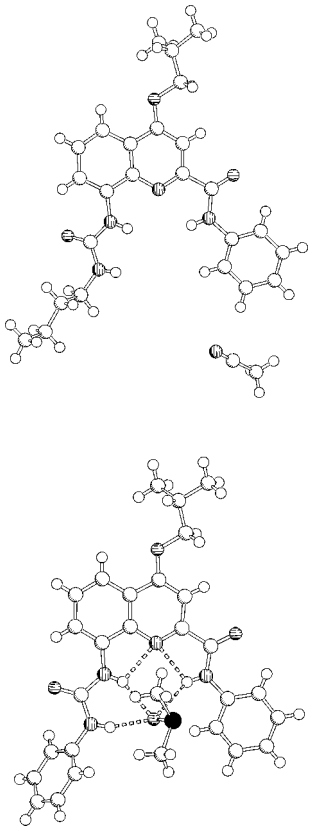


Figure 2. Solid-state structure of **1c**·CH_3CN (top) and **1e**·DMSO (bottom).

The two internal NH units provide the conformational rigidity that positions the remaining NH to form a small cleft. Therefore, this pyridine-bridged amido–urea unit is predisposed to act as an anchor for the fixation of guest species. In the solid phase, the carbonyl oxygen of a second molecule of urea binds in the pocket, which leads to a 1D hydrogen-bonded chain. Acetonitrile is not involved in the H-bonding.

Involvement of solvent molecules in the hydrogen bonding to the receptor is observed in the solid-state structure of **1e**·DMSO. The conformation of receptor **1e** is very similar to that described for **1c**. However, now one molecule of DMSO is bound to the three hydrogen-bond donors and it shows long contacts to the internal hydrogen atoms with the H···O bond lengths equal to 2.48 Å (amide), 2.21 Å (urea) and a shorter one to the external urea proton of 2.00 Å. In addition, one *ortho* proton of the phenyl ring that is attached to the amide is located at a distance of 2.56 Å from the DMSO oxygen atom. This phenyl ring is in the same plane as the amide and quinoline moieties, which probably introduces some steric hindrance, whereas the phenyl group at the urea is twisted out of plane and therefore does not interfere with the binding guest. The DMSO

molecule is located somewhat above the plane of the binding site owing to the size of the oxygen atom, which is too big to allow binding inside the cavity.

Determination of Binding Affinities

In our earlier study, we used receptor **1a** to determine its binding affinities with fluoride, chloride, bromide and nitrate anions by NMR as well as fluorescence spectroscopy in chloroform. Only in the case of fluoride did NMR spectroscopy not allow the determination of the binding constants. With the other anions, only relative binding constants could qualitatively be estimated because of self-aggregation of the receptors at the concentration of the measurement (0.0125 M).

Fluorescence spectroscopy, alternatively, was carried out at a much lower concentration (1 μM) were no self-aggregation of the receptor could take place. Therefore, the observed values are much higher, but they show similar trends in their selectivities.

Following this, we investigated modified receptors **1b**–**e** to determine their anion binding abilities using both spectroscopic methods. In addition, benzoate as a bigger "organic" anion was studied.

NMR Spectroscopic Investigations

Before starting the titration experiments, we determined the binding stoichiometry between receptors and anions by Jobs method. It was found to be 1:1 (Figure 3).[12]

Titration experiments were performed at a receptor concentration of 0.0125 M in $CDCl_3$ by the successive addition of tetrabutylammonium salts of the anions, and the amide signals, as well as the urea NH signals, were followed. The observation of three different signals allows to estimate the error of the titration to be <25%. The titration curves (e.g. Figure 3) were fitted by standard nonlinear regression methods as described in the literature.[12] The results of the NMR studies are summarised in Table 1. Again, no reliable data could be obtained for fluoride by NMR spectroscopy.

All receptors **1** have a strong preference for the smaller anions over the bigger ones. Therefore, decreasing binding constants can be observed in the series chloride, bromide and nitrate. However, a strong dependence of K_a on the substituents at the receptor side chains can be observed. Starting from our initial receptor **1a**, we introduced a phenyl group at the amide unit to obtain receptors **1b** and **1c**. This does not influence the binding of the anions significantly. In **1d**, we added a phenyl substituent to the urea moiety. This led to a slight increase in the binding affinity of the chloride anion. The most significant increase is found for receptor **1e** with two phenyl substituents. With chloride, a K_a = 7700 M^{-1} was found. This effect is probably due to the increase in the acidity of the two protons close to the phenyl groups and is most effective with chloride, which, because of its size, can come in close contact with the protons.

In the case of benzoate binding,[13] the association constants seem to unsystematically vary with the different receptors **1a**–**e**. Here, not only the binding of the anionic part is important, but it is additionally influenced by steric interactions of the phenyl group with the receptor and by aromatic–aromatic interactions between the benzoate anion and the receptors.

To summarise the NMR titration experiments, it is seen that quinoline receptors **1a**–**e** can be used for the binding of anions in chloroform, which shows some selectivity for

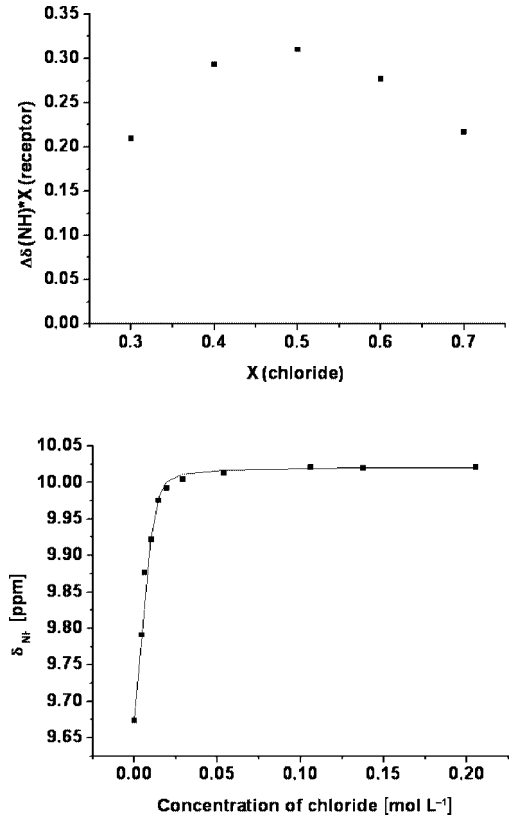
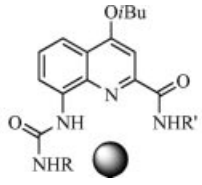


Figure 3. Representation of a selected example of the Jobs plot of receptor **1d** with chloride anions and the corresponding NMR titration curve observed for the amide NH. The solid line represents the simulated curve.

Table 1. Binding constants K_a [M^{-1}] for the 1:1 binding of various anions (as tetrabutyl ammonium salts) with receptors **1a**–**e** determined by ^1H NMR spectroscopy in $CDCl_3$ at a concentration of 0.0125 M and 296 K. All data are the result of at least two independent measurements. Errors are estimated to be <25%.



	R	R′	Cl^-	Br^-	NO_3^-	Benzoate
1a	C_8H_{17}	C_6H_{13}	1000	500	420	450
1b	C_8H_{17}	Ph	830	260	320	4000
1c	C_4H_9	Ph	2110	353	412	390
1d	Ph	C_6H_{13}	3333	337	322	600
1e	Ph	Ph	7700	1100	1100	3000

smaller chloride anions over the larger halides. Introduction of phenyl groups increases the acidity of neighbouring NH protons and thus increases the binding affinities of the anions.

Fluorescence Spectroscopic Investigations[14]

As mentioned above, fluorescence spectroscopy has the advantage that the measurements are performed at a concentration where no aggregation of the receptor can occur. This can be shown by concentration-dependent fluorescence studies. In addition, fluoride anion binding can be investigated.

The addition of halide or nitrate anions to receptors **1a**–**e** leads in all cases to fluorescence enhancement (Figure 4). Only with benzoate quenching occurs probably by the aromatic carboxylate.

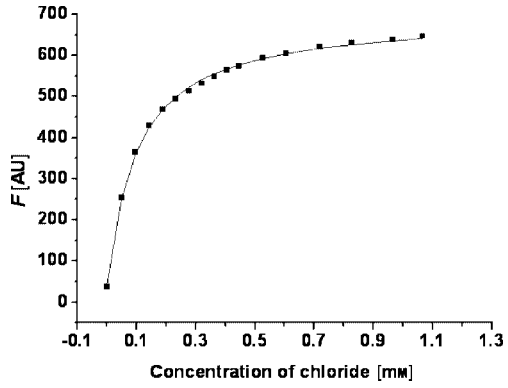


Figure 4. Enhancement of the fluorescence intensity of receptor **1d** (concentration: 1 μM) in chloroform upon addition of tetrabutyl ammonium chloride (excitation wavelength: 323 nm, emission wavelength: 438 nm).

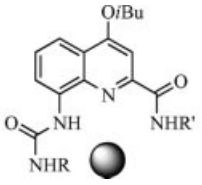
As a disadvantage, no reliable titration curves could be obtained for easily photooxidised receptor **1e**.

The results of the fluorescence titrations are summarised in Table 2. Without competition of receptor self-aggregation, the obtained K_a's are usually higher than the ones obtained by NMR spectroscopy. The relative selectivities of chloride, bromide and nitrate anion binding by **1a**–**d** are in the same range as observed by NMR spectroscopy (see for comparison Table 1).

The fluoride anion already shows a moderately high binding with receptor **1a** (K_a = 14400 M^{-1}) as well as with **1b** (K_a = 14300 M^{-1}). The K_a = 5000 M^{-1} of **1c** with fluoride seems to be very low, but can be reproduced.

Receptor **1d**, in contrast, shows a very high affinity for the small fluoride anion with K_a = 150000 M^{-1}. This is probably due to the fact that F^- is the ideal size to fit in the cavity of the receptor. In this case, enhancement of the acidity at the urea moiety increases the binding affinity because of the close contact to the anion. Enhancement of the acidity at the amide moiety (receptor **1b/1c**) does not lead to related effects. This binding unit is blocked by the intramolecular hydrogen bonding to the quinoline nitrogen atom. Unfortunately we were not able to obtain association constants of the biphenylated receptor **1e** with fluoride.

Table 2. Binding constants K_a [M^{-1}] for the 1:1 binding of various anions (as tetrabutyl ammonium salts) with receptors **1a**–**e** determined by fluorescence spectroscopy in $CHCl_3$ at a concentration of 1 μM at 296 K. All data are the result of at least two independent measurements. Errors are estimated to be <25%. Excitation/emission wavelength [nm]: 403/471 (**1a**), 350/462 (**1b**), 387/461 (**1c**), 323/438 (**1d**), and 299/456 (**1e**).



	R	R′	F^-	Cl^-	Br^-	NO_3^-	Benzoate
1a	C_8H_{17}	C_6H_{13}	14400	3100	640	400	6000
1b	C_8H_{17}	Ph	14300	7700	340	1510	4700
1c	C_4H_9	Ph	5000	4630	1050	1630	5080
1d	Ph	C_6H_{13}	150000	10380	1887	1672	
1e	Ph	Ph	receptor is light unstable				

Computational Considerations

Quantum-chemical calculations were performed to acquire some insight into the size-complementarity between model receptor **A** and different halide anions. Although the applied method is appropriate to gain an impression of the geometry of the interaction between host and guest, it does not allow an estimation of entropic influences or solvent effects.

Unconstrained optimisation for all structures were initially carried out at the Hartree–Fock level of ab initio theory by using the 6-31++G** basis set (HF/6-31++G**). Calculation and diagonalisation of the corresponding force constant matrices showed that all resulting structures were local minima. Starting from these geometries, we then performed final optimisations at the correlated level by employing Møller–Plesset perturbation theory to the second order and the 6-31+G* basis set (MP2/6-31+G*). The Gaussian03 suite of quantum-chemical routines[15] running on the facilities of the Computing and Communication Centre of the RWTH Aachen was used for all of the calculations. Selected structural parameters of the minima are given in Table 3, and the structures optimised at the MP2 level of theory are shown in Figure 5.

The $–C(=O^2)–N^4H_2$ segment of free receptor molecule **A** has a significantly pyramidalised amino group; it is distinctively turned out of the plane defined by the atoms of the condensed ring system. Except for a pyramidalisation of the N^4H_2 group, the complex **A**·F^- (Figure 5, a) is essentially planar. Whereas the structural features of the host unit are widely retained in **A**·Cl^-, the chlorine atom lies significantly (1.114 Å) above the least-squares plane defined by the non-hydrogen atoms of the acceptor part of the complex (cf. Table 3). Elevation of the halogen atom from this plane is even stronger in **A**·Br^- (1.674 Å), where rotation of the $N^3–C(=O)–N^4H_2$ side chain about the bond to the ring system is more pronounced than in the other complexes. The $H^{1a}\cdots X\cdots H^{4a}$ bond angles decrease in the order F > Cl >

Table 3. Selected structural parameters for **A**·F$^-$, **A**·Cl$^-$ and **A**·Br$^-$ obtained at the MP2/6-31+G* level (HF/6-31++G** values in parentheses) (Interatomic distances measured in Å, angles in °). The parameter *h* is the largest perpendicular distance of an atom (≠X$^-$) from the least-squares plane defined by the non-hydrogen atoms of the host part of the complex. The parameter *h*′ is the largest perpendicular distance of the halide anion from the same plane.

	A·F$^-$	**A**·Cl$^-$	**A**·Br$^-$
$H^{1a}\cdots X$	1.663(1.718)	2.216(2.418)	2.416(2.560)
$H^{3}\cdots X$	1.758(1.826)	2.401(2.834)	2.534(3.059)
$H^{4a}\cdots X$	1.728(1.753)	2.195(2.283)	2.403(2.426)
$H^{1a}\cdots H^{3}$[a]	2.491(2.559)	2.779(2.833)	2.822(2.840)
$H^{1a}\cdots X\cdots H^{3}$	93.4(92.4)	73.9(64.7)	69.5(59.9)
$H^{3}\cdots X\cdots H^{4a}$	69.5(68.2)	54.9(48.9)	51.7(45.3)
$H^{1a}\cdots X\cdots H^{4a}$	162.9(160.6)	123.8(113.3)	111.6(105.2)
$H^{1a}\cdots N^{2}\cdots H^{3}$[b]	66.4(67.4)	72.9(73.6)	73.7(73.9)
$N^{4}\cdots C\cdots N^{3}\cdots C$[d]	–177.0(179.8)	178.7(178.1)	–173.4(–179.9)
h[c]	0.355(0.013)	0.418(0.101)	0.585(0.002)
h′	0.064(0.007)	1.114(0.332)	1.674(0.003)

[a] 2.744 Å in acceptor molecule **A**. [b] 75.30° in acceptor molecule **A**. [c] 0.886 Å in acceptor molecule **A**. [d] 173.8° in acceptor molecule **A**.

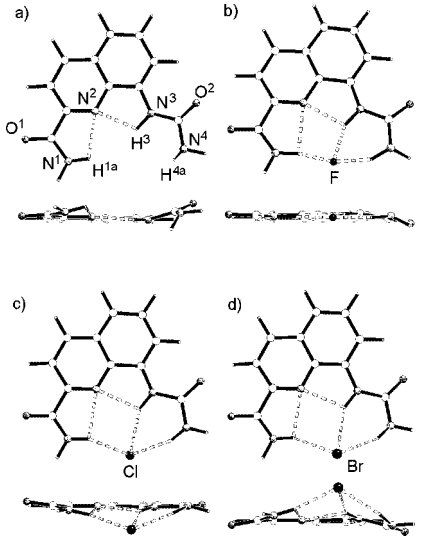


Figure 5. Calculated structures (MP2, top view and side view) of simplified receptor **A** (a), and its host–guest complex with fluoride **A**·F (b), chloride **A**·Cl (c) and bromide **A**·Br (d).

Br. The bond lengths between the atoms of the heavy-atom skeletons obtained at the MP2/6-31+G* level are very similar in all three complexes. Except for the side chains where the C–NH_2 and the C=O bonds are about 0.020 Å shorter and 0.013 Å longer than in the acceptor molecule, the bonds in **A** and **A**·X$^-$ are of comparable lengths.

At all levels of accuracy, bonding is the strongest for X = F, followed by X = Cl and finally X = Br.

The energies of the reaction **A** + X$^-$ → **A**·X$^-$ [ΔE_b = E_{tot}(**A**·X$^-$) – E_{tot}(**A**) – E_{tot}(X$^-$)] obtained at different levels of theory are given in Table 4. The interactions between the halogen anions and **A** are stabilising even at the HF level. To roughly estimate how much of ΔE_b might be due to a basis set superposition error (BSSE), we applied counterpoise corrections using the method suggested by Boys and Bernardi.[16] These corrections are small at the Hartree–Fock level (cf. Table 4), and although the calculated ΔE_b values are most likely too negative as a result of an overpolarisation of the molecules at the Hartree–Fock level, strong electrostatic and polarisation components are likely to contribute to the total binding energy. As to be expected, the counterpoise corrections are significantly larger when MP2 corrections are included in single-point calculations at the Hartree–Fock-optimised geometries (MP2/6-311++G**//HF/6-31++G**).

Table 4.Energy changes associated with the reaction **A** + X$^-$ → **A**·X$^-$ (ΔE_b; all energies in kcal mol^{-1}); ZPE is the zero-point vibrational energy.

	A·F$^-$	**A**·Cl$^-$	**A**·Br$^-$
HF/6-311++G**//HF/6-31++G**	–66.56	–40.67	–35.60
HF/6-311++G**//HF/6-31++G**[a]	–65.16	–40.04	–35.48
MP2/6-311++G**//HF/6-31++G**	–55.73	–34.21	–28.76
MP2/6-311++G**//HF/6-31++G**[a]	–50.46	–28.21	–24.39
MP2/6-31+G*//MP2/6-31+G*	–62.34	–40.97	–40.38
MP2/6-311++G**//MP2/6-31+G*	–61.84	–41.94	–36.32
ZPE+MP2/6-311++G**//HF/6-31++G**	–53.78	–32.61	–26.80
ZPE+MP2/6-311++G**//HF/6-31++G**[a]	–48.51	–26.61	–22.43
ZPE+MP2/6-31+G*//MP2/6-31+G*	–60.39	–39.37	–38.42
ZPE+MP2/6-311++G**//MP2/6-31+G*	–59.89	–40.34	–34.36

[a] Including a counterpoise correction.[16]

NBO calculations[17,18] with the 6-31G** basis set at the HF/6-31++G**- and the MP2/6-31+G*-optimised geometries were performed to elucidate binding between the anions and the acceptor molecule. Independent of the geometry and the halogen atom, the NBO results are qualitatively the same for all three complexes in that *this* analysis of the molecular wave function does not give classical bonds between X and the host unit of the complex. Each of the anions carries four lone pairs (*n*) with occupation numbers between 1.910 and 2.000 *e*. These lone pairs strongly interact predominantly with the σ_{NH}* orbitals of the receptor unit, whereas the interaction of highly occupied σ orbitals of the host molecule with *Rydbergs* of the halogen atoms are very weak and can safely be neglected. The energy lowering due to the $n \rightarrow \sigma^*$ interaction ($\Delta E_{n\sigma^*}^{(2)}$) can be estimated by using an energy expression derived from second-order perturbation theory $\Delta E_{n\sigma^*}^{(2)} = -q_n \cdot \langle n|\boldsymbol{F}|\sigma^*\rangle^2 / (\varepsilon_{\sigma^*} - \varepsilon_n)$, where $\boldsymbol{F}$ is the Fock operator of the molecule and q_n is the occupation number of the lone pair. The parameters ε_{σ^*} and ε_n are the NBO orbital energies of the σ* and nonbonding orbital *n*, respectively.[17,18] The corresponding values are given in Table 5.

Table 5.Natural atomic charges *q*(X$^-$), charge transfer energies (ΔE_{ct}) and $\Delta E_{n\sigma^*}$ calculated at the HF/6-31G**//MP2/6-31+G* level. The numbers in parentheses were obtained at the HF/6-31G**//HF/6-31++G** level (charges in *e* and energies in kcal mol^{-1}).

X$^-$	*q*(X$^-$)	ΔE_{ct}	$\Delta E_{n\sigma^*}^{(2)}$
F$^-$	–0.8304(–0.8492)	–105.1(–91.1)	–108.5(–91.4)
Cl$^-$	–0.8870(–0.9283)	–53.5(–31.8)	–61.8(–35.4)
Br$^-$	–0.8868(–0.9211)	–47.7(–32.4)	–52.2(–33.4)

At –108.5 kcal mol^{-1}, the $n \rightarrow \sigma^*$ interactions are the strongest for X = F, significantly weaker for X = Cl (–61.8kcal mol^{-1}) and the weakest for X = Br (–52.2kcal mol^{-1}). As to be expected, these energies are similar to the energies associated with charge transfer from X$^-$ to acceptor molecule **A** upon formation of the complex (charge-transfer energy, ΔE_{ct}). The charge-transfer energy was obtained as the difference between the SCF energy of the complex (**A**·X$^-$) calculated with the full Fock matrix and the total energy obtained in a single iteration after deletion of the Fock matrix elements between the donor orbitals of X and the acceptor orbitals of **A**.[17] The amount of charge transferred to the acceptor molecule (Δq) is relatively small (F: 0.1696 *e*, Cl = 0.1130 *e* and Br: 0.1132 *e*), and the largest transfer occurs from the fluoride anion, which also gives the most negative charge-transfer energy. Owing to similar geometries for **A**·F$^-$ at the Hartree–Fock and the MP2 levels, Δq, ΔE_{ct} and $\Delta E_{n\sigma^*}{}^{(2)}$ are not too different for both sets of structural parameters. The structural differences between the geometries obtained with the HF and MP2 methods are larger for **A**·Cl$^-$ and **A**·Br$^-$. Consequently, the values that were obtained for Δq, ΔE_{ct} and $\Delta E_{n\sigma^*}{}^{(2)}$ for both geometries differ much more for these two molecules than they do for **A**·F$^-$. In general, more negative values of ΔE_{ct} and $\Delta E_{n\sigma^*}{}^{(2)}$ and a more positive Δq value are obtained for the structures optimised at the correlated level.

Conclusions

Starting from solid-state structures such as **5**·DMSO, which show the host–guest behaviour of 2-acid substituted 8-hydroxyquinolines, we developed an efficient and selective receptor for the fluoride anion in chloroform. Substitution of the amide moiety for an acid functionality and a urea group instead of the hydroxy group in **5** led to potent halide receptors **1a**–**c**. However, variation of the substituents at the amide group as well as at the urea caused an enhancement in the acidity of the NH protons and an enhancement in the binding of fluoride anions in chloroform at room temperature to K_a = 150000 M^{-1} for **1d**.

Computational considerations using model **A** indicate that the binding of the anion is mainly electrostatic and show that receptors **1a**–**e** provide a cavity that is most appropriate for the binding of the small fluoride. The larger halides (chloride and bromide) do not fit in the provided cavity and therefore have to be located above the plane of receptor molecule **A**.

From our comparative studies by NMR and fluorescence techniques, we can see that fluorescence at lower concentrations leads to more accurate data than the corresponding NMR spectroscopic methods. However, NMR spectroscopy allows an estimation of relative affinities for different anions, if measurements are performed at the same concentration of the receptor.

As pointed out,[19] deprotonation of the receptors by a fluoride anion always has to be considered as a competitive process to the binding of this anion with high basicity. This prevents the determination of reliable data for fluoride anionic binding by NMR spectroscopy. In our computational calculations, this process was not taken into account and only binding of the fluoride anion to the pocket of the receptor was considered.

In an additional preliminary study, the binding of carboxylate anions to the receptors can be shown, which opens up a way for organocatalytic reactions. Therefore, we are now preparing enantiomerically pure chiral derivatives of **1**.

Experimental Section

NMR spectra were recorded with a Varian Mercury 300 or Inova 400 spectrometer. FTIR spectra were recorded with a Perkin–Elmer FTIR 1760 spectrometer (KBr). MS were measured with a Varian MAT 212 spectrometer. Elemental analyses are obtained with a Heraeus CHN-O-Rapid analyser. Melting points were measured with a Büchi B-540 apparatus and are uncorrected. Fluorescence measurements were performed with a Perkin–Elmer LS 50-B spectrofluorometer.

CCDC-633847 to -633849 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

5,7-Dibromo-8-hydroxyquinoline-2-carboxylic Acid (5): 5,7-Dibromo-8-hydroxyquinoline-2-carboxaldehyde[20] (0.25 g, 0.72 mmol) was dissolved in formic acid (10 mL, 0.26 mol, 1 equiv.) and the suspension was cooled to 0 °C. Cold hydrogen peroxide (16 mL; 30% solution in water, 0.52 mol, 2 equiv.) was slowly added, and the mixture was warmed to room temperature. After stirring for 3 d, water (200 mL) was added, the precipitate was collected by filtration, washed with cold water and dried. The first recrystallisation from DMF/*i*PrOH allowed the recovery of 0.06 g (24%) of the starting material; the second recrystallisation from methanol provided **5** as a yellow solid. Yield: 0.096 g (37%). M.p. 265 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 13.00 (br. s, 1 H), 11.07 (br. s, 1 H), 8.55 (d, J = 7.0 Hz, 1 H), 8.24 (d, J = 8.8 Hz, 1 H), 8.15 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.70 (C), 151.70 (C), 146.15 (C), 138.29 (CH), 137.34 (C), 136.03 (CH), 128.06 (C), 122.23 (CH), 109.29 (C), 106.08 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3309, 1706, 1613, 1572, 1451, 1376, 1245, 1194, 936, 839 cm^{-1}. MS (EI): m/z = 346.8 [M + H]$^+$. $C_{10}H_5Br_2NO_3$·CH_3OH (379.01): calcd. C 34.86, H 2.39, N 3.70; found C 35.09, H 2.68, N 4.08. X-ray quality crystals were obtained from DMSO: Crystal data ($C_{10}H_5NO_3Br_2$)-(SC_2H_6O): FW = 425.10, plate, 0.20 × 0.10 × 0.04 mm^3, triclinic, space group $P\bar{1}$, a = 8.6570(17) Å, b = 10.524(2) Å, c = 17.694(4) Å, α= 96.72(3)°, β = 102.80(3)°, γ = 109.81(3)°, V = 1446.1(5) Å^3, Z = 4, $D_{calcd.}$ = 1.952 g cm^{-3}, F(000) = 832, Mo-K_α radiation, λ = 0.71073 Å, μ = 5.761 mm^{-1}, T = 173(2) K, $2\theta_{max}$ = 55.0°, 12587 reflections collected, 3638 unique (R_{int} = 0.1006), 2158 with $I_o > 2\sigma(I_o)$. Solved by using SHELXS and refined with SHELX-97,[21] full-matrix least-squares on F^2, 392 parameters, 492 restraints, GoF = 1.128, R_1 = 0.1800, wR_2 = 0.2391 (all reflections), 1.24 < $\Delta\rho$ < –1.24 e Å^{-3}.

4-Isobutoxy-8-nitroquinoline-2-carboxylic Acid Hexylamide (3a): A solution of 4-isobutoxy-8-nitroquinoline-2-carboxylic acid (**2**; 0.6 g, 2.07 mmol, 1.0 equiv.) and carbonyl diimidazole (0.57 g, 3.5 mmol, 1.75 equiv.) in chloroform (20 mL) was heated at reflux for 1.5 h under an atmosphere of Ar. A solution of *n*-hexylamine (0.32 g, 3.18 mmol, 1.5 equiv.) in chloroform (2 mL) was added, and the mixture was heated at reflux for an additional 2 d. After cooling

to room temperature, the organic phase was washed with water and dried ($MgSO_4$), and the solvent was removed in vacuo. After column chromatography (silica gel, CH_2Cl_2) **3a** was obtained in 92% (0.71 g) as a yellow solid. M.p. 97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (dd, J = 1.5, 8.5 Hz, 1 H), 8.20 (s, NH), 8.11 (dd, J = 1.5, 7.5 Hz, 1 H), 7.81 (s, 1 H), 7.62 (t, J = 8.5 Hz, 1 H), 4.11 (d, J = 6.6 Hz, 2 H), 3.47 (q, J = 7.5 Hz, 2 H), 2.30 (m, 1 H), 1.67 (m, 2 H), 1.37 (m, 2 H), 1.33 (m, 4 H), 1.14 (d, J = 6.6 Hz, 6 H), 0.90 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 163.1, 153.4, 126.7 (2 C), 124.9 (2 C), 124.8 (2 C), 123.1, 99.8, 75.6, 39.7, 31.6, 29.7, 28.1, 26.7, 22.5, 19.1, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3301 (s), 2959 (s), 2928 (s), 2859 (m), 1667 (vs), 1539 (vs), 1501 (m), 1465 (m), 1354 (s), 1240 (m), 1142 (m), 1014 (s), 873 (m), 758 (m), 729 (m) cm^{-1}. MS (EI, 70 eV): m/z (%) = 373 (7) [M, $C_{20}H_{27}N_3O_4$]$^+$, 355 (92) [$C_{20}H_{25}N_3O_3$]$^+$, 300 (22) [$C_{18}H_{26}N_2O$]$^+$, 282 (17) [$C_{17}H_{20}N_3O$]$^+$, 246 (100) [$C_{13}H_{14}N_2O_3$]$^+$, 230 (40) [$C_{13}H_{12}NO_3$]$^+$, 217 (14) [$C_{12}H_{11}NO_3$]$^+$, 200 (12) [$C_{12}H_8O_3$]$^+$, 190 (21) [$C_9H_6N_2O_3$]$^+$, 173 (6) [$C_9H_5N_2O_3$]$^+$, 144 (5) [C_9H_6NO]$^+$, 57 (9) [C_4H_9]$^+$. $C_{20}H_{27}N_3O_4$ (373.45): calcd. C 64.32, H 7.29, N 11.25; found C 64.60, H 7.63, N 11.71.

4-Isobutoxy-8-nitroquinoline-2-carboxylic Acid Phenylamide (3b): A solution of 4-isobutoxy-8-nitro-quinoline-2-carboxylic acid (**2**; 0.2 g, 0.69 mmol, 1.0 equiv.) and carbonyl diimidazole (0.196 g, 1.21 mmol, 1.75 equiv.) in chloroform (20 mL) was heated at reflux for 1.5 h under an atmosphere of Ar. A solution of aniline (0.01 g, 0.76 mmol, 1.1 equiv.) in chloroform (2 mL) was added, and the mixture was heated at reflux for an additional 2 d. After cooling to room temperature, the organic phase was washed with water and dried ($MgSO_4$), and the solvent was removed in vacuo. After column chromatography (silica gel, CH_2Cl_2), **3b** was obtained in 80% (0.2 g) as a white solid. M.p. 188.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.18 (s, NH), 8.52 (dd, J = 1.4, 8.5 Hz, 1 H), 8.19 (dd, J = 1.4, 7.4 Hz, 1 H), 7.88 (s, 1 H), 7.81 (d, J = 7.4 Hz, 2 H), 7.66 (t, J = 7.9 Hz, 1 H), 7.42 (t, J = 7.9 Hz, 2 H), 7.19 (t, J = 7.4 Hz, 1 H), 4.15 (d, J = 6.7 Hz, 2 H), 2.33 (m, 1 H), 1.17 (d, J = 6.7 Hz, 6 H) ppm. IR (KBr): $\tilde{\nu}$ = 3743 (m), 3350 (w), 2958 (m), 2361 (vs), 2339 (vs), 1692 (s), 1525 (vs), 13674 (m), 1110 (m), 1018 (m), 752 (m), 669 (m) cm^{-1}. MS (EI, 70 eV): m/z (%) = 365 (85) [M, $C_{20}H_{19}N_3O_4$]$^+$, 309 (7) [$C_{16}H_{13}N_3O_4$]$^+$, 280 (2) [$C_{15}H_{12}N_3O_3$]$^+$, 262 (5) [$C_{16}H_{10}N_2O_2$]$^+$, 246 (40) [$C_{13}H_{14}N_2O_3$]$^+$, 190 (100) [$C_9H_6N_2O_3$]$^+$, 173 (4) [$C_9H_5N_2O_2$]$^+$, 143 (3) [C_9H_5NO]$^+$, 115 (5) [C_8H_5N]$^+$, 93 (3) [C_6H_5O]$^+$, 77 (4) [C_6H_5]$^+$, 57 (5) [C_4H_9]$^+$. $C_{20}H_{19}N_3O_4$ (365.39): calcd. C 65.75, H 5.21, N 11.5; found C 65.37, H 5.73, N 11.96.

8-Amino-4-isobutoxyquinoline-2-carboxylic Acid Hexylamide (4a): A mixture of nitro precursor **3a** (0.6 g, 1.66 mmol) dissolved in EtOAC (20–30 mL) and 10% Pd/C was stirred at ambient temperature under an atmosphere of hydrogen (5 bar) for 4 h. The solution was filtered through Celite, and the solvent was evaporated. Yield:0.55 g (1.60 mmol, 98%). M.p. 121 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (s, NH), 7.67 (s, 1 H), 7.60 (dd, J = 1.0, 8.2 Hz, 1 H), 7.36 (t, J = 8.2 Hz, 1 H), 6.99 (dd, J = 1.0, 6.9 Hz, 1 H), 4.91 (br. s, 2 H), 4.05 (d, J = 6.5 Hz, 2 H), 3.52 (q, J = 6.9 Hz, 2 H), 2.27 (m, 1 H), 1.69 (m, 2 H), 1.36 (m, 4 H), 1.13 (d, J = 6.5 Hz, 6 H), 0.92 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8, 164.8, 163.1 (2 C), 148.9, 143.7, 127.5, 111.3, 110.6, 108.4, 98.8, 75.0, 39.7 (2 C), 31.6, 29.8, 28.2, 26.7, 22.6, 19.2, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3491 (m), 3332 (s), 3257 (m), 2957 (s), 2926 (s), 2851 (m), 1650 (s), 1614 (m), 1510 (m), 1510 (vs), 1469 (m), 1422 (m), 1355 (m), 1275 (m), 1150 (m), 1065 (m), 1012 (m), 878 (m), 747 (s) cm^{-1}. MS (EI, 70 eV): m/z (%) = 343 (82) [M, $C_{20}H_{29}N_3O_2$]$^+$, 300 (1) [$C_{18}H_{26}N_3O$]$^+$, 286 (4) [$C_{18}H_{26}N_2O$]$^+$, 272 (8) [$C_{17}H_{24}N_2O$]$^+$, 258 (3) [$C_{16}H_{22}N_2O$]$^+$, 243 (5) [$C_{13}H_{11}N_2O_3$]$^+$, 216 (100) [$C_{11}H_8N_2O_3$]$^+$, 187 (10) [$C_{10}H_7N_2O_2$]$^+$, 160 (27) [$C_9H_6NO_2$]$^+$, 130 (4) [C_9H_6O]$^+$, 100 (9) [C_8H_4]$^+$, 77 (1) [C_6H_5]$^+$, 57 (1) [C_4H_9]$^+$. $C_{20}H_{29}N_3O_2 \cdot 1/2H_2O$ (352.47): calcd. C 68.15, H 8.58, N 11.92; found C 68.17, H 8.67, N 11.82.

4-Isobutoxy-8-amine-quinoline-2-carboxylic Acid Phenylamide (4b): A mixture of nitro precursor **3a** dissolved in CH_2Cl_2 (20–30 mL) and 10% Pd/C was stirred at ambient temperature under an atmosphere of hydrogen (5 bar) for 1 d. The solution was filtered through Celite. The solution was used in the next step without isolation of the amine.

4-Isobutoxy-8-(3-octylureido)quinoline-2-carboxylic Acid Hexylamide (1a): A solution of 8-amino-4-isobutoxyquinoline-2-carboxylic acid hexylamide (**4a**; 0.53 g, 1.55 mmol, 1.0 equiv.) and *n*-octyl isocyanate (0.51 g, 3.29 mmol, 1.5 equiv.) in chloroform (30 mL) was heated at reflux for 3 h. After cooling to room temperature, the solvent was removed in vacuo. After column chromatography (silica gel, CH_2Cl_2), **1a** was obtained as a yellow solid. Yield: 0.66 g (1.32 mmol, 85%). M.p. 135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, NH), 9.23 (s, NH), 8.73 (d, J = 7.7 Hz, 1 H), 7.75 (d, J = 8.5 Hz, 1 H), 7.67 (s, 1 H), 7.49 (t, J = 8.2 Hz, 1 H), 6.37 (s, NH), 3.98 (d, J = 6.6 Hz, 2 H), 2.32 (q, J = 6.7 Hz, 2 H), 2.25 (m, 1 H), 1.64 (s, 4 H), 1.39 (m, 4 H), 1.15 (d, J = 6.6 Hz, 6 H), 1.10 (d, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 163.5, 163.2, 137.4, 136.3, 127.9, 123.5, 121.9, 100.2, 98.4, 76.1, 40.2, 31.6, 31.4, 30.4, 30.2, 29.2, 29.1, 28.2, 26.9, 26.7, 22.5, 22.4, 19.0, 14.0, 13.8 ppm. IR (KBr): $\tilde{\nu}$ = 3348 (vs), 2928 (vs), 2858 (s), 1646 (s), 1528 (vs), 1460 (m), 1416 (m), 1384 (w), 1360 (m), 1321 (m), 1274 (m), 1224 (m), 1144 (w), 1045 (m), 865 (w), 817 (w), 762 (m), 725 (w), 544 (w) cm^{-1}. MS (EI, 70 eV): m/z (%) = 498 (7) [M, $C_{29}H_{46}N_4O_3$]$^+$, 370 (22) [$C_{21}H_{30}N_4O_2$]$^+$, 343 (100) [$C_{20}H_{29}N_3O_2$]$^+$, 314 (10) [$C_{19}H_{28}N_3O$]$^+$, 242 (42) [$C_{15}H_{20}N_3$]$^+$, 216 (53) [$C_{12}H_{20}N_2$]$^+$, 185 (12) [$C_{10}H_5N_2O_2$]$^+$, 159 (13) [$C_9H_5NO_2$]$^+$, 100 (11) [C_8H_4]$^+$, 85 (1) [C_6H_{13}]$^+$, 57 (4) [C_4H_9]$^+$. $C_{29}H_{46}N_4O_3 \cdot 1/2H_2O$ (509.71): calcd. C 68.60, H 9.33, N 11.04; found C 68.83, H 9.03, N 10.90.

8-(3-Octylureido)-4-isobutoxy-quinoline-2-carboxylic Acid Phenylamide (1b): A solution of 4-isobutoxy-8-aminoquinoline-2-carboxylic acid phenylamide (**4b**; 0.28 g, 0.89 mmol, 1.0 equiv.) and *n*-octyl isocyanate (0.179 g, 1.155 mmol, 1.5 equiv.) in dichloromethane (30 mL) was heated at reflux for 1 d. After cooling to room temperature, the solvent was removed in vacuo. After column chromatography (silica gel, CH_2Cl_2), **1b** was obtained as a yellow solid. Yield: 0.302 g (0.62 mmol, 80%). M.p. 155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.02 (s, NH), 8.95 (s, NH), 8.58 (dd, J = 1.0, 8.0 Hz, 2 H), 7.74 (dd, J = 1.0, 6.7 Hz, 2 H), 7.67 (s, NH), 7.43 (t, J = 8.0 Hz, 1 H), 7.21 (t, J = 7.4 Hz, 2 H), 7.04 (t, J = 7.4 Hz, 1 H), 5.87 (s, 1 H), 3.95 (d, J = 6.5 Hz, 2 H), 3.11 (m, 2 H), 2.23 (q, J = 6.7 Hz, 1 H), 1.33 (m, 2 H), 1.19 (m, 10 H), 1.09 (d, J = 6.5 Hz, 6 H), 0.83 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 148.9, 137.3, 135.7, 134.9, 128.6 (2 C), 127.7, 124.4, 122.0, 120.5 (2 C), 116.0 (2 C), 113.9, 98.8, 75.1, 40.5, 31.7 (2 C), 30.1, 29.2 (2 C), 28.1, 26.9, 22.6, 19.2 (2 C), 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3746 (w), 3335 (s), 2928 (s), 1686 (s), 1643 (m), 1526 (vs), 1449 (m), 1320 (m), 1042 (m), 755 (m), 695 (m) cm^{-1}. MS (EI, 70 eV): m/z (%) = 490 (9) [M, $C_{29}H_{38}N_4O_3$]$^+$, 361 (36) [$C_{21}H_{21}N_4O_2$]$^+$, 335 (100) [$C_{19}H_{19}N_4O_2$]$^+$, 306 (3) [$C_{17}H_{14}N_4O_2$]$^+$, 279 (14) [$C_{15}H_{11}N_4O_2$]$^+$, 242 (13) [$C_{12}H_{10}N_4O_2$]$^+$, 216 (5) [$C_{11}H_8N_2O_3$]$^+$, 186 (11) [$C_{10}H_6N_2O_2$]$^+$, 160 (9) [$C_9H_6NO_2$]$^+$, 130 (2) [C_9H_6O]$^+$, 99 (4) [C_8H_3]$^+$, 55 (3) [C_4H_7]$^+$. $C_{29}H_{38}N_4O_3 \cdot 1/2H_2O$ (499.65): calcd. C 69.71, H 7.87, N 11.21; found C 69.31, H 7.03, N 11.10.

8-(3-Butylureido)-4-isobutoxy-quinoline-2-carboxylic Acid Phenylamide (1c): A solution of 4-isobutoxy-8-aminoquinoline-2-car-

boxylic acid phenylamide (**4b**; 0.3 g, 0.89 mmol, 1.0 equiv.) and *n*-butyl isocyanate (0.133 g, 1.335 mmol, 1.5 equiv.) in dichloromethane (30 mL) was heated at reflux for 1 d. After cooling to room temperature, the solvent was removed in vacuo. After column chromatography (silica gel, CH_2Cl_2), **1c** was obtained as a yellow solid. Yield: 0.29 g (0.69 mmol, 75%). M.p. 210 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.93 (s, NH), 8.83 (s, NH), 8.53 (dd, J = 1.0, 7.2 Hz, 2 H), 7.72 (dd, J = 1.0, 7.4 Hz, 2 H), 7.64 (s, NH), 7.43 (t, J = 8.0 Hz, 1 H), 7.24 (t, J = 7.2 Hz, 2 H), 7.07 (d, J = 8.0 Hz, 1 H), 5.57 (s, NH), 3.94 (d, J = 6.5 Hz, 2 H), 3.20 (m, 2 H), 2.23 (m, 1 H), 1.41 (m, 2 H), 1.21 (m, 2 H), 1.10 (d, J = 6.5 Hz, 6 H), 0.83 (t, J = 7.4 Hz, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 3681 (s), 3441 (vs), 2961 (s), 2360 (vs), 1687 (m), 1650 (m), 1532 (s), 1458 (w), 1388 (w), 1322 (w), 1043 (m), 754 (m), 668 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 434 (15) [M, $C_{25}H_{30}N_4O_3$]$^+$, 361 (39) [$C_{21}H_{21}N_4O_2$]$^+$, 335 (100) [$C_{19}H_{19}N_4O_2$]$^+$, 306 (5) [$C_{17}H_{14}N_4O_2$]$^+$, 279 (23) [$C_{15}H_{11}N_4O_2$]$^+$, 242 (19) [$C_{12}H_{10}N_4O_2$]$^+$, 216 (7) [$C_{11}H_8N_2O_3$]$^+$, 187 (5) [$C_{10}H_7N_2O_2$]$^+$, 160 (17) [$C_9H_6NO_2$]$^+$, 130 (3) [C_9H_6O]$^+$, 104 (1) [C_8H_8]$^+$, 57 (2) [C_4H_9]$^+$. $C_{25}H_{30}N_4O_3 \cdot 1/2H_2O$ (443.54): calcd. C 67.70, H 7.04, N 12.63; found C 67.45, H 6.95, N 12.53. X-ray quality crystals were obtained from acetonitrile: Crystal data ($C_{25}H_{30}N_4O_3$)(CH_3CN): *FW* = 475.58, plate, 0.60 × 0.15 × 0.03 mm^3, monoclinic, space group *P* 2$_1$/*n*, *a* = 15.454(3) Å, *b* = 8.2659(17) Å, *c* = 21.183(4) Å, β = 105.44(3)°, *V* = 2608.2(9) Å^3, *Z* = 4, $D_{calcd.}$ = 1.211 g cm^{-3}, *F*(000) = 1016, Mo-K_α radiation, λ = 0.71073 Å, μ = 0.081 mm^{-1}, *T* = 173(2) K, $2\theta_{max}$ = 55.0°, 6723 reflections collected, 2641 unique (R_{int} = 0.0650), 1020 with $I_o > 2\sigma(I_o)$. Solved by using SHELXS[21] and refined with SHELX-97, full-matrix least-squares on F^2, 317 parameters, 0 restraints, *GoF* = 1.070, R_1 = 0.2447, wR_2 = 0.3109 (all reflections), 0.29 < $\Delta\rho$ < –0.28 e Å^{-3}.

4-Isobutoxy-8-(3-phenylureido)quinoline-2-carboxylic Acid Hexylamide (1d): A solution of 8-amino-4-isobutoxyquinoline-2-carboxylic acid hexylamide (**4a**; 0.22 g, 0.59 mmol, 1.0 equiv.) and phenyl isocyanate (0.11 g, 0.89 mmol, 1.5 equiv.) in chloroform (30 mL) was heated at reflux for 3 h. After cooling to room temperature, the solvent was removed in vacuo. After column chromatography (silica gel, CH_2Cl_2), **1d** was obtained as a yellow solid. Yield: 0.15 g (0.32 mmol, 56%). M.p. 153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.83 (s, NH), 8.76 (d, J = 7.2 Hz, 1 H), 8.35 (s, NH), 7.81 (d, J = 7.7 Hz, 1 H), 7.76 (s, 1 H), 7.54 (t, J = 8.03 Hz, 1 H), 7.35 (d, J = 7.7 Hz, 2 H), 7.15 (t, J = 7.67 Hz, 2 H), 6.96 (t, J = 7.15 Hz, 1 H), 3.94 (d, J = 6.43 Hz, 2 H), 2.22 (m, 1 H), 1.35 (m, 3 H), 1.07 (d, J = 6.70 Hz, 6 H), 0.73 (m, 4 H), 0.51 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 163.7, 163.4 (2 C), 137.4, 136.3, 131.6, 128.8 (2 C), 128.2, 121.9, 113.9, 100.2, 98.6, 75.2, 40.4 (2 C), 31.3, 30.5, 29.2, 28.1, 26.7, 22.3, 19.1 (2 C), 14.2, 13.7 ppm. IR (KBr): $\tilde{\nu}$ = 3328 (m), 2958 (m), 2929 (m), 2869 (m), 1642 (m), 1602 (m), 1531 (vs), 1499 (m), 1440 (m), 1418 (m), 1315 (s), 1269 (w), 1198 (m), 1072 (m), 1014 (m), 966 (w), 894 (w), 754 (m), 696 (m) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 462 (7) [M, $C_{27}H_{34}N_4O_3$]$^+$, 370 (100) [$C_{21}H_{30}N_4O_2$]$^+$, 343 (18) [$C_{20}H_{29}N_3O_2$]$^+$, 314 (30) [$C_{19}H_{28}N_3O$]$^+$, 242 (9) [$C_{15}H_{20}N_3$]$^+$, 216 (24) [$C_{12}H_{20}N_2$]$^+$, 185 (14) [$C_{10}H_5N_2O_2$]$^+$, 159 (7) [$C_9H_5NO_2$]$^+$, 100 (5) [C_8H_4]$^+$. $C_{27}H_{34}N_4O_3 \cdot 1/4H_2O$ (467.09): calcd. C 69.43, H 7.44, N 11.99; found C 69.42, H 7.26, N 11.95.

4-Isobutoxy-8-(3-phenylureido)quinoline-2-carboxylic Acid Phenylamide (1e): A solution of 4-isobutoxy-8-aminoquinoline-2-carboxylic acid phenylamide (**4b**; 0.2 g, 0.6 mmol, 1.0 equiv.) and phenyl isocyanate (0.1 g, 0.9 mmol, 1.5 equiv.) in dichloromethane (30 mL) was heated at reflux for 1 d. After cooling to room temperature, the solvent was removed in vacuo. After column chromatography (silica gel, CH_2Cl_2), **1e** was obtained as a white solid. Yield: 0.21 g, (0.46 mmol, 77%). M.p. 236 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.62 (s, NH), 9.18 (s, NH), 8.54 (d, J = 7.9 Hz, 1 H), 8.00 (s, NH), 7.64 (d, J = 8.5 Hz, 4 H), 7.50 (s, 1 H), 7.48 (d, J = 7.9 Hz, 1 H), 7.30 (t, J = 8.5 Hz, 1 H), 7.13 (t, J = 7.8 Hz, 2 H), 7.06 (t, J = 7.8 Hz, 2 H), 6.93 (t, J = 7.4 Hz, 1 H), 6.87 (t, J = 7.4 Hz, 1 H), 3.83 (d, J = 6.4 Hz, 2 H), 2.18 (m, 1 H), 1.06 (d, J = 6.4 Hz, 6 H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0, 162.8 (2 C), 153.3, 148.8, 137.8, 137.4.136.8, 134.8, 128.9 (2 C), 128.5, 127.4, 124.5, 123.9, 121.7, 121.0, 120.7, 116.8, 114.4, 98.6, 75, 28.1, 19.1 (2 C) ppm. IR (KBr): $\tilde{\nu}$ = 3909 (w), 3851 (m), 3737 (vs), 3448 (s), 2940 (w), 2856 (w), 2361 (vs), 1843 (w), 1649 (s), 1542 (vs), 1315 (w), 667 (vs) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 454 (1) [M, $C_{27}H_{26}N_4O_3$]$^+$, 362 (64) [$C_{21}H_{20}N_3O_3$]$^+$, 363 (15) [$C_{21}H_{21}N_3O_3$]$^+$, 335 (21) [$C_{20}H_{21}N_3O_2$]$^+$, 306(29) [$C_{19}H_{20}N_3O$]$^+$, 278 (7) [$C_{16}H_{12}N_3O_2$]$^+$, 242 (7) [$C_{13}H_{12}N_3O_2$]$^+$, 216 (4) [$C_{11}H_{10}N_3O_2$]$^+$, 186 (21) [$C_{10}H_6N_2O_2$]$^+$, 160 (17) [$C_9H_6NO_2$]$^+$, 130 (6) [C_9H_6O]$^+$, 119 (100) [$C_7H_3O_2$]$^+$, 93 (61) [C_6H_5O]$^+$, 77 (5) [C_6H_5]$^+$, 64 (23) [C_5H_5]$^+$, 51 (10) [C_4H_3]$^+$. $C_{27}H_{26}N_4O_3 \cdot 1/2H_2O$ (463.53): calcd. C 69.96, H 5.87, N 12.08; found C 70.14, H 5.55, N 11.26. X-ray quality crystals were obtained from DMSO: Crystal data ($C_{27}H_{26}N_4O_3$)(C_2H_6SO): *FW* = 532.65, block, 0.20 × 0.10 × 0.10 mm^3, monoclinic, space group *P* 2$_1$/*n*, *a* = 9.3881(19) Å, *b* = 11.631(2) Å, *c* = 13.968(3) Å, α = 109.68(3)°, β = 101.96(3)°, γ = 100.26(3)°, *V* = 1353.2(5) Å^3, *Z* = 2, D_c = 1.307 g cm^{-3}, *F*(000) = 564, Mo-K_α radiation, λ = 0.71073 Å, μ = 0.162 mm^{-1}, *T* = 173(2) K, $2\theta_{max}$ = 55.0°, 4689 reflections collected, 4689 unique (R_{int} = 0.0710, before merging), 3793 with $I_o > 2\sigma(I_o)$. Solved by using SHELXS[21] and refined with SHELX-97, full-matrix least-squares on F^2, 343 parameters, 0 restraints, *GoF* = 1.081, R_1 = 0.0769, wR_2 = 0.1251 (all reflections), 0.22 < $\Delta\rho$ < –0.31 e Å^{-3}.

Acknowledgments

Financial support by the DFG, the Fonds der Chemischen Industrie, COST D31, and the Academy of Finland (proj. no. 205729; K. R. and L. R.) is gratefully acknowledged. We thank Prof. E. Weinhold and M. Bahr for their help with the fluorescence spectroscopy.

[1] a) I. Stibor (Ed.), *Topics in Current Chemistry Vol. 255: Anion Sensing*, Springer, Heidelberg, **2005**; b) P. D. Beer, P. A. Gale, *Angew. Chem.* **2001**, *113*, 502; *Angew. Chem. Int. Ed.* **2001**, *40*, 486; c) A. Bianchi, K. Bowman-James, E. Garcia-Espana (Eds.), *Supramolecular Chemistry of Anions*, Wiley-VCH, New York, **1997**; d) K. Gloe (Ed.), *Macrocyclic Chemistry*, Springer, Berlin, **2005**.

[2] S. M. Rowe, S. Miller, E. J. Sorscher, *New Engl. J. Med.* **2005**, *352*, 1992.

[3] K. Bowman-James, *Acc. Chem. Res.* **2005**, *38*, 671.

[4] R. Herges, A. Dikmans, U. Jana, F. Köhler, P. G. Jones, I. Dix, T. Fricke, B. König, *Eur. J. Org. Chem.* **2002**, 3004.

[5] a) G. Müller, J. Riede, F. P. Schmidtchen, *Angew. Chem.* **1988**, *100*, 1574; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1516; b) A. Metzger, V. M. Lynch, E. V. Anslyn, *Angew. Chem.* **1997**, *109*, 911; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 862; c) C. Schmuck, *Chem. Commun.* **1999**, 843; d) C. Schmuck, *Chem. Eur. J.* **2000**, *6*, 709; e) R. Martinez-Manez, F. Sancanon, *Chem. Rev.* **2003**, *103*, 4419; f) J. Yoon, S. K. Kim, N. J. Singh, K. S. Kim, *Chem. Soc. Rev.* **2006**, *35*, 355.

[6] a) P. J. Gale, J. L. Sessler, V. Kral, V. Lynch, *J. Am. Chem. Soc.* **1996**, *118*, 5140; b) F. P. Schmidtchen, *Org. Lett.* **2002**, *4*, 431; c) J. L. Sessler, D. E. Gross, W.-S. Cho, V. M. Lynch, F.-P. Schmidtchen, G. W. Bates, M. E. Light, P. A. Gale, *J. Am. Chem. Soc.* **2006**, *128*, 12281; d) J. M. Llinares, D. Powell, K.

Bowman-James, *Coord. Chem. Rev.* **2003**, *204*, 57; e) K. Kavallieratos, S. R. de Gala, D. J. Austin, R. H. Crabtree, *J. Am. Chem. Soc.* **1997**, *119*, 2325; f) K. Kavallieratos, C. M. Bertao, R. H. Crabtree, *J. Org. Chem.* **1999**, *64*, 1675; g) P. A. Gale, *Acc. Chem. Res.* **2006**, *39*, 465.

[7] M. Albrecht, Triyanti, M. de Groot, M. Bahr, E. Weinhold, *Synlett* **2005**, 2095.

[8] a) H. Jiang, J.-M. Leger, P. Guionneau, I. Huc, *Org. Lett.* **2004**, *6*, 2985; b) H.-Y. Hu, C.-F. Chen, *Tetrahedron Lett.* **2006**, *47*, 175.

[9] M. Albrecht, K. Witt, E. Wegelius, K. Rissanen, *Tetrahedron* **2000**, *56*, 591.

[10] H. Jiang, J.-M. Leger, C. Dolain, P. Guionneau, I. Huc, *Tetrahedron* **2003**, *59*, 8365.

[11] a) P. Roychowdury, P. N. Das, B. S. Basak, *Acta Crystallogr., Sect. B* **1978**, *34*, 1047; b) T. Banerjee, N. N. Saha, *Acta Crystallogr., Sect. C* **1986**, *42*, 1408; c) M. Albrecht, K. Witt, R. Fröhlich, O. Kataeva, *Tetrahedron* **2002**, *58*, 561.

[12] a) K. A. Connors, *Binding Constants*, Wiley, New York, **1987**; b) C. S. Wilcox in *Frontiers in Supramolecular Chemistry and Photochemistry* (Eds.: H.-J. Schneider, H. Dürr), Wiley-VCH, Weinheim, **1991**, p. 123.

[13] A. Tejeda, A. I. Oliva, L. Simon, M. Grande, M. C. Caballero, J. R. Moran, *Tetrahedron Lett.* **2000**, *41*, 4563.

[14] O. S. Wolfbeis, *Fluorescence Spectroscopy: New Methods and Applications*, Springer, Berlin, **1993**.

[15] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, Revision D.02, Gaussian, Inc., Wallingford, CT, **2004**.

[16] S. F. Boys, F. Bernardi, *Mol. Phys.* **1970**, *19*, 553.

[17] A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *88*, 899.

[18] E. D. Glendening, A. E. Reed, J. E. Carpenter, F. Weinhold, *NBO 3.0 Program Manual*, Theoretical Chemistry Institute and Department of Chemistry, University of Wisconsin, Madison, Wisconsin.

[19] V. Amendola, M. Bonizzoni, D. Esteban-Gomez, L. Fabbrizzi, M. Licchelli, F. Sancenon, A. Taglietti, *Coord. Chem. Rev.* **2006**, *250*, 1451.

[20] M. Hassani, W. Cai, D. C. Holley, J. P. Lineswala, B. R. Maharjan, G. R. Ebrahimian, H. Seradj, M. G. Stocksdale, F. Mohammadi, C. C. Marvin, J. M. Gerdes, H. D. Beall, M. Behforouz, *J. Med. Chem.* **2005**, *48*, 7733.

[21] G. M. Sheldrick, *SHELXTL 6*, Bruker AXS Inc., Madison, Wisconsin, USA.

Received: February 13, 2007
Published Online: April 17, 2007

