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# Synthesis of Quinoline-Based Anion Receptors and Preliminary Anion Binding Studies with Selected Derivatives

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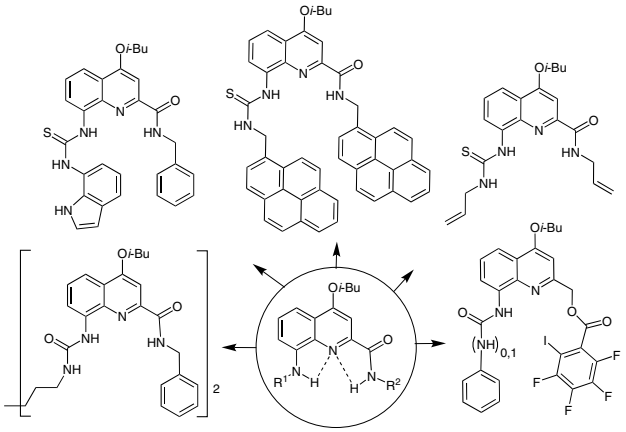

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**Abstract** Six quinoline-based anion receptors were designed, prepared, and characterized, among which the crystal structure of an indole derivative was obtained. Selected receptors were tested for the recognition of halide anions in solution and showed some selectivity of chloride over bromide and iodide.

**Key words** supramolecular chemistry, receptors, halides, quinolines, indoles

Supramolecular chemistry, 'the chemistry of molecular assemblies and of the intermolecular bond', is the basis for molecular sensing and recognition as well as molecular self-assembly.[2] Hereby, selectivity and specificity are most crucial. Anions are negatively charged chemical species, and are ubiquitous in human bodies and nature. For instance, the balance of chloride concentrations plays a vital role in the metabolism of human beings. Once disrupted, it will lead to certain diseases, such as cystic fibrosis, and even death.[3] Therefore, the specific binding of anions helps to understand binding mechanisms and to control anion concentrations. Yet, selective recognition of anionic species still is highly challenging. Reasons include the mainly electrostatic interaction, undefined shape, and low resistance to pH and solvents. Anion chemistry has slowly progressed since its birth in the late 1960s and its significance has been gradually recognized. Consequently, the sensing and recognition of various anions has substantially progressed from the beginning of 1990. As examples, Beer and co-workers extensively prepared anion-templated interlocked structures and applied them to sense and recognize anions.[4] Sessler and co-workers used calixpyrrole derivatives to sense and recognize anions.[5] Gale and his team focused on the build-up and applications of structurally simple but functionality-rich aromatic compounds.[6] Flood and co-workers applied click chemistry to generate shape-persistent CH hydrogen bonding arrays to sense and recognize anions.[7] However, it is still of tremendous significance to develop more anion receptors and utilize them to selectively sense and recognize anions.

4-Isobutoxy-8-aminoquinoline-2-carboxylic acids were first synthesized by Huc and Jiang in 2003 as building blocks for foldamers.[8] Due to their intriguing intra/intermolecular hydrogen bonding networks, they have been widely utilized in material and nanotechnology science, such as the aforementioned foldamers,[9] helical molecular capsules,[10] as well as molecular shuttles.[11] In 2005, based on observations of the solid state structure of an 8-hydroxyquinoline derivative,[12] we incorporated urea and amide moieties as anion binding sites attached to the quinoline backbone to obtain a fluorescent anion sensor.[13] The sensor showed 'turn-on' fluorescent properties upon the addition of anions and tremendously higher binding affinities towards fluoride anions than to other halide anions, which suggested that the two tails at the quinoline backbone can cooperatively participate in the anion binding. Subsequently, a detailed study of quinoline-based anion receptors with various substituents was performed.[14] Recently, the anion binding properties of a series of quinoline-based anion receptors in both $CDCl_3$ and DMSO-$d_6$ were further explored and the role of anion-π interactions for anion association has been probed.[15] Among the receptors, fluorinated ones show enhanced anion binding affinities over nonfluorinated ones. This presumably results from the increased acidity of the NH protons. Anion-π interactions might additionally contribute. More recently, a crown ether was introduced as a cation-binding site at the quinoline backbone to obtain an ion pair receptor and salt solubilizer.[16] The receptor can rec-

ognize ion pairs and shows positive cooperative effects. It solubilizes inorganic salts into organic solvents, such as $CHCl_3$ or DMSO.

Herein, we report the convenient synthesis of some novel quinoline-based receptors for the recognition of anions. Our approach shows how different functional groups can be established in the periphery of the quinoline backbone using amides and thioureas as linkers. The side groups are selected in order to introduce some functionality like additional hydrogen bonding units, halogen bonding groups, photoactive groups, linkers, or allyl units, which allow further derivatization. Selected compounds are tested in preliminary studies to recognize halide anions in $CDCl_3$ and DMSO-$d_6$ with satisfactory selectivity.

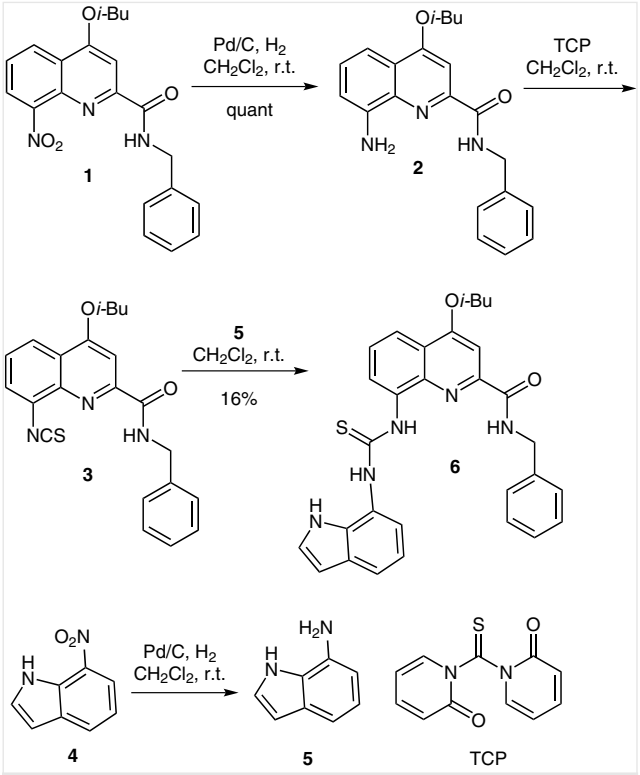
## An Indole-Substituted Quinoline Derivative

Indoles act as hydrogen bond donors and thus are potential anion binding sites.[17] They are able to transport anions through cell membranes.[18] In contrast to this, amide or urea groups as binding sites act as both, hydrogen bond donors as well as acceptors. Here, a 7-aminoindole was attached to the quinoline backbone to increase the anion associating ability. The synthesis started with 2-amido-4-isobutoxy-8-nitroquinoline **1**, which was prepared according to a previous report.[15] Initially, nitro compound **1** was reduced to amine **2** catalyzed by Pd/C using $H_2$ in dichloromethane at room temperature. Subsequently, amine **2** reacted with TCP (1,1′-thiocarbonyldi -2,2′-pyridone) to afford isothiocyanate **3** in dichloromethane at room temperature. 7-Nitro-1*H*-indole (**4**) was reduced to 7-amino-1*H*-indole (**5**) under the same conditions as described for **1**. Finally, the freshly prepared isothiocyanate **3** was coupled with amine **5** to obtain the target compound **6** in 16% yield (over two steps) (Scheme 1).

Single crystals of receptor **6**, which were appropriate for X-ray diffraction analysis were grown from a DMSO solution. Intramolecular hydrogen bonding is observed in the quinoline **6** between protons at the amide fragment and at the thioureido group and the nitrogen atom in the quinoline backbone. The corresponding distances are 2.253 Å and 2.139 Å, respectively (Figure 1). A molecule of quinoline **6** binds a molecule of DMSO. Three NH protons from the amide group and the thioureido group participate in the binding of the O atom of DMSO. The distances range from 1.956 to 2.480 Å. The NH proton of the indolyl group turns out of the quinoline plane and does not participate in the association of DMSO. It is found that this NH proton is bound by an $O_{amide}$ atom of another molecule of **6** via intermolecular hydrogen bonding showing a distance of 1.904 Å.

## A Dipyrene-Substituted Quinoline Derivative

Due to their characteristic photophysical and photochemical properties, such as high quantum yields of fluorescence, relatively long lifetimes, or controllable aromatic




**Scheme 1** Synthesis of indole-modified quinoline **6**

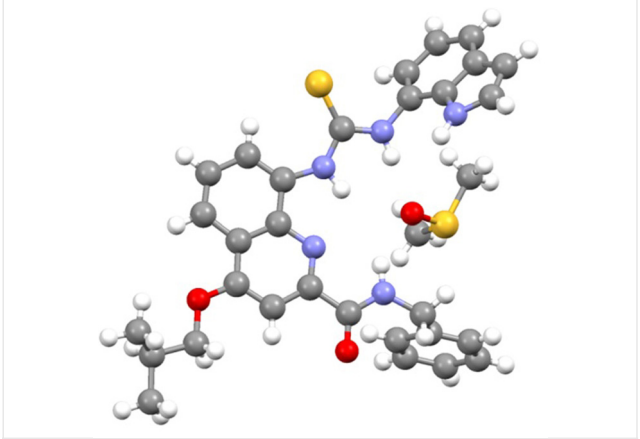
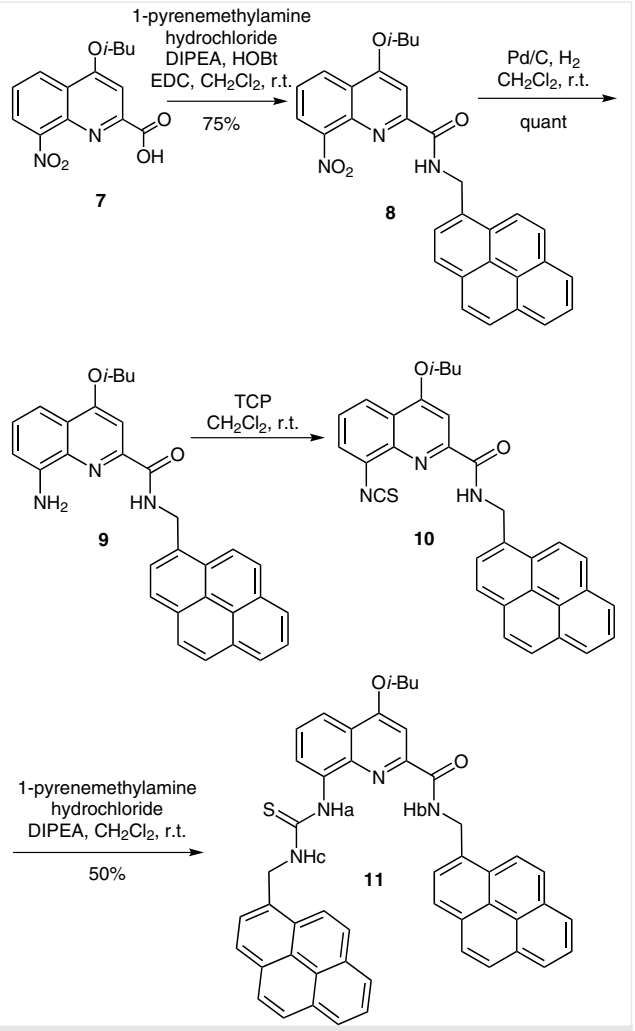


**Figure 1** The crystal structure of receptor **6**·DMSO (gray, C; white, H; blue, N; red, O; yellow, S).

aggregation,[19] pyrenes are widely used in supramolecular chemistry and biochemistry to sense anions,[20] cations,[21] or to functionalize oligonucleotides.[22]

Here, two pyrenyl moieties were attached to the quinoline backbone. The preparation of dipyrenyl decorated quinoline **11** started with 4-isobutoxy-8-nitroquinoline-2-carboxylic acid (**7**), which was synthesized according to the literature.[23] Initially, acid **7** was coupled with 1-pyrenemethylamine hydrochloride using DIPEA as a base and HOBt and EDC as coupling reagents in dichloromethane at

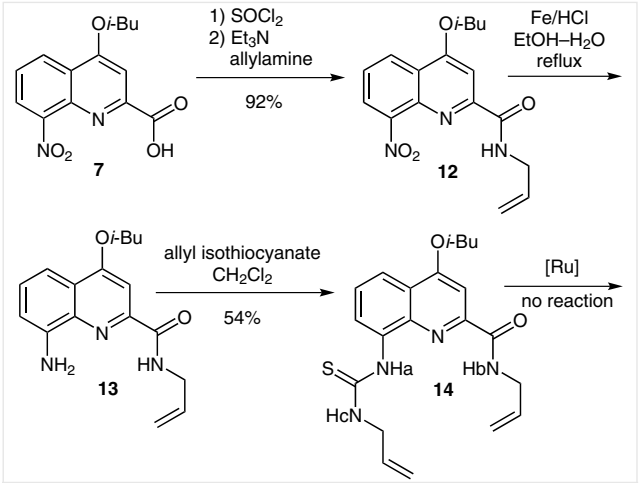
room temperature affording the pyrenemethyl-substituted quinoline **8**. The nitro group of **8** was hydrogenated to the amine **9**, which subsequently reacted with TCP in dichloromethane to isothiocyanate **10**. Finally, **10** was coupled with pyrenemethylamine hydrochloride using DIPEA as a base in dichloromethane to result in the dipyrenyl-substituted quinoline **11** in 50% yield (Scheme 2).




**Scheme 2** Synthesis of dipyrenyl-modified quinoline **11**

## A Diallyl-Substituted Quinoline Derivative

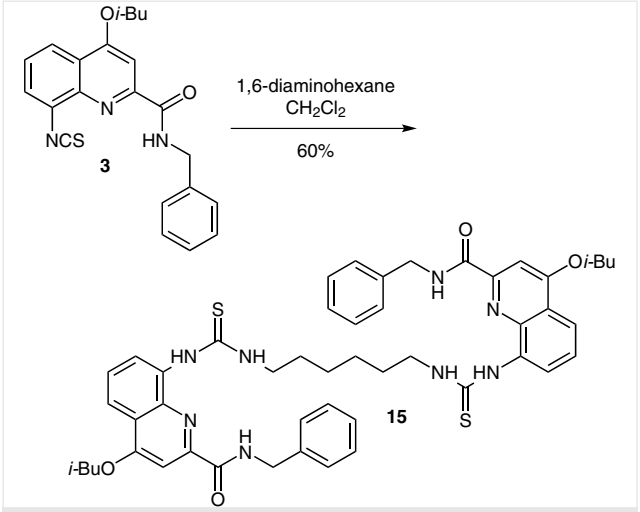
The preparation of a diallyl-substituted quinoline is described in Scheme 3. The starting material **7** was prepared according to literature. Initially, acid **7** was activated to acid chloride, which coupled with allylic amine using triethylamine as a base in dichloromethane at room temperature. Subsequently, the nitroquinoline **12** was reduced to the corresponding amine with Fe/HCl.[24] Finally, amine **13** reacted with allyl isothiocyanate to provide receptor **14** in 54% yield. The construction of macrocycles through Ru-catalyzed alkene metathesis was unsuccessful.




**Scheme 3** Synthesis of diallylic modified quinoline **14** and attempt of macrocyclization via alkene metathesis

## Synthesis of an Alkyl-Bridged Bisquinoline

Dicarboxylates, acting as intermediates in Krebs cycles, play a significant role in metabolism and many other biological processes.[25] Their accumulation in aerobic organisms can lead to some diseases. Consequently, it is of great use to selectively associate dicarboxylates using ditopic receptors. We already reported the high binding affinities of quinoline-based anion receptors towards benzoates in solution.[14] Herein, a compound bearing two quinoline-based anion binding sites was prepared as a potential receptor for dicarboxylates. Bisquinoline receptor **15** was obtained from the above described benzyl 8-isothiocyanatoquinoline-2-carboxamide **3** reacting with 1,6-diaminohexane in 60% yield (Scheme 4). The hexyl linker was selected due to solubility consideration as well as increasing its lipophilicity for further intracellar applications.




**Scheme 4** Preparation of bisquinoline **15**

**Quinolines Containing Halogen Bond Donors**

Halogen bonding refers to the noncovalent attractive interaction between halogen atoms (typically Cl, Br, and I) acting as acceptors and electron-rich atoms and groups.[26] It is regarded as a significant addition to hydrogen bonding. Its application is widely found in biological processes, crystal engineering, molecular sensing and recognition, and construction of supramolecular architectures.[27] Resnati and co-workers reported the applications of halogen bonding in molecular recognition in 2005. A tripodal heteroditopic receptor was prepared, and was utilized to recognize halide sodium salts in solid and solution.[28] Subsequently, the Taylor group has substantially used halogen bonding in molecular recognition in solution and provides significant and intriguing results.[29] Here, as an extension of our quinoline-based anion receptors, a halogen bond donor is introduced to the quinoline-backbone. The preparation is depicted in Scheme 5.

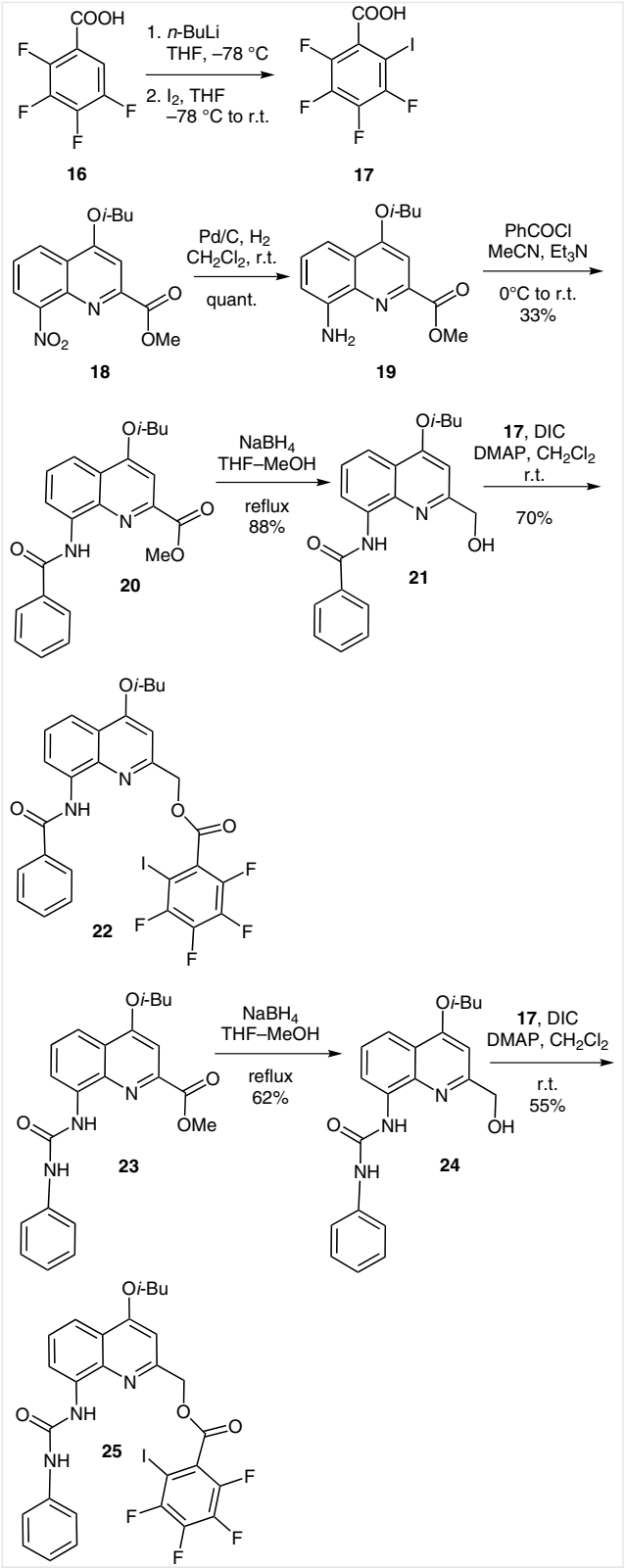
As a precursor of halogen bond donors, 2,3,4,5-tetrafluoro-6-iodobenozic acid was synthesized according to literature.[30] The nitroquinoline was reduced to the amine and subsequently reacted with benzoyl chloride to afford 8-amidoquinoline **20** in 33% yield. Afterwards, **20** was reduced to 2-hydroxymethylquinoline **21** in 88% yield.[31] After that, 2-hydroxymethylquinoline **21** was coupled with acid **17** catalyzed by *N*,*N*′-diisopropylcarbodiimide (DIC) and 4-dimethylaminopyridine (DMAP) in dichloromethane to afford the target compound **22** in 70% yield. Its analogue **25** was synthesized in 55% yield from quinoline **23** using a similar reaction procedure.

**Preliminary Anion-Binding Studies with Receptors 11, 14, 22 and 25**

The anion binding properties of **11**, **14**, **22**, and **25** were tested in $CDCl_3$ and DMSO-$d_6$ solution using $^1$H NMR spectroscopy.

Initially, the change of the chemical shift of receptor **14** upon addition of halide anions was explored in $CDCl_3$ at room temperature. The NH protons of receptor **14** shifted downfield when tetrabutylammonium bromide was added in $CDCl_3$ (Figure 2). The peaks in $^1$H NMR corresponding to Ha, Hb and Hc (for the assignment of protons, see Scheme 3) shifted downfield by 1.56, 1.76, and 3.40 ppm, respectively, which indicated strong interactions between bromide anions and receptor **14**.

The anion binding properties of compound **14** for bromide anion binding were investigated by $^1$H NMR titration experiments in $CDCl_3$ and DMSO-$d_6$. Figure 3 shows the titration curves of **14** in $CDCl_3$. Based on Job plots, the obtained data were fitted to a 1:1 ratio using standard methods of nonlinear regression. The binding constants in $CDCl_3$ were provided as $K_{ass}$ = 1040, 248, 55 $M^{-1}$, for **14** towards $Cl^-$, $Br^-$, $I^-$ anions, respectively. After the same treatment, the association behavior between **14** and halide anions in DMSO-$d_6$ were studied and summarized in Table 1.




**Scheme 5** Synthesis of quinolines **22** and **25**

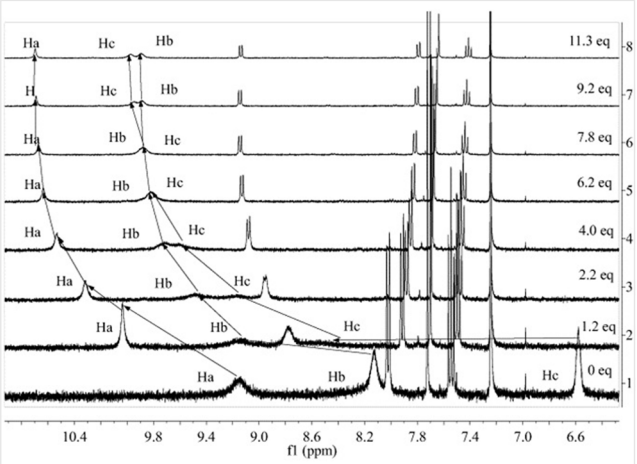



**Figure 2** Changes of the chemical shift of compound **14** upon addition of tetrabutylammonium bromide in $CDCl_3$ at 298.15 K

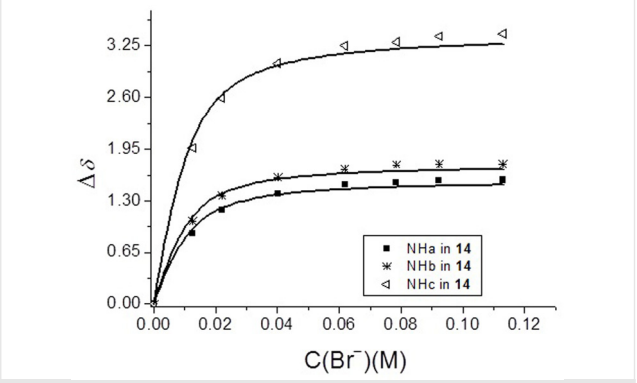



**Figure 3** Titration curves of compound **14** and tetrabutylammonium bromide in $CDCl_3$ at 298.15 K

Due to the poor solubility of **11** in $CDCl_3$, its binding behavior was only monitored in DMSO-$d_6$. The Job plots showed that the stoichiometric ratios between receptor **11** and chloride and bromide anions in DMSO-$d_6$ were 1:1. As a consequence, the titration curves were fitted according to a 1:1 ratio and provided corresponding binding constants of $K_{ass}$ = 238 and 75 $M^{-1}$, respectively, which was very similar to the ones observed for **14** (Figure 4).

Afterwards, the anion binding properties of compound **22** and **25** were investigated in $CDCl_3$ and DMSO-$d_6$ through $^1$H NMR spectra. For compound **22**, no bind affinities were detected towards halide anions in solution using the NMR spectra method. This is due to the ester linkage, which reduces the number of H-bond donors at the receptor. Halogen bonding is not strong enough to compensate for the lack of this unit.

The binding constants of compound **25** towards halide anions in chloroform were obtained for a 1:1 ratio and are reported in Table 1. The binding constants between compound **25** and halide anions using $^1$H NMR spectra were

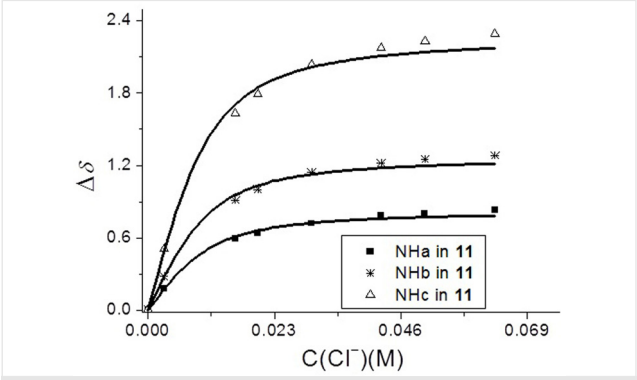



**Figure 4** Titration curves between receptor **11** and chloride anions in DMSO-$d_6$ at 298 K

measured as 19, 89, and 83 $M^{-1}$, for chloride, bromide, and iodide anions, respectively. In DMSO-$d_6$, no reliable data could be collected for **25**. The proton chemical shifts of urea groups in compound **25** went proportionally downfield with the addition of tetrabutylammonium chloride and bromide salts, and the chemical shifts were not affected by the addition of tetrabutylammonium iodide salts.

**Table 1** Binding Constants ($K$, $M^{-1}$) of Receptors **11**, **14**, and **25** with Halide Anions in $CDCl_3$ and DMSO-$d_6$ at 298.15 K[a]

| | $Cl^-$ | $Br^-$ | $I^-$ |
|---|---|---|---|
| in $CDCl_3$ | | | |
| **14** | 1040 | 248 | 55 |
| **25** | 19 | 89 | 83 |
| in DMSO-$d_6$ | | | |
| **11** | 238 | 75 | –[b] |
| **14** | 223 | 42 | –[b] |

[a] The binding constants were determined by $^1$H NMR titration experiments in $CDCl_3$ and DMSO-$d_6$, and fitted according to a 1:1 binding ratio based on Job plots. Errors are estimated to be less than 20%.
[b] No binding observed.

All of the obtained binding constants are summarized in Table 1. Both receptors of **11** and **14** show decreasing binding affinities towards halide anions in the order: $Cl^- > Br^- > I^-$. The trend presumably results from the inherent basicity of halide anions and complementary size. Receptor **14** shows somewhat weaker binding affinities towards chloride and bromide anions in DMSO-$d_6$ than in $CDCl_3$, which is predominantly ascribable to strong competition of DMSO due to its good hydrogen acceptance ability and strong solvation of anions. Interestingly, receptor **11** shows slightly higher binding affinities towards chloride and bromide anions than receptor **14**. This might be attributed to a possible intramolecular π-π stacking of two pyrenyl moieties, leading to a size reduction of the anion binding site. Association constants of up to 238 $M^{-1}$ in highly competitive DMSO are

relatively high taking into account that the receptor is neutral and binding is predominantly based on hydrogen bonding.

Compound **25**, which contains a bigger cavity for anion association, shows low but unusual selectivity towards halide anions in chloroform, decreasing in the order $Br^- \geq I^- > Cl^-$. Presumably, this sequence results from a compromise of basicity and size fitting. From the basicity aspect, bromide anions are stronger bases than iodide anions and can be more strongly bound by urea groups through hydrogen bonding. On the other hand, from size fitting aspect, iodide anions are larger and are better fitting to the cavity size. As a consequence, compound **25** shows similar binding affinities towards bromide and iodide anions. While, although chloride anions are the strongest base among the three anions, their size is too small to fit in the cavity. This makes chloride anions to be bound loosely through a combination of hydrogen bonding and halogen bonding or sole hydrogen bonding.

In conclusion, a series of novel quinoline-based compounds are designed, prepared, and characterized. The compounds contain various functionalities and are likely to serve as anion receptors to recognize anions in solution. In addition, some compounds are tested to recognize halide anions in solution and show satisfactory binding affinities and selectivities. In the case of **25**, an unusual selectivity sequence via a combination of hydrogen bonding and halogen bonding is observed. Further studies on modulation of the system in order to obtain better anion binding specificity and selectivity are underway.

Commercially available reagents were used as received. All solvents were used after distillation without further purification, unless otherwise indicated. $CH_2Cl_2$ and MeCN were stirred with $CaH_2$ overnight and distilled. All NMR spectra were recorded in $CDCl_3$, $CD_3CN$, or DMSO-$d_6$ by using a Varian Mercury 300, Varian 400, or Varian 600 spectrometer. Mass spectra were measured by using EI (70 eV) or ESI techniques on a Finnigan SSQ 7000 or Thermo Deca XP spectrometer. IR spectra were obtained on a Perkin-Elmer FTIR spectrometer 100. The samples were recorded as KBr pellets (4000–650 $cm^{-1}$). Elemental analyses were performed on CHN-O-Rapid Vario EL instrument from Heraeus. Melting points were obtained on Büchi B-540 melting point apparatus. X-ray diffraction data were collected at 100 K on a Bruker D8 goniometer equipped with an APEX CCD detector using MoKα radiation (λ = 0.71073 Å). The radiation source was an INCOATEC I-μS microsource. A cooling device Oxford Cryosystems 700 controller was used to ensure temperature stability during data collection. The SAINT software[32] was used for integration and SADABS[33] for multi-scan absorption correction. The structures were solved with direct methods (SHELXS97) and refined by full-matrix least squares on $F^2$ (SHELXL97).[34] Anisotropic displacement parameters were assigned to non-hydrogen atoms. H atoms bonded to N were localized in Difference Fourier maps; their positions were refined freely.

**7-Amino-1*H*-indole (5)**

A mixture of 7-nitroindole (**4**; 99 mg, 0.61 mmol) dissolved in $CH_2Cl_2$ (20 mL) and 10% Pd/C (30 mg) was stirred at r.t. under an atmosphere of $H_2$ (20 bar) overnight. The solution was filtered through Celite and the filtrate was evaporated to dryness. The residue was used directly in the next step.

**Compound 6**

7-Aminoindole (**5**; ca. 0.61 mmol, 1.0 equiv) was added to a solution of **3** (ca. 0.61 mmol) in anhydrous $CH_2Cl_2$ (15 mL) in a round-bottomed flask filled with $N_2$. The mixture was stirred overnight and then the solvent was evaporated. The residue was chromatographed on silica gel with $CH_2Cl_2$ as an eluent to afford **6**; yield: 50 mg (M = 523.65 g·mol$^{-1}$, n = 0.095 mmol, 16%), light yellow solid; mp 168–169 °C.

IR (KBr): 3405, 3263, 2962, 2031, 1668, 1535, 1422, 1345, 1218, 1163, 1057, 954, 860, 790, 727 $cm^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 11.17 (s, 1 H), 10.62 (s, 1 H), 10.42 (s, 1 H), 9.51 (dd, *J* = 7.80, 1.20 Hz, 1 H), 9.29 (s, 1 H), 7.87 (dd, *J* = 8.10, 2.50 Hz, 1 H), 7.71 (s, 1 H), 7.65 (t, *J* = 8.10 Hz, 1 H), 7.50 (d, *J* = 7.80 Hz, 1 H), 7.35 (m, 5 H), 7.24 (m, 1 H), 7.15 (d, *J* = 6.90 Hz, 1 H), 7.01 (t, *J* = 7.80 Hz, 1 H), 6.48 (m, 1 H), 4.66 (d, *J* = 6.60 Hz, 2 H), 4.18 (d, *J* = 6.60 H, 2 H), 2.23 (m, 1 H), 1.11 (d, *J* = 6.90 Hz, 6 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 179.37, 164.34, 163.22, 149.92, 139.56, 138.56, 136.25, 132.59, 129.83, 128.80, 127.55, 127.32, 126.08, 123.11, 121.80, 120.14, 119.40, 119.28, 118.37, 115.41, 102.11, 99.91, 75.16, 43.08, 28.11, 19.40.

MS (EI): *m*/*z* (%) = 174.1 (100.00, $[C_9H_6N_2S]^+$), 349.3 (19.11, $[C_{21}H_{23}N_3O_2]^+$), 132.2 (25.52, $[C_8H_8N_2]$), 391.3 (5.17, $[C_{22}H_{21}N_3O_2S]$).

Anal. Calcd for $C_{30}H_{29}N_5O_2S$: C, 68.81; H, 5.58; N, 13.37. Found: C, 68.26; H, 5.65; N, 13.25.

**X-ray Data**[35]

X-ray quality crystals were obtained from DMSO: $C_{30}H_{29}N_5O_2S{\cdot}(CH_3)_2SO$; *Mr* = 601.77; crystal size 0.43 × 0.36 × 0.25 $mm^3$; orthorhombic; space group *Fdd*2, *a* = 28.616 (2) Å, *b* = 33.622 (2) Å, *c* = 12.8697 (9) Å; *β* = 90°; *V* = 12382.3 (15) Å$^3$; *Z* = 16; $\rho_{cal}$ = 1.291 g $cm^{-3}$; *μ* = 0.21 $mm^{-1}$; *F*(000) = 5088; 36864 collected reflections ($\theta_{max}$ = 22.2306°) of which 6333 were independent ($R_{int}$ = 0.061); $T_{max}$ = 0.949; $T_{min}$ = 0.914; *T* = 100 K; full-matrix least-square on $F^2$ with 1 restraint and 383 parameters; GOF = 1.05; *R*1 = 0.038 ($I > 2\sigma(I)$); *wR*2 (all data) = 0.088; peak/hole = 0.21/–0.17 e Å$^{-3}$.

**Compound 8**

To an anhydrous $CH_2Cl_2$ (20 mL) solution of a mixture of 4-isobutoxy-8-nitroquinoline-2-carboxylic acid (**7**; 232 mg, 0.8 mmol, 0.8 equiv) and 1-pyrenemethylamine hydrochloride (267 mg, 1.0 mmol, 1.0 equiv) were successively added DIPEA (0.5 mL), HOBt (135.13 mg, 1.0 mmol, 1.0 equiv), and EDC·HCl (191 mg, 1.0 mmol, 1.0 equiv). The progress of the reaction was monitored by TLC (eluent: $CH_2Cl_2$). Upon completion after stirring for 6 h under $N_2$ at r.t., the reaction mixture was washed with sat. aq $NH_4Cl$ (ca. 20 mL). The organic extract was dried ($Na_2SO_4$) and filtered. The solvent was evaporated to dryness and the residue was purified by recrystallization from $CH_2Cl_2$–MeOH (2:1 v/v) to afford **8**; yield: 300 mg (M = 503.18 g·mol$^{-1}$, n = 0.60 mmol, 75%). light yellow solid; mp 210–212 °C.

IR (KBr): 3822, 3381, 2961, 2877, 2324, 2099, 1893, 1679, 1519, 1358, 1135, 1017, 874, 832, 754 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.75 (t, *J* = 5.40 Hz, 1 H), 8.44 (m, 2 H), 8.18 (m, 4 H), 8.06, (m, 5 H), 7.88 (s, 1 H), 7.59 (m, 1 H), 5.46 (d, *J* = 6.00 Hz, 2 H), 4.15 (d, *J* = 6.60 Hz, 2 H), 2.31 (m, 1 H), 1.16 (d, *J* = 6.90 Hz, 6 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 190.32, 163.44, 163.20, 153.09, 147.58, 138.93, 131.26, 131.11, 130.93, 130.76, 128.84, 128.16, 127.39, 126.68, 126.55, 125.92, 125.23, 125.13, 124.91, 123.30, 122.71, 100.10, 41.78, 28.07, 19.14.

MS (EI): *m*/*z* (%) = 230.3 (100.00, $[C_{17}H_{12}N]^+$), 399.2 (20.03, $[C_{27}H_{16}N_2O_2]^+$), 503.3 (28.00, $[M]^+$).

Anal. Calcd for $C_{31}H_{25}O_4N_3$: C, 73.94; H, 5.00; N, 8.34. Found: C, 73.39; H, 5.11; N, 8.09.

### Compound 9

A mixture of **8** (85 mg, 0.169 mmol, 1.0 equiv) dissolved in $CH_2Cl_2$ (20 mL) and 10% Pd/C (30 mg) was stirred at r.t. under an atmosphere of $H_2$ (20 bar) overnight. The solution was filtered through Celite and the filtrate was evaporated to dryness. The residue was used directly in the next step.

### Compound 10

To an anhydrous $CH_2Cl_2$ (20 mL) solution of **9** (ca. 0.169 mmol, 1.0 equiv) was added TCP (43 mg, 0.186 mmol, 1.1 equiv). After stirring for 8 h under $N_2$ atmosphere at r.t., the solvent was evaporated to dryness, and the residue was chromatographed on silica gel with hexane as an eluent to allow the isolation of **10** as a yellow solid, which was used for the next reaction without characterization.

### Compound 11

To an anhydrous $CH_2Cl_2$ (20 mL) solution of 1-pyrenemethylamine hydrochloride (75 mg, 0.279 mmol, 1.6 equiv) in a round-bottomed flask filled with $N_2$ were successively added DIPEA (0.5 mL) and **10** (ca. 0.169 mmol, 1.0 equiv) . The mixture was stirred overnight and then the solvent was evaporated. The residue was chromatographed on silica gel with $CH_2Cl_2$ as an eluent to give **11**; yield: 63 mg (M = 746.92 g·mol$^{-1}$, n = 0.084 mmol, 50%); light yellow solid; mp 186–188 °C.

IR (KBr): 3289, 3041, 2927, 2325, 2108, 1733, 1646, 1516, 1458, 1314, 1228, 1178, 1037, 915, 842, 755, 701, 680 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 10.49 (s, 1 H), 9.72 (t, *J* = 5.70 Hz, 1 H), 9.33 (d, *J* = 7.50 H, 1 H), 9.21 (t, *J* = 4.50 Hz, 1 H), 8.42 (d, *J* = 9.30 Hz, 2 H), 8.33 (d, *J* = 7.50 Hz, 1 H), 8.24 (m, 4 H), 8.08 (m, 8 H), 7.93 (m, 3 H), 7.84 (d, *J* = 8.40 Hz, 1 H), 7.66 (m, 2 H), 5.52, 5.51 (d, *J* = 4.20 Hz, 2 H), 5.25, 5.23 (d, *J* = 5.70 Hz, 2 H), 4.12 (d, *J* = 6.30 Hz, 2 H), 2.18 (m, 1 H), 1.08 (d, *J* = 3.90 Hz, 6 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 163.18, 138.91, 136.36, 136.32, 132.67, 131.99, 131.16, 130.74, 130.60, 130.42, 128.93, 128.34, 127.73, 127.43, 126.64, 125.87, 125.77, 125.69, 125.55, 125.20, 124.98, 123.60, 123.43, 121.85, 119.25, 115.37, 99.75, 75.15, 45.83, 28.09, 19.38 (some signals were found to be overlapping).

MS (ESI): *m*/*z* (%) = 780.80 (100.00, $[M + H_2O + OH]^-$), 745.07 (52.48, $[M - H]^-$).

Anal. Calcd for $C_{49}H_{38}N_4O_2S{\cdot}0.5H_2O$: C, 77.85; H, 5.20; N, 7.41. Found: C, 77.83; H, 4.85; N, 7.24.

### Compound 12

A solution of the acid **7** (250 mg, 0.86 mmol, 1.0 equiv) in $SOCl_2$ (10 mL) was heated to reflux for 3 h. The excess of $SOCl_2$ was blown out using $N_2$ gas. The acid chloride was dissolved in anhydrous $CH_2Cl_2$ (5 mL), and added over a period of 10 min to a solution of allylamine (0.128 mL, 1.72 mmol, 2.0 equiv) and $Et_3N$ (478 mg, 4.73 mmol, 5.5 equiv) in $CH_2Cl_2$ (10 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred overnight. The solvent was removed and the residue was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$ to afford the pure product **12**; yield: 260 mg (M = 329.14 g·mol$^{-1}$, n = 0.79 mmol, 92%); light yellow solid; mp 105–106 °C.

IR (KBr): 3390, 3058, 2965, 2079, 1679, 1588, 1526, 1421, 1356, 1260, 1139, 1015, 865, 795, 759 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.51 (dd, *J* = 8.40, 1.50 Hz, 1 H), 8.30 (br, 1 H), 8.13 (dd, *J* = 7.20, 1.80 Hz, 1 H), 7.81 (s, 1 H), 7.66 (m, 1 H), 5.97 (m, 1 H), 5.28 (m, 2 H), 4.13 (m, 4 H), 2.30 (m, 1 H), 1.15 (d, *J* = 6.60 Hz, 6 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 163.46, 163.19, 153.13, 147.69, 138.91, 133.59, 126.65, 125.15, 124.95, 123.26, 116.46, 99.98, 91.88, 41.98, 28.06, 19.13.

MS (ESI): *m*/*z* (%) = 330.14481 (100.00, $[M + H]^+$).

Anal. Calcd for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.81; N, 12.76. Found: C, 62.12; H, 5.63; N, 12.75.

### Compound 13

Iron powder (220 mg, 3.93 mmol, 13.0 equiv) and concd HCl (ca. 14 µL) were added to a solution of nitroquinoline **12** (100 mg, 0.304 mmol, 1.0 equiv) in EtOH (10 mL) and $H_2O$ (ca. 2 mL) and the mixture was heated to reflux for 90 min. After cooling the mixture to r.t., $CH_2Cl_2$ (ca. 15 mL) was added, and the organic layer was dried ($MgSO_4$). After filtration through Celite and evaporation of the solvent, the residue was used directly in the next step without further purification and characterization.

### Compound 14

Allyl isothiocyanate (0.090 mL, 0.912 mmol, 3.0 equiv) was added to a solution of **13** (ca. 0.304 mmol, 1.0 equiv) in anhydrous $CH_2Cl_2$ (15 mL) in a round-bottomed flask filled with $N_2$. The mixture was heated to reflux and stirred for 8 h, and then the solvents were evaporated. The residue was purified by flash chromatography on silica gel eluting with $CH_2Cl_2$–EtOAc (15:1 v/v) to afford the pure product **14**; yield: 65 mg (M = 398.52 g·mol$^{-1}$, n = 0.163 mmol, 54%); light yellow solid; mp 177–178 °C.

IR (KBr): 3293, 2964, 1640, 1534, 1356, 1316, 1229, 1026, 920, 761, 695 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 10.30 (s, 1 H), 9.27 (br, 1 H), 9.20 (dd, *J* = 8.00, 1.20 Hz, 1 H), 8.88 (t, *J* = 5.20 Hz, 1 H), 7.82 (dd, *J* = 8.40, 1.20 Hz, 1 H), 7.62 (s, 1 H), 7.59 (t, *J* = 8.00 Hz, 1 H), 5.95 (m, 2 H), 5.17 (m, 4 H), 4.23 (t, *J* = 5.40 Hz, 2 H), 4.12 (d, *J* = 6.40 Hz, 1 H), 4.05 (t, *J* = 5.60 Hz, 2 H), 2.19 (m, 1 H), 1.05 (d, *J* = 6.10 Hz, 6 H).

$^{13}$C NMR (151 MHz, $CDCl_3$): δ = 180.54, 164.17, 163.48, 150.25, 139.53, 134.20, 133.72, 132.80, 126.66, 122.81, 120.20, 117.97, 117.70, 116.73, 99.71, 75.36, 47.48, 42.12, 28.08, 19.13.

MS (ESI): *m*/*z* (%) = 56.3 (100.00, $[C_3H_6N]^+$), 341.9 (80.19, $[C_{18}H_{20}N_3O_2S]^+$), 285.9 (60.96, $[C_{17}H_{21}N_2O_2]^+$), 398.0 (23.04, $[M]^+$).

Anal. Calcd for $C_{21}H_{26}N_4O_2S$: C, 63.29; H, 6.58; N, 14.06. Found: C, 63.09; H, 6.74; N, 13.80.

**Compound 15**

1,6-Diaminohexane (27 mg, 0.23 mmol, 1.0 equiv) was added to a solution of **3** (ca. 0.46 mmol) in anhydrous $CH_2Cl_2$ (15 mL), in a round-bottomed flask filled with $N_2$. The mixture was stirred overnight and then the solvent was evaporated. The residue was recrystallized from MeOH– $CH_2Cl_2$ (1/2 v/v) to give **15**; yield: 124 mg (M = 899.18 g·mol$^{-1}$, n = 0.138 mmol, 60%); light yellow solid; mp 219–221 °C.

IR (KBr): 3310, 2963, 2929, 1643, 1544, 1457, 1353, 1316, 1258, 1140, 1039, 1003, 869, 816, 757, 699 cm$^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 10.29 (s, 2 H), 9.69 (s, 2 H), 9.16 (dd, *J* = 8.10, 1.20 Hz, 2 H), 8.75 (s, 2 H), 7.84 (dd, *J* = 8.40, 1.20 Hz, 2 H), 7.66 (s, 2 H), 7.59 (t, *J* = 8.10 Hz, 2 H), 7.34 (m, 10 H), 4.65 (d, *J* = 6.00 Hz, 4 H), 4.16 (d, *J* = 6.60 Hz, 4 H), 3.54 (s, 4 H), 2.22 (m, 2 H), 1.60 (s, 4 H), 1.38 (m, 4 H), 1.10 (d, *J* = 6.60 Hz, 12 H).

$^{13}$C NMR (151 MHz, DMSO-$d_6$): δ = 180.19, 164.38, 163.10, 149.88, 139.67, 138.78, 136.55, 128.71, 127.64, 127.30, 121.80, 119.10, 114.93, 99.64, 75.07, 43.80, 42.99, 28.67, 28.10, 26.64, 19.40.

MS (ESI): *m*/*z* (%) = 896.93 (100.00, [M – H]$^-$), 933.00 (12.05, [M + $H_2O$ + OH]$^-$).

Anal. Calcd for $C_{50}H_{58}N_8O_4S_2$·$H_2O$: C, 65.48; H, 6.59; N, 12.22. Found: C, 65.03; H, 6.45; N, 12.15.

**Methyl 8-Amino-4-isobutoxyquinoline-2-carboxylate (19)**

A mixture of methyl 4-isobutoxy-8-nitroquinoline-2-carboxylate (**18**; 300 mg, 0.99 mmol) dissolved in $CH_2Cl_2$ (10 mL) and 10% Pd/C (50 mg) was stirred at r.t. under an atmosphere of $H_2$ (20 bar) for 5 h. The solution was filtered over Celite and the filtrate was evaporated to dryness. The residue was used directly in the next step.

**Methyl 8-Benzamido-4-isobutoxyquinoline-2-carboxylate (20)**

To a 100 mL two-necked round-bottomed flask equipped with a magnetic stirrer was added **19** (270 mg, 0.99 mmol) under $N_2$ atmosphere. Then, MeCN (ca. 40 mL) and $Et_3N$ (0.33 mL) were added to the flask. After cooling the mixture to 0 °C, benzoyl chloride (140 mg, 1 mmol) was added dropwise by using a syringe. The suspension was allowed to reach r.t. and stirred overnight. When the reaction was complete, the solvent was evaporated; the residue was dissolved in $CH_2Cl_2$ (ca. 50 mL) and washed with sat. aq $NH_4Cl$ (ca. 50 mL). The organic extract was dried ($Na_2SO_4$), filtered, and the filtrate was evaporated to dryness. The residue was purified by silica gel column chromatography using $CH_2Cl_2$–hexane (5:2) as eluent; yield: 122 mg (33%); colorless solid; mp 124 °C.

IR (KBr): 3845, 3328, 2922, 2858, 2658, 2302, 2095, 1911, 1722, 1675, 1533, 1365, 1244, 1110, 1028, 981, 914, 771, 694 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 10.87 (s, 1 H), 8.95 (dd, *J* = 7.50, 1.50 Hz, 1 H), 8.11 (m, 2 H), 7.96 (dd, *J* = 8.40, 1.20 Hz, 1 H), 7.58 (m, 5 H), 4.07 (m, 5 H), 2.31 (m, 1 H), 1.17 (d, *J* = 6.90 Hz, 6 H).

$^{13}$C NMR (150 MHz, $CDCl_3$): δ = 165.74, 165.22, 163.13, 146.72, 138.97, 135.19, 134.94, 133.62, 131.86, 130.14, 128.78, 128.46, 128.44, 127.30, 122.07, 117.35, 115.63, 101.22, 52.91, 28.19, 19.21.

MS (EI, 70 eV): *m*/*z* (%) = 377.9 (100, [M]$^+$).

Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.94; H, 6.03; N, 7.22.

***N*-[2-(Hydroxymethyl)-4-isobutoxyquinolin-8-yl]benzamide (21)**

A mixture of **20** (122 mg, 0.32 mmol) and $NaBH_4$ (122 mg, 3.22 mmol) in THF (10 mL) was stirred at 65 °C for 30 min. Then, MeOH (2.6 mL) was added dropwise during 30 min and effervescence was observed. Stirring was maintained for further 60 min. The reaction mixture was cooled to r.t. and then evaporated to give the crude solid, which was dissolved in $CH_2Cl_2$ (ca. 20 mL). The organic layer was washed with $H_2O$ (ca. 20 mL) and brine (ca. 20 mL), and dried ($Na_2SO_4$). The solvent was evaporated to afford the crude product. This was purified by silica gel column chromatography using $CH_2Cl_2$–2% MeOH as eluent;[31] yield: 99 mg (88%); colorless solid; mp 147 °C.

IR (KBr): 3881, 3322, 2928, 2325, 2089, 1894, 1549, 1313, 1151, 1037, 914, 819, 699 cm$^{-1}$.

$^1$H NMR (600 MHz, $CDCl_3$): δ = 10.46 (s, 1 H), 8.92 (d, *J* = 7.80 Hz, 1 H), 8.02 (d, *J* = 7.20 Hz, 2 H), 7.91 (dd, *J* = 8.40, 1.20 Hz, 1 H), 7.55 (m, 4 H), 6.76 (s, 1 H), 4.91 (s, 2 H), 3.98 (d, *J* = 6.60 Hz, 2 H), 3.38 (br, 1 H), 2.27 (m, 1 H), 1.14 (d, *J* = 6.60 Hz, 6 H).

$^{13}$C NMR (150 MHz, $CDCl_3$): δ = 165.37, 159.30, 138.18, 137.94, 137.38, 137.31, 136.04, 135.09, 133.58, 131.85, 129.05, 127.09, 125.99, 120.72, 117.71, 116.16, 98.00, 64.96, 29.68, 27.96, 19.12.

MS (EI, 70 eV): *m*/*z* (%) = 349.7 (100, [M]$^+$).

Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 8.0. Found: C, 70.85; H, 7.91; N, 7.40.

**(8-Benzamido-4-isobutoxyquinolin-2-yl)methyl 2,3,4,5-Tetrafluoro-6-iodobenzoate (22)**

To a 50 mL two-necked round-bottomed flask were added **21** (90 mg, 0.267 mmol), 2,3,4,5-tetrafluoro-6-iodobenzoic acid (**17**; 125 mg, 0.390 mmol), DIC (0.1 mL), and DMAP (5.0 mg) in $CH_2Cl_2$ (25 mL). The reaction mixture was stirred for 18 h under $N_2$ atmosphere. The resulting solution was quenched with sat. aq $NH_4Cl$ (ca. 15 mL) and extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic extracts were washed with brine (ca. 30 mL), dried ($Na_2SO_4$), and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography using $CH_2Cl_2$–hexane (10:1) as eluent; yield: 119 mg (70%); light yellow solid; mp 135–136 °C.

IR (KBr): 3832, 3351, 3157, 3071, 2961, 2877, 2643, 2325, 2107, 1991, 1919, 1739, 1662 (s), 1596, 1526, 1457, 1366, 1319, 1256, 1199, 1106, 1040, 983, 901, 799, 757, 695 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 10.65 (s, 1 H), 8.93 (dd, *J* = 7.60, 1.20 Hz, 1 H), 8.02 (m, 2 H), 7.91 (dd, *J* = 8.40, 1.20 Hz, 1 H), 7.52 (m, 4 H), 6.92 (s, 1 H), 5.66 (s, 2 H), 3.99 (d, *J* = 6.40 Hz, 2 H), 2.28 (m, 1 H), 1.12 (d, *J* = 6.80 Hz, 6 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 177.45, 165.31, 163.07, 153.89, 138.93, 135.19, 134.12, 131.73, 128.73, 127.18, 126.60, 120.56, 117.40, 115.81, 99.44, 69.52, 28.14, 19.21. Due to the coupling with $^{19}$F, C-atoms at the fluorinated ring system were not observed.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –112.18 (m, 1 F), –136.35 (m, 1 F), –148.76 (m, 1 F), –151.89 (m, 1 F).

MS (EI, 70 eV): *m*/*z* (%) = 652.0 (96.42, [M]$^+$).

Anal. Calcd for $C_{28}H_{21}F_4IN_2O_4$·0.5 $H_2O$: C, 50.85; H, 3.35; N, 4.24. Found: C, 51.01; H, 3.70; N, 4.29.

**1-[2-(Hydroxymethyl)-4-isobutoxyquinolin-8-yl]-3-phenylurea (24)**

A mixture of methyl 4-isobutoxy-8-(3-phenylureido)quinoline-2-carboxylate (**23**; 121 mg, 0.31 mmol) and $NaBH_4$ (116 mg, 3.07 mmol) in THF (10 mL) was stirred at 65 °C for 30 min. Then, MeOH (2.5 mL) was added dropwise during 30 min and effervescence was observed. Stirring was maintained for further 60 min. The reaction mixture was cooled to r.t. and then evaporated to give the crude product, which was dissolved in $CH_2Cl_2$ (ca. 25 mL). The organic layer was washed with $H_2O$ (ca. 20 mL) and brine (ca. 20 mL), and dried ($Na_2SO_4$). The

solvent was evaporated to give the product, which was purified by silica gel column chromatography using $CH_2Cl_2$–2% MeOH as eluent; yield: 70 mg (62%); colorless solid; mp 192–194 °C.

IR (KBr): 3870 (w), 3332 (m), 3258 (m), 3080 (m), 2956 (m), 2879 (m), 2638 (w), 2319 (w), 2079 (w), 1926 (w), 1669 (m), 1603 (s), 1520 (s), 1429 (m), 1311 (s), 1233 (m), 1176 (m), 1065 (s), 973 (m), 841 (m), 747 (s) $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.73 (s, 1 H), 9.48 (s, 1 H), 8.49 (dd, *J* = 12.00, 1.28 Hz, 1 H), 7.66 (dd, *J* = 8.40, 1.20 Hz, 1 H), 7.52 (s, 1 H), 7.50 (s, 1 H), 7.44 (t, *J* = 8.00 Hz, 1 H), 7.28 (t, *J* = 7.80 Hz, 2 H), 7.12 (s, 1 H), 6.98 (t, *J* = 7.40 Hz, 1 H), 5.48 (t, *J* = 5.80 Hz, 1 H), 4.76 (d, *J* = 5.69 Hz, 2 H), 4.03 (d, *J* = 6.40, 2 H), 2.18 (m, 1 H), 1.05 (d, *J* = 6.80 Hz, 6 H).

$^{13}C$ NMR (150 MHz, $CDCl_3$): δ = 158.34, 158.27, 152.93, 137.96, 129.55, 126.15, 124.83, 124.73, 123.72, 123.61, 123.11, 122.73, 122.12, 120.68, 116.71, 116.64, 114.65, 97.81, 64.37, 27.87, 19.14.

MS (EI, 70 eV): *m*/*z* (%) = 365.4 (2.9, $[M]^+$), 273.3 (79.2, $[C_{21}H_{23}N_3O_3 - NH_2C_6H_5]^+$).

Anal. Calcd for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.5. Found: C, 67.73; H, 6.58; N, 11.28.

### [4-Isobutoxy-8-(3-phenylureido)quinoline-2-yl]methyl 2,3,4,5-Tetrafluoro-6-iodobenzoate (25)

To a 50 mL two-necked round-bottomed flask were added **24** (60 mg, 0.16 mmol), 2,3,4,5-tetrafluoro-6-iodobenzoic acid (**17**; 81 mg, 0.25 mmol), DIC (0.08 mL) and DMAP (5.2 mg) in $CH_2Cl_2$ (25 mL). The reaction mixture was stirred for 18 h under $N_2$ atmosphere. The resulting solution was quenched with sat. aq $NH_4Cl$ (ca. 15 mL) and extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic extracts were washed with brine (ca. 30 mL), dried ($Na_2SO_4$), and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography using $CH_2Cl_2$–hexane (10:1) as eluent; yield: 60 mg (55%); light yellow solid; mp 161–164 °C.

IR (KBr): 3393, 3328, 3061, 2960, 2873, 2162, 2117, 1977, 1935, 1857, 1792, 1722, 1699, 1598, 1531, 1498, 1466, 1441, 1424, 1377, 1314, 1265, 1222, 1197, 1113, 1071, 1022, 976, 893, 794, 752, 690 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 9.30 (s, 1 H), 8.59 (dd, *J* = 8.00, 0.08 Hz, 1 H), 7.79 (dd, *J* = 8.40, 1.20 Hz, 1 H), 7.47 (m, 3 H), 7.37 (t, *J* = 8.00 Hz, 2 H), 7.14 (t, *J* = 7.40 Hz, 1 H), 6.87 (s, 1 H), 6.75 (s, 1 H), 5.53 (s, 2 H), 3.96 (d, *J* = 6.40 Hz, 2 H), 2.26 (m, 1 H), 1.12 (d, *J* = 6.80 Hz, 6 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 45.26, 139.40, 138.05, 129.28, 126.74, 124.24, 121.25, 107.65, 100.12, 93.68, 28.14, 26.50, 19.20. Due to the coupling with $^{19}F$, C-atoms at the fluorinated ring system were not observed.

$^{19}F$ NMR (376 MHz, $CDCl_3$): δ = –112.19 (m, 1 F), –136.65 (m, 1 F), –148.70 (m, 1 F), –151.82 (m, 1 F).

MS (ESI): *m*/*z* (%) = 668.06421 (95, $[M + H]^+$).

Anal. Calcd for $C_{28}H_{22}F_4IN_3O_4$: C, 50.39; H, 3.32; N, 6.30. Found: C, 50.12; H, 3.67; N, 6.17.

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## Supporting Information

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(35) CCDC 1013128 contains 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.