Quinoline-based Anion Receptors and Anion-π Interactions

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Herrn Prof. Dr. D. Enders danke ich herzlich für die freundliche Übernahme des Korreferates.

For my parents & Junhong

For my family

What are the important problems of your field?
What important problems are you working on?
If what you are doing is not important
and if you don't think it is going to
lead to something important,
why are you working on it?

Dr. Richard Hamming

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List of Abbreviations

18-crown-6: 1,4,7,10,13,16- hexaoxacyclooctadecane

2D: two dimensional

Å: Ångström, 0.1 nm

Ac: acetyl

aq/aq.: aqueous

m.p./mp: melting point

br: broad

Bu: butyl

Bu_4N^+,: tetrabutylammonium cations

$Bu_4NX/Bu_4N^+X^-$: tetrabutylammonium halide

calcd. cal: calculated

$CDCl_3$: deuterated chloroform, deuterochloroform

CD_3CN: deuterated acetonitrile, trideuteroacetonitrile

Celite: a form of diatomaceous earth

CH_3CN: acetonitrile

CI: chemical ionization

concd.: concentrated

d: doublet

dd: doublet of doublet

DCM/CH_2Cl_2: dichloromethane

DIAD: diisopropyl azodi carboxylate

DIPEA: N,N-diisopropylethyl amine

DMF: N,N-dimethylformamide

DMSO: dimethyl sulfoxide

DMSO-d_6: deuterated dimethyl sulfoxide, hexadeuterodimethyl sulfoxide

EDC/ EDC·HCl: N-(3-dimethyl aminopropyl) -N′-ethylcarbo diimide hydrochloride

EI: electron ionization

eq./equiv.: equivalent(s)

ESI-MS: electrospray ionization mass spectrometry

h: hour(s)

HBTU: O-(Benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate

HClcc: concentrated hydrochloric acid

Hz: Hertz

HOBt: 1-hydroxybenzotriazole

i-: *iso*-

IR: infrared

i-Bu-: *iso*-butyl-

K: binding constant(s)

m: multiplet

M: molarity [mol L^{-1}]; molecular mass [g mol^{-1}]

min: minute(s)

MeOH: methanol

MS: mass spectrometry

n-Bu: *n*-butyl

nd/not det.: not determined

NMR: nuclear magnetic resonance

NOESY: Nuclear Overhauser Enhancement Spectroscopy

Pd/C: palladium on carbon

Ph: phenyl

PPA: polyphosphoric acid

ppm: part(s) per million

Pr: propyl

quant.: quantitative

recryst.: recrystallization

rt/rt.: room temperature

s: singlet

t: triplet

t: *tert*-; tertiary-

TCP: 1,l'-thiocarbonyldi-2,2'-pyridone

TEA: triethylamine

tert-: tertiary-

TFA: trifluoroacetic acid

THF: tetrahydrofuran

TLC: thin layer chromatography

TMS: tetramethylsilane

v: volume

Chapter 1 Introduction

1.1 Supramolecular Chemistry

Since Charles Pedersen found accidently crown ethers in 1967, supramolecular chemistry has developed rapidly and grown into a very interesting and useful field. In a broad sense, the beginning of supramolecular chemistry was recorded as the appearance of Charles Pedersen's seminal paper in *Journal of the American Chemical Society*, entitled "Cyclic Polyethers and Their Complexes with Metal Salts", in 1967.[1] It marked the significance of supramolecular chemistry that Charles J. Pedersen, Donald J. Cram and Jean-Marie Lehn were awarded the Nobel Prize in Chemistry 1987 "for their development and use of molecules with structure-specific interactions of high selectivity". Supramolecular chemistry has been defined by Jean-Marie Lehn as the "chemistry beyond the molecule" and "chemistry of molecular assemblies and of the intermolecular bond". It focuses on molecular assemblies of various chemical species based on weak non-covalent interactions.

Charles J. Pedersen discovered crown ethers by chance, yet he won the Nobel Prize in Chemistry not by chance. Initially, he designed and tried to synthesize a multidentate phenolic ligand as "a metal deactivator" to protect petroleum products from autoxidation through converting metal salts into inactive multidentate complexes.[2] He carried out the designed reactions, as shown in Figure 1. Though Pedersen knew that the partially protected catechol was not pure and was contaminated with about 10 percent unreacted catechol, he went on carrying out the next reaction using the impure compounds as starting material because he thought he need to purify the target compound anyway. To his surprise, he obtained only a small quantity (about 0.4% yield) of white crystals after purification. Pedersen was innovative because he did not follow dogma but followed his natural curiosity and intuition, and without hesitation, he studied the unknown through ultraviolet spectroscopy. With his genuine curiosity and persistence, Pedersen hypothesized and determined the structure of the unknown

compound and investigated the cation complexation behavior. During the next nine years staying in Du Pont until his retirement, Pedersen focused on studying the crown ethers' synthesis and cation complexation properties. Consequently, he deserved the Nobel Prize in Chemistry as a pioneer in supramolecular chemistry, a new uncharted territory of chemistry.

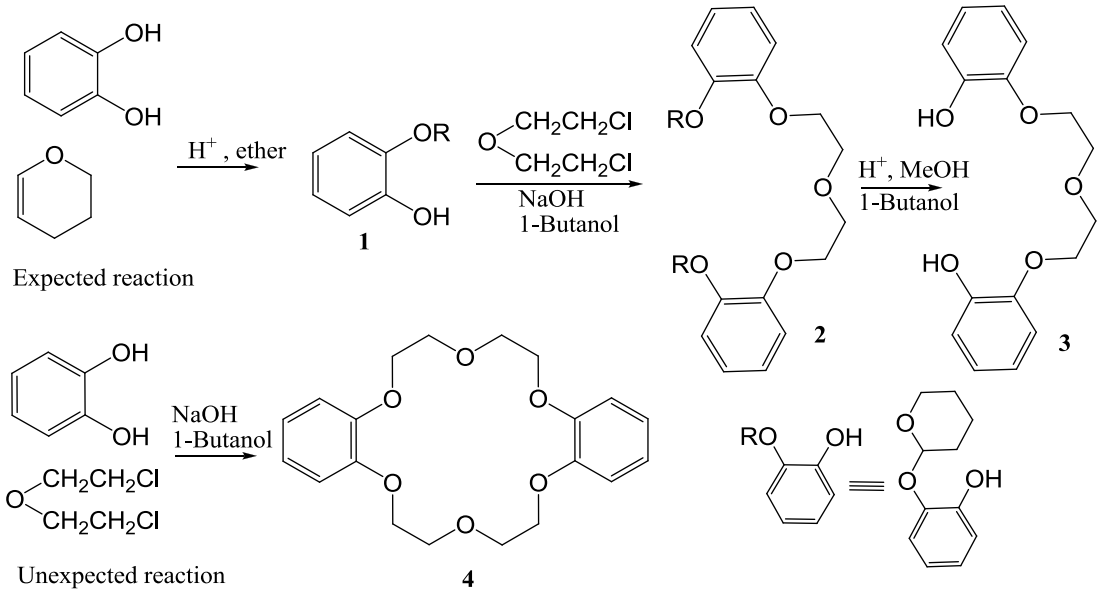


Figure 1 The serendipitous discovery of crown ether by Pedersen.

Inspired by Pedersen's pioneering work, Donald J. Cram and J. M. Lehn carried out a lot of excellent work in this field.[3]

Based on Charles Pedersen's breakthrough findings, Donald J. Cram developed host-guest chemistry and expanded crown ethers into two-dimensional and three-dimensional organic compounds, which were synthesized through principle of preorganization and could bind selectively certain metal cations through structural recognition. With the help of CPK molecular models, Donald J. Cram and coworkers designed and synthesized a series of ligands as depicted in Figure 2. They reported the syntheses of spheraplex **5**, complexes of **5** with Na^+ and **5** with K^+.[4] In spheraplex **5**, the binding oxygen atoms are preorganized in an octahedral array, ready to receive a metal cation due to the rigid structures. As a result of preorganization, the spherand **5** binds Na^+ more than 10^{10} more effectively than the analogous podand **6**. Moreover, Donald J. Cram et al. have investigated extensively a transacylase mimic. They com-

bined aryloxy, cyclic urea, pyridyl, biphenyl, ethylene, methylene, and oxygen units into certain 20-membered macrocycle hosts, which mimic serine transacylases.[5] Their studies have shown that the design and preparation of systems mimicking some properties of enzymes, such as to enhance reaction rates via complexation, is possible. In addition, Donald J. Cram developed synthetic receptors made from spheraplex building blocks: 3-dimensional synthetic molecular vessels – cavitands.[6] A series of target cavitands with large internal surfaces were designed and readily prepared. Most of the cavitands were derived via rigidification from a simple cavitand **7**, which was synthesized in good yield through treatment of resorcinol with acetaldehyde and acid.[6-7] They determined the association constant for a derivative of **7** with CS_2 and observed a cocrystal, which showed that CS_2 had occupied the cavity in the expected manner. As the development of cavitands, they also reported certain synthetic molecular containers – carcerands.[8] As an expert and talented professor in organic chemistry, he managed to catch the cutting edge of chemistry and was good at thinking about the receptors' design and skilled at long-pathway multiple-step synthesis. Cram successfully utilized his substantial knowledge in organic chemistry into the cutting-edge field—supramolecular chemistry. He has made seminal and great contributions to the seedling-like field and has been regarded as a cofounder of supramolecular chemistry.

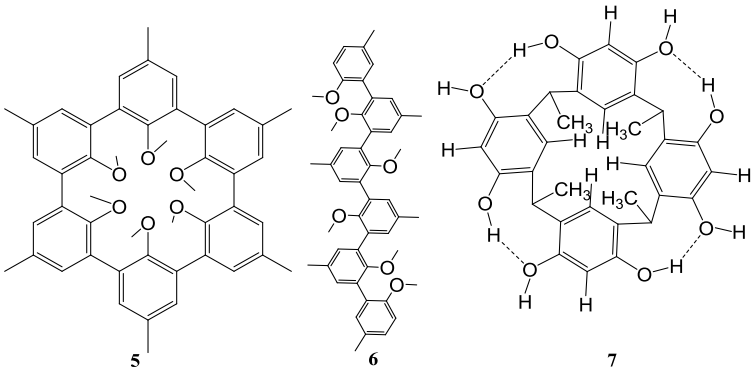


Figure 2 The structures of spheraplex **5**, podand **6** and cavitand **7**.

Jean-Marie Lehn, a further visionary leader in supramolecular chemistry, is known for cryptands and is still specializing and active in this field. Lehn[9] began his research on natural products, where he learned to focus on the general importance of

individual molecular details at the University of Strasburg in France. He and coworkers devised and developed a type of new molecules, called cryptands. Cryptands, a three-dimensional analogues of Pedersen's crown ethers, are more selective receptors and bind more strongly for certain metal ions due to "precise spatial organization of donor atoms". In general, cryptands are apt to bind a variety of "hard cations", such as NH_4^+, alkali metal cations, alkaline earth metal cations and lanthanoid cations. In particular, the resulting complexes are lipophilic, which makes the ionic reactions occur in organic solvents and is crucial in both chemistry and biology.[10] As a general example, Figure 3 shows the structures of 2.2.2-Cryptand and its complex encapsulating a potassium cation. His group is also investigating anion chemistry and the recognition of anionic substrates. They have studied extensively anionic species' (inorganic anions, carboxylates, phosphates, etc.) binding and recognition of macrocycles and macropolycycles resulting from both electrostatic, structural effects, and complementarities. For example, they devised and obtained cryptands with positively charged or neutral electron-deficient groups to serve as receptors to bind and recognize anions. As shown in Figure 3, receptor **10**[11] is formed by protonated macrobicyclic polyamines with an ellipsoidal pattern and is perfect complementary to azide anions but not fit well to halide anions. They studied the properties of macrobicyclic receptor **10** to recognize linear triatomic species, such as azide anions, through ^{13}C FT NMR as well as to stabilize unstable species like F_2H^-, Cl_2H^-, F_3^-, Cl_2F^-, etc.

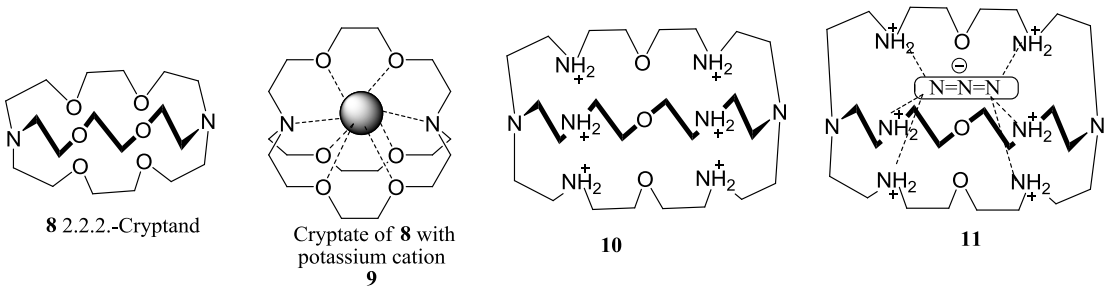


Figure 3 Structures of 2.2.2-Cryptand **8** and its potassium complex **9** as well as macrobicyclic polyamines **10** and its schematic diagram towards binding azide anions **11**.[12]

In addition, Lehn and coworkers attached appropriate functional groups into receptors to act as supramolecular catalysts.[13] For instance, they reported both the su-

pramolecular catalysis in the hydrolysis of ATP facilitated by macrocyclic protonated polyamines and the pyrophosphate synthesis from acetyl phosphate mediated by macrocyclic polyamines.[14] Furthermore, they studied self-assembly based on metal-ligand interactions for biological or material applications.[15] As a general and classic example,[15a] they described the self-recognition, self-organization and self-selection in helicate self-assembly. Firstly, they treated mixtures of four types of different chain-length the [oligo (2, 2′)-bipyridine] strands with copper(I) ions to yield spontaneously double helicates without significant crossover. Secondly, they treated the mixture of two types of tris-bipyridine ligands (with different substitutions) with a mixture of copper(I) and nickel(II) to form spontaneously mere the double helicate for copper(I) and the triple helicate for nickel(II), as shown in Figure 4. The processes can manage to yield spontaneous double and/or triple helical assembly species from mixtures of ligands and metal ions, which are attributed to the realm of programmed supramolecular systems.

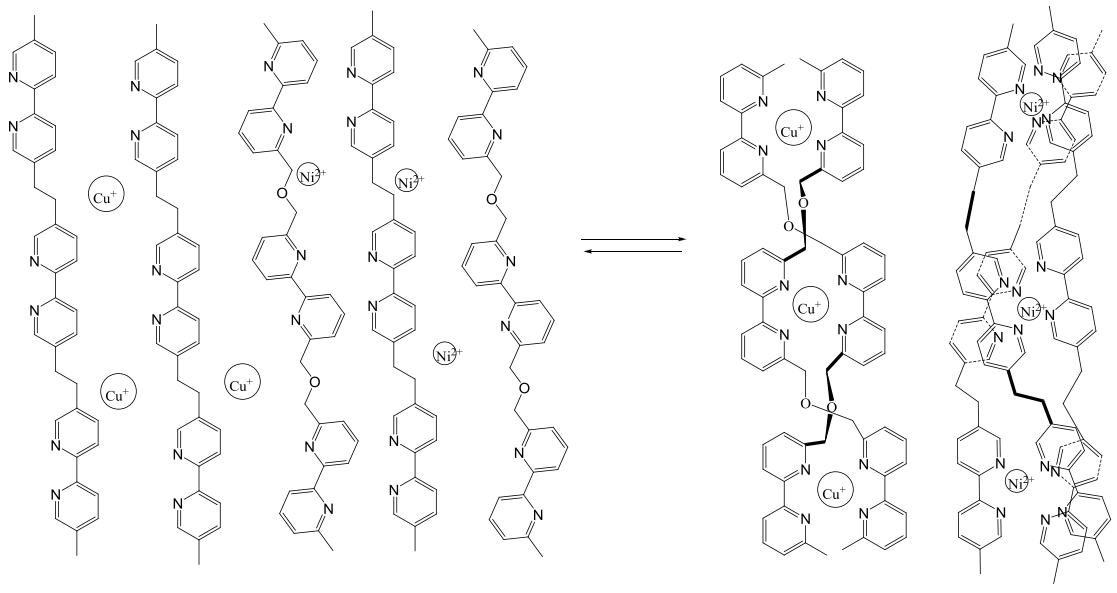


Figure 4 The schematic diagram for the self-recognition, self-organization, and self-selection in helicate self-assembly.

Lehn has been contributing original and a great deal of contributions to the fledging supramolecular chemistry, in particular molecular recognition and self-assembly.[9, 16]

Besides the three founders, their peers and descendants have also been cease-

lessly exploring and substantially developing supramolecular chemistry into applications in many fields, such as supramolecular catalysis.

Julius Rebek Jr.,[17] Makoto Fujita[18] and Kenneth N. Raymond[19] have made significant contributions to supramolecular catalysis in confined cavities.

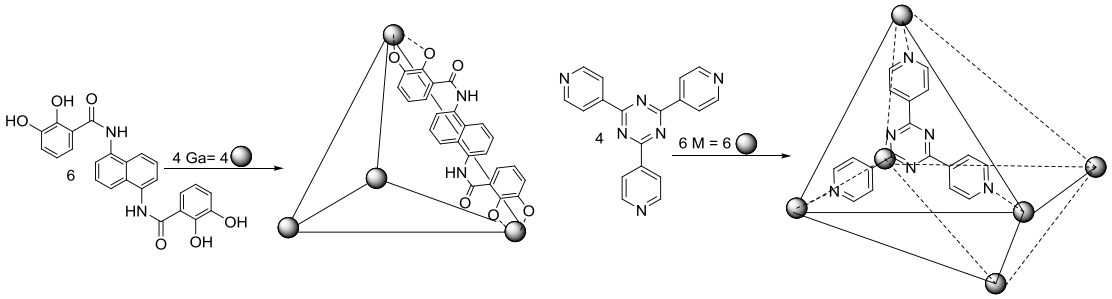


Figure 5 Representative nanocages for reactions.[20]

George Whitesides, Fraser Stoddart, Peter Stang, Fritz Vögtle, Jean-Pierre Sauvage, Fran çois Diederich, Chad A. Mirkin, Vincenzo Balzani, Eric Anslyn, and Jerry Atwood have also made significant contributions to the development of supramolecular chemistry.

With the untiring efforts of these pioneers as well as descendants, supramolecular chemistry has progressed into an interdisciplinary, serviceable, function-oriented domain.

1.2 Anion Chemistry

Compared to cation chemistry, anion chemistry is not explored extensively. Its birth dates back to the late 1960s, halide anions were encapsulated by protonated diazabicycloalkane ammonium ions reported by Park and Simmons,[21] almost the same period of the beginning as cation chemistry. In contrast to the fully developed and extensively investigated cation chemistry, anion chemistry is in a fledging stage and needs more efforts to be made. The research on anion chemistry is more difficult. The reasons are various.

Firstly, compared to the monotonous spherical shapes of most cations, anions really have various shapes, 1) all of the monoatomic anions are spherical, including ha-

lide anions and O^{2-}, S^{2-} etc; 2) N_3^-, CN^-, SCN^-, OH^-, O_2^-, S_2^-, I_3^-, etc. are linear; 3) CO_3^{2-}, NO_3^-, HSO_3^-, SO_3^{2-} etc are trigonal planar; 4) HOO^-, NH_2^-, RCO_2^-, NO_2^- etc are V-shaped; 5) ClO_4^-, BrO_4^-, HSO_4^-, SO_4^{2-}, $H_2PO_4^-$, HPO_4^{2-}, PO_4^{3-}, MnO_4^-, BF_4^- etc are tetrahedral; 6) $Fe(CN)_6^{4-}$, $Co(CN)_6^{3-}$, PF_6^- etc are octahedral; (7) some anions have complex structures. Polyoxometalate anions have various and characteristic structures, for example, $XM_{12}O_{40}^{n-}$ anions belong to Keggin structure, and $Mo_6O_{19}^{2-}$ anions are Lindqvist structures; 8) poly charged DNAs are double helix structures,[22] and some RNAs are hairpin loop structures.[23]

Secondly, compared to corresponding cations, anions are more apt to be affected by solvents due to higher electron polarizability. In solution, anions are strongly solvated through hydrogen bonding, polar moment and polarizability.

Thirdly, pH can dramatically influence anions as Lewis bases. The changes of pH perhaps lead to the presence of different species of anions in solution, which makes the sensing and recognition of anions more difficult.

Fourthly, many metal cations, as Lewis acids, can catalyze many reactions in organic chemistry. Thus, plenty of reaction-based indicator systems[24] are ingeniously devised and utilized into recognition and sensing of cations,[25] especially for mercury(II) ions,[26] copper(II) ions,[27] and so on. On the contrary, only a few reaction-based receptors are synthesized and used in anion sensing and recognition.[28]

Until recently, most anion receptors mainly rely on electrostatic interactions (positive charged receptors, such as ammoniums), hydrogen bonds (acidic X-H groups, X = N, O, S, C etc), metal or Lewis acid coordination (electron-deficient metal cations or Lewis acidic receptors, such as receptors containing boron, mercury, silicon, germanium, and tin etc), hydrophobic effects (receptors based on cyclodextrins etc) and a combination of two or more interactions.[29]

The most significant backbones for anion receptors are N-H containing aromatic systems, including pyrroles,[30] indoles,[31] carbazoles,[31-32] indolocarbazole[33] etc. Due to the existence of acidic protons, once they are modified with other anion binding sites, such as amide or (thio)urea groups etc, or are cyclized,[34] they are likely to

tightly bind anions. Some significant aromatic receptors containing N-H are displayed in Figure 6.

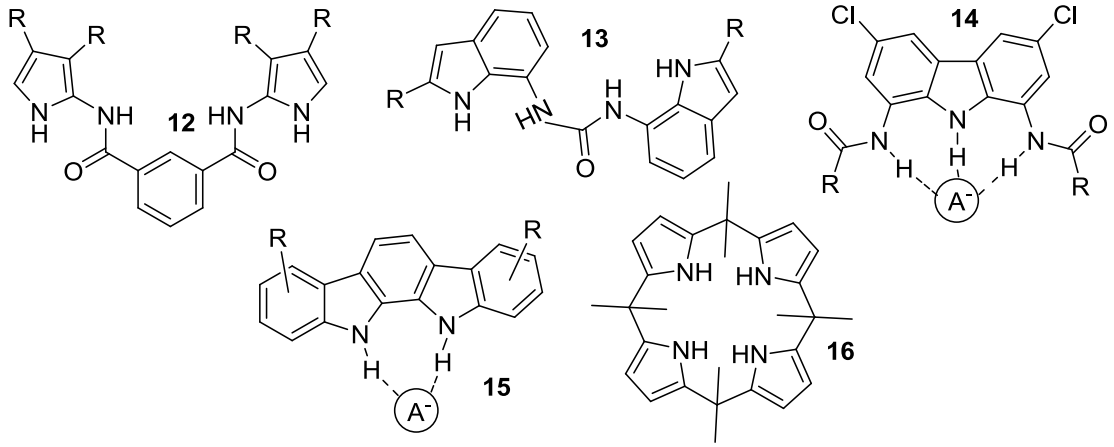


Figure 6 Receptors containing aromatic N-H moiety: 1) pyrrole-based receptors **12**, 2) indole-based receptors **13**, 3) carbazole-based receptors **14**, 4) indolocarbazole-based receptors **15**; 5) a calix[4]pyrrole-based receptor **16**.

Philip A. Gale has been making vital contributions to the development of anion chemistry, and he has been summarizing the advances of anion chemistry frequently.[35]

Some novel receptors, binding modes, and sensing mechanisms are developed gradually recently.

In 2005, Resnati and coworkers reported the halogen-bonding-based heteroditopic receptors for alkali metal halides, such as NaI, KI, KBr and KCl, for the first time.[36] Due to the tris[2-(2-hydroxyethoxy)ethyl]amine as metal binding sites and the iodotetrafluorophenyl groups as anion binding sites, the receptor can bind alkali cations and halide anions simultaneously and shows an unusual affinity order, decreasing in the order $I^- > Br^- > Cl^-$, due to charge-transfer contributions to halogen bonding. More recently, Taylor and coworkers have further developed the application of halogen bonds in recognition of anions.[37] They designed and synthesized a tridentate receptor with a combination of three *ortho*-substituted iodoperfluoroarenes and a hexasubstituted benzene derivative, which acted as a preorganized tridentate receptor for anions. The results demonstrated that the receptor achieved high-affinity molecu-

lar recognition exploiting the halogen-bonding interactions alone. The affinities towards anions are consistent with Resnati's results, decreasing in the order $I^- > Br^- > Cl^-$. Subsequently, they combined distinct non-covalent interactions, hydrogen and halogen bonding, and demonstrated that the two interactions can bind anions cooperatively and achieve high affinity and unusual selectivity towards anions.[38]

Amar H. Flood and co-workers have carried out extensive research on the application of weak C-H hydrogen bonds in anion sensing and recognition.[39] Due to the well-designed preorganization and the shape-persistent macrocycle, the C-Hs of 1,2,3-triazoles function perfectly as hydrogen bond donors to efficiently complex chloride with strong affinity in solution.[40] In addition, they have demonstrated that the preorganization of intramolecular hydrogen bonds enhanced the affinity of 1,2,3-triazoles towards chloride binding.[41]

Kochi and collaborators intelligently employed anion-π interactions to recognize halide anions with olefinic and aromatic receptors.[42] Upon addition of bromide salt into tetracyanopyrazine in acetonitrile, a new peak immediately appeared at roughly 400 nm and rose with the increase of bromide concentrations, which indicated the formation of a charge-transfer complex between bromide anions and tetracyanopyrazine. Notably, a cocrystal of tetracyanopyrazine and tetrabutyl ammonium bromide was obtained and showed that the bromide anions laid 0.3 nm over the periphery of electron-deficient aromatic rings, showing the anion-π interactions in solid. Later, Johnson and collaborators reported that anion-π interactions can augment halide binding in solution.[43] They devised and prepared two receptors with a pentafluorophenyl as well as phenyl group, respectively. The phenyl group receptor showed no affinities towards halide anions in $CDCl_3$, while the one with a pentafluorophenyl group showed moderate affinities towards halide anions with binding constants in the range of 20-34 M^{-1}, in the order $I^- > Cl^- > Br^-$ in $CDCl_3$ through the ^1H NMR spectroscopic method. This study highlighted the utilization of anion-π interactions to bind anions by design.

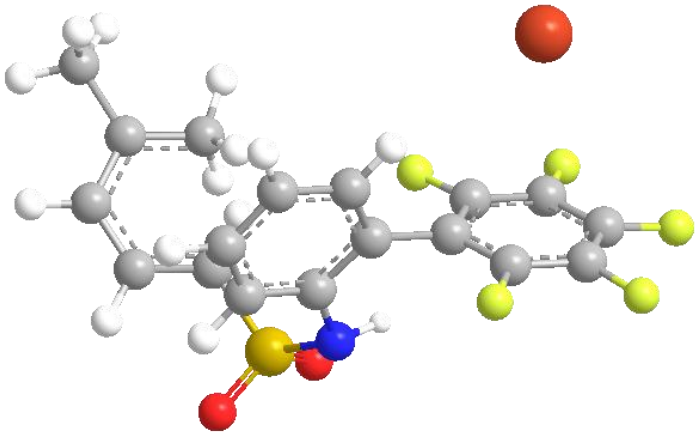
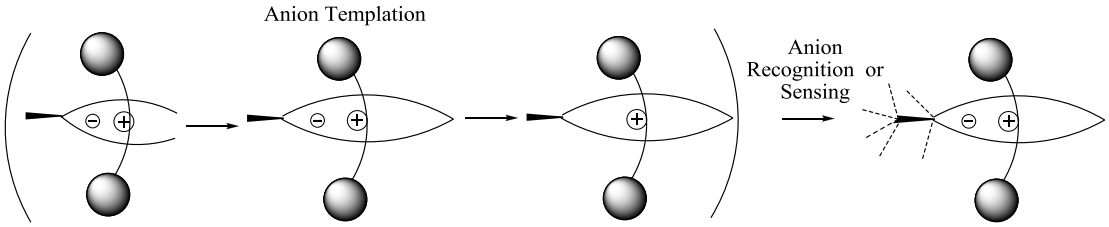


Figure 7 Proposed schematic diagram for Johnson's anion receptor and an anion (drawing from Chem-Bio 3D Ultra).

Beer and coworkers are considerably concerned to synthesize novel interlocked molecular architectures using anionic species as templating motifs and in turn use them to sense and recognize anions, mainly including halides (Scheme 1).[44] Firstly, they prepared orthogonal complexes using anionic species as a template through hydrogen or halogen bonding, similar to Sauvage's copper(I) templated systems. Secondly, they transformed the orthogonal complexes to pseudorotaxanes with anionic species as templates. They often employed Grubbs ring closing metathesis. Thirdly, the anionic species, templates during the construction of pseudorotaxane process, were removed through ion exchange and left perfect binding sites for the templating anionic species. Finally, the interlocked structures were utilized as anion receptors and showed enhanced anion binding properties and high selectivity, especially towards the anionic species as templates, due to the preorganization and perfect complementarity.



Scheme 1 Beer's interlocked sensors and complex architectures for anions.

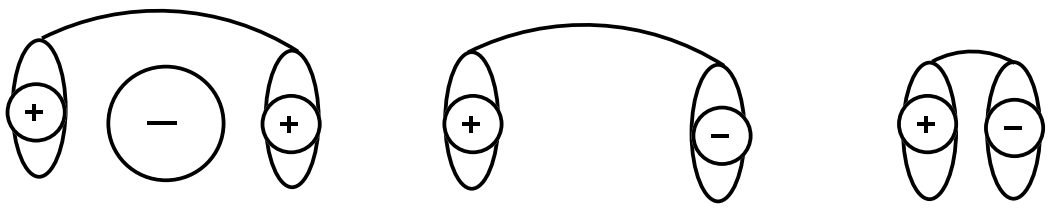
In 2010, V. Sindelar and co-workers described the preparation of a novel hexameric macrocycle (bambus[6]uril) through acid-catalyzed condensation of 2,4-dimethylglycoluril with formaldehyde.[45] The results showed that bambus[6]uril

can bind halide anions inside the cavity through twelve weak C-H···anion bonds between methylene carbon atoms on the convex face of glycoluril units and the corresponding anion with high affinity and selectivity in the following order: $I^- > Br^- > Cl^- > F^-$.

1.3 Ion-pair Chemistry

The concept of ion pairs was first introduced in mechanistic consideration of substitution reactions. Winstein et al. discussed the acetolysis of 3-anisyl-2-butyl arylsulfonates and of some other compounds.[46] The concept is used to explain many phenomena in stereochemistry, especially for S_N1 substitution.

Ion-pair recognition as a fledging field, emerging from simultaneous anion and cation coordination, has become an interesting field in supramolecular chemistry[47] and its investigation helps us to understand further the mechanisms of catalysis and to design catalysts on target. Some elegant studies in the field were described by e.g. Reinhoudt,[48] Beer,[47c, 49] Smith,[50] Barboiu,[51] Sessler[47a, 47b, 52] and their co-workers. Due to the conformational features of calix[4]diquinones, Beer and collaborators have investigated cooperative AND ion-pair recognition by a series of various calix[4] diquinone receptors.[49c] Smith and coworkers focused on the ion pair binding properties of macrobicyclic receptors and used them in selective solid-liquid extraction as well.[50b, 50e] Recently, Sessler and collaborators described the recognition behavior of ion pairs of KF and CsF by a calix[4]pyrrole and obtained the respective co-crystal structures.[52b]



Scheme 2 Three types of ditopic receptors a) cascade complex (left), b) heteroditopic receptor for separated ion pairs (middle), and c) contact ion pairs (right).

Salt extraction and solubilization has developed with the advances of ion pair

recognition and stabilization and is an inadequately explored area. It permits ionic reactions to occur in aprotic media.[2] In 1996, Reinhoudt et al. reported a bifunctional calix[4]arene which was capable of binding anions and cations simultaneously and solubilized sodium halide salts into chloroform.[48c] In 1999, White and Tasker et al. studied a series of ditopic ligands for the simultaneous extraction of cations and anions.[53] Smith et al. ingeniously designed and investigated ion pair binding and solubilization of KCl salts into DMSO.[50b]

1.4 Anion-π Interactions

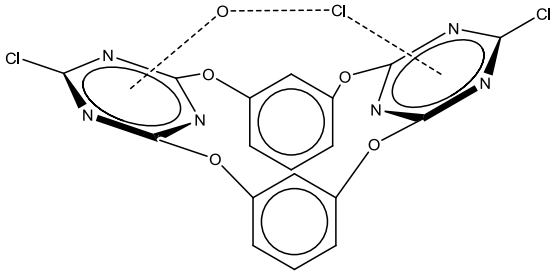
Although cation-π interactions have been investigated and applied in various fields for several decades,[54] only few reports on the anion-π interactions appeared. Most people believed that anions and π-aromatic ring systems would repulse each other until the year of 2002. Indeed, contrary to the chemical intuition, the interactions between anions and π systems can be attractive *via* umpolung or polarity inversion, namely converting electron-rich aromatic rings to electron-deficient aromatic ones. In the year of 2002, M. Mascal et al.,[55] I. Alkorta et al.,[56] and A. Frontera collaborated with P. M. Deyá[57] et al. put intelligently forward the concept of anion-π interactions and investigated it through quantum chemical calculations and the crystallographic experiments simultaneously. Since then, anion-π interactions have been investigated broadly *via* theoretical calculations and single crystal structures due to their essential role in chemical processes/systems in form of catalysis and transport.[58]

Anion-π interactions are defined as favorable non-covalent contacts between electron-rich anions and electron-deficient aromatic systems (π-acid). Typically, the anions, such as halide anions, ClO_4^-, BF_4^-, PF_6^-, SCN^-, SO_4^{2-}, NO_3^- etc and aromatic systems, e.g. hexafluorobenzene, pentafluorobenzene, triazine, trinitrobenzene, tetranitrobenzene and their derivatives are exploited in the study on anion-π interactions.

Antonio Frontera is a pioneer on anion-π interactions and has made plenty of contributions to this fledging field with his collaborators.[58d] He and coworkers investigated the directionality of anion-π interactions through comparison of the energetic

changes of moving the anions from the exact centre of electron-deficient aromatic rings to different directions with changes of corresponding cations by means of theoretical calculations.[59] In addition, they reported the combined experimental and theoretical study of anion-π interactions in N^5-and N^9- decyladenine and bis (pyridine) salts, complexes of Zinc(II) with *N*-imidazolyl- and *N*-pyrazolylpyrimidine donor ligands. The results of theoretical calculations are perfect in accordance with the experimental findings.[60] Since asking the question "Anion-π interactions: do they exist?" in 2002, they have been answering that anion-π interactions exit and are favorable.[61]

Meixiang Wang et al. have made elegant work on anion-π interactions through investigating tetraoxacalix[2]arene[2]triazine's electron-deficient and self tunable nature.[62] They have studied the interactions between tetraoxacalix[2]arene[2]triazine receptors and halide anions and showed that the electron-deficient receptors interacted strongly in solution and solid state.[63] Recently, collaborating with Dexian Wang, Meixiang Wang reported the generality, strength and structure between electron-rich anions and an electron-deficient tetraoxacalix[2]arene[2]triazine by the use of electrospray ionization mass spectrometry, fluorescence titration and X-ray crystal structures. The perfect cooperation of anion-π interactions and lone pair electron-π interactions was used in anion binding. The authors claimed that this way provided a new dimension on studying molecular recognition and self-assembly and potentiated the effect of anion-π interactions in chemical and biological systems.[62e]



Scheme 3 Schematic drawing of anion-π interactions between a tetraoxacalix[2]arene[2]triazine receptor and an anion.

Reedijk, Gamez and co-workers reported the first host for anionic guest (a dendritic octadendate N ligand) and its encapsulation behavior of chloride anions by

anion-π interactions.[64]

Matile, Schalley and collaborators provided direct experimental evidences for anion-π interactions through electrospray tandem mass spectrometry in combination with theoretical calculations and exerted anion-π interactions on selective transport of anions across lipid bilayer membranes.[65]

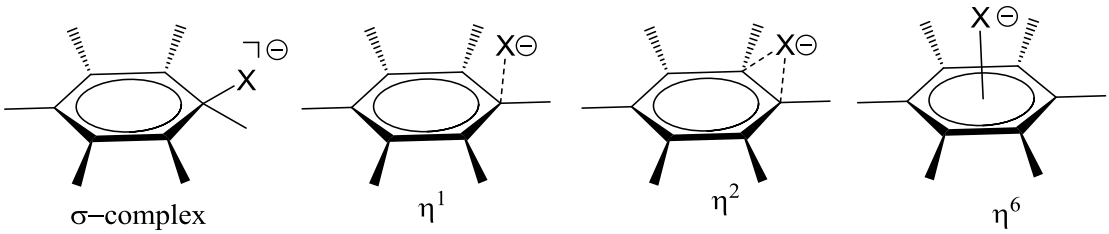
Ballester and co-workers evaluated quantitatively anion-π interactions through ^{1}H NMR spectroscopy in solution and X-ray crystallographic studies using a series of *meso*-tetraaryl calix[4]pyrrole receptors and halide anions.[66]

Olefinic and aromatic receptors were used to recognize halide anions by Kochi and collaborators, which showed the applications of anion-π interactions in anion recognition.[42] Afterwards, Johnson and co-workers augmented halide binding ability in solution using anion-π interactions.[43]

Kim R. Dunbar, Helen T. Chifotides and their group focus on using anion-π interactions and other non-covalent interactions to construct cationic metallasupramolecular architectures.[58a] Most of their studies are involved in exceptional π-acidic ligands, such as 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (bptz)[67] or 3,6-bis(2-pyrimidyl)-1,2,4,5-tetrazine (bmtz)[68] or 1,4,5,8,9,12-hexaazatriphenyl enehexacarbonitrile (HAT(CN)$_6$)[69], as π-electron receptors. The anion-π interactions play a vital role in stabilizing the supramolecular architectures.[67-68, 70]

Since 2008, Albrecht group has been conducting detailed studies on anion-π interactions of various anions with fluorophenyl moieties in the solid state as well as in solution.[71] Initially, a series of pentafluorophenyl substituted ammonium, iminium, amidinium, and phosphonium halides were investigated and it was found that they showed extensive anion-π interactions.[71b] Meanwhile, the new η^2-type coordination between anions and electron-deficient aromatic rings were reported. Subsequently, CH-directed anion-π interactions in the crystals of pentafluorobenzyl-substituted ammonium and pyridinium salts were studied and it was found that the symmetric hydrogen bonding facilitated η^6-type binding between anions and electron-deficient aromatic rings while asymmetric hydrogen bonding benefited other types (such as

η^1-type) binding.[71h] Furthermore, the anion-π interactions were implemented in salts to stabilize the rarely observed and unstable tetraiodide anion I_4^{2-}.[71g]



Scheme 4 Interactions between anions and aromatic π-systems.

Chapter 2 Objectives

The work of this dissertation will be divided into five parts.

2.1 Quinoline-based Anion Receptors

Anion species play a vital role in human bodies and biological and physiological science. The study on recognition and sensing of anions are not as mature as cation's study and there is more space to explore in this field. Urea as well as thiourea groups, particularly *N*, *N*′-substitution modified ones, represent excellent hydrogen-bond donors and binding sites for anion recognition and sensing.[72] In proteins, the amide units, which are widely employed in anion recognition and binding, play an important role for the binding of anions and other functions.[23] As electron-deficient moieties, pentafluorophenyl groups are used in anion sensing and recognition in order to enhance the positive polarity of the receptor binding sites and to introduce the possibility for anion-π interactions.[71b, 71g, 71h, 71j] Therefore, a series of quinoline-based halide receptors (**1**-**6**, Figure 8) were designed, in which pentafluorophenyl groups were introduced as electron-withdrawing π-acidic groups. In order to mimic oligopeptides in proteins, two amides were designed to attach to the quinoline backbone to form a preorganized bisamide cleft for binding halide anions (**7**-**10**, Figure 8). The novel anion receptors are based on a functionalized quinoline backbone capable for halide binding mainly through hydrogen bonding, perhaps somewhat with the help of anion-π interactions. It is planned to tune the affinity of quinoline-based receptors towards halide anions by virtue of mediating the electronic, solvent, and fluoro-substitution effects. As an effective method, ^{1}H and ^{19}F NMR spectroscopy in $CDCl_3$ and DMSO-d_6 will be used in this study.

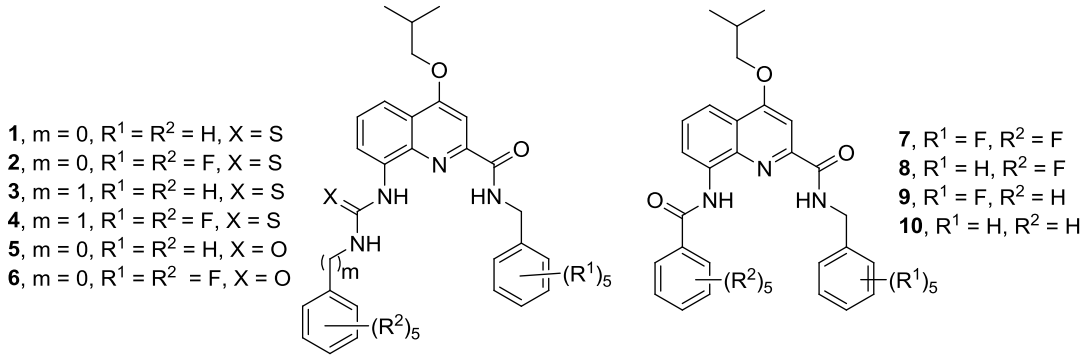


Figure 8 Designed receptors towards anions to tune halide affinity in solution.

2.2 A Quinoline-substituted Crown Ether

Crown ethers, unintentionally prepared by C. J. Pedersen in 1960s,[2] have been widely applied in cation-sensing,[1] ditopic recetpors,[50c] rotaxane-construction,[73] salt extraction,[74] and phase transfer catalysis.[75] Ion-pair recognition, emerging from cation and anion coordination, has become an interesting, ongoing but not fully understood field in supramolecular chemistry.[47] Due to their intra-/intermolecular hydrogen binding sites, 2-amido-8-aminoquinolines are utilized as backbones for anion-sensing[76] and foldamer-construction.[77] Our group studied various types of 2-amido-8-aminoquinoline derivatives to recognize anions in solution.[78]

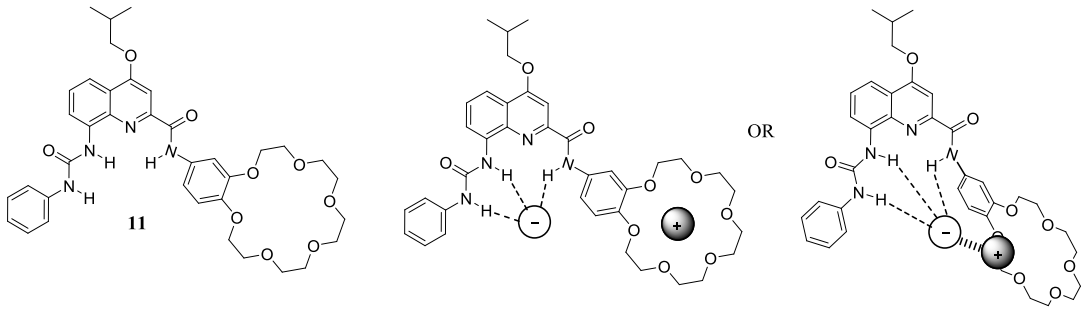


Figure 9 Molecular structure of receptor **11** and scheme for **11** binding ion pairs and salts.

Herein, based on previous work,[79] a combination of anion binding sites (2-amido-8-aminoquinolines) and cation binding sites (crown ether) was achived to form a novel ditopic receptor for ion-pairs or salts and to study solution behavior in chloroform and DMSO (Figure 9).[79] Due to the presence of both an anion binding site and a cation binding moiety, receptor **11** has potential applications in catalysis and

selective separation.

2.3 Anion Receptors Based on Biphenyl-substituted Quinoline

Biphenyl is an interesting moiety due to the torsional angle between the two phenyl planes. The torsional angle depends on the energetic competition between favorable π-conjugation and the repulsion of the two C-H_{ortho} atoms.[80] Herein, a combination of two kinds of biphenyls (biphenyl and 2,3,4,5,6-pentafluorobiphenyl) and a 2-amido-8-aminoquinoline derivative is designed to investigate anion binding properties and to probe anion-π interactions in solution, respectively. Due to the torsion of the biphenyl and preorganization of 8-amino-2-quinolinecarboxylic amide, the receptors are likely to form cavities for halide anions.

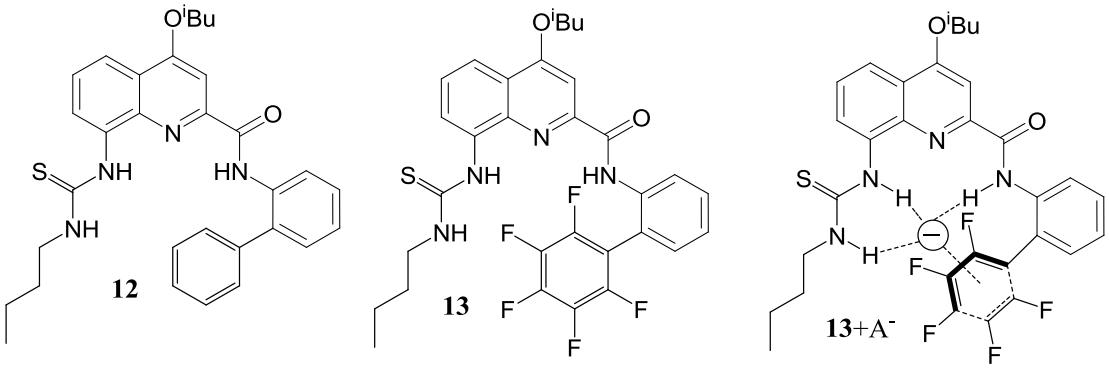
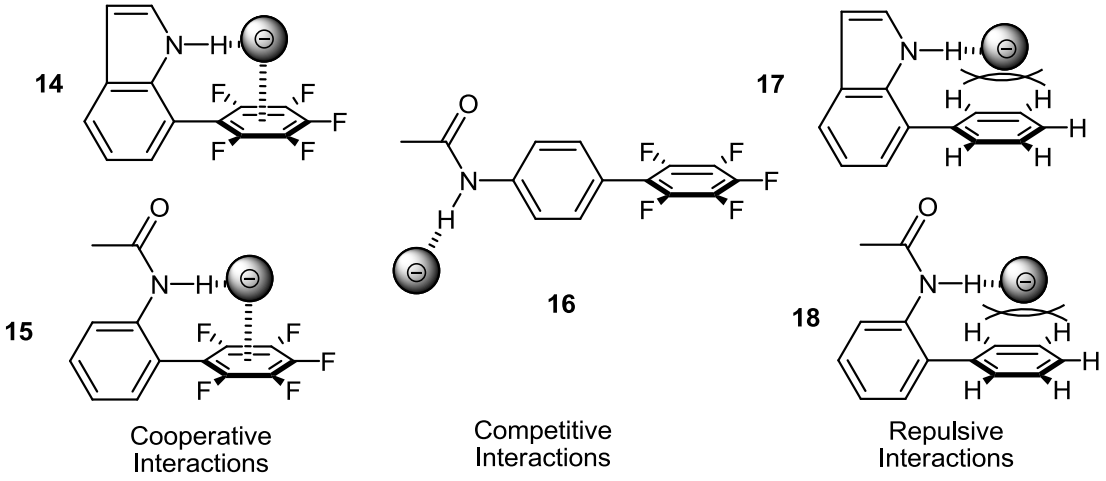


Figure 10 Designed anion receptors **12**, **13** and schematic diagram of **13** binding of an anion.

2.4 Exploration of Anion-π Interactions in Solution

Compared to cation-π interactions, the anion-π interaction is still regarded as a fledging domain. There is infinite space to explore in this topic, such as its nature, its directionality and its applications in sensing and recognition of anions in solution. Indoles are hydrogen bond donors for anion binding in biological systems. They have been widely exploited for the design of anion receptors.[81] Pentafluorophenyl groups are perfect electron-deficient aromatic groups and have been delicately devised into receptors to track anion-π interaction by many scientists.[43, 71a, 71b, 71e, 71g, 71h, 71j] Inspired by Johnson and co-workers' work[43], three groups of receptors were devised.

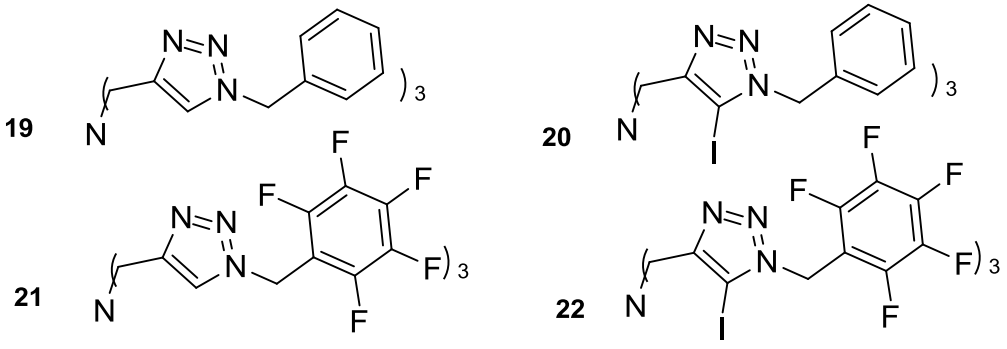
The focus is to probe the probability to capture anion-π interactions in solution through ^{1}H NMR and ^{19}F NMR spectroscopic methods and to study their relevance.



Scheme 5 Molecular structures of receptors **14**-**18** and concept of cooperative, competitive and repulsive interactions.

2.5 Syntheses of Further Receptors for Anions

In order to probe the anion binding behavior in solution, some other receptors for halide and biscarboxylate anions were designed and prepared. Their binding of anions will be measured in solution by means of NMR and UV-vis spectroscopy.



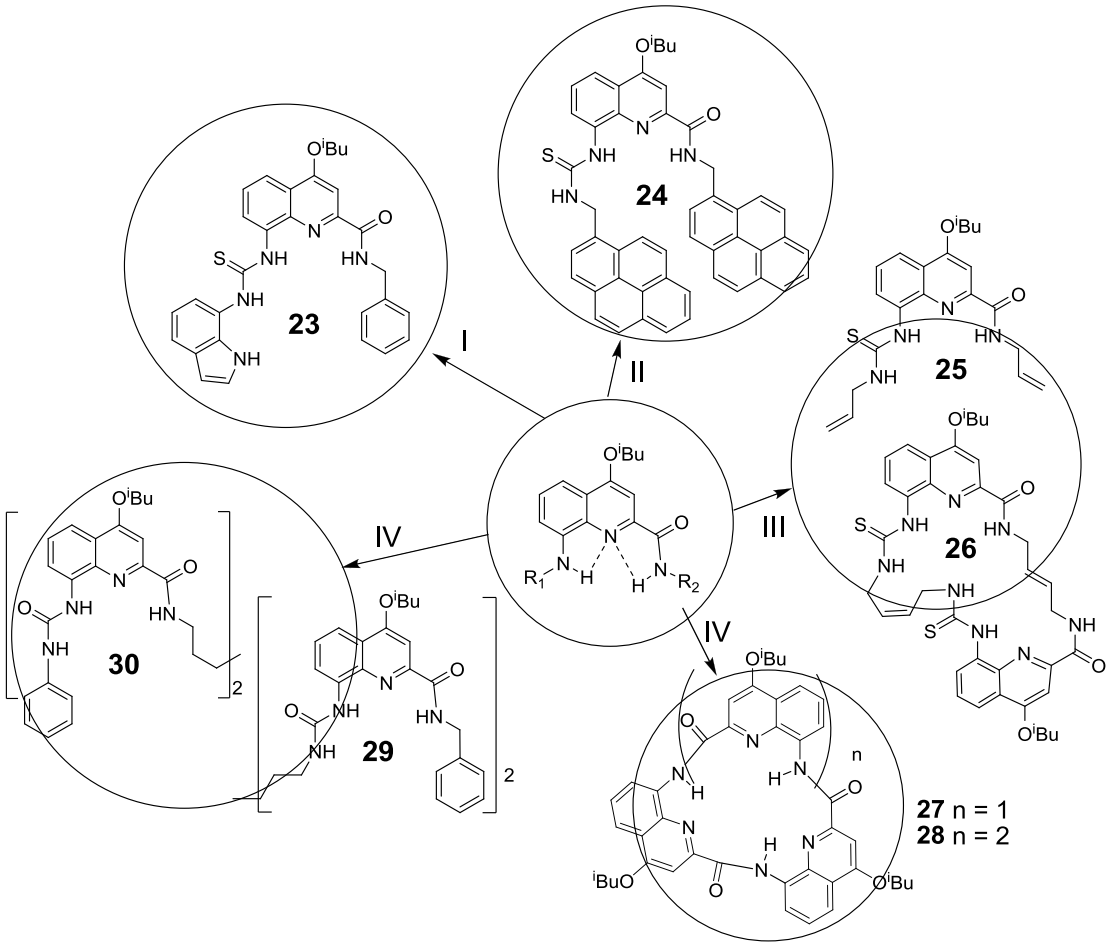


Figure 11 A series of designed receptors towards anions.

Chapter 3 Tuning the Halide Affinity of Quinoline-based Anion Receptors

3.1 Introduction

Supramolecular chemistry is defined as "the chemistry beyond the molecule" and "chemistry of molecular assemblies and of the intermolecular bond" by Jean-Marie Lehn.[82] Molecular assemblies are achieved through highly selective association between similar or different molecules. The design and accomplishment of molecular assembly are based on the development and applications of knowledge on molecular recognition. The knowledge on molecular recognition is vital for the molecular assembly in supramolecular chemistry. Moreover, molecular recognition plays a prominent role in physiological processes. The balance of ion concentrations in human body liquids relies on the selective recognition of ion carriers. Therefore, it is becoming more and more significant to foster molecular recognition knowledge and to develop molecular receptors with high selectivity and sensitivity. Compared to cation chemistry, recognition and sensing of anions has been a less explored domain in supramolecular chemistry. There are infinite space in the recognition and sensing of anion and anionic species. Halide anions are a group of anionic species and inextricably bound to human beings. For example, everyone acquires chloride anions in the form of table salt. The advances of anion chemistry have tremendously progressed recently. Beer and co-workers developed an anion template synthesis of interlocked structures, which are able to sense and recognize anions in solution, especially towards anions used as templates.[44a] In addition, they ingeniously incorporated halogen bonding into the interlocked architectures as anion binding sites and achieved expressively high selectivity and high binding constants in solution.[83] Meanwhile, Taylor et al extensively investigated the binding behavior of halide and other anions through halogen-bonding interactions alone or incorporation of halogen/hydrogen bonding interactions in solution.[37b, 38, 84] The tridentate halogen-bonding receptors showed interest-

ing selectivity towards halide anions in the order $I^- > Br^- > Cl^-$ and bound halide anions strongly in solution through halogen binding alone.[37a]

Anion-π interactions are attractive interactions between electron-rich anions and electron-deficient π aromatic systems. The interest in anion-π interactions has gained tremendously in the last couple of decades. However, there are many problems to solve in this field, such as their nature, their directionalities, and their applications in anion sensing and recognition and molecular assemblies. Our group has been studying the anion-π interactions between pentafluorophenyl groups and various anions in the solid state[71b, 71g, 71h] as well as by NMR titration studies in solution.[71e]

Due to their excellent properties as hydrogen bond donors, (thio)urea groups, especially *N*,*N*′-substitution ones, are widely exploited in the design of anion receptors and showed superior binding affinities towards anions.[72] As functional groups in proteins, amides (peptide bonds) play a significant role in the functions of proteins. Amides are comprehensively used in binding and association of anions.[23]

The intramolecular hydrogen bond networks of 2-amido-8-hydroxyquinoline were found by our group in 2000.[78a] After much thought, it was managed to introduce 2-amido-8-aminoquinoline derivatives, which were constructed by Jiang and Huc et al,[77c, 85] as fluorescent anion receptors for fluoride anions.[78a] The receptor showed high selectivity for fluoride in solution. Subsequently, various amide and urea groups were introduced into the backbone to provide receptors for halide and other anions in solution,[78b, 86] as shown in Figure 12.

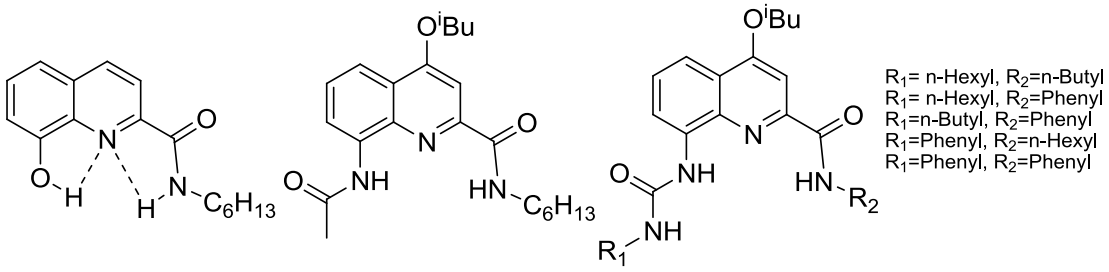


Figure 12 The structures of a representative 2-amido-8-hydroxyquinoline derivative and some receptors from previous research.

Based on previous research, two novel kinds of anion receptors were designed.

The first group combines (thio)urea and amide as anion binding sites in a cooperative fashion. The second group combines two amide groups in a receptor to bind anions in a cooperative type, which has the potential to mimic oligo peptides. In addition, the second group is regarded as better receptors to observe anion-π interactions due to the relatively weak binding ability of amide groups in solution.

The introduction of pentafluorophenyl groups offers the opportunity to investigate the interplay of anion-π interactions and hydrogen bonding in solution. The presence of phenyl and pentafluorophenyl groups provides the possibility to probe the electronic effects in solution. Different (thio)urea groups give a chance to compare their anion binding affinities in solution. Due to intramolecular hydrogen bonds, the acidic protons in amide and (thio)urea groups are likely to associate anions in a cooperative fashion, which facilitates the anion binding process. The presence of the isobutyl ether group is resulting from the synthesis requirement, and it should increase the solubility of compounds in common solvents.

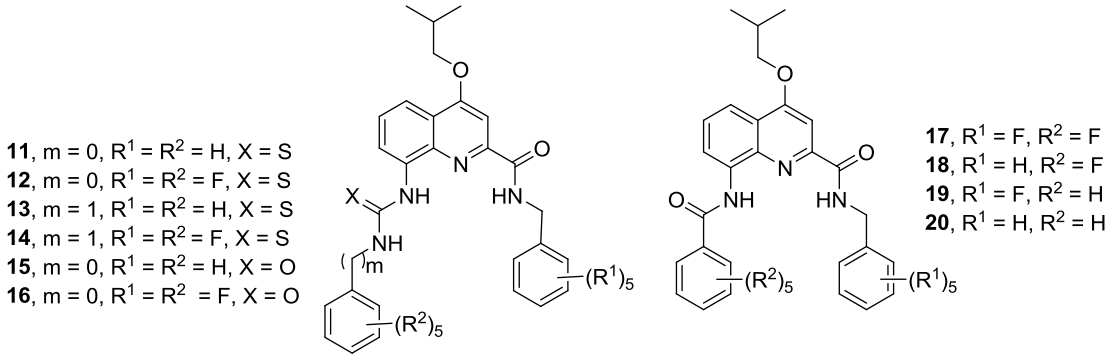


Figure 13 The structures of targeted quinoline-based receptors.

3.2 Syntheses of Receptors

Quinoline-based receptors are prepared by following the depicted processes (Figure 14, 15 and 16). The synthetic pathway is easy-to-operate, high yielding, and highly flexible in terms of structural modification. Nitroquinoline carboxylic acid is obtained from 2-nitroaniline according to the reported procedure by Huc and Jiang et al.[87] Firstly, 2-nitroaniline reacts with dimethyl acetylenedicarboxylate in methanol for 16 h at room temperature, and then the reaction mixture is heated for 6 h to afford

2-[(2-nitrophenyl)amino]-2-butenedioic acid dimethyl ester **1** in a high yield. Secondly, ester **1** is cyclized to 1,4-dihydro-8-nitro-4-oxo-2-quinolinecarboxylic acid methyl ester **2** with PPA (polyphosphoric acid) dehydration at 120°C for 1 h. Thirdly, ester **2** reacts with iso-butanol under Mitsunobu conditions with the catalysis of DIAD in the presence of triphenyl phosphorus in dried THF overnight to provide methyl 4-isobutoxyl-8-nitroquinoline-2-carboxylate **3**. Finally, the saponification of **3** is accomplished in alkaline methanol and THF solution for 20 h and the product is neutralized using an excess of acetic acid to provide 4-isobutoxyl-8-nitroquinoline -2-carboxylic acid **4**, as shown in Figure 14.

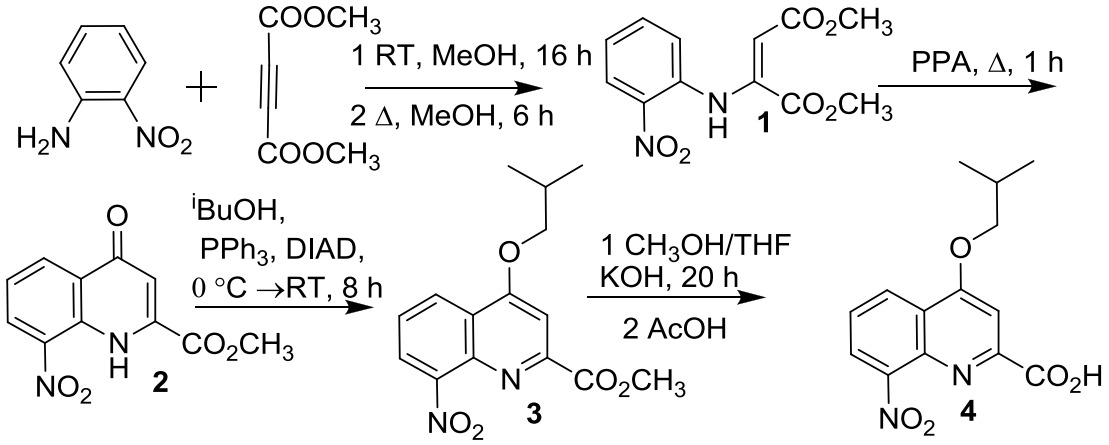


Figure 14 Syntheses of nitroquinoline carboxylic acid **4**.

To construct electron-deficient clefts, the precursor of pentafluorobenzyl amine is synthesized according to literature.[88] 2,3,4,5,6-Pentafluorobenzyl bromide reacts with tritylamine in DMF at room temperature for 1 h to afford *N*-trityl-2,3,4,5,6-penta fluorobenzyl amine **5**. Subsequently, *N*-trityl-2,3,4,5,6-pentafluorobenzyl amine **5** is deprotected in TFA/CH_2Cl_2 solution for 10 minutes and then reacts with concentrated hydrochloric acid to provide 2,3,4,5,6-pentafluorobenzyl amine hydrochloride **6**, which is used as the source of 2,3,4,5,6-pentafluorobenzyl amine in the presence of DIPEA.

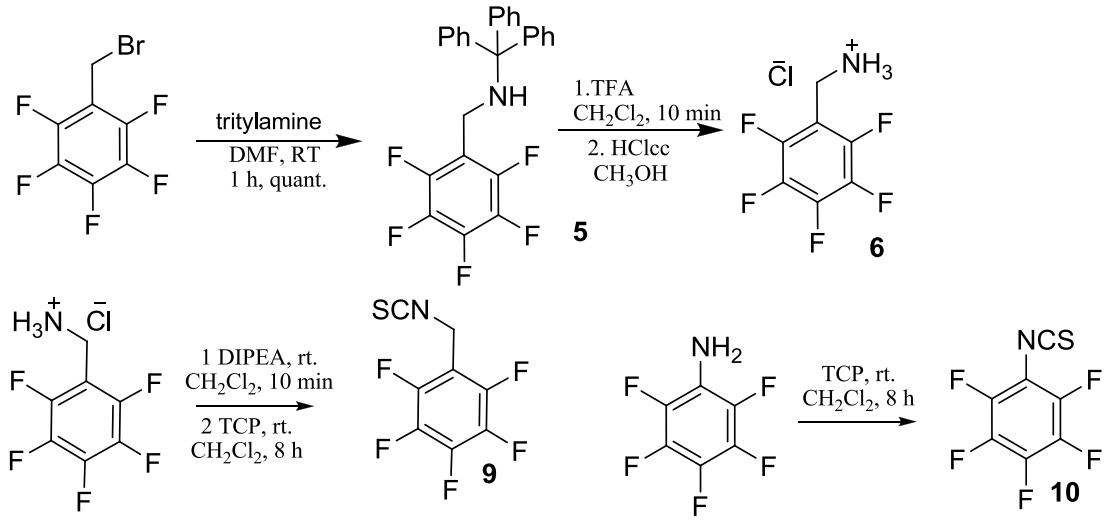


Figure 15 Syntheses of salt **6** and pentafluoroaryl isothiocyanates **9** and **10**.

It is notable that pentafluorobenzyl isothiocyanate is not commercially available and is prepared from pentafluorobenzyl amine hydrochloride salts. Initially, precursor **6** is transformed to pentafluorobenzyl amine in the presence of DIPEA. Subsequently, pentafluorobenzyl amine reacts with TCP (1,l'-thiocarbonyldi-2,2'-pyridone)[89] to produce pentafuorobenzyl isothiocyanate **9** in good yield. The pentafluorophenyl isothiocyanate **10** is prepared directly from pentafluoroaniline and TCP in DCM.

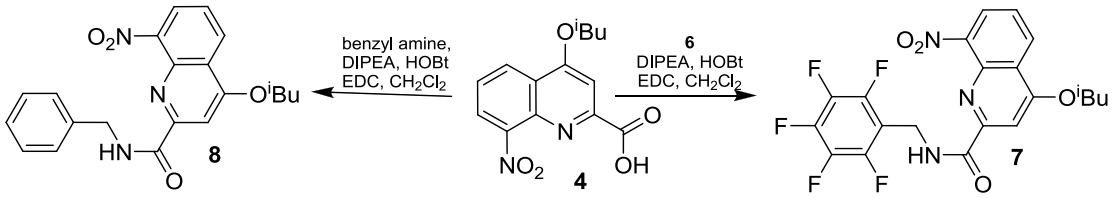


Figure 16 Syntheses of 4-isobutoxyl-8-nitroquinoline-2-carboxylic benzylamides **7** and **8**.

Two amides **7** and **8** are synthesized from appropriate amines with nitroquinoline carboxylic acid **4** in the presence of DIPEA, HOBt and EDC ·HCl in good yield. Nitro groups of the respective amides are reduced under the catalysis of Pd/C at the hydrogen gas atmosphere (20 bar) to afford the corresponding amines in nearly quantitative yield. The latter react with appropriate aryl isothiocyanates or isocyanates to form the (thio)urea receptors **11**-**16**. In addition, reactions of the amines with pentafluorobenzoyl or benzoyl chloride in the presence of TEA (triethylamine) in dry acetonitrile afford the corresponding four diamide receptors **17**-**20**, possessing only two amides as hydrogen bond donors bearing fluorosubstituted or non-fluorosubstituted aromatic

rings.

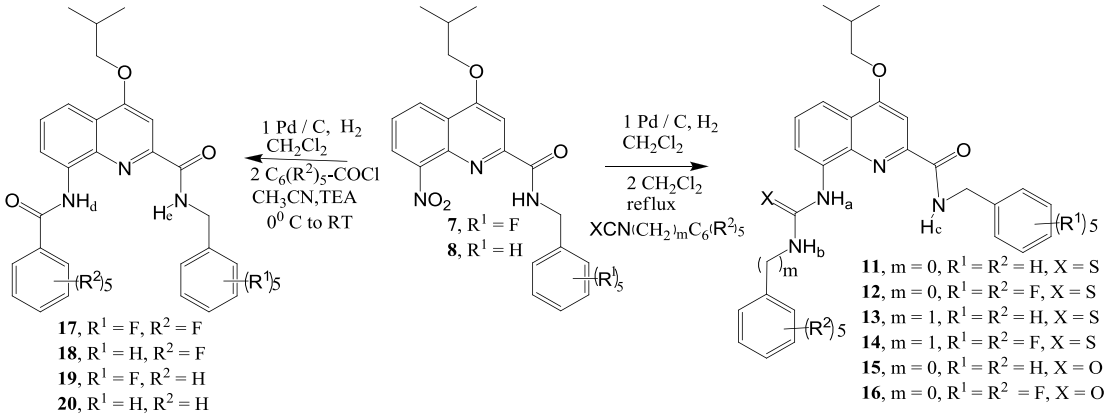


Figure 17 Syntheses of quinoline-based receptors.

The above compounds are fully characterized by ^{1}H NMR, ^{19}F NMR (if possible), ^{13}C NMR, IR, mass spectra, melting points and elemental analysis. In addition, for compounds **7**, **11**, **12**, **13**, **14**, **16**, and **18**, single crystals are obtained and analyzed by X-ray diffraction (see Experimental Section for details).

3.3 Solid State Structures and Conformational Considerations

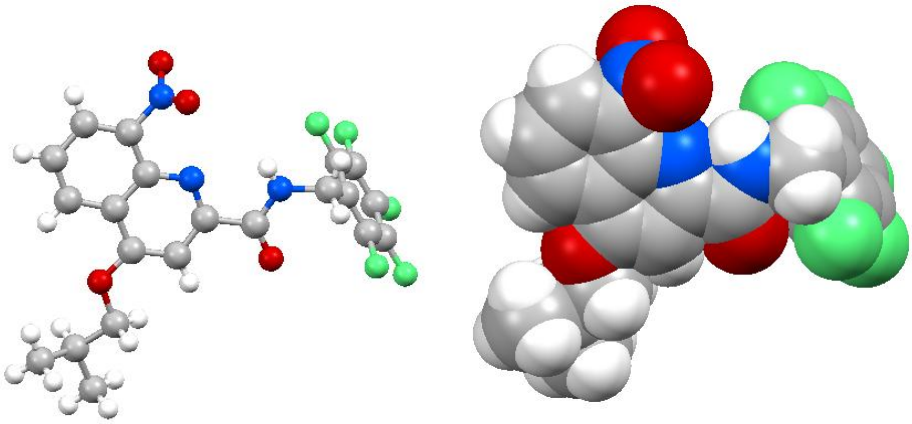


Figure 18 Single crystal structures of compound **7** (gray, C; white, H; green, F; blue, N; red, O).

An X-ray crystal structure of intermediate **7** is obtained by slow evaporation of a solution of **7** in CH_3OH/CH_2Cl_2, as shown in Figure 18. As anticipated, the NH proton is positioned in the front of the quinoline nitrogen rim via intramolecular hydrogen bonding.

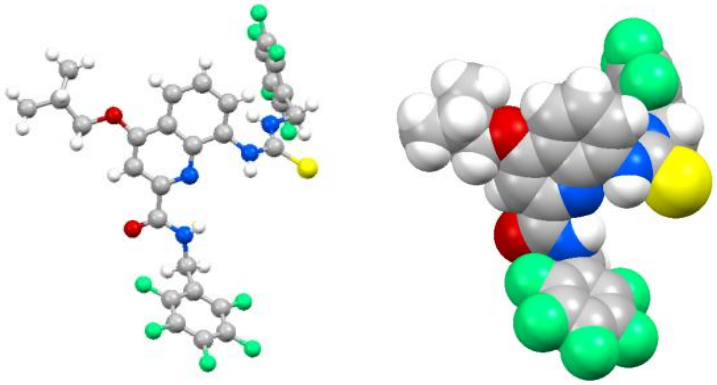


Figure 19 Structures of receptor **14** in solid (gray, C; white, H; green, F; blue, N; red, O; yellow, S).

Yellow crystals of receptor **14** are grown by slow evaporation of a CH_3OH/CH_2Cl_2 solution of the receptor. The structure is elucidated by single crystal X-ray diffraction and is shown in Figure 19. The amide proton points to the nitrogen atom of the quinoline moiety with a distance of 2.263 Å and one of thiourea protons with a distance of 2.733 Å, well preorganized for anion complexation. On the other hand, the second hydrogen atom of the thiourea moiety and the attached electron-deficient arene are turned away from the front of the molecule. However, since the N-C single bond between the pentafluorobenzyl and the amide group is flexible, the pentafluorophenyl group is able to participate in the binding of anions by anion-π interactions. The distance between the two protons, which are pointing to the direction of the quinoline N part, is 2.473 Å. Receptor **14** is a good receptor towards anions by preorganization.

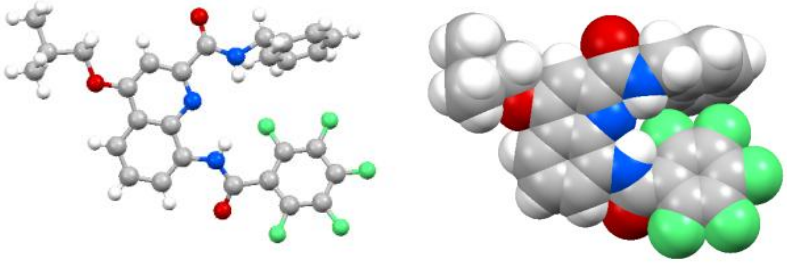


Figure 20 Single crystal structures of receptor **18** (gray, C; white, H; green, F; blue, N; red, O).

Crystals of receptor **18** are obtained by slow evaporation of a solution of **18** in CH_3OH/CH_2Cl_2. Figure 20 shows the structure of receptor **18** in the solid. Similar to **14**, the two hydrogen atoms of the amides create a cleft which should be appropriate

for the binding of anions. The distances between the two amide hydrogen atoms and the quinoline nitrogen atom are 2.232 and 2.267 Å, respectively.

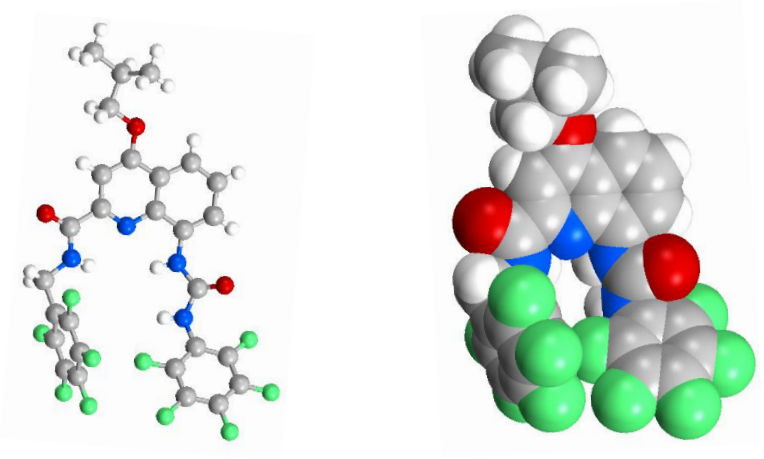


Figure 21 Structures of receptor **16** in solid (gray, C; white, H; green, F; blue, N; red, O; yellow, S).

Besides, crystals of receptor **16** were grown from a DMSO solution of the receptor, because it has very poor solubility in $CHCl_3$ and other common solvents. Notably, all of the three NHs point to the front of the quinoline nitrogen rim in a convergent fashion to form a hydrogen donor cavity by means of intra/intermolecular hydrogen bonding. Amazingly, the lone pair-π interactions involved in a fluorine atom are observed in this molecule. Lone pair-π interactions between a neutral electron-rich molecule (i.e. possessing one or more lone pairs) and a six-membered aromatic ring are very common in solid structure.[90] Here, the intramolecular lone pair-π interactions are observed. As shown in Figure 22, one fluorine atom of the pentafluorophenyl group close to thiourea is positioned in close proximity to another pentafluorophenyl unit. It has to be mentioned that in the crystal the fluorine atom does not exactly locate above the center of the π-system but shifts towards the rim of the pentafluorophenyl moiety. One short close contact F-C 2.923 Å (sum of vdW radii = 3.17 Å) is observed. It can be described as a "η^1" type lone pair π interaction.

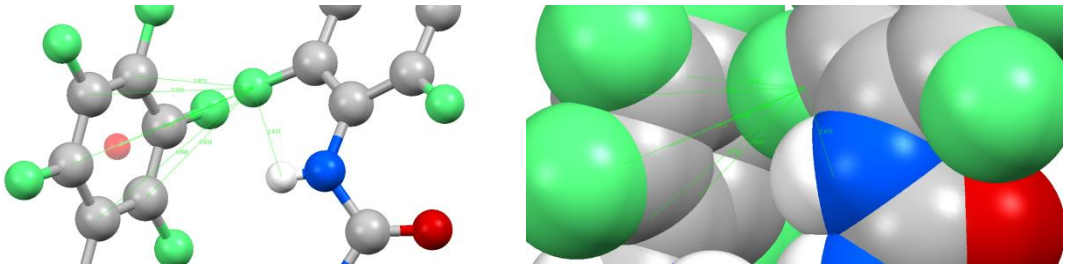


Figure 22 Part of the X-ray structures of receptor **16** showing interactions between a fluorine atom and its neighboring pentafluorophenyl group (gray, C; white, H; green, F; blue, N; red, O; yellow, S).

Table 1 Comparison of the F-C contacts [Å] in receptor **16**.

Bond distance	F-centroid$_{Ph}$	F-C1	F-C2	F-C3	F-C4	F-C5	F-C6
	3.268	2.923	3.204	3.772	4.098	3.834	3.267

The X-ray diffraction data for corresponding compounds are reported in the Experimental Section in detail.

3.4 ^{1}H NMR and ^{19}F NMR Studies in Solution

As an effective method to explore solution properties, NMR titrations are tremendously applicable for host-guest systems.[91] ^{1}H, ^{19}F, ^{13}C NMR spectroscopies are widely used in supramolecular chemistry. Here, the binding behavior of receptors towards halide anions is studied by ^{1}H NMR and ^{19}F NMR spectroscopic methods in solution.

Job plot (method of continuous variation or Job's method) has been applied to determine the binding ratio between hosts and guests since P. Job developed it in 1928.

3.4.1 Interactions of (Thio)urea-based Receptors with Halide Anions

First of all, the interactions between the novel receptors and halide anions are examined in $CDCl_3$. Considerable changes of ^{1}H NMR spectra are observed with the successive addition of halide anions (as Bu_4NX, tetrabutylammonium halide) in $CDCl_3$. For receptor **14** and chloride anions as typical example, the changes are discussed in detail. Similar cases are observed for other receptors and halide anions.

The signals of N-H protons of the amide and thiourea groups significantly shift

downfield, up to 2.280, 2.23, and 4.16 ppm, respectively. These data indicate that chloride anions are tightly bound by receptor **14**, proposed in a cooperative fashion by the acidic protons, in $CDCl_3$. Moreover, it is interesting to note that the saturation occurs when the amount of chloride anions reaches 1.1 equivalents. It signifies that the binding ratio between the receptor and chloride anions is 1:1, which is further confirmed by a Job plot.

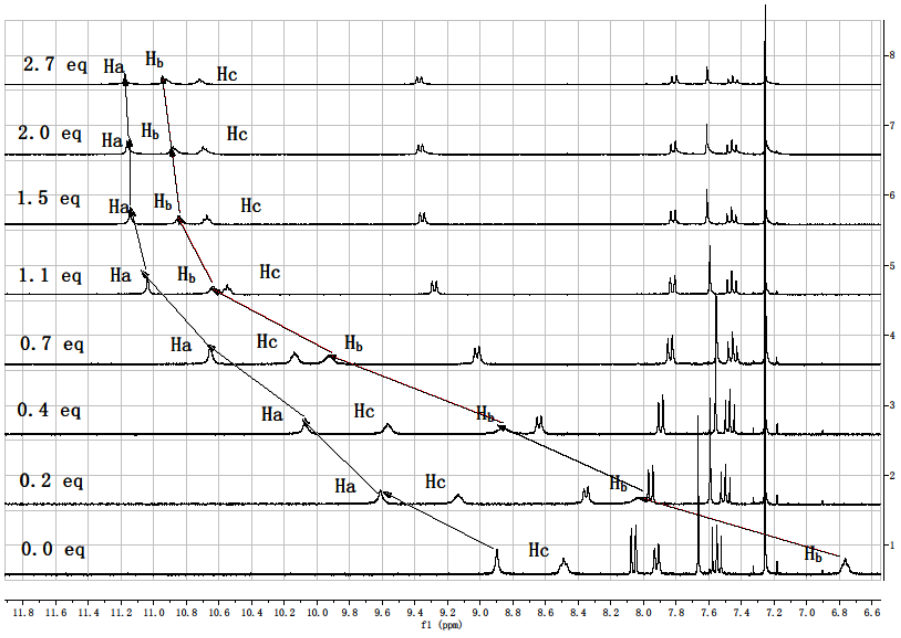


Figure 23 Partial ^{1}H NMR spectra ($CDCl_3$, 300 MHz, 298 K) of receptor **14** after successive addition of Bu_4NCl (the assignment of protons see Figure 17).

Although above data provide useful information on the binding ratio, the associating stoichiometry between receptor **14** and chloride anions is further examined by Job's method. The variation of the weighted chemical shifts as a function of molar ratio clearly shows a 1:1 receptor: anion binding ratio between receptor **14** and chloride anions (Figure 24, top left). Meanwhile, the ^{1}H NMR titration experiments between receptor **14** and chloride anions are conducted in $CDCl_3$ with a concentration of 0.01 M of receptor **14** and successive addition of Bu_4NCl. The corresponding titration curves are shown in Figure 24, top right. The data are obtained and fitted using standard methods of nonlinear regression treatment[92] to give the binding constant K = $1.67*10^4$ M^{-1} between receptor **14** and chloride anions in $CDCl_3$ at 298 K. The interactions of receptor **14** towards bromide and iodide anions are also examined and the

binding constants were obtained for a 1:1 binding ratio.

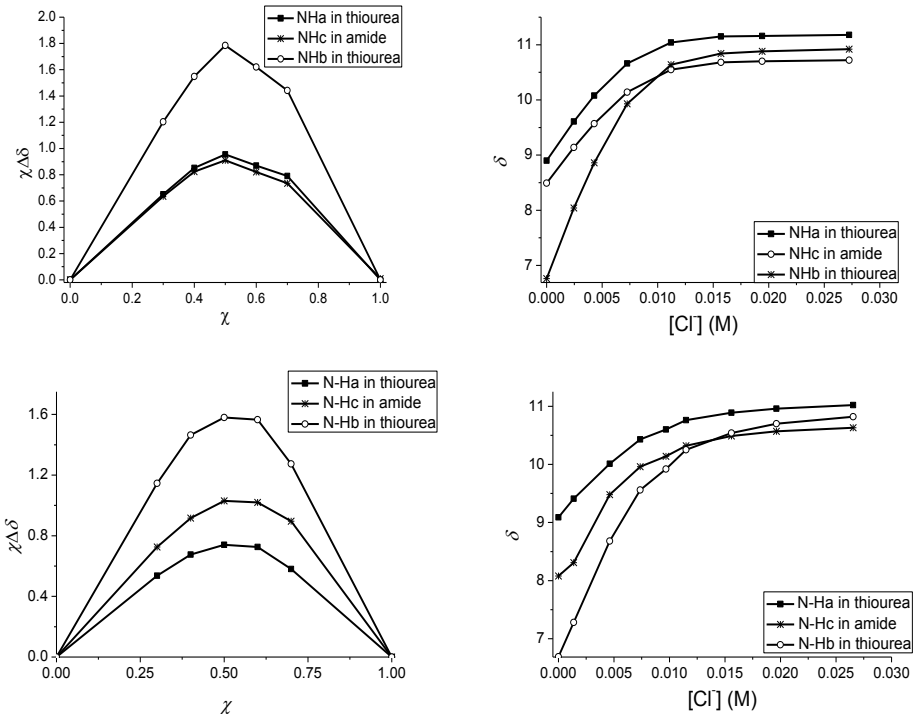


Figure 24 Titration curves of receptors **14** (right top) and **13** (right bottom) towards chloride anions in $CDCl_3$ and corresponding Job plots in $CDCl_3$ for receptors **14** (left top) and **13** (left bottom) towards chloride anions at 298 K (the total concentrations kept on 0.01 M).

The presence of pentafluorobenzyl groups in receptor **14** is assumed to cause the protons to be more acidic than ones in its analog **13**. To evaluate the effect of fluorination, the binding properties of receptor **13** towards halide anions are inquired by virtue of ^{1}H NMR titration experiments and Job plots in $CDCl_3$. Job plots clearly show 1:1 binding stoichiometry between receptor **13** and chloride anions in $CDCl_3$ (Figure 24, bottom left). The data obtained from ^{1}H NMR titration experiments are fitted with standard methods of nonlinear regression[92] (Figure 24, bottom right). The binding constant is reported as $K = 3.11*10^3$ M^{-1} between receptor **13** and chloride anions in $CDCl_3$ at 298 K.

To survey the associating behavior of different kinds of thiourea groups, receptor **12** is used to bind halide anions in $CDCl_3$. The ^{1}H NMR titration and Job plot experiments in $CDCl_3$ between receptor **12** and halide anions are carried out, too. An association constant of $K > 5*10^4$ M^{-1} is estimated for a 1:1 binding situation between receptor **12** and Cl^- in $CDCl_3$ at 298 K.

Generally speaking, the solution NMR data are readily applicable to the host-guest systems whose binding constants are in the range of 10 – 10^4 M^{-1}.[91a] In above investigations, the binding constant between receptor **12** and chloride anions is beyond this range. In order to acquire more reliable data between receptors and halide anions in solution, the binding behavior of the host-guest systems is pursued in DMSO-d_6. Due to its more polar and more competitive nature as a solvent, the binding affinities of receptors for halide anions would become low and the binding constants are likely to go to the range of 10 – 10^4 M^{-1}.

As a representative case, the binding behavior of receptor **14** towards chloride anions in DMSO-d_6 is discussed. Initially, the Job plots of receptor **14** and chloride anions from ^{1}H NMR spectroscopy are achieved and apparently show a 1:1 binding stoichiometry in DMSO-d_6 (Figure 25 right). Afterwards, the ^{1}H NMR titration experiments are conducted in DMSO-d_6 and the obtained data are fitted using standard methods of nonlinear regression treatment (Figure 25, left). A binding constant K = 744 M^{-1} is determined in DMSO-d_6 at 298 K. The binding properties of all receptors **11** - **16** and halide anions are also explored and provide the corresponding binding constants in DMSO-d_6 at 298 K.

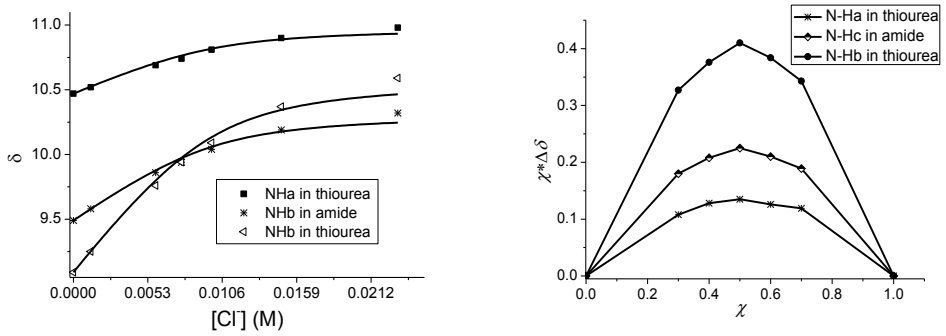


Figure 25 Titration curves of receptor **14** towards chloride anions in DMSO-d_6 (left) and corresponding Job plots in DMSO-d_6 at 298 K (right).

In order to compare the binding constants of different receptors and to analyze the changing trends, the binding constants of all receptors (**11** - **16**) with halide anions (Cl^-, Br^- and I^-, as Bu_4NX) in $CDCl_3$ and DMSO-d_6 are summarized in Table 2.

Table 2 Binding constants (K, M^{-1}) of receptors **11** – **16** with halide anions (as tetrabutylammonium salts) in $CDCl_3$, and DMSO-d_6 containing 0.5% water at 298 K. The binding constants are determined by ^1H 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%.

host	Cl^-	Br^-	I^-	host	Cl^-	Br^-	I^-
	$CDCl_3$				DMSO-d_6		
11	969	218	65	**11**	600	87	_ (b)
12	$> 5 \cdot 10^4$	$3.52 \cdot 10^4$	$1.65 \cdot 10^3$	**12**	845	21	_ (b)
13	$3.11 \cdot 10^3$	471	106	**13**	831	66	_ (b)
14	$1.67 \cdot 10^4$	$3.22 \cdot 10^3$	465	**14**	744	50	_ (b)
15	$3.17 \cdot 10^4$	$4.32 \cdot 10^3$	593	**15**	408	62	_ (b)
16	_(a)	_ (a)	_ (a)	**16**	809	73	_ (b)

[a] The receptor is not soluble in this solvent. [b] No significant shift observed.

Comparison of these binding constants of various (thio)urea/amide-based quinoline receptors **11** - **16** towards halide anions in solution reveals some interesting findings:

Firstly, all of the receptors, no matter fluorination or not, no matter in $CDCl_3$ or in DMSO-d_6, show increasing affinities towards halide anions in the order of $I^- < Br^- < Cl^-$. This result is ascribable to a combination of the basicity of halide anions and their size effects. Steiner stated that "all hydrogen bonds can be considered as incipient proton transfer reactions, and for strong hydrogen bonds, this reaction can be in a very advanced state."[93] The binding affinities depend on the basicity of the anions for a given receptor. In addition, the size effect makes a contribution to the trend as well. As mentioned above, the distance between the two protons, which are pointing to the direction of the quinoline N atom, is 2.473 Å. The diameters corresponding to chloride, bromide, and iodide anions are 3.62, 3.92, and 4.40 Å, respectively. The smaller the diameter of an anion is, the fitter it is for a receptor. Therefore, a combination of these two effects leads to the binding trend.

Secondly, receptors exhibit higher binding affinities toward a given anion in $CDCl_3$ than in DMSO-d_6. DMSO-d_6 is a more polar solvent and it is bound more strongly by receptors through hydrogen bonds. That DMSO-d_6 occupies the binding sites of receptors causes the receptors to show relatively low binding affinities for anions. The binding process between receptors and halide anions in DMSO-d_6 is proposed to be less entropically favored than in $CDCl_3$ because the separation of receptors and DMSO-d_6 consumes extra energies.

Thirdly, the fluorinated receptors, such as **12** and **14**, display higher binding abilities than the non-fluorinated ones, such as **11** and **13**. The first component that perhaps leads to the difference is based on electronic effects. Due to the strong electron-withdrawing ability of pentafluorophenyl groups, the N-Hs in thiourea and amide groups attaching to fluorinated receptors are stronger polarized and therefore more acidic. The second component might be based on an anion-π interaction. The anion-π interaction perhaps contributes to the binding ability of fluorinated receptors towards anions in solution.

Fourthly, receptor **12** binds each halide anion more strongly than receptor **14** does. It is ascribable to the difference of substituted thioureas. In receptor **12**, the pentafluorophenyl group, which is electron-deficient and withdraws electrons strongly, is directly attached to the thiourea; while in receptor **14**, the pentafluorophenyl group is anchored to the thiourea moiety through a methylene linker. Consequently, the N-Hs in the thiourea group in receptor **12** are induced to be more acidic than in receptor **14**.

Fifthly, it occurrs in $CDCl_3$ that the slight modification of receptors generate vast differences in binding ability; while the various receptors with different modifications in DMSO-d_6 display similar binding ability towards a given anion. It is proposed that the stronger solvation of anions in DMSO-d_6 decreases the selectivity of guests towards the receptors. The signals of all receptors in ^{1}H NMR spectra in DMSO-d_6 do not change with the successive addition of iodide anions. Due to their weak basicity and bulk sizes, all receptors exhibit no binding affinities towards iodide anions in

DMSO-d_6.

3.4.2 Interactions of Diamide-based Receptors with Halide Anions

(Thio)urea groups are excellent and strong binding sites for anions, while anion-π interactions are severely weak and extremely difficult to observe in solution. In above receptors, even if anion-π interactions exist, their contributions will submerge in the titanic contributions of (thio)urea groups. Amide groups are relatively weak binding moieties. Amide groups as peptide bond in proteins play countless functions, such as forming secondary or higher structures and transporting anions within the human body. Many receptors containing amide groups as binding sites have been designed and exploited to coordinate, bind, recognize and sense anions.[23]

In order to mimic oligo peptides and to explore the contributions of anion-π interactions in the binding process, receptors **17** - **20** are used to recognize halide anions in solution. As discussed above, the two N-H protons in receptor **18** point to the front of the N atom of the quinoline backbone and are likely to bind anions cooperatively. The binding behavior of receptors **17** - **20** towards halide anions in $CDCl_3$ is studied by means of ^{1}H NMR spectroscopic titration and Job plots with Bu_4N^+ halide salts. The Job plots of receptor **17** towards chloride anion in $CDCl_3$ are recorded in Figure 26 right, exhibiting a 1:1 binding stoichiometry. With the addition of chloride anions, the chemical shifts go downfield in the ^{1}H NMR spectra. The titration curves of receptor **17** towards chloride anions are also depicted in Figure 26. The fitted data provide a binding constant of K = 44 M^{-1} between receptor **17** and chloride anions in $CDCl_3$ at 298 K. All of the titration curves and Job plots between receptors **17** - **18** and halide anions are conducted in $CDCl_3$ at 298 K. The signals of receptors **19** and **20** in ^{1}H NMR spectra do not change with the addition of halide anions. No binding constants data are obtained and recorded. All the obtained data are listed in Table 3.

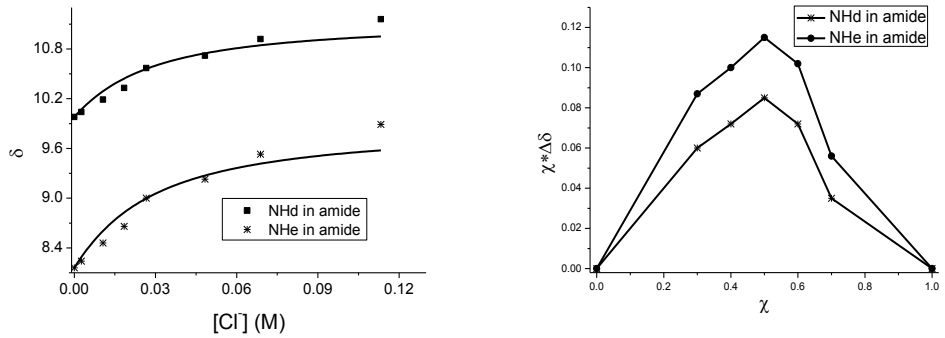


Figure 26 ^{1}H NMR titration curves of receptor **17** towards chloride anions in $CDCl_3$ (left) and corresponding Job plots in $CDCl_3$ (right).

Table 3 Binding constants (K, M^{-1}) of receptors **17** and **18** with halide anions in $CDCl_3$ at 298 K. The binding constants are measured by ^{1}H NMR titration experiments in $CDCl_3$ and fitted according to a 1:1 binding ratio. Errors are estimated to be less than 20%.

host	Cl^-	Br^-	I^-
17	44	35	18
18	34	30	15

The determined data are analyzed in brief.

As expected, receptors **17** - **18** display lower binding affinities towards a given anion than receptors **10** - **16** do. This is attributed to the absence of stronger hydrogen donor groups (urea/thiourea).

The selectivity of receptors **17** and **18** towards anions shows the same trend, in the sequence of $Cl^- \geq Br^- > I^-$ (considering of the estimated errors), which is in agreement to receptors **11** - **16**. This is ascribable to the differences of basicity and sizes of halide anions. The binding pockets of these receptors are fitter to small anions in solution.

Receptor **17**, containing two pentafluorophenyl groups, shows a somewhat stronger binding affinity than receptor **18**, containing only one pentafluorophenyl group. The effect of fluorination can account for this. The electronic differences between receptors **17** and **18** resulting from the fluoro substituent influence the p*Ka* of the N-H protons. In addition anion-π interactions might contribute. So far it is not clear which effect is the dominant one and the amount of participation of each interaction.

It is of interest to note that the pentafluorobenzoyl substituent is the prerequisite for the receptors. Compounds **19** and **20**, which do not contain pentafluorobenzoyl substituents, show no detectable binding affinities for anions in $CDCl_3$ at 298 K.

3.4.3 ^{19}F NMR Studies in Solution

Interactions between (thio)urea-based receptors and halide anions.

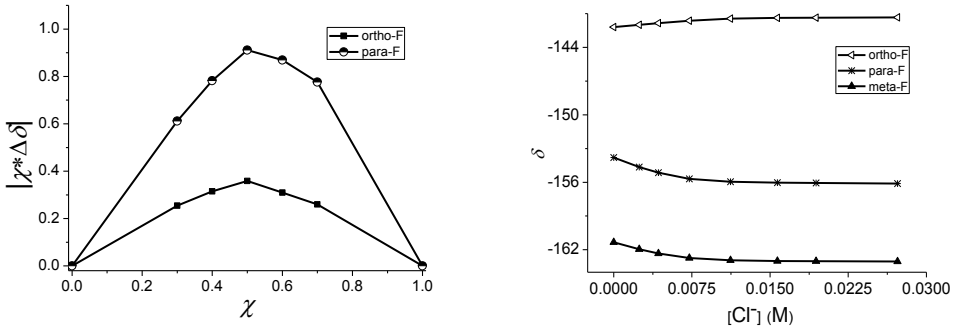


Figure 27 ^{19}F NMR titration curves of receptor **14** towards chloride anions in $CDCl_3$ (right) and corresponding Job plots in $CDCl_3$ (left).

^{19}F NMR spectroscopic method is widely used to analyze and determine the structures of organofluorine compounds due to its favorable nuclear properties and high natural abundance. Recently, Metrangolo, Resnati, Taylor and their co-workers[38, 94] used ^{19}F NMR spectroscopic method to investigate halogen bonding and/or anion sensing in solution and provided excellent results. The anion binding behavior of fluorinated receptors is likewise investigated by means of ^{19}F NMR spectroscopic method in solution. To find the binding stoichiometry between receptor **14** and chloride anions, a ^{19}F NMR Job plot is depicted in Figure 27 (left). It shows a 1:1 binding stoichiometry in $CDCl_3$, which is consistent with the result of related proton NMR studies. ^{19}F NMR titration spectra of receptor **14** upon the addition of varying equivalents of Bu_4NCl are plotted in Figure 27 (right). Standard methods of nonlinear regression treatment of the obtained data leads to the binding constant $K = 1.82*10^4$ M^{-1} between receptor **14** and chloride anions in $CDCl_3$ at 298 K.

Likewise, the anion binding properties of receptor **14** in DMSO-d_6 by means of ^{19}F NMR spectroscopy are examined. Initially, the Job plots experiments are carried

out in DMSO-d_6 to check the binding ratio between receptor **14** and anions via ^{19}F NMR spectra. The Job plots apparently show a 1:1 binding ratio between receptor **14** and chloride anions through ^{19}F NMR in DMSO-d_6 (Figure 28, left), which is good agreement with the results of the ^{1}H NMR studies. Titration curves are also plotted according to ^{19}F NMR spectra in DMSO-d_6. Standard methods of nonlinear regression treatment of the obtained data leads to the binding constant K = 711 M^{-1} between receptor **14** and chloride anions in DMSO-d_6 at 298 K , which is perfect accord with the results obtaining from ^{1}H NMR studies.

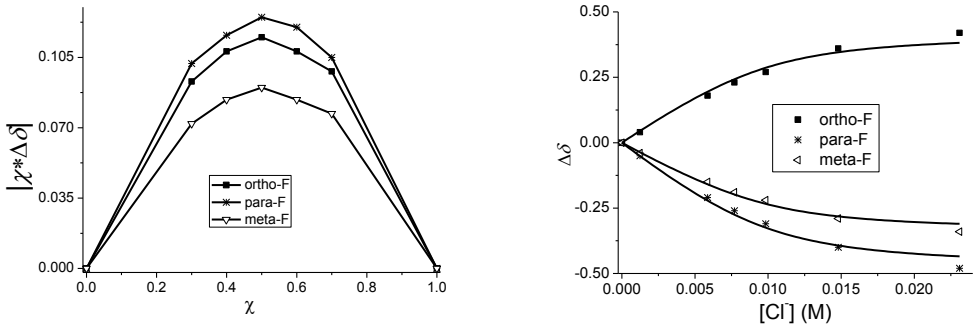


Figure 28 ^{19}F NMR titration curves of receptor **14** towards chloride anions in DMSO-d_6 (right) and corresponding Job plots in DMSO-d_6 (left).

It shows that the results obtained from ^{1}H NMR studies and ^{19}F NMR studies are in accord with one another.

3.5 Conclusions

A series of quinoline-based receptors towards anions has been synthesized successfully in good yield, and is fully characterized by ^{1}H NMR, ^{19}F NMR, ^{13}C NMR, mass spectra, infrared spectra, and elemental analyses. Some single crystals of the key compounds are prepared from appropriate solvents, and elucidated by single crystal X-ray diffraction. Their single crystal structures reveal that each receptor forms an appropriate preorganized structure for the binding of anions by virtue of intra/intermolecular hydrogen bonding. Their binding abilities towards halide anions are investigated by ^{1}H NMR and ^{19}F NMR and they show from moderate to strong affinities towards anions decreasing in the order of Cl^- > Br^- > I^- in $CDCl_3$ and DMSO-d_6

solution. In addition, tuning the halide binding affinities is achieved by modulating the electronic effects, functional groups, and fluorosubstituent effects. Thereby, the fluoro substituted receptors are stronger binders than the corresponding non-fluorinated derivatives. Anion-π interactions potentially contribute to the enhanced binding affinities. Furthermore, a rough general sequence of NH-containing binding sites towards halide anions is found, as shown in Figure 29. This rough trend should offer useful information and suggestion for the design of further receptors in anion recognition, sensing chemistry and catalysis science.

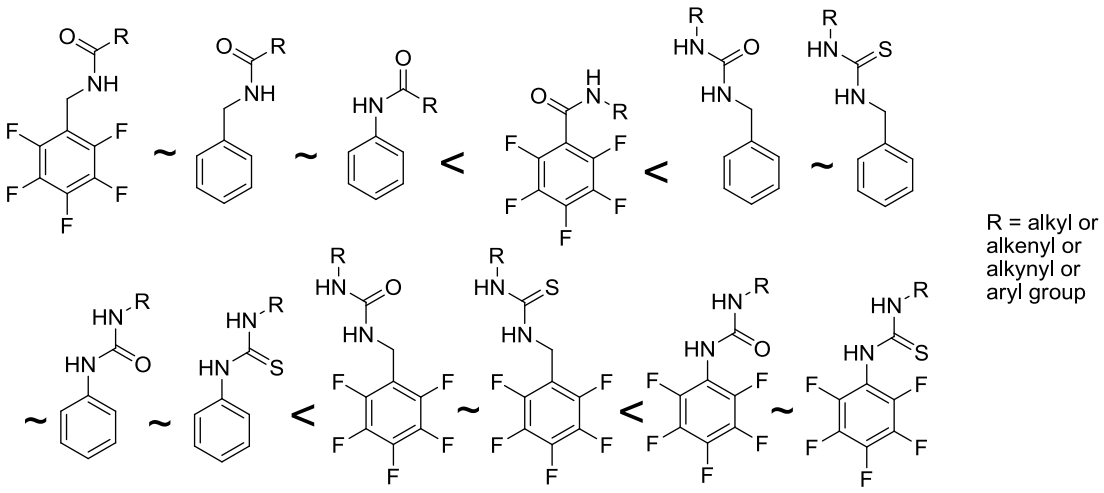


Figure 29 The general sequence of various NH-containing anion binding sites in solution.

Chapter 4 Salt-solubilization and Ion Pair Recognition through a Quinoline-substituted Crown Ether

4.1 Introduction

Crown ethers, the first generation marocyclic hosts, were first prepared and described by C. J. Pedersen in the late 1960s.[2] Since then, they have been widely applied in cation-sensing,[1] ditopic recetpors,[50c] rotaxane-construction,[73] salt extraction,[74] phase transfer catalysis[75] and many other fields. Ion-pair recognition, emerging from binding of anions and cations at the same time, has become an interesting field in supramolecular chemistry.[47] Ion-pairs widely appear in organic reaction processes. Reinhoudt,[48] Beer,[47c, 49] Smith,[50] Barboiu,[51] Sessler[47a, 47b, 52] and their co-workers have extensively explored the ion-pair recognition in solution and provide elegant results. Beer's group has developed a cooperative AND ion-pair recognition fashion by virtue of the conformational features of calix[4]diquinones.[49c] Smith and collaborators have made significant contributions to investigate the ion-pair binding properties of macrobicyclic receptors.[50b, 50e] Recently, J. L. Sessler and collaborators demonstrated the recognition behavior of ion pairs of KF and CsF by a calix[4]pyrrole in both solution and the solid state.[52b]

Inorganic salts play a vital role in many organic reactions, e.g. as reducing or oxidizing reagents. For example, sodium or potassium hypochlorite are exploited in enantioselective epoxidation of α,β-unsaturated ketones.[95] In addition, it permits ionic reactions to occur in aprotic media.[2] However, most inorganic salts are not soluble in common organic solvents. Consequently, salt extraction and solubilization are developed to solve this problem. Although it has progressed in past couple years, it is still an inadequately explored area. In 1996, a bifunctional calix[4]arene-based receptor was reported by Reinhoudt et al, which was capable of binding anions and cations simultaneously and solubilizing sodium halide salts into chloroform.[48c] In 1999, a

series of ditopic ligands for the simultaneous solvent extraction of cations and anions were demonstrated by White and Tasker et al.[53] The solubilization of KCl into DMSO were revealed by Smith and co-workers.[50b]

Due to their intra- and intermolecular hydrogen bonding networks, 2-amido-8-aminoquinolines are utilized as backbones for anion-sensing[76] and foldamer-construction.[77] Our group has systematically studied various types of 2-amido-8-aminoquinoline derivatives to tune anion affinity.[78, 96]

In this chapter, the synthesis and solution behavior of a novel ion-pair ditopic quinoline-based receptor is reported. The solubilization of chloride salts into organic solvents, such as chloroform or DMSO, is described.

4.2 Syntheses

The ditopic receptor is synthesized according to previous reports, as shown in the following scheme.[79] Firstly, catalytic hydrogenation of methyl 4-isobutoxyl-8-nitroquinoline-2-carboxylate **3** in CH_2Cl_2 with the catalysis of Pd/C in H_2 gas atmosphere affords the corresponding amine, which is subsequently coupled with phenyl isocyanate in CH_2Cl_2 at reflux to afford methyl 4-isobutoxy-8-(phenylureido)quinoline-2-carboxylate **21** in good yield. Secondly, the saponification of **21** is carried out in alkaline CH_3OH/THF solution overnight and then neutralized using ice acetic acid to afford 4-isobutoxy-8-(phenylureido) quinoline-2-carboxylic acid **22**, which reacts with freshly reduced 4′-aminobenzo-18-crown-6 **23** in the presence of HBTU (O-(Benzotriazol -1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate) and DIPEA in a mixture of CH_2Cl_2 and CH_3CN solution to afford the ditopic receptor **24** in satisfactory yield. 4′-Aminobenzo-18-crown-6 **23** is prepared by catalytic reduction of 4′-nitrobenzo-18-crown-6 in CH_2Cl_2 in the presence of Pd/C and H_2 gas atmosphere overnight in near to quantitative yield.

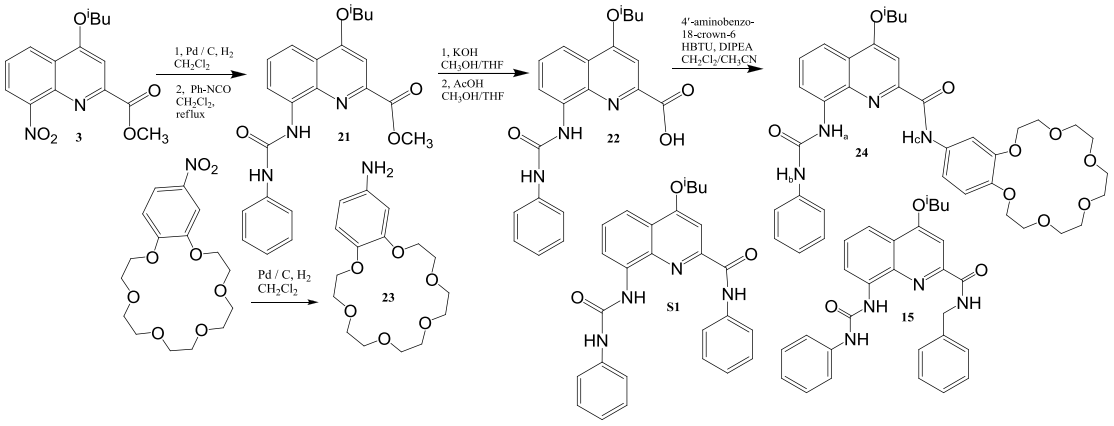


Figure 30 Syntheses of the ditopic receptor **24** and the structures of control compounds **S1** and **15**.

The above compounds are fully characterized by ^{1}H NMR, ^{13}C NMR, IR, mass spectra, melting points and elemental analysis. In addition, compound **24** is crystallized and analyzed by X-ray diffraction from DMSO (see Experimental Section for details).

4.3 Solid State Structures and Conformational Considerations

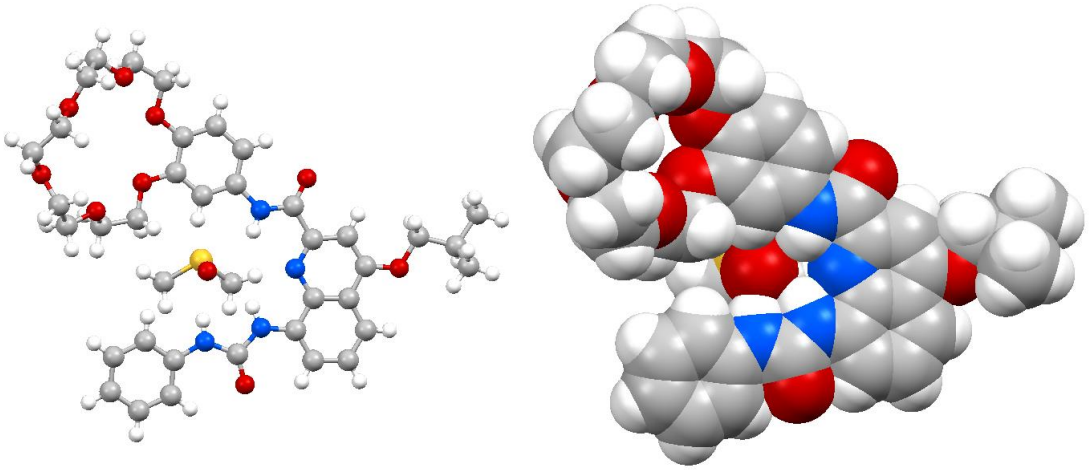


Figure 31 Crystal structures of ditopic receptor **24** (gray, C; white, H; blue, N; red, O; yellow, S).

Crystals of ditopic receptor **24** are grown from a solution of receptor **24** in DMSO. The structure is elucidated by single crystal X-ray diffraction and is shown in Figure 31. As shown in Figure 31, **24** contains both an anion-binding site and a cation-binding site held in close proximity. As anticipated, the acidic hydrogen atom of the amide and one of urea groups are oriented to the front of the quinoline nitrogen

atom with a distance of 2.275 Å and 2.269 Å, respectively. Another proton in thiourea group points also to the cavity. This geometry facilitates the anion binding. The 18-crown-6 has been well studied as an excellent binding site for cations, especially for potassium ions.[1-2] The presence of both an anion binding site and a cation binding site should ensure the possibility of binding ion pairs in solution.

4.4 ^{1}H NMR Studies in Solution

4.4.1 Study of Substituent Effects

First of all, the binding behavior of receptor **24** towards bromide anions (as tetrabutylammonium Bu_4N^+ halide salts) in $CDCl_3$ is examined by virtue of ^{1}H NMR spectroscopic studies. With the successive addition of bromide anions, the changes of chemical shifts in ^{1}H NMR spectra for N-H protons are observed, up to 0.35, 0.67 and 0.34 ppm, respectively. It exhibits that there are interactions between the receptor **24** and bromide anions in solution.

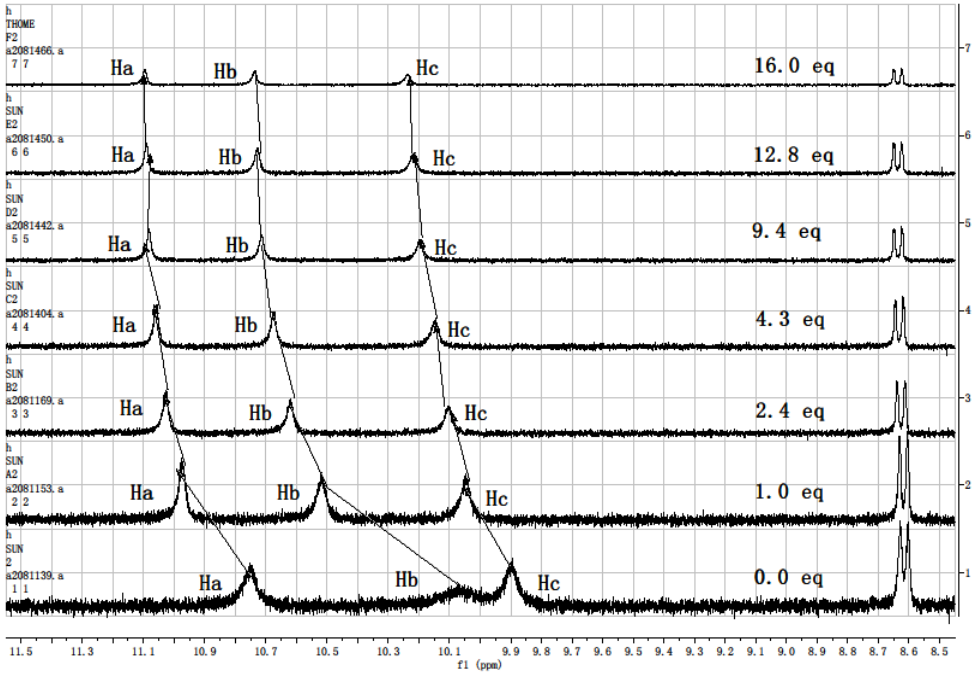


Figure 32 Partial ^{1}H NMR spectra ($CDCl_3$, 300 MHz, 298 K) of receptor **24** after successive addition of Bu_4NBr (the assignment of protons see Figure 30).

Secondly, Job plots of receptor **24** towards bromide anions in solution are obtained by virtue of ^{1}H NMR spectroscopic method. The 1:1 binding stoichiometry is validated between receptor **24** and bromide anions in $CDCl_3$ (Figure 33 right).

Thirdly, anion binding investigations are conducted using Bu_4N^+ halide salts as anion sources in $CDCl_3$ through ^{1}H NMR spectroscopic method. The ^{1}H NMR titration experiments are performed in 0.005 M solution of receptor **24** in $CDCl_3$ by successive addition of corresponding Bu_4N^+ halide salts. Titration curves of receptor **24** towards bromide anions are shown in Figure 33. The data obtained from ^{1}H NMR titration curves are fitted by standard methods of nonlinear regression treatment[92] to provide a binding constant of K = 525 M^{-1} between bromide anions and receptor **24**. The binding constants of receptor **24** towards chloride and iodide anions are also acquired through the similar treatment.

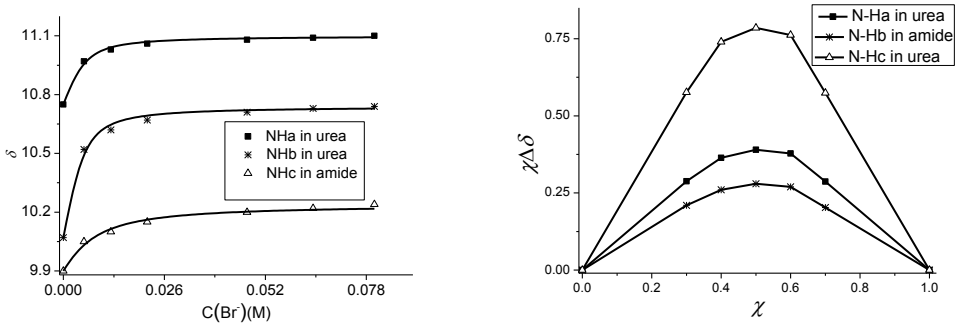


Figure 33 Titration curves of receptor **24** towards bromide anions (left) in $CDCl_3$ at 298 K and corresponding Job plots in $CDCl_3$ (right the total concentration kept 0.005 M) at 298 K.

The binding constants of receptor **24** towards various halide anions in $CDCl_3$ are listed in Table 4. In order to discuss the substituent effect on the binding ability, the data for control **S1**, which was reported previously, are also recorded in Table 4.[78b] The binding affinities of receptor **24** towards halide anions are becoming strong in the order: $I^- < Br^- < Cl^-$, which is consistent with previous report. This tendency is hypothesized to arise from the higher basicity of chloride anions, the size of the receptor binding pocket and the fitter size of small anions. Furthermore, receptor **24** displays weaker binding ability for given anions compared to analog **S1**. Presumably, the N-H_{amide} proton in **24** is less acidic due to the existence of extra alkyl-oxy groups at

the phenyl group as well as due to the steric hindrance effect of the bulky crown ether moiety. The existence of the bulky 18-crown-6 moiety makes receptor **24** show slightly weaker binding affinities for anions, but receptor **24** is still a good receptor for anions due to the preorganized hydrogen cavity.

Table 4 Binding constants (K, M^{-1}) of receptor **24** and control **S1** with halide anions (Bu_4N^+ salts) in $CDCl_3$ at 298 K. The binding constants are determined by ^1H NMR titration experiments in $CDCl_3$ at 298 K and fitted according to a 1:1 binding ratio based on Job plots. Errors are estimated to be less than 15%.

host	Cl^-	Br^-	I^-
24	1008	525	236
S1[78b]	7700	1100	___[a]

(a): Not reported.

4.4.2 Complexation of Ion Pairs in DMSO-d_6

Due to the existence of both an anion binding site and a cation binding moiety, receptor **24** is likely to associate ion pairs simultaneously in solution. The ability of binding ion pairs for receptor **24** are evaluated by means of ^1H NMR spectroscopic studies in DMSO-d_6 due to solubilizition reasons. The binding behavior of receptor **24** towards anions is studied in the absence and presence of a suitable coordinating cation in DMSO-d_6. Bu_4N^+ halide salts and $KBPh_4$ (potassium tetraphenylborate) are used to provide halide anions and potassium cations, respectively. Receptor **24** has negligible affinity for Bu_4N^+ and BPh_4^-. The binding ratio between receptor **24** and halide anions both in the presence and absence of potassium cations are examined in DMSO-d_6. As a representative example, the Job plots are shown in Figure 34. In both cases, the binding stoichiometries are checked as 1:1 irrespective of the presence of potassium ions or not. Afterwards, the titration curves between receptor **24** and halide anions are operated and fitted using non-linear curve fitting method.[92] The typical titration curves of receptor **24** for chloride anions are presented in Figure 34 in the presence and absence of potassium cations in DMSO-d_6. The obtained binding constants are calculated as 212 M^{-1} and 397 M^{-1} in DMSO-d_6 at 298 K corresponding to the absence and presence of potassium cations, respectively. To evaluate the cooperativity effect,

$K_{\text{ion pair}}/K_{\text{anion, free}}$ is defined as coopeativity factor in ion-pair recognition field by Beer.[49c] For chloride anions, the cooperativity factor is calculated as 1.87. Other binding constants of receptor **24** for halide anions with and without potassium cations are also determined in DMSO-d_6 at 298 K and other cooperativity factors are also acquired. All of the obtained data are recorded in Table 5.

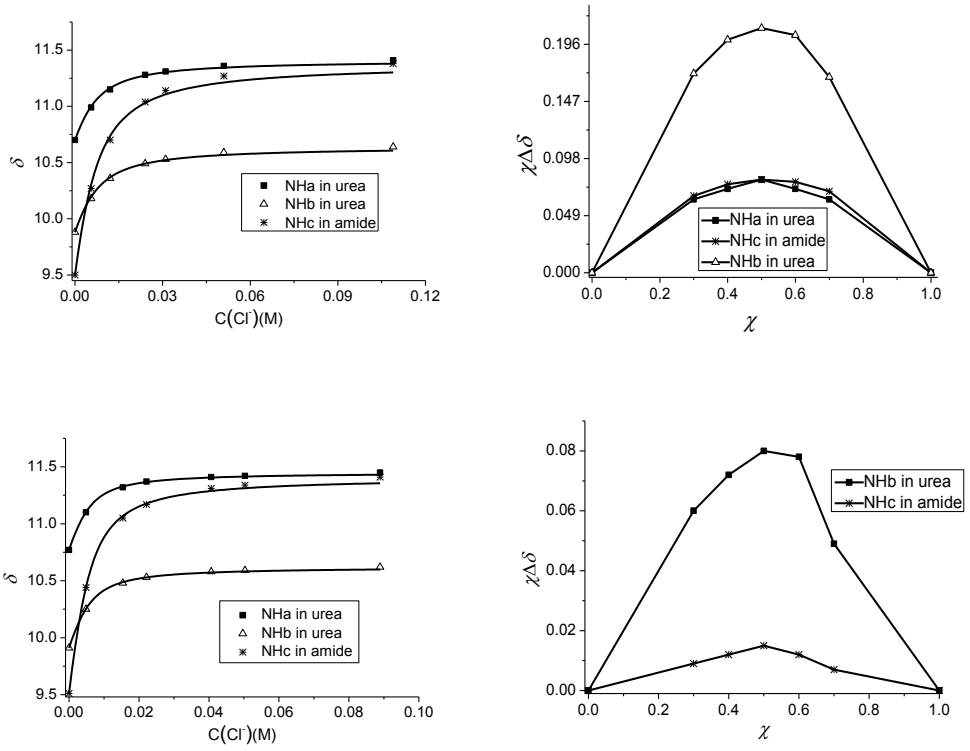


Figure 34 Titration curves of receptor **24** in the absence (left top) and presence (left bottom) of potassium cations (as $KBPh_4$) towards chloride anions in DMSO-d_6 and corresponding Job plots in DMSO-d_6 at 298 K (right top and right bottom).

Table 5 Binding constants (K, M^{-1}) of receptor **24** with halide anions (as Bu_4N^+ salts) in the absence and presence of $KBPh_4$ in DMSO-d_6 and in mixed solvent (v/v/v 8/1/1, $CD_3CN/CDCl_3$/DMSO-d_6) at 298 K and cooperativity factors. The binding constants are determined by ^1H NMR titration experiments and fitted according to a 1:1 binding ratio based on Job plots. Errors are estimated to be less than 15%.

guest	solvent host	K	cooperativity factor	solvent host	K	cooperativity factor
	DMSO-d_6			$CD_3CN/CDCl_3$/DMSO-d_6		
Cl^-	free **24**	212	1.87	free **24**	470	3.31
	24 + K^-	397		**24** + K^-	1556	
Br^-	free **24**	45	1.13	free **24**	106	2.39
	24 + K^-	51		**24** + K^-	253	
I^-	free **24**	__a	__	free **24**	__a	__
	24 + K^-	__a		**24** + K^-	__a	

a: No shift observed.

A slight enhancement of binding affinity is detected in chloride and bromide recognition when potassium cations are present in solution. Presumably, there are two effects to facilitate the anion binding properties when potassium cations are present in solution. Firstly, the ion-dipole interactions between potassium cations and crown ether moieties are likely to induce a higher acidity of the amide N-H proton than the free receptor **24**. Consequently, the binding ability increases. Secondly, an extra electrostatic cation-anion interaction appears once potassium cations are bound by receptor **24**, which is favorable for stabilization of the receptor-anion complex. This factor also perhaps makes the binding ability increase in solution. Supposedly, the high polar solvents DMSO cause the cooperativity factors to be relatively small. It is possibly to determine bigger cooperativity factors in less competitive solvents.

4.4.3 Complexation of Ion Pairs in Mixed Solvents

In order to further probe the cooperativity effect, the ion-pair binding properties of receptor **24** are examined in less polar and competitive solvents. Considering of solubility, the mixture of CD_3CN, $CDCl_3$ and DMSO-d_6 (v/v/v: 8/1/1) is chosen. All of the titration experiments between receptor **24** and halide anions in the presence and absence of potassium cations are conducted in these solvents. The corresponding ti-

tration curves are displayed in Figure 35. The binding constants are obtained by the fitted data and are also listed in Table 5.

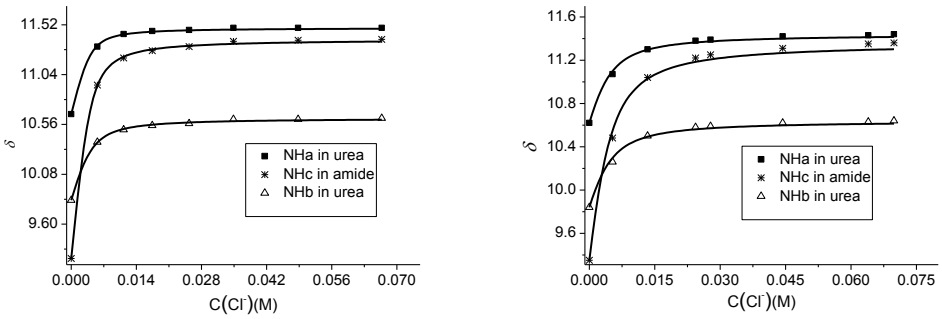


Figure 35 Titration curves of receptor **24** in the absence(left) and presence (right) of $KBPh_4$ towards chloride anions in mixed solvent of CD_3CN /$CDCl_3$/DMSO-d_6 (v: 8/1/1).

After examination of the data in Table 5, some trends are exhibited.

Firstly, the binding constants between receptor **24** and anions in both the absence and the presence of potassium cations become bigger in these less competitive solvents than in DMSO-d_6. This is anticipated to result from the decrease of polarity of solvents.

Secondly, the binding affinities of receptor **24** towards halide anions in this mixed solvent also decrease in the order: $Cl^- > Br^- > I^-$. The basicity of halide anions and the size of the cavity of receptor **24** lead to the sequence. The basicity of halide anions decreases in the order: $Cl^- > Br^- > I^-$. Moreover, the smaller the anion is, the fitter it is for the hydrogen cavity in receptor **24**.

Thirdly, a higher enhancement of binding affinities is obtained in the form of cooperativity factors for Cl^-/Br^- 1.87/1.13 in DMSO-d_6 and 3.31/2.39 in mixed solvents. Presumably, it results from the solvent effects on extra interactions between receptor **24** in the presence potassium cations and anions in mixed solvents relative to DMSO-d_6. The decrease of solvent polarity not only facilitates the original hydrogen bonding interactions between anions and receptor **24**, but also benefits the extra interactions, including induced acidity and electrostatic attractions. Consequently, the cooperativity factors rise.

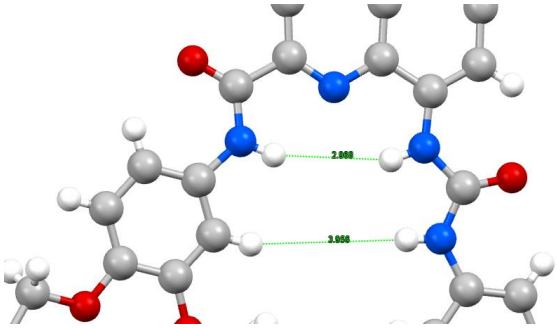
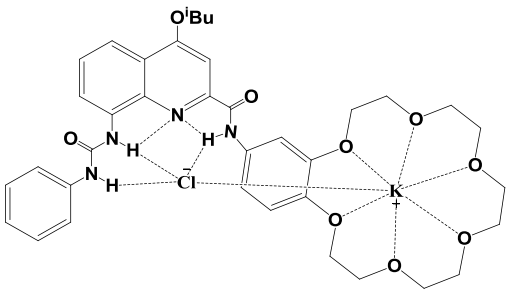


Figure 36 Partial of the single crystal structure of receptor **24**.

Fourthly, receptor **24** does not show detectable affinity towards iodide anions in DMSO-d_6, irrespective of the presence of potassium cations or not, which is in accord with previous report. Unexpectedly, receptor **24** does not show affinity towards iodide anions in the less polar mixed solvents either. It is hypothesized to result from the size matching rules. As shown in Figure 36, the distances between the two acidic hydrogen atoms are 2.968 Å and 3.956 Å, respectively. The diameters of chloride, bromide and iodide anions are 3.62 Å, 3.92 Å and 4.40 Å, respectively.[97] The hydrogen cavity fits chloride anions well, and receptor **24** matches bromide anions not quite well. While the size of iodide (4.40 Å) is too big to fit into the hydrogen cavity (size: 2.968 Å and 3.956 Å) in receptor **24**.

4.4.4 Predicted Binding Mode

Owing to the small cooperativity factors, the binding mode between receptor **24** and ion pairs is classified as separated heteroditopic ion pair recognition,[47c, 49c] as shown in Scheme 6. Presumably, the rigid phenyl spacer between the quinoline-backbone and crown ether moiety leads to the small cooperativity factors.



Scheme 6 The possible binding mode of receptor **24** with ion-pair K^+/Cl^-.

4.4.5 Solubilizing of Salts into $CDCl_3$

Due to the existence of a cation binding site (crown ether moiety) and an anion complexation part (quinoline backbone), receptor **24** has an ability of binding ion pairs (such as K^+/Cl^-, K^+/Br^-) simultaneously. It is hypothesized to solubilize inorganic salts into organic salts. This hypothesis is validated by ^1H NMR spectroscopic and mass spectra method.

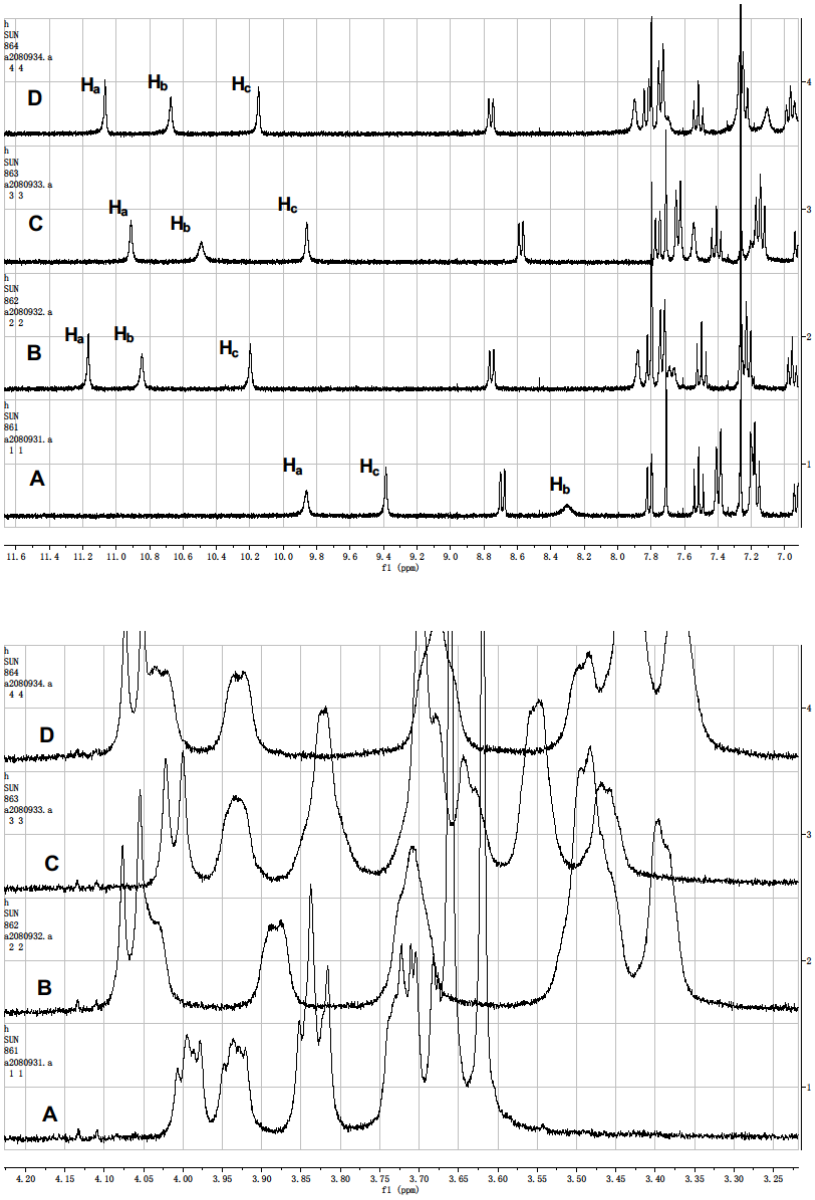
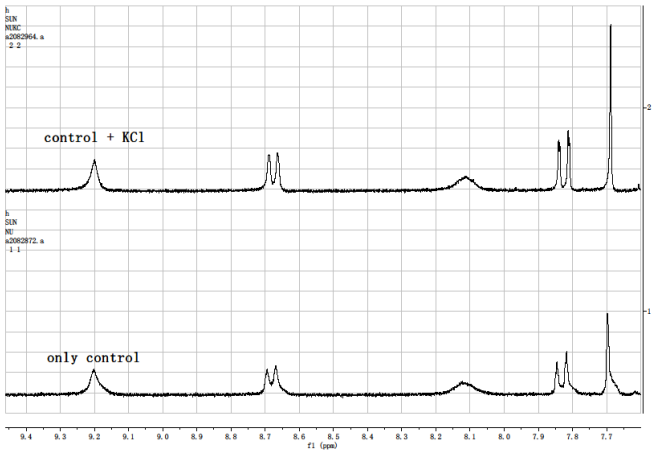


Figure 37 The N-Hs regions (top) and the crown ether regions (bottom) of the ^1H NMR spectra of A) only **24**, B) **24** in the presence of KCl, C) **24** in the presence of NaCl, D) **24** in the presence of NH_4Cl in $CDCl_3$ at 298 K.

The complex samples for ^{1}H NMR are obtained by mixing of receptor **24** and an excess of solid salts (KCl, NaCl and NH_4Cl) followed by stirring for 12 h in the NMR test tubes. The interacting behavior of receptor **24** and KCl in $CDCl_3$ as a representative example is discussed here in detail. The ^{1}H NMR spectrum of receptor **24** is displayed in Figure 37 A. After interacting with KCl, the peaks corresponding to N-H protons shift downfield dramatically, up to 1.31, 2.54 and 0.81 ppm (Figure 37, top A and B). This phenomenon is pretty similar to the presence of soluble chloride salts, such as Bu_4NCl. Moreover, tremendous changes take place for the peaks corresponding to the crown ether moiety. Presumably, they result from the interactions between receptor **24** and KCl in $CDCl_3$. The crown ether moiety is flexible and shows overlapping multiplets in the range of 3.60-4.05 ppm in the absence of KCl in $CDCl_3$ (Figure 37, bottom A). The peaks become less overlapping and expanded to 3.35 - 4.10 ppm region due to the existence of KCl, indicating the rigidification of crown ether moiety.[98] It is ascribed to the host reorganization and desolvation. The effect of ionic strength is ruled out, see below. All of these phenomena support the solubilization properties of receptor **24**, capable of solubilizing KCl into $CDCl_3$.

Similar results are obtained for NaCl and NH_4Cl in $CDCl_3$, Figure 37.



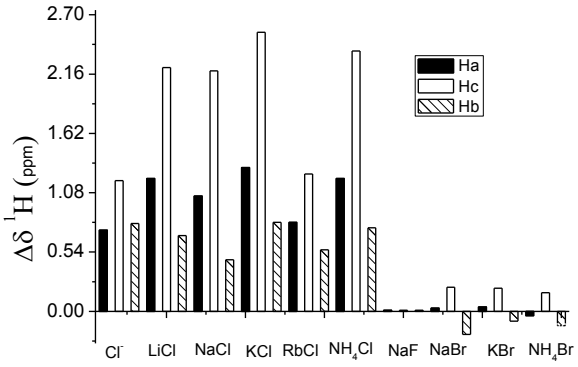


Figure 38 The acidic proton regions of the ^{1}H NMR spectra of a) only control **15** (bottom) and b) control **15** (top) in the presence of KCl in $CDCl_3$ at 298 K and ^{1}H NMR chemical shift changes of receptor **24** in the presence of KCl, $\Delta\delta = \delta$(in the presence of salts) - δ(free receptor).

To examine the role of the 18-crown-6 fragment in receptor **24**, the solubilization properties of a control compound **15**[99] are tested. After a similar treatment process, the ^{1}H NMR spectra are acquired in the absence and presence of KCl (Figure 38, top). The existence of KCl only causes negligible changes in ^{1}H NMR for the control **15**. The result shows that there are no detectable interactions between compound **15** and KCl salts in $CDCl_3$ at 298 K. Control **15** is not capable of solubilizing KCl into $CDCl_3$. The existence of a crown ether part serving as binding sites for cations is indispensible for the ditopic receptor.

Afterward, the ability of extracting other inorganic salts into chloroform of receptor **24** is also examined by ^{1}H NMR spectroscopic methods. The chemical shift changes of receptor **24** for various inorganic salts are summarized in Figure 38 bottom.

After examination and analysis of above data, some conclusions are drawn.

1. Receptor **24** prefers chloride salts over other salt. The bigger downfield shifts in ^{1}H NMR of receptor **24** towards alkali metal and ammonium chloride salts suggest stronger interactions between receptor **24** and chloride salts. Interestingly, the anion fragments are the vital control factors. Receptor **24** serves as a splendid solubilizer of chloride salts into $CDCl_3$, irrespective of which cation part is used in salts. It shows relatively weak binding affinities toward bromide salts. This is consistent with the

preference order of $Cl^- > Br^- > I^-$ in both $CDCl_3$ and DMSO-d_6.

2. After comparison of the changes of chemical shifts in the presence of soluble Bu_4NCl and KCl, it is found that receptor **24** extracts an almost stoichimetric amount of chloride salts into chloroform and almost all of the receptor **24** act as solubilizers for chloride salts.

3. The benzo-18-crown-6 fragment is known to act as a splendid binder for potassium cations. Consequently, the addition of potassium salts causes the biggest chemical shift changes. The rubidium cations are too big to fit the crown ether moiety well.

4. Fluoride anions are strongly basic and can easily deprotonate species containing acidc protons to form HF and HF_2^- in solution. In solid, the fluoride part still keeps this property. With the addition of KF salts, the three N-H protons disappear in ^1H NMR spectrum.

4.4.6 Solubilizing of Salts into DMSO-d_6

Furthermore, the extraction ability of receptor **24** towards chloride salts into DMSO-d_6 is studied. The results are illustrated in Figure 39. It exhibits that receptor **24** is also able to solubilize chloride salts into DMSO-d_6.

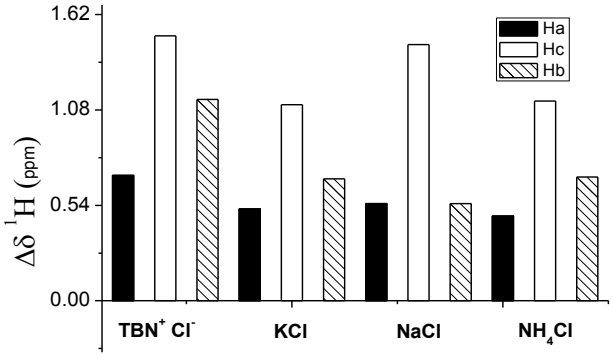


Figure 39 ^1H NMR chemical shift changes of receptor **24** in the presence of various chloride salts in DMSO-d_6 [$\Delta\delta$ = δ(in the presence of salts) - δ(free receptor)].

Compared to the results in $CDCl_3$, the ability of solubilizing salts into DMSO-d_6

is weaker than that in $CDCl_3$. This is also consistent with binding affinities of ditopic receptor **24** in solution. DMSO-d_6 is a good hydrogen bonding partner and has stronger ability to compete with the guests than $CDCl_3$ does. Due to the competition between bulk solvent molecules and guest molecules, the binding affinities in DMSO-d_6 are weaker than those in $CDCl_3$ for a given anion. Consequently, the binding affinity and solubilizing ability towards salts in DMSO-d_6 are weaker than in $CDCl_3$ due to the more polar nature of DMSO-d_6.

In addition, the "titration" experiments of receptor **24** towards KCl are carried out in DMSO-d_6 at room temperature (Figure 40). As shown, the ^{1}H NMR signals corresponding to respective NH protons in receptor **24** go downfield dramatically with the addition of KCl in DMSO-d_6. However, the binding constant between receptor **24** and KCl salts cannot be obtained due to lack of the accurate solubility reasons. The cases for NaCl and NH_4Cl are similar as for KCl.

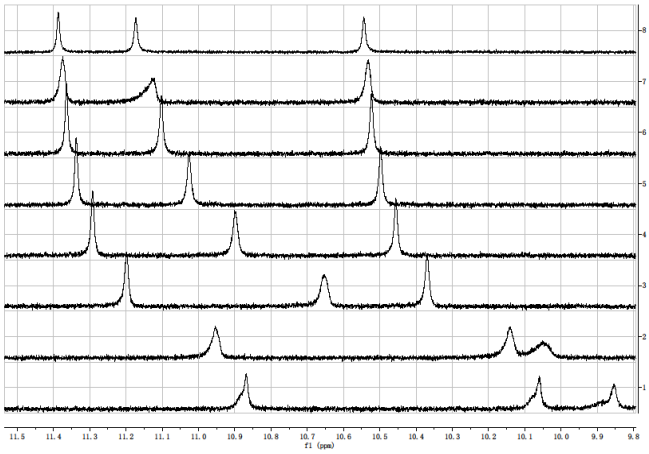


Figure 40 Partial ^{1}H NMR regions of the receptor **24** with the successive addition of KCl in DMSO-d_6.

4.4.7 MS Study

In order to further investigate the solubilization properties of receptor **24** towards salts, the complexes of receptor **24** and salts have also been confirmed by ESI mass spectrometry. After solid-liquid extraction, the mixtures are filtered, concentrated, dried in *vacuo* and measured in chloroform by ESI mass spectra. The potassium chloride complex is discussed as a representative example. In the positive ESI mass spec-

tra region of the **24**-KCl complex, two main peaks at 727.27875(100.00%) and 1489.52856(80.00%) are clearly observed, corresponding to [**24** + K]$^+$ and [2 **24**+2 K + Cl]$^+$ or in the form of [2 **24**+ K + KCl]$^+$, respectively. In addition, the peak at 723.28241(100.00%) clearly appear in the negative region, corresponding to [**24** + Cl]$^-$ (Figure 41).

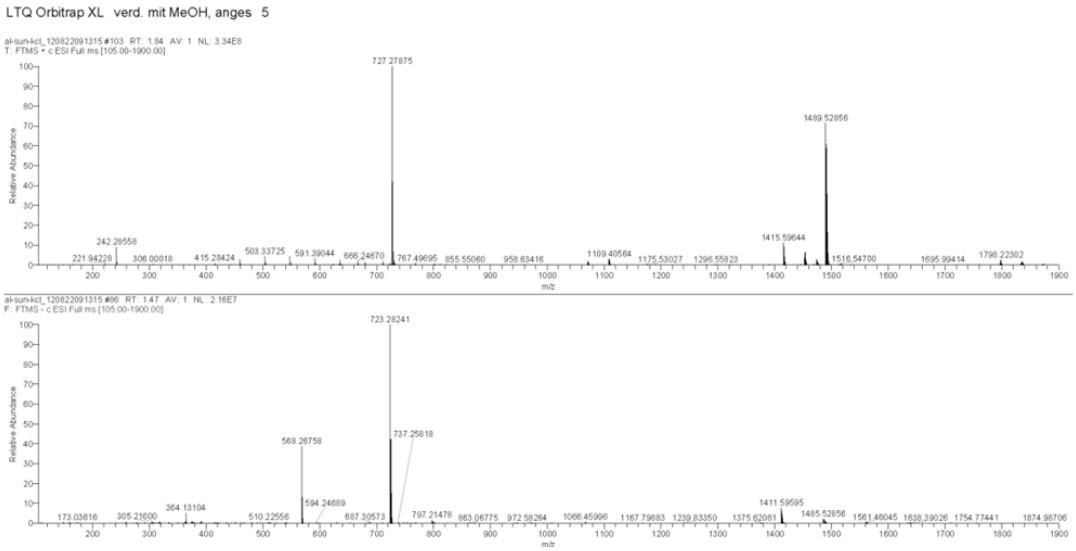


Figure 41 The ESI mass spectra of positive region (top) and negative region (bottom) for **24**-KCl.

The case for NaCl is similar to that of KCl. Two peaks at 711.30175 (100.00%) and 1457.57471 (46.43%) are clearly observed in the positive region, corresponding to [**24** + Na]$^+$ and [2 **24**+2 Na + Cl]$^+$ or in the form [2 **24**+ Na + NaCl]$^+$, respectively. Furthermore, two peaks at 723.28021(100.00%) and 1411.59180 (93.03%) are clearly appeared in the negative region, corresponding to [**24** + Cl]$^-$ and [2 **24** + Cl]$^-$, respectively.

The case for NH_4Cl is similar to that of KCl and NaCl, it will not be discussed here.

These mass spectral results afford supportive proof of solubilization of MCl salts into chloroform by receptor **24**.

4.4.8 Extraction-release Solid-$CHCl_3$-water-solid Cycle

Moreover, the extraction-release of KCl in solid-$CHCl_3$-water-solid cycles is

tested. Based on ^{1}H NMR analysis, KCl is easily transferred into chloroform by receptor **24** and released by water-washing in a controlled fashion. First of all, a solution of receptor **24** (0.01 M) in 0.80 mL $CDCl_3$ is analyzed by ^{1}H NMR at 298 K, and the peaks of receptor **24** in $CDCl_3$ solution corresponding to H_a, H_b and H_c are 10.01, 8.55 and 9.48, respectively (Figure 42,top a). Secondly, an excess of KCl salts are added into the NMR test tubes and stirred for 12 h and then ^{1}H NMR spectra are measured. The peaks of receptor **24** after treatment corresponding to H_a, H_b and H_c shifted downfield to 11.12, 10.75 and 10.14, respectively (Figure 42, top b).

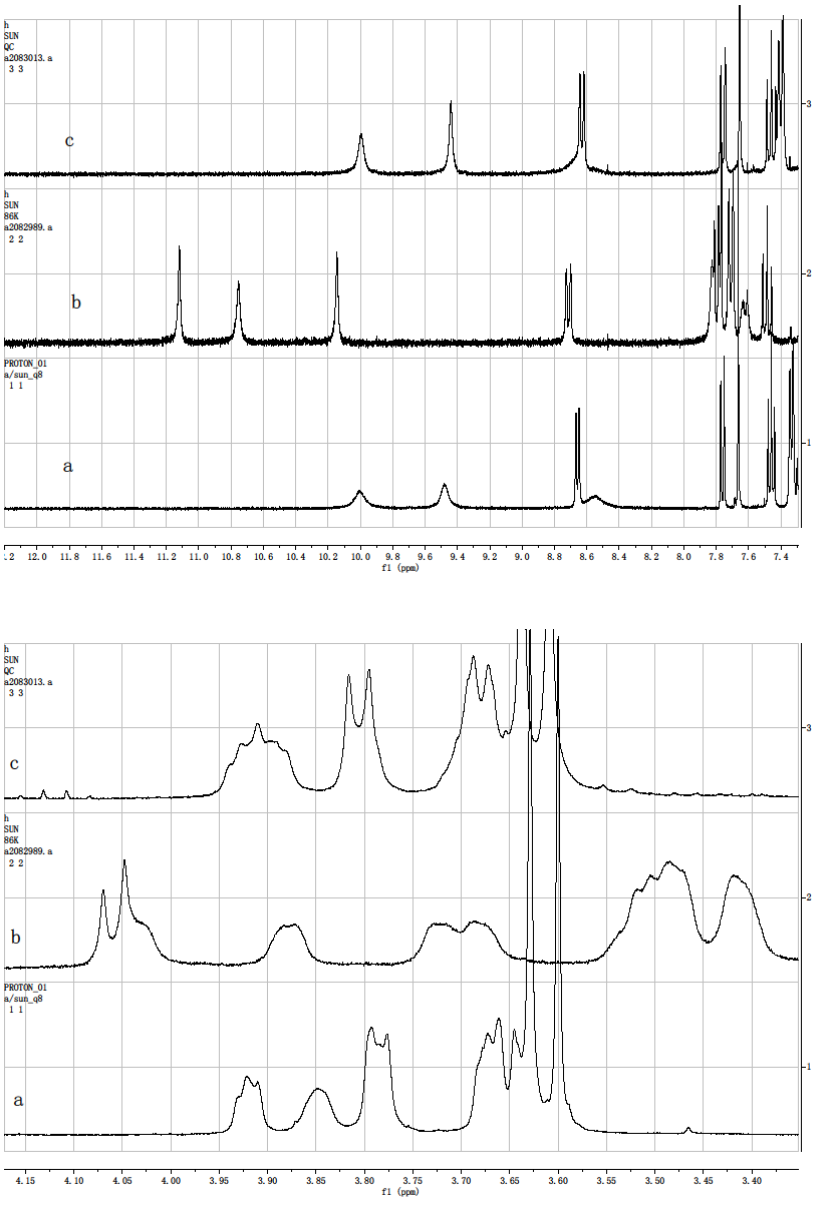
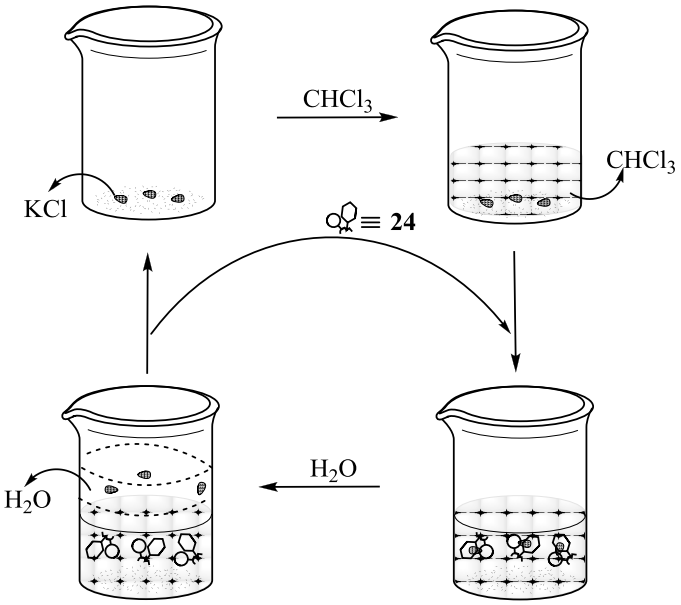


Figure 42 The ^{1}H NMR spectra of a) only **24**, b) **24** in presence of KCl, c) after water-washing **24**-KCl complex in $CDCl_3$.

Finally, receptor **24** and potassium chloride are conveniently recovered through a water-washing fashion. The ^{1}H NMR spectra of the recovered receptor **24** in $CDCl_3$ is measured. It is found that all of the signals corresponding to the N-H protons return, as shown in Figure 42.

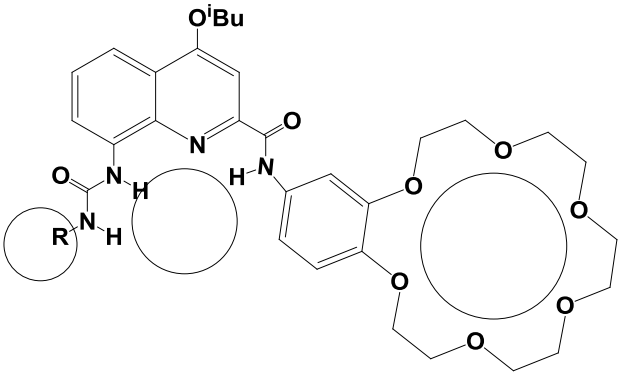
Similar case is observed for the crown ether part. In the absence of guests, the crown ether is flexible and shows overlapping multiples at the 3.60 - 3.95 ppm region of the ^{1}H NMR spectrum (Figure 42, right bottom). In the presence of KCl salts, the corresponding ^{1}H NMR partial become less overlapped and expand to 3.40 - 4.10 ppm range due to the interaction between the receptor and salts. It is ascribable to the host reorganization and desolvation. After a water-washing process, the corresponding signals return to the range of 3.60-3.95 ppm. These chemical shift changes are consistent with that of the low field region. These experiments exhibit that receptor **24** is able to solubillize salts (KCl) into organic media ($CDCl_3$) and the salts can be conveniently removed through water-washing, as shown in Scheme 7. In addition, the remaining solution of the receptor **24** in chloroform can be used again for the solubilization of KCl for several times.



Scheme 7 Extraction-release solid-$CHCl_3$-water-solid cycle of KCl and recovering of receptor **24**.

4.4.9 Discussion of the Receptor as a Catalyst Precursor

Many reactions involve in ion-pair type intermediates or transition states whose stabilization are critical for the realization of these type reactions, such as the catalyzed ring-opening of episulfonium ions with indole.[100] Chiral (thio)urea derivatives as privileged chiral catalysts have been broadly used in accelerating of this type of reactions through stabilization of the anions by means of hydrogen bonding.[101] As far as the scaffold is concerned, the chiral centre can be easily introduced into the R group (Scheme 8), the preorganized hydrogen cavity (Scheme 8) for stabilization of anionic guests and the crown ether (Scheme 8) for stabilization of cationic species.



Scheme 8 The diagram of receptor **24** as a catalyst precursor for enantioslective reactions.

4.5 Conclusions

In conclusion, a new ditopic receptor has been designed and prepared successfully, characterized fully by ^{1}H NMR, ^{13}C NMR, mass spectra, infrared spectra, X-ray diffraction, and elemental analyses. Its single crystals are obtained and elucidated by X-ray diffraction, and show perfect preorganization for ion pairs. It has been applied to bind simultaneously anions and cations and to solubilize chloride salts into chloroform and DMSO. The results show that the receptor is ideal for ion pair recognition, such Cl^-/K^-, Br^-/K^-, in DMSO-d_6 and mixed solvents and show positive cooperative effects in both cases. Cooperativity factors rise with the decrease of polarity of solvents. In addition, the receptor is able to solubilize inorganic halide salts into aprotic solvents, such as $CDCl_3$ and DMSO-d_6, and can be recycled repeatedly. Due to its

stabilization ability of ion pairs and solubilization of inorganic salts, this ditopic receptor should have wide potential applications in catalysis, separation, and transporting anions and cations through membranes. Furthermore, this study potentiates the method that a straightforward combination of a common anion receptor and a well-studied cation-complexation moiety enables the formation of ion-pair receptors and solubilizers for salts in organic phases.

Chapter 5 Biphenyl-substituted Quinolines as Receptors for Anions

5.1 Introduction

Anions almost exist ubiquitously in the earth and play a vital role in daily life and industry. The birth of anion chemistry was marked by the encapsulation of halide anions by protonated diazabicycloalkane ammonium ions in the late 1960s.[21] It is still a relatively "fledging" domain in chemistry. The significance of the study on anion recognition is clear without doubt. Chloride channels, which represent a relatively under-explored field, are involved the recognition of chloride ions with high selectivity.[102] Chemists on catalysis have learned much from anion recognition.[103] For example, Jacobsen and coworkers have utilized extensively the (thio)urea catalysts to accelerate organic enantioselective reactions by means of binding counteranions of cationic species.[100, 104]

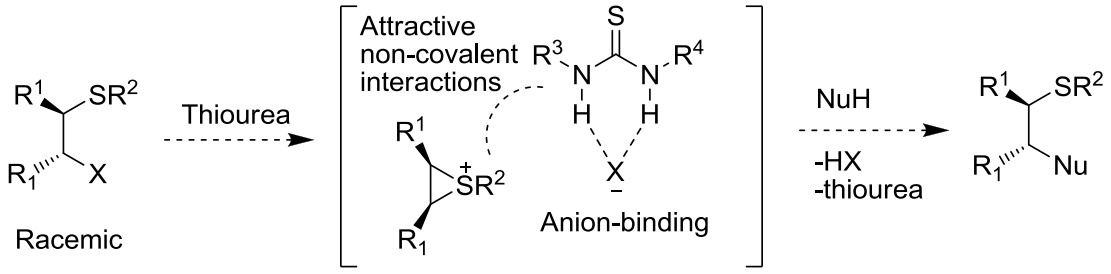


Figure 43 Proposed thiourea-catalysed ring-opening of episulfonium ions with indole via anion binding.

8-Amino-2-quinolinecarboxylic acid was initially synthesized by Huc and Jiang et al and utilized as a backbone for oligoamide foldamers.[77a, 77c, 85] Inspired by the crystallographic data of amide substituted 8-hydroxyquinoline derivatives and their hydrogen bonding behavior, our group has developed a series of 8-amino-2-quinolinecarboxylic acid derivatives and investigated systematically the binding and sensing properties towards anions and ion-pairs in a tweezer-like form.[78, 99, 105] Chen et al devised and prepared a fluorescent chemosensor towards anions using a cyclic

tetrapeptide based on 8-amino-2-quinolinecarboxylic acid backbones and the fluorescence quenched with the addition of fluoride anions as well.[76] Biphenyl is an interesting molecule due to the torsional angle. The torsional angle depends on a energertic balance of π-conjugation between the two planes and repulsion of two *ortho*-position protons.[80]

Herein, the synthesis, single crystal structure features and anion-binding properties of two types of biphenyl decorated 8-amino-2-quinolinecarboxylic acid derivatives through ^{1}H NMR study are reported. In addition, the thermodynamic origin of the binding process between one receptor and chloride anions in $CDCl_3$ and DMSO-d_6 through variable-temperature ^{1}H NMR study is investigated.

5.2 Syntheses

The receptors are synthesized according to the following schematic diagram. Firstly, 2,3,4,5,6-pentafluoro-2'-nitro-1,1'-biphenyl **25** is prepared by Pd-catalyzed decarboxylative arylation of pentafluorobenzene with 2-nitrobenzoic acid in DMSO at 130°C. Secondly, 2,3,4,5,6-pentafluoro-2'-nitro-1,1'-biphenyl **25** and 2'-nitro-1,1'-bi phenyl are reduced in dichloromethane with the catalysis of Pd/C at a hydrogen gas atmosphere to afford the corresponding amines **(26a** and **26b**). Thirdly, the obtained amines react with 8-nitro-quinoline-2-carboxylic acid **4** to afford corresponding 8-nitro-quinoline-2-carboxylic acid (pentafluoro)benzylamide **(27** and **28**). Fourthly, each 8-nitro-quinoline-2-carboxylic acid amide **(27** and **28**) is reduced in dichloromethane with the catalysis of Pd/C at hydrogen gas atmosphere to afford corresponding 8-aminoquinoline-2-carboxylic acid amide **(29** and **32**), which, subsequently, reacts with TCP to provide corresponding 8-isothiocyanatoquinoline-2-carboxylic acid amide **(30** and **33**). Finally, respective 8-isothiocyanatoquinoline-2-carboxylic acid amide **(30** and **33**) reacts with *n*-butyl amine in dichloromethane at room temperature to afford the respective target receptor **(31** and **34**).

The above compounds are fully characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR IR, mass spectra, melting points and elemental analysis. In addition, for the key com-

pounds **28**, **31** and **34**, single crystals are obtained and analyzed by X-ray diffraction (see Experimental Section for details).

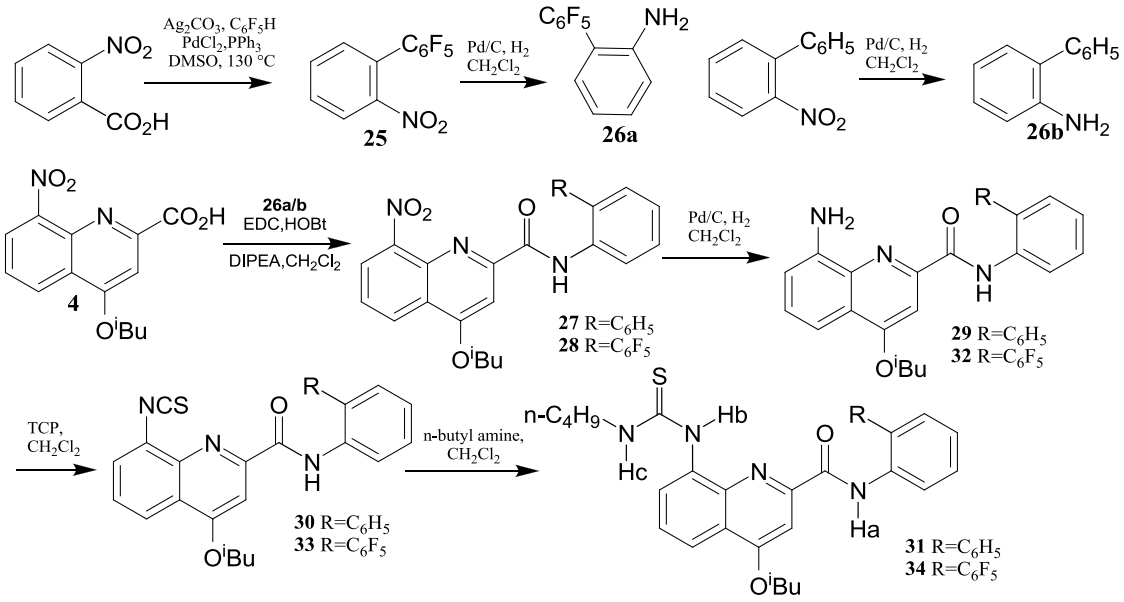


Figure 44 Syntheses of quinoline-based receptors towards anions.

5.3 Solid State Structures and Conformational Considerations

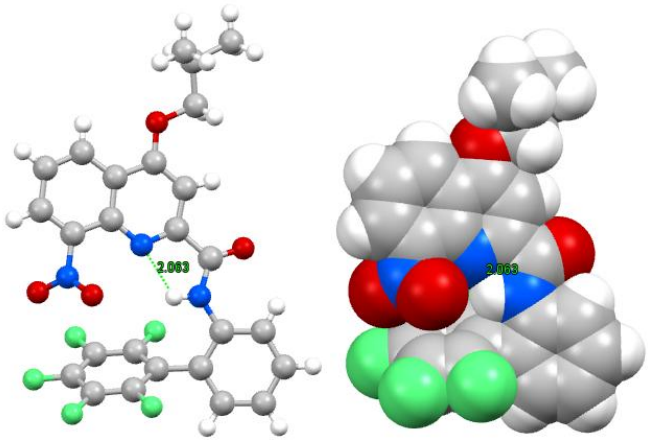


Figure 45 X-ray structures of receptor **28** (gray, C; white, H; green, F; blue, N; red, O).

Crystals of intermediate **28** are obtained by slow evaporation of a solution of **28** in CH_3OH/CH_2Cl_2, and the structure is elucidated by single crystal X-ray diffraction, as shown in Figure 45. As anticipated, the amide NH proton is positioned in the front of the quinoline nitrogen rim via intramolecular hydrogen bonding in a distance of 2.063 Å. Moreover, the pentafluorophenyl group of the biphenyl is pointing to the

front of the quinoline, which benefits the probing of anion-π interactions by means of the directionality of amide NH group.

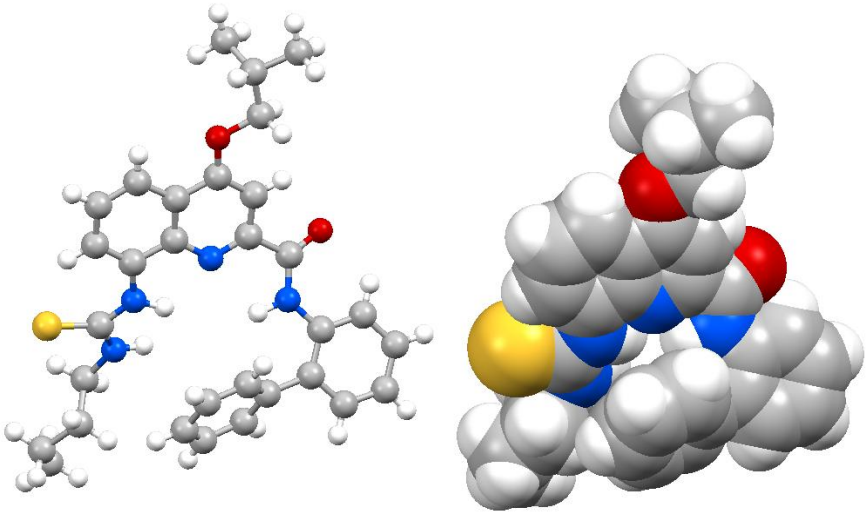


Figure 46 X-ray structures of receptor **31** (gray, C; white, H; blue, N; red, O; yellow, S).

Yellow crystals of receptor **31** are grown by slow evaporation of a CH_3OH/CH_2Cl_2 solution of the receptor. The structure is elucidated by single crystal X-ray diffraction and shown in Figure 46. The amide proton points to the nitrogen atom of the quinoline moiety with a distance of 2.237 Å and one of thiourea group protons with a shorter distance of 2.154 Å, well preorganized for anion recognition. In addition, the second hydrogen atom of the thiourea moiety also points to the front of the quinoline unit. The three N-Hs convergently form a cavity towards anion binding by design and preorganization. The configuration of biphenyl group is ascribable to the π-π interaction between C_6H_5 of the biphenyl group and the C=S double bonds of thiourea group. Those are roughly parallel to each other and held in close proximity (Figure 47). One feature of this receptor is that the hydrogen networks are embraced by biphenyl groups, which may affect the anion-binding.

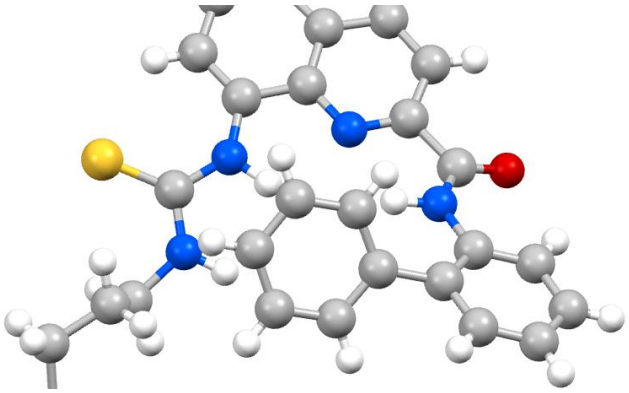


Figure 47 Part of the X-ray structures of receptor **31**.

Crystals of receptor **34** for single crystal X-ray diffraction are obtained by slow evaporation of solvent from a solution of receptor **34** in CH_2Cl_2/MeOH and its structures are shown in Figure 48. Similar to receptor **31**, the NH in amide and one NH in thiourea are positioned in close proximity to the quinoline N atom, in a distance 2.246 Å and 2.321 Å, respectively. In sharp contrast to the configuration of receptor **31** in which the biphenyl group is located in the front of the molecule due to the π-π interaction between C_6H_5 and S=C, the biphenyl in receptor **34** is turned away from the front of the molecule. The configuration is hypothesized to result from a lone pair-π interaction between a carbonyl group in the amide and the pentafluorophenyl group (Figure 49).

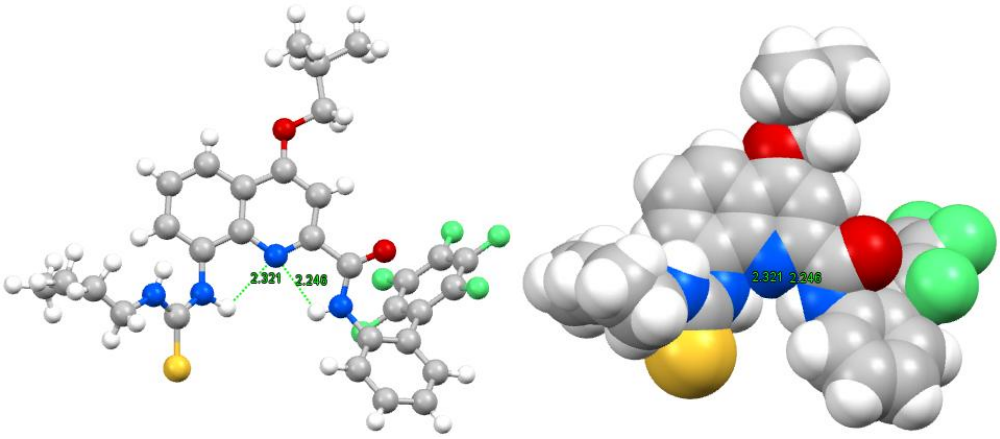


Figure 48 X-ray structures of receptor **34** (gray, C; white, H; green, F; blue, N; red, O, yellow, S).

Lone pair-π contacts are very common supramolecular bonding interactions in solid-state structures.[90] The parameters of lone pair-π interactions between C=O and C_6F_5 are examined, listed in Table 6 and illustrated in Figure 49. Since two of the dis-

tances separating the electron-rich atom O from each atom of the aromatic ring (O-C^1 = 2.805 Å, O-C^2 = 2.978 Å) are below the sum of the van der Waals radii (O-C = 3.22 Å) and α = ~66.31 °, this lone pair-π interaction belongs to moderate ones according to the empirical rule.[90]

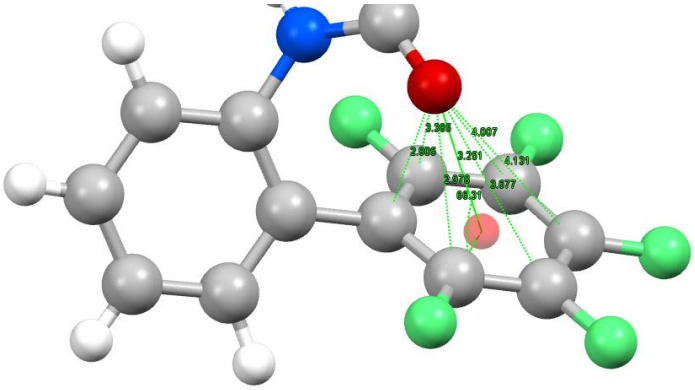


Figure 49 Part of the X-ray structures of receptor **34** (gray, C; white, H; green, F; blue, N; red, O, yellow, S).

Table 6 Parameters of the O-C contacts [Å] in receptor **34.**

Bond	O-centroid	O-C1	O-C2	O-C3	O-C4	O-C5	O-C6
distance	3.251	2.805	2.978	3.677	4.131	4.007	3.385

5.4 ^{1}H NMR Study in Solution

First of all, ^{1}H NMR spectroscopic investigations are conducted in $CDCl_3$ in 0.01 M. The changes of the ^{1}H NMR spectra of receptors **31** and **34** in $CDCl_3$ upon addition of chloride, bromide and iodide ions are examined to study the halide-binding properties at 298 K. Tetrabutylammonium (Bu_4N^+) halide salts are added as halide anion sources.

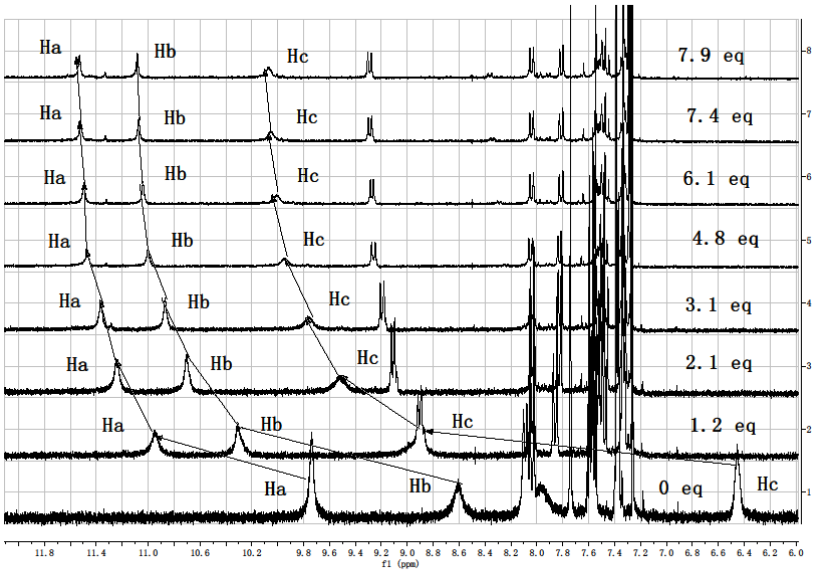
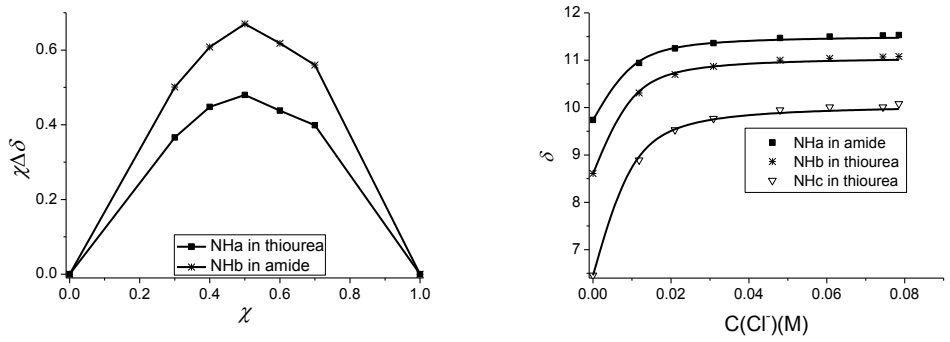


Figure 50 Partial ^{1}H NMR spectra ($CDCl_3$, 300 MHz, 298 K) of receptor **34** after successive addition of Bu_4NCl (the assignment of protons see Figure 44)

The titration of **34** with $Bu_4N^+Cl^-$ is discussed in detail. With the successive addition of chloride salt, the signals of NH protons of the amide and of the thiourea of **34** are significantly shifted downfield (Figure 50) from 9.74, 8.61, and 6.46 ppm to 11.53, 11.08 and 10.08 ppm, respectively. This means that chloride ions are tightly associated with the acidic hydrogen atoms (see below).

Prior to titration experiments, the binding stoichiometry between receptors and anions are determined by Job plots. The variation of the weighted chemical shift as a function of molar ratio shows a 1:1 ratio of receptor to anion stoichiometry for **34** as well as **31** in $CDCl_3$ at 298 K (Figure 51, top left and bottom left).



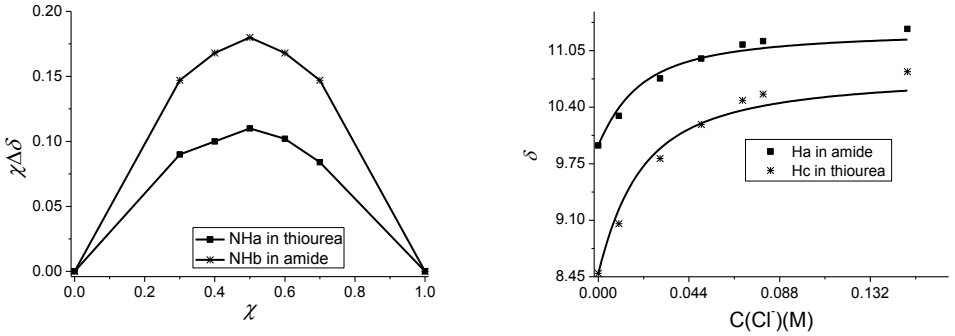


Figure 51 Titration curves of receptors **34** (right top) and **31** (right bottom) towards chloride anions in $CDCl_3$ and corresponding Job plots in $CDCl_3$ for receptors **34** (left top) and **31** (left bottom) at 298 K.

Subsequently, the titration experiments are carried out in $CDCl_3$ with a concentration of 0.01 M of receptor **34** and successive addition of $Bu_4N^+Cl^-$. The titration curves are shown in Figure 51 (right top). Standard methods of nonlinear regression treatment[106] of the obtained data provide the binding constant of K = 467 M^{-1} for receptor **34** and chloride anions in $CDCl_3$ at 298 K. The binding constants for receptor **34** towards other halide anions in $CDCl_3$ 298 K are obtained through similar treatment as well, which are listed in Table 7.

To probe the fluoro-substitute effects, the anion binding behavior of receptor **31** is also studied in $CDCl_3$ at 298 K. The data for receptor **31** towards halide anions in $CDCl_3$ at 298 K are also gained and summarized in Table 7.

To investigate the solvent effects, the anion binding properties of the receptors are also studied in DMSO-d_6. First of all, the binding stoichiometry is determined through Job plots analysis in DMSO-d_6 using ^{1}H NMR spectra at a total concentration of 0.01 M at 298 K. The Job plots clearly show a 1:1 binding stoichiometry between receptors **34** and **31** for the investigated anions (Figure 52 top left and bottom left). Afterwards, titration experiments are conducted in DMSO-d_6 with a concentration of 0.01 M of receptor **34** and successive addition of Bu_4N^+ halide salts at 298 K. Standard methods of nonlinear regression treatment[106] of the obtained data yield the binding constant of K = 160 M^{-1} between receptor **34** and chloride anions in DMSO-d_6 at 298 K. The data for other halide anions are also listed in Table 7. All of the binding constants for receptor **31** towards halide anions are obtained through ^{1}H

NMR study and listed in Table 7 as well.

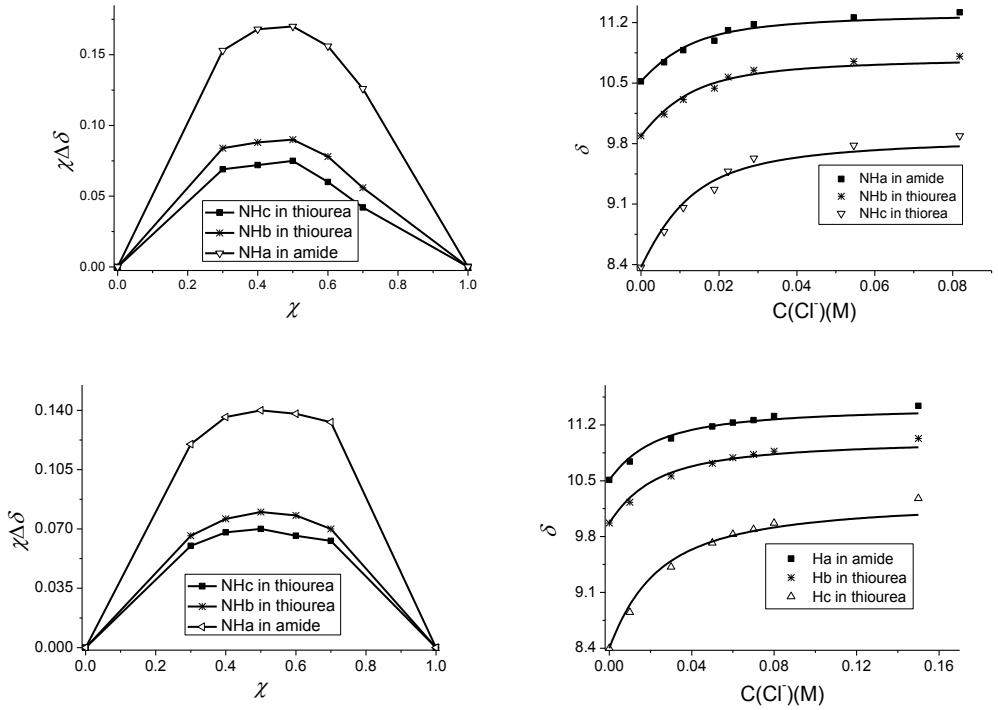


Figure 52 Titration curves of receptors **34** (right top) and **31** (right bottom) towards chloride anions in DMSO-d_6 and corresponding Job plots in DMSO-d_6 for receptors **34** (left top) and **31** (left bottom).

For comparison purposes, all binding constants of receptors **34** and **31** towards halide anions (Cl^-, Br^- and I^-) in $CDCl_3$ and DMSO-d_6 at 298 K are summarized in Table 7.

Table 7 Binding constants (K, M^{-1}) of receptors **34** and **31** with halide anions in $CDCl_3$ and in DMSO-d_6 at 298 K. The binding constants are determined by ^1H 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%.

	Cl^{-a}	Br^{-a}	I^{-a}
In $CDCl_3$			
34	467	129	67
31	70	32	20
In DMSO-d_6			
34	160	48	--[b]
31	60	42	--[b]

a: added as tetrabutylammonium salts. b: no detectable data observed.

After examination of the obtained data, some trends are summarized based on the two receptors:

For both receptors, the binding affinity towards halide anions decreases in the order: $Cl^- > Br^- > I^-$ in both $CDCl_3$ and DMSO-d_3.This is mainly ascribable to the basicity of halide anions. Steiner stated, "All hydrogen bonds can be considered as incipient proton transfer reactions…".[93] That is to say, the binding affinity for a given NH containing receptor relies on the basicity of anions. The more basic the anion is (i.e. the less acidic the conjugate acid is), the higher the binding affinity is.[107] Moreover, the size of the hydrogen cavity also contributes to the sequence. The cavity is fitter for smaller size of anions. Consequently, the binding affinity towards halide anions is decreasing in this sequence due to a combination of these two effects.

The fluorinated receptor shows considerably stronger binding affinities for halide anions than the nonfluorinated receptor does in $CDCl_3$ solution, while both show similar affinities towards halide anions in DMSO-d_6. It mainly results from the fluoro-substituted effect. Anion-π interactions perhaps make some contributions to it as well. Owing to the pentafluorosubstitution, the amide in **34** is more acidic than its counterpart in **31**. Since the binding affinity is a combination of interactions between three N-H groups and anions, one stronger anion binding hydrogen donor is likely to make the corresponding receptor exhibit a higher binding ability. The presence of pentafluorophenyl groups facilitates anion-π interactions to make contributions for the binding affinity. Moreover, presumably, the differences of configurations for the two receptors affect the binding constants. Given the shielding effect of the biphenyl group, the anion binding for receptor **31** is entropically unfavored compared to receptor **34**. Due to a combination of these effects, receptor **34** shows a higher binding affinity towards a given anion than receptor **31** does in $CDCl_3$. While these effects are not so significant for receptors in DMSO-d_6. This is consistent with our previous results.[99]

As anticipated, receptor **34** displays higher binding affinity towards a given anion in $CDCl_3$ than in DMSO-d_6. It shows no detectable binding affinity towards iodide anions in DMSO-d_6. This is attributable to the more polar nature of DMSO-d_6 and its stronger binding ability to compete as a hydrogen bonding partner. Unexpectedly, receptor **31** shows similar binding affinities towards chloride and bromide

anions in $CDCl_3$ and in DMSO-d_6. This phenomenon is inconsistent with our previous results. Usually, the binding constants in $CDCl_3$ are often bigger than in DMSO-d_6. To elucidate this, the thermodynamic origin of the host-guest binding process between receptor **31** and chloride anions by means of variable-temperature ^{1}H NMR study in both solvents is investigated.

5.5 Thermodynamics of Receptor 31 Binding Chloride Anions in $CDCl_3$ and DMSO-d_6 Solution

Rebek,[108] Dougherty,[109] Wilcox[110] and coworkers have applied single-point variable-temperature ^{1}H NMR studies to elucidate host-guest binding and provide valuable thermodynamic parameters.

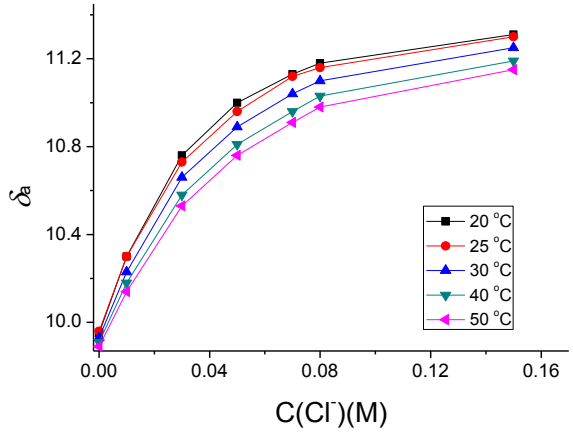


Figure 53 Titration curves of receptor **31** (0.01 M) towards chloride anions at 20 °C, 25 °C, 30 °C, 40 °C and 50 °C in $CDCl_3$.

Here the variable-temperature ^{1}H NMR study is used to investigate the thermodynamic origin of the binding process between receptor **31** and chloride anions. The binding constants are obtained in $CDCl_3$ at different temperatures: 20 °C (293 K), K = 74 M^{-1}, 25 °C (298), K = 70 M^{-1}, 30 °C (303 K), K = 64 M^{-1}, 40 °C (313 K), K = 58 M^{-1}, and 50 °C (323 K), K = 53 M^{-1}.

A van't Hoff plot for the binding process between receptor **31** and chloride anions in $CDCl_3$ is obtained, as shown in Figure 54 (□). After similar treatment of re-

ceptor **31** and chloride anions in DMSO-d_6, the corresponding van't Hoff plot is obtained and also illustrated in Figure 54 (∇).

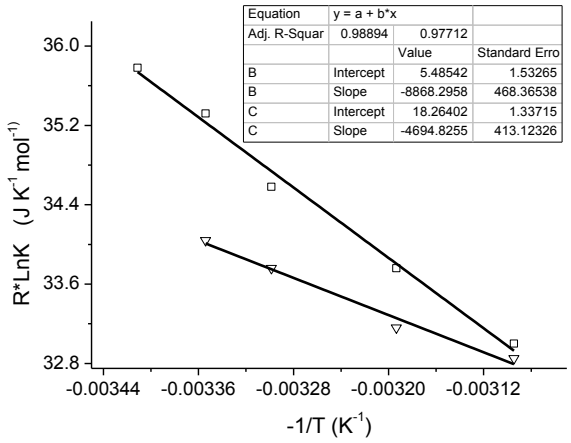


Figure 54 The van't Hoff plots for the binding process between receptor **31** and chloride anions in $CDCl_3$ (□) and in DMSO-d_6 (∇).

In $CDCl_3$, $\Delta H = -8.86 \pm 0.46$ kJ mol^{-1} and $\Delta S = 5.49 \pm 1.52$ J mol^{-1} K^{-1} are obtained from the van't Hoff plot; in DMSO-d_6, $\Delta H = -4.69 \pm 0.41$ kJ mol^{-1} and $\Delta S = 18.26 \pm 1.34$ J mol^{-1} K^{-1} are obtained from the van't Hoff plot. They show that the binding of receptor **31** and chloride is both enthalpically favored and entropically favored, but it is primarily enthalpically driven at room temperature (when T = 298 K, $\Delta H = -8.86 \pm 0.46$ kJ mol^{-1}, $-T\Delta S = -1.636 \pm 0.453$ kJ mol^{-1}). The loss of 4.17 kJ/mol of enthalpy is ascribable to DMSO-d_6 as a competitive binding partner. However, this loss is considerably compensated by the changes of entropy of 12.77 J mol^{-1} K^{-1} at room temperature. In DMSO-d_6, the binding behavior is driven by both enthalpy and entropy, and they make comparable contributions (when T = 298 K, $\Delta H = -4.69 \pm 0.41$ kJ mol^{-1}, $-T\Delta S = -5.44 \pm 0.399$ kJ mol^{-1}). Therefore, the binding process between receptor **31** and chloride anions in $CDCl_3$ are mainly enthalpically driven, while the process in DMSO-d_6 is both enthalpically and entropically driven.

5.6 Conclusions

Two kinds of biphenyl-conjugated quinoline receptors towards halide anions were successfully prepared and fully characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR

IR, mass spectra, melting points and elemental analysis. In addition, the crystals of compounds **28**, **31** and **34** are obtained and analyzed by X-ray diffraction. Both receptors are utilized to recognize halide anions in $CDCl_3$ and DMSO-d_6. Variable-temperature ^1H NMR study is used to evaluate the thermodynamics of host-guest binding. The fluorinated receptor shows higher binding affinities towards a give anion than the non-fluorinated receptor.

Chapter 6 Solution Investigation of Competitive Interactions in Anion Binding: NH-, CH-, Anion-π and Lone-pair π Supported NH-anion Interactions

6.1 Introduction

6.1.1 What Are Anion-π Interactions?

Cation-π interactions have been extensively studied and exploited in various fields for couples of decades,[54] but nobody has paid attention to the existence of anion-π interactions. In 2002, M. Mascal et al.[55], I. Alkorta et al.[56] and P. M. Deyà[57] et al. ingeniously presented the anion-π interactions concept and studied them through a combination of computational and crystallographic experimental studies almost at the same time as pioneers.

Anion-π interactions are defined as the attractions between electron-rich anions and electron-deficient systems.

6.1.2 Why Do Chemists Study Anion-π Interactions?

Due to their essential role in chemical and biological processes/systems in form of catalysis and transport,[58] anion-π interactions have been broadly investigated by virtue of theoretical calculations and crystallographic experiments.

6.1.3 Who Are and How Are Investigated Anion-π Interactions?

Wang et al. have studied the anion-π interactions between tetraoxacalix[2]arene[2]triazine receptors and halide anions and showed that the electron-deficient

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[1] I am extremely grateful to Dr. Michael Giese for his helpful discussion and communications on this work.

receptor bound strongly in both solution and solid state through anion-π interactions.[63] Reedijk, Gamez and co-workers reported a dendritic octadentate N ligand as a host for anionic guests and exhibited its encapsulation behavior of chloride through anion-π interactions.[64] Matile, Schalley and collaborators afforded direct experimental evidence for anion-π interactions through electrospray tandem mass spectrometry collaborating with theoretical calculations.[65] Ballester group appraised quantitatively anion-π interactions through ^{1}H NMR spectroscopic methods in solution using a series of *meso*-tetraaryl calix[4]pyrrole receptors and halide anions.[66] Very recently, Lopez-Garzon and Bianchi et al studied thermodynamics of anion-π interactions in aqueous solution through potentiometric and isothermal titration calorimetry methods.[111] Since 2008, our group has performed detailed studies on the interactions of various anions with fluorophenyl moieties in the solid state as well as in solution.[71b, 71h, 71i]

6.1.4 Why to Study Anion-π Interactions in Solution?

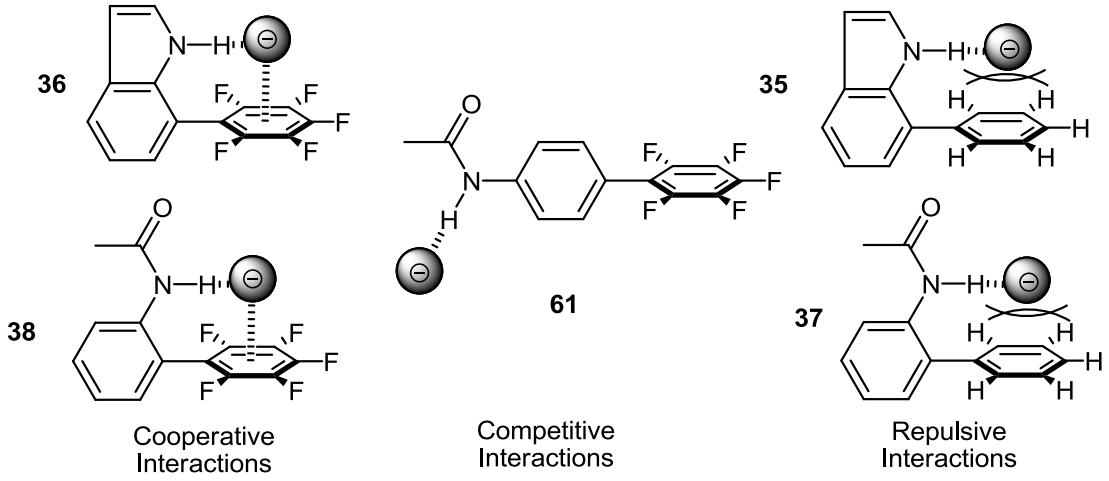
Although a variety of important studies in this fledging area in supramolecular chemistry are performed,[58a, 58d, 112] anion-π interactions have not been well and fully understood and not explored sufficiently yet. Especially their role in the anion-sensing process and their nature in solution are unclear.[112b] To gain more insight on anion-π interactions in solution, the following study is planned and conducted.

6.1.5 How to Study Anion-π Interactions in Solution?

After much thought, five simple yet novel receptors, **35**-**38** and **61**, are designed and prepared, as shown in Scheme 9. Their anion-binding properties are explored in solution and the influence of three binding modes is probed.

There are one hydrogen bond donor and one pentafluorophenyl/phenyl group in all of the receptors. Due to the different interactions between halide anions and pentafluorophenyl/phenyl groups, there are three possible binding fashions, named as cooperative interactions, competitive interactions and repulsive interactions, as shown

in Scheme 9. This study focuses on quantifying the differences between the five receptors and halide anions in solution through ^{1}H NMR and ^{19}F NMR spectroscopic methods. Comparing the different binding abilities of the receptors towards halide anions in solution, it is likely to give a further apprehension in the strength and relevance of anion-π interactions.



Scheme 9 Concept of cooperative, competitive and repulsive interactions.

6.2 Syntheses

First of all, receptor **35** is obtained through a palladium-catalyzed Suzuki-Miyaura coupling reaction of potassium phenyltrifluoroborates and 7-bromo-1*H*-indole in satisfactory yield (Figure 55 left).[113] Afterward, according to relevant literature, receptor **36** is tried to be prepared by a palladium mediated Ullmann coupling reaction,[43] a copper mediated Ullmann coupling reaction,[114] a palladium catalyzed Suzuki−Miyaura Coupling reaction using pentafluorophenylboronic acid as starting material,[115] a palladium-catalyzed Suzuki-Miyaura coupling reaction of potassium pentafluorophenyltrifluoroborates and 7-bromo-1*H*-indole,[116] a palladium-catalyzed Suzuki-Miyaura coupling reaction of 7-(4,4,5,5-Tetramethyl -1,3,2-dioxaborolane-2-yl)-1*H*-indole[117], reactions of hexafluorobenzene[118] and so on. However, none of them works. After many failures and much thought, it is gradually recognized that these methods are monotomous ways that a pentafluorophenyl group is tried to introduce into an existing indolyl group (Figure 55 right I) though the

mother backbones are attached with different reactive sites. Presumably, the strong electron-withdrawing effect of five fluorine atoms causes that the substitution of C_6F_5-group occurs difficultly. Maybe there is an alternative pathway. Finally, an alternate pathway is put forward for the first time: first introduction of the pentafluorophenyl group (Figure 55 right II1) and then construction of the indolyl ring (Figure 55 right II2). After literature research, a practicable pathway is designed, shown in Figure 55 right. Initially, 2,3,4,5,6-pentafluoro-2'-nitro-1,1'-biphenyl is prepared through Pd-catalyzed decarboxylative arylation of pentafluorobenzene with 2-nitrobenzoic acid.[119] Subsequently, 7-pentafluorophenyl-1*H*-indole (**36**) is successfully synthesized directly in excellent yield by Bartoli indole synthesis.[120] Receptor **36** is synthesized for the first time.

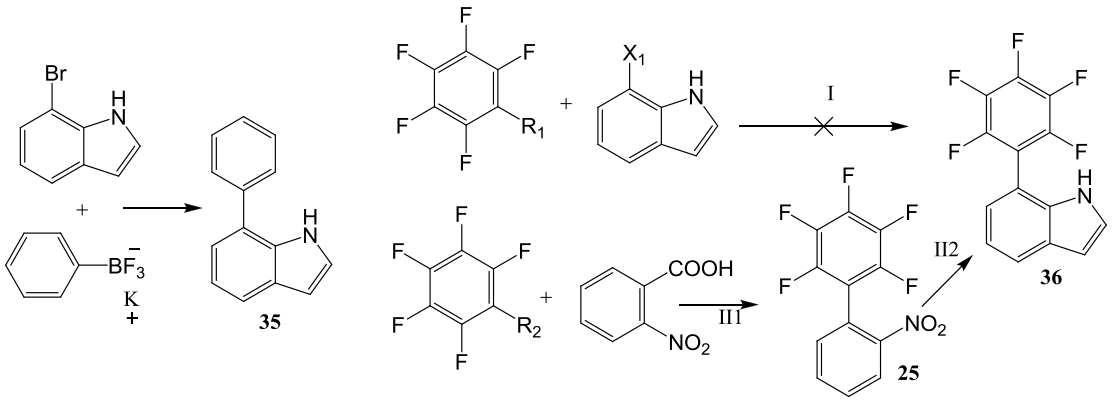


Figure 55 Syntheses of receptors **35** and **36**.

The synthesis of receptor analogues **37** and **38** starts with catalytic hydrogenation of the corresponding nitro compound to afford the appropriate amine. The appropriate amine reacts with acetyl chloride in the presence of pyridine in dichloromethane to afford the receptors **37** and **38** in high yield. 2,3,4,5,6-Pentafluoro-4′-nitro -1,1′-biphenyl **60** is prepared from Pd-catalyzed direct arylation of pentafluorobenzene with 1-iodo-4-nitrobenzene in water.[121] It is reduced in CH_2Cl_2 in the presence of Pd/C and 20 bar H_2 gas and then reacts with acetyl chloride in CH_2Cl_2 in the presence of pyridine to provide receptor **61** in high yield.

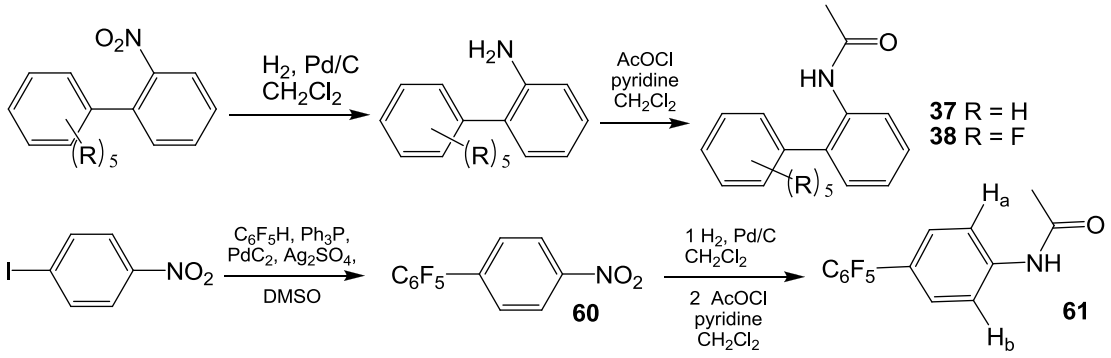


Figure 56 Syntheses of receptors **37**, **38** and **61**.

All the compounds are fully characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR (if possible), MS, IR and elemental analysis (see Experimental Section for the detailed synthesis operations and characterizations).

6.3 ^{1}H NMR Study in CD_3CN

First of all, the binding ratios between receptors and halide anions (as tetrabutylammonium halide, Bu_4NX) are examined in solution. All cases are measured by means of ^{1}H NMR spectroscopic method.[92] For receptors containing pentafluorophenyl groups, the corresponding binding ratios are also checked through ^{19}F NMR spectroscopic method. The titration experiments of **36** with Bu_4NX are discussed as a representative example. The Job plots between receptor **36** and chloride anions in CD_3CN are recorded in Figure 57 top. They both clearly show the 1:1 binding ratio between receptor **36** and chloride anions in CD_3CN.

Subsequently, to explore the binding behavior of these five receptors, ^{1}H NMR and ^{19}F NMR titration experiments are carried out in 0.01 M solution of each receptor in CD_3CN at 298 K with the successive addition of halide anions. Once the data are collected, the titration curves are recorded and analyzed by non-linear regression to afford corresponding binding constants.[92] The titration curves between receptor **36** and chloride anions in CD_3CN from ^{1}H NMR and ^{19}F NMR spectroscopic methods are exhibited in Figure 57 bottom.

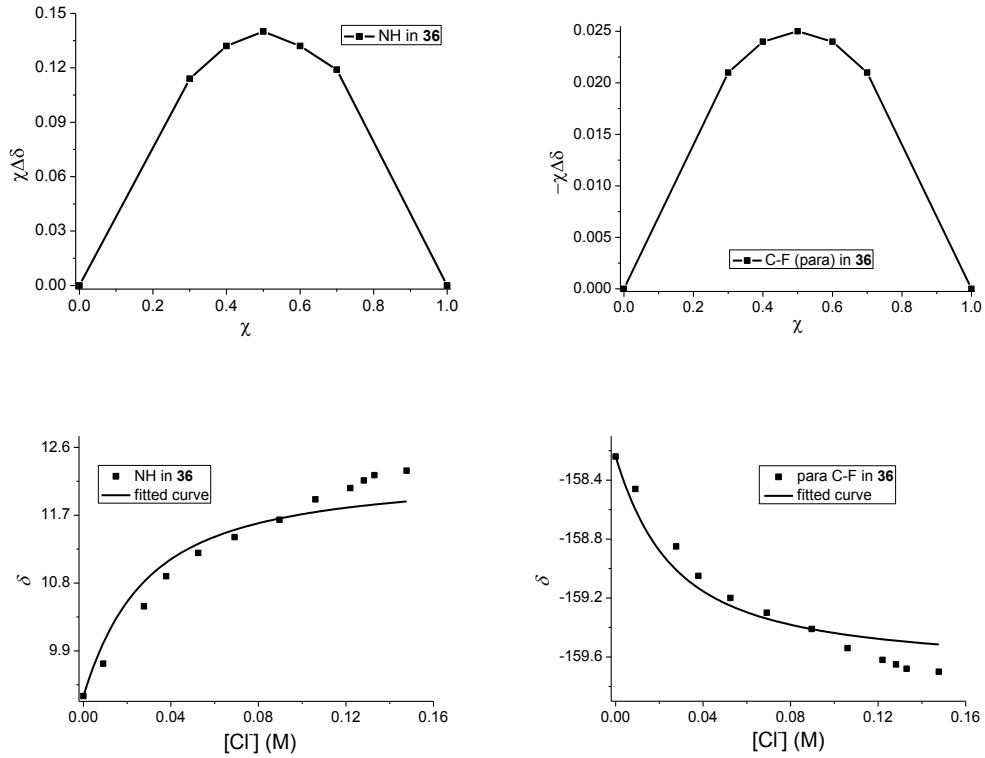


Figure 57 Job plots for receptor **36** towards chloride anions in CD_3CN obtained from ^1H NMR (top, left) and obtained from ^{19}F NMR (top right) and corresponding titration curves of receptor **36** (0.01 M, bottom). The total concentrations for Job plots were kept at 0.01 M.

During the titration process, a dramatic change of ^1H NMR spectra for receptor **36** is observed with the successive addition of chloride anions, up to 2.99 ppm; while the change of receptor **35** is smaller than with receptor **36**, (1.31 ppm).

In addition, an interesting phenomenon is observed for receptor **61**. Not only the N-H proton but also the C-$H_{a/b}$ protons dramatically move downfield with the addition of anions. The double protons $H_{a/b}$ close to amide group in receptor **61** shift dramatically downfield (0.35 ppm) with the addition of Bu_4NCl salts, while their counterparts in other receptors go slightly high field. Presumably, the C-H protons participate the anion binding. Therefore, the gradual changes of the C-H protons with the addition of halide anions are also used to calculate the binding constants. The titration curves and Job plots between receptor **61** and chloride anions are displayed in Figure 58. A 1:1 binding ratio is obtained from the Job plots. Both the N-H signal and C-H signal are used to calculate the binding constants and the results are fit to each other well. The similar treatments are performed for other halide anions.

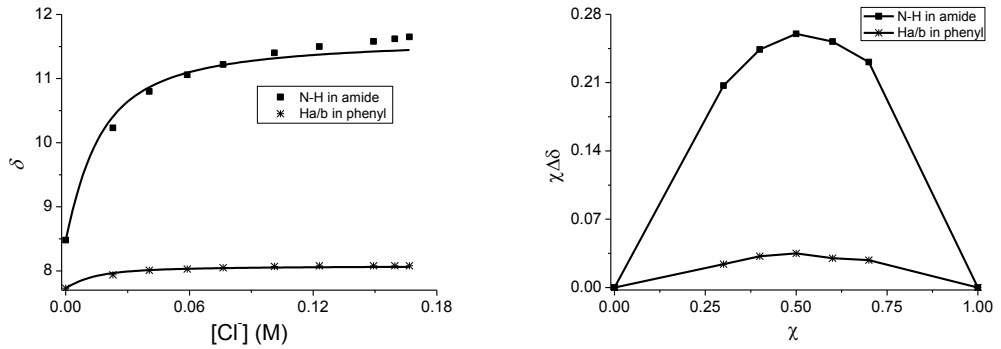


Figure 58 Titration curves of receptor **61** towards chloride anions obtained from ^{1}H NMR in CD_3CN and corresponding Job plots in CD_3CN. The total concentrations for Job plots were kept at 0.01 M.

In order to analyze the results, the binding constants for each receptor are summarized in Table 8, obtained from N-H signals, C-H signals, or C-F signals.

Table 8 Binding constants (K, M^{-1}) of receptors **35** – **38** and **61** with halide anions in CD_3CN at 298 K. The binding constants were determined by ^{1}H NMR and ^{19}F NMR titration experiments in CD_3CN and fitted according to a 1:1 binding ratio. Errors are estimated to be less than 20%.

		Cl^-	Br^-	I^-
35	^{1}H NMR	16.5	14.1	-[a]
36	^{1}H NMR	45.5	28.1	17.7
	$-\Delta\Delta G$[b] (kcal/mol)	0.60	0.40	1.69
	^{19}F NMR	49.6	28.8	20.7
37	^{1}H NMR	27.9	26.0	23.6
38	^{1}H NMR	51.9	37.7	24.0
	^{19}F NMR	55.4	38.8	28.0
61	^{1}H NMR (N-H)	92.1	44.4	21.4
	^{1}H NMR (C-H)	128.0	47.3	23.7

[a] No detective shift observed. [b] $\Delta\Delta G = \Delta G_{X@\mathbf{2}} - \Delta G_{X@\mathbf{1}}$

The above data were examined and compared to draw some useful conclusions, discussed as below:

All receptors show decreasing affinities towards halide anions in the order $Cl^- > Br^- > I^-$. Presumably, they are resulting from the Lewis basicity of halide anions in solution.[93] The Lewis basicity of halide anions decreased in the sequence of $Cl^- > Br^- > I^-$. The binding affinity depends on the Lewis basicity and a given receptor shows

higher binding affinity for a more basic anion. Consequently, the binding sequence appeared.

Receptor **36** exhibits somewhat higher binding abilities towards anions than receptor **35** does. It is attributed to either the electronic effect, resulting from the different electron-withdrawing ability of phenyl and pentafluorophenyl groups, or the anion-π interactions or a combination of both effects. Until now, it is not clear what the leading factor is and how many it accounts for. The changes of free energy value (ΔG) show the thermodynamics of the binding process. Ballester et al introduced ΔΔG to examine the substituent effects and to measure anion-π interactions in solution.[66] Here, the difference in binding energies $\Delta\Delta G = \Delta G_{X@2} - \Delta G_{X@1}$ is calculated to estimate the differences of the two binding affinities for a given halide anion (Table 8). Their absolute values are 0.6 and 0.4 kcal/mol for chloride and bromide anions, respectively, which both are lower than the results of Johnson's system.[112b] It is presumably resulting from the avoidance of inter/intramolecular lone pair-π interactions.

Receptor **38** is a stronger binder for halide anions than receptor **36** and **37** in solution. The differences between receptor **37** and **38** are contributed to either the electronic effects or the anion-π interactions or a combination of these two effects. Presumably, the enhanced binding affinity of **38** is perhaps due to an additional effect - lone-pair π interactions. The O_{amide} atom is likely to interact with the pentafluorophenyl group by lone-pair π contacts. This will polarize the amide group and cause a higher acidity of the H_{amide} proton, which results in a higher binding affinity to anions (Figure 59). Lone-pair π contacts are common supramolecular bonding interactions in solid state structures,[90] and are proven in solution as well.[122] This weak non-covalent interaction might contribute to the binding of anions in receptor **38**. In order to prove this concept of cooperative effect of lone-pair π and NH···anion interactions, simple force field calculation using ChemBio 3D Ultra (MMFF94) are performed, which reveal the O_{amide} atom for receptor **38** locates closely above the centre of the pentafluorophenyl group; while the O_{amide} atom for receptor **37** is positioned far away from the centre of the phenyl group. The binding constants of **36** are slightly

lower than that of **38** towards a given anion. This might be attributed to the higher flexibility of **38** which facilitates its lone-pair π interactions. In contrast, receptor **36** is not able to form lone-pair π interactions.

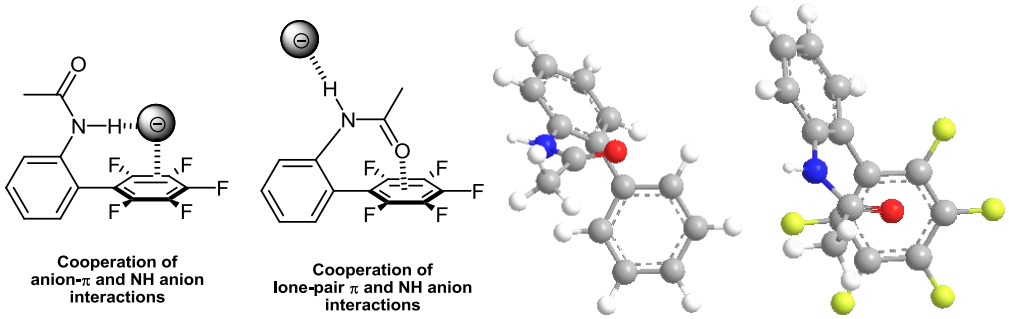


Figure 59 Possible binding modes between **38** and anions (left 1 and 2) and optimized molecular models for receptors **37** (right 2) and **38** (right 1)

Receptor **61** shows higher binding affinities towards halide anions than any other receptors, which is unexpected. Surprisingly, dramatic changes of both C-H protons close to amide group are detected with the addition of halide salts, such as $\Delta\delta_{max}$ = 0.35 ppm for chloride anions. Presumably, the enhanced binding ability of receptor **61** is ascribed to the participation of C-$H_{a/b}$ protons as extra complexation sites due to the strong electron-withdrawing ability of a pentafluorophenyl group. ^{1}H NMR, 2D NOESY experiments and the single crystal structure of an analogue support this explanation. The peaks of N-H and C-$H_{a/b}$ of **61** in ^{1}H NMR spectra are singlet and doublet in the absence of chloride anions, respectively. They both split into multiplet upon the addition of chloride anions, as shown Figure 60. In addition, the cross-peak intensities between N-H and its closest C-$H_{a/b}$ dramatically increase with the addition of chloride anions in 2D NOESY spectra. Furthermore, the participation of C-H proton in the anion binding behavior is observed in a single crystal structure, which interacts with anions in the same mode as receptor **61**, as shown in Figure 60 right. Therefore, the binding mode for receptor **61** towards anions is proposed to associate anions through the cooperation of N-H and C-$H_{a/b}$, as shown in Figure 61. The appearance of the 4′-acetamide group is indispensible for the C-$H_{a/b}$ to serve as anion binding site. The counterpart of C-$H_{a/b}$ in receptor **38** goes slightly high field with the addition of anions and shows no binding affinities towards anions in solution.

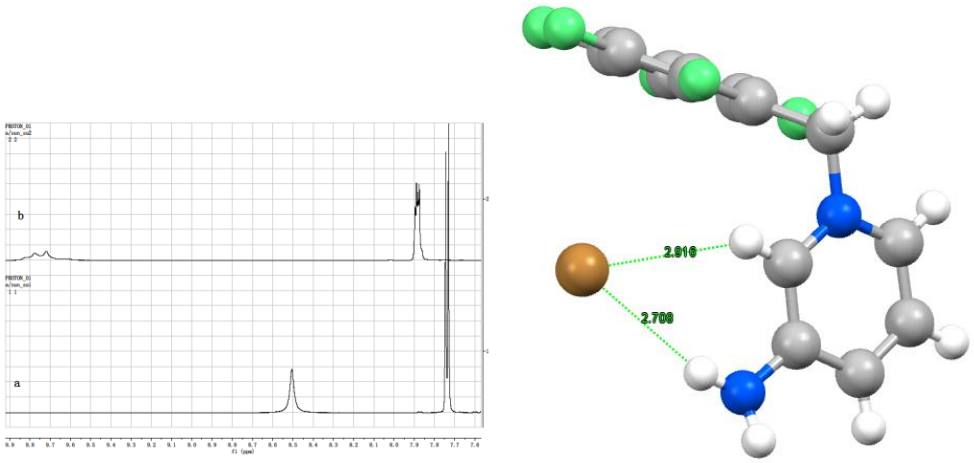


Figure 60 Partial ^{1}H NMR of N-H and C-$H_{a/b}$ protons of receptor **61** in the absence of chloride anions (left bottom, a) and in the presence of chloride anions in CD_3CN (left top, b) and single crystal structure of 3-amino-1-(pentafluorophenylmethyl)-pyridinium bromide[2] (right).[123]

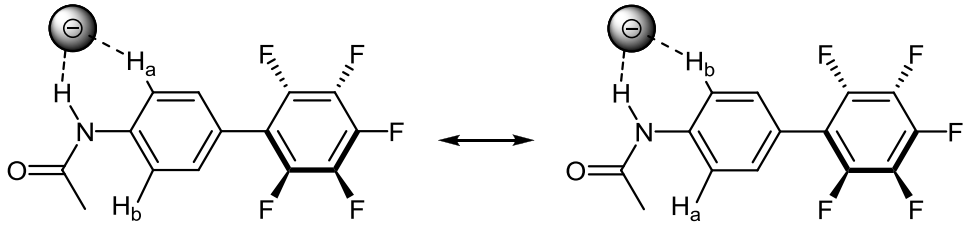


Figure 61 The proposed binding mode for receptor **61** towards an anion.

6.4 MS Study

ESI-MS provides more evidence on the anion-binding behavior. A mixture of **35**, **36** (1.0 equiv. each) and one equivalent of $Bu_4N^+Cl^-$ is mixed in chloroform for 10 min, and subsequently the sample is measured in chloroform and acetonitrile using ESI-MS to monitor the binding behavior. The main peak 318.00969 corresponding to [**36** + Cl]$^-$ is observed; while no peak corresponding to [**35** + Cl]$^-$ is detected.

[2] This single crystal structure was kindly recommended and provided by Dr. Michael Giese.

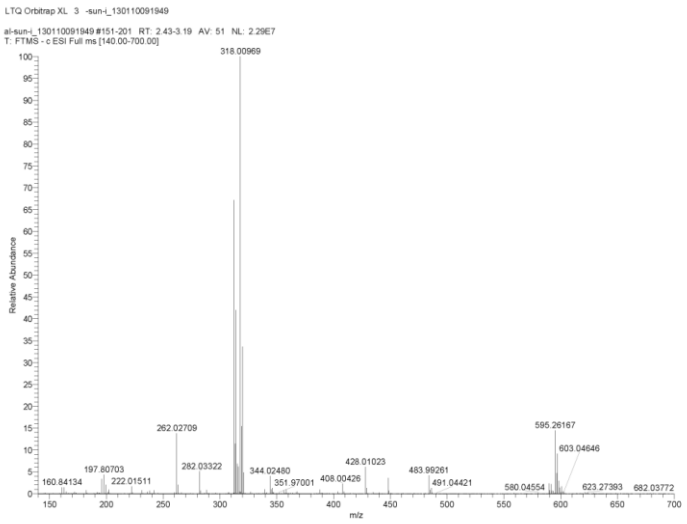


Figure 62 ESI MS of a mixture of equimolar solution of receptors **35**, **36** and $Bu_4N^+Cl^-$ in $CHCl_3/CH_3CN$.

Two more samples are measured on ESI MS. One sample, equimolar solution of receptor **35** and $Bu_4N^+Cl^-$ are electrosprayed under as mild as possible ionization conditions. No peaks corresponding to $[\mathbf{35}+Cl]^-$ or its oligomers are detected. On the contrary, the main peak 318.01523 (100%) corresponding to $[\mathbf{36}+Cl]^-$ is found for the sample **36** and $Bu_4N^+Cl^-$ in $CHCl_3$ and CH_3CN after the same treatment. The fragment ions produced by collision-induced dissociation (CID) are used to explore the peak 318.01523. After collision-induced dissociation, two peaks, 297.98561 and 282.03379, are detected, corresponding to $[C_{14}H_5ClF_4N]^-$ and $[C_{14}H_5F_5N]^-$, respectively. Scheme 10 is used to describe the process as bellow.

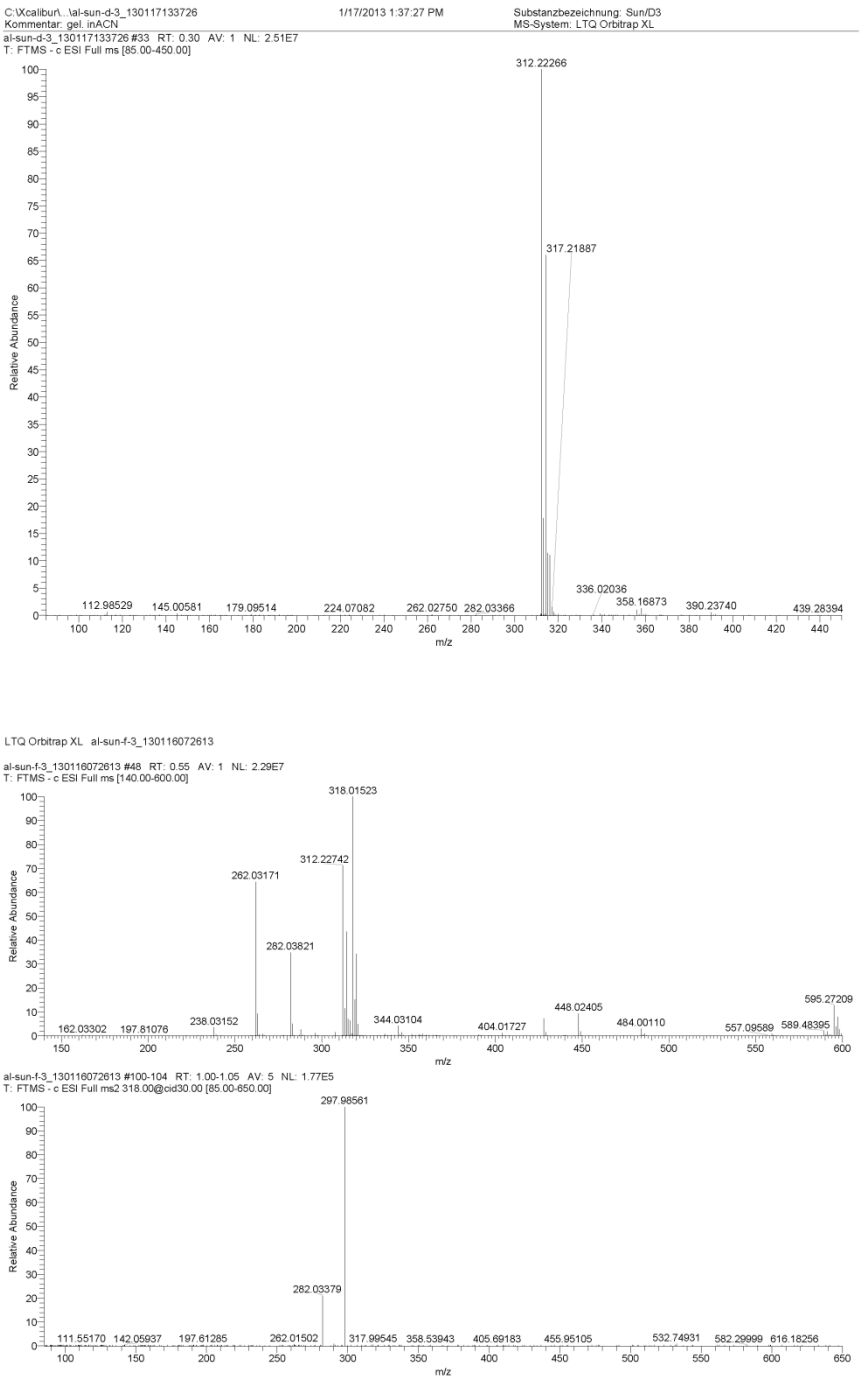
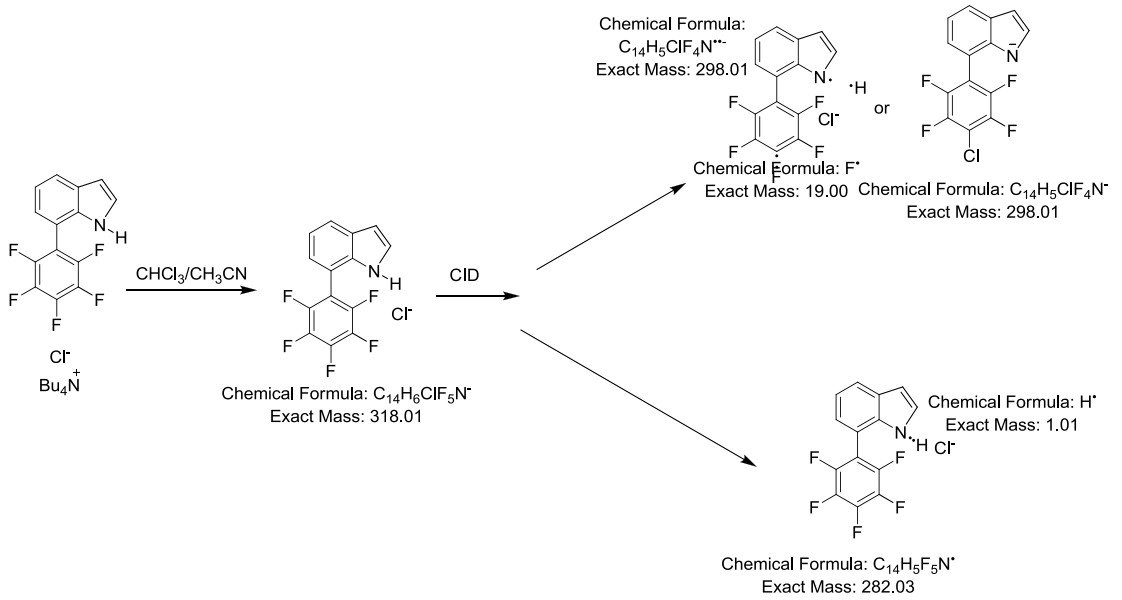


Figure 63 ESI MS spectra of equimolar solution of receptor **35** and $Bu_4N^+Cl^-$ (top) and equimolar solution of receptor **36** and $Bu_4N^+Cl^-$ in $CHCl_3$ (bottom).



Scheme 10 Proposed reactions in gas phase for receptor **36** and $Bu_4N^+Cl^-$.

Similar results are obtained for the sample from receptors **37**, **38** and $Bu_4N^+Cl^-$. A sample of equimolar receptors **37**, **38** and $Bu_4N^+Cl^-$ in $CHCl_3$ is stirred for 10 min and then measured using ESI-MS. There are no peaks corresponding to $[\mathbf{37}+Cl]^-$ or its oligomers in the spectrum, while a peak 336.02005 corresponding to $[\mathbf{38}+Cl]^-$ is detected.

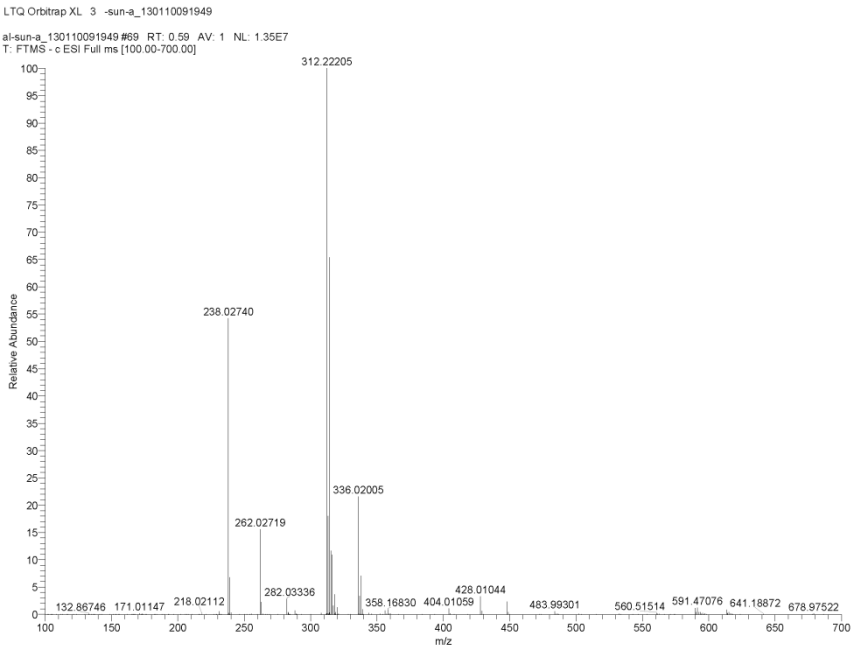


Figure 64 ESI MS spectrum of a mixture of equimolar solution of receptor **37**, **38**, and $Bu_4N^+Cl^-$ in $CHCl_3/CH_3CN$.

6.5 Conclusions

In summary, a series of new receptors based on indole and biphenyl scaffolds are elaborately designed, prepared successfully and used to explore anion-π interactions in solution. The fluorinated receptors show slightly higher binding ability towards a given halide anion. Due to the elaborate design and preparation, the effects of lone-pair π interactions in competition to anion-π interactions are effectively prevented, presumably. In addition, a new type of binding anions incorporating an amide and C-H_{phenyl} is found in solution and shows good anion binding ability in solution. Due to the small differences of binding affinities for receptors and many influencing factors, the relevance of anion-π interactions are not fully explored.

Chapter 7 Synthetic Receptors for Anions

Owing to the vital roles of anions in our daily life, physiological process and industrial field, it is becoming more and more fascinating to investigate the binding behavior of various receptors towards anions in solution. Herein, a series of receptors based on 2-amido-8-aminoquinolines and tripodal structures are devised and prepared.

7.1 Anion Receptors Based on 2-Amido-8-aminoquinolines

7.1.1 Synthesis and Structure of Indolyl-substituted Quinoline

8-Nitroquinoline **8** is catalytically reduced into corresponding amine **39** in DCM in the presence of Pd/C and 20 bar H_2 gas in an almost quantitative yield. It subsequently reacts with TCP to provide 8-isothiocyanatoquinoline **40**. 7-Nitroindole is reduced to 7-aminoindole catalyzed by Pd/C in the presence of 20 bar H_2 gas, which reacts with **40** to provide the indolyl decorated 2-amido-8-aminoquinoline **42** in moderate yield.

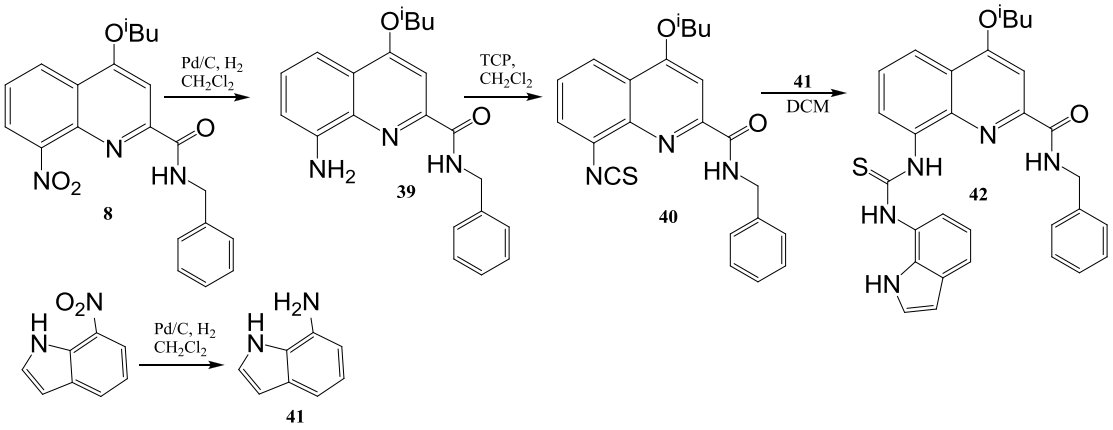


Figure 65 Synthesis of indolyl decorated quinoline **42**.

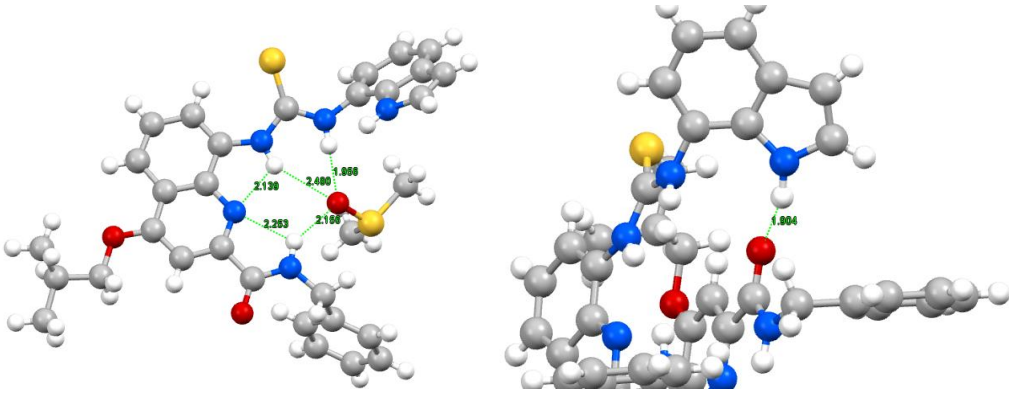


Figure 66 The hydrogen networks in solid structure of receptor **42** (left) and the intermolecular hydrogen bond between two receptors **42** (right) (gray, C; white, H; blue, N; red, O; yellow, S).

Due to intramolecular hydrogen bonding, the proton in amide and one proton in thiourea group are positioned in the front of the quinoline nitrogen site and the observed N-H distances are 2.253 Å and 2.139 Å, respectively, shown as Figure 66 left. The presence of a DMSO molecule makes certain contributions to the formation of the hydrogen network. The observed NH-S_{DMSO} distances for amide and thiourea groups are 2.480 Å and 2.156 Å, respectively. While another NH in thiourea group also locates in the hydrogen donor network primarily resulting from the coordination of a DMSO bound by NH-S_{DMSO} interaction with a distance of 1.956 Å. While the proton of the indole group turns out of the hydrogen network. After examining the stacking interaction in crystals, the proton in indolyl group is observed to form an intermolecular NH-O_{amide} hydrogen bond in a distance of 1.904 Å with a neighboring receptor molecule, shown as Figure 66 right.

7.1.2 Synthesis of Bispyrenyl-substituted Quinoline

Bispyrenyl decorated quinoline is prepared as shown in Figure 67. Initially, quinoline acid **4** couples with 1-pyrenemethylamine hydrochloride in the presence of DIPEA, HOBt and EDC in DCM to provide 1-pyrenemethyl 8-nitroquinoline-2-carboxamide **49**, which is catalytically reduced to 1-pyrenemethyl 8-aminoquinoline-2-carboxamide **50** catalyzed by Pd/C with 20 bar H_2 gas in DCM in almost quantitive yield. Subsequently, **50** is transferred to 1-pyrenemethyl 8-isothiocyanatoquinoline-2-carboxamide **51** by reaction with TCP in DCM at room

temperature. Finally, **51** couples with 1-pyrenemethylamine hydrochloride in the presence of DIPEA in DCM to provide bispyrenyl decorated quinoline **52** in moderate yield.

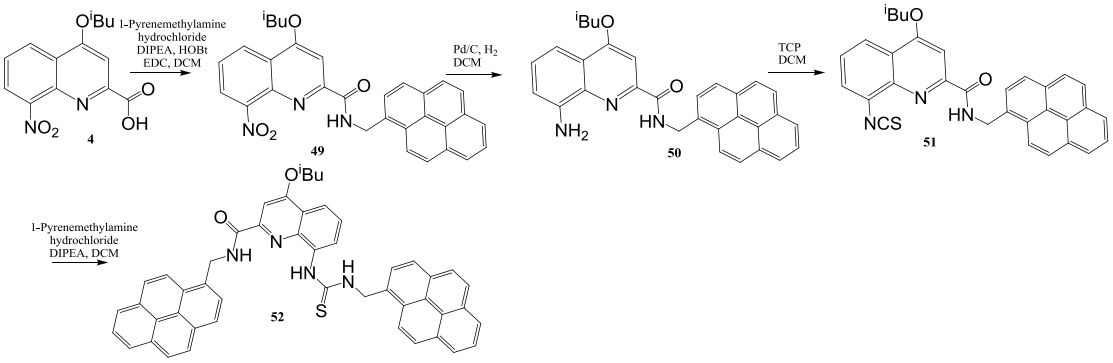


Figure 67 Synthesis of bispyrenyl decorated quinoline **52**.

7.1.3 Synthesis of Diallyl-substituted Quinoline

The synthesis of diallyl substituted quinoline receptor **47** is depicted in Figure 68 as follows. Compound **45** is prepared from quinoline acid **4** and allylamine in the presence of DIPEA, HOBt and EDC in DCM. Subsequently, it is reduced in the presence of Pd/C and 20 bar H_2 gas to provide allyl 8-aminoquinoline-2-carboxamide **46**, which couples with allyl iothiocyanate in DCM to afford diallyl substituted quinoline receptor **47** in good yield.

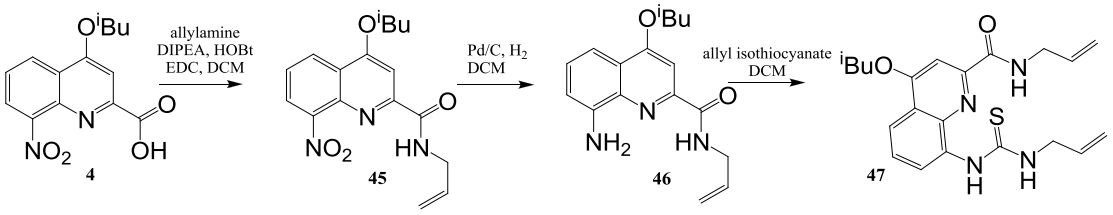


Figure 68 Synthesis of receptor **47**.

7.1.4 Synthesis of a Bisthiourea-conjugated Quinoline

Receptor **43** is prepared from above described benzyl 8-isothiocyanato quinoline-2-carboxamide **40** and 1,6-diaminohexane in DCM in high yield. Due to the multiple and preorganized hydrogen donors, receptor **43** is hypothesized to be a good receptor towards bis-carboxylate guests, such as isophthalate, oxalate, malonate, succi-

nate anions.

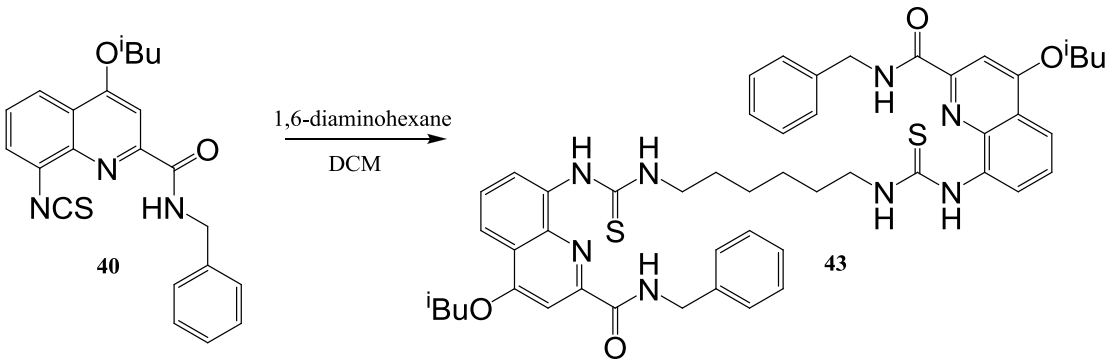


Figure 69 Synthesis of receptor **43**.

7.2 Syntheses of Anion Receptors Based on Pyrrole and Tren Backbone

7.2.1 Synthesis of a Pyrrole-backbone Receptor

Receptor tris(pentalfuorobenzyl) pyrrole **57** is synthesized as shown in Figure 70. The direct alkylation of pyrrole by nucleophilic substitution reaction in an ionic liquid is used to prepare receptor **57**.[124] A mixture of pentafluorobenzyl bromide, pyrroles, and [bmim][SbF_6] is heated at 80 ℃ for 36 h to provide receptor **57**.

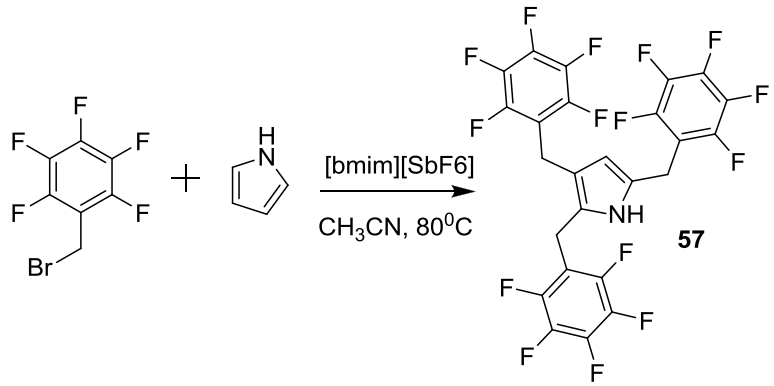


Figure 70 Synthesis of receptor **57**.

7.2.2 Syntheses of Tren-based Receptors

The syntheses[3] of receptors **58** and **59** are shown in Figure 71. [125] The method of copper(I)-catalyzed azide-alkyne click (CuAAC) reaction is used to prepare receptors **58** and **59**. Initially, the appropriate benzyl bromide reacts with sodium azide in DMSO or mixed acetone/water at room temperature to afford corresponding benzyl azide. Subsequently, tripropargylamine reacts with the appropriate benzyl azide in the presence of TEA using H_2O/DCM/THF as solvents to provide receptor **58** and **59** in excellent yield.

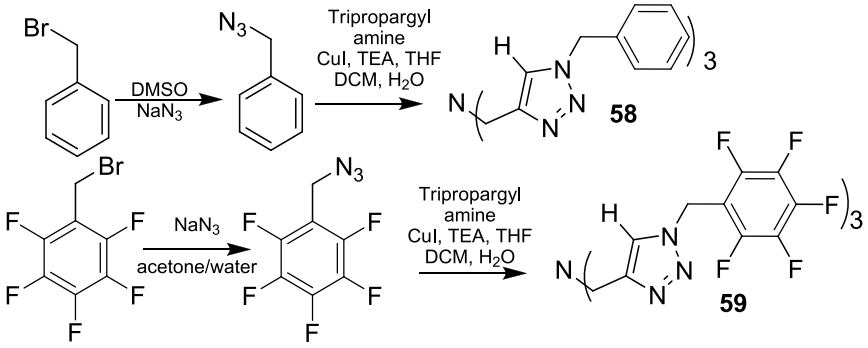


Figure 71 Synthesis of receptors **58** and **59**.

[3] The syntheses of **58** and **59** were conducted with the help of my research student Thomas Traill.

Chapter 8 Conclusions and Perspectives

This thesis focuses on developing novel quinoline-based anion receptors and investigation of the applications of anion-π interactions in anion sensing in solution. It has presented the construction of a series of anion and ion-pair receptors and their applications in supramolecular chemistry, as shown in Figure 72. Furthermore, five simple yet novel anion receptors were elaborately designed, prepared, and employed to study the relevance of anion-π interactions in solution, as shown in Scheme 11.

8.1 Conclusions for Quinoline-based Anion and Ion-pair Receptors

First of all, the modulation of affinities of receptors towards halide anions in solution was achieved through a series of quinoline-based receptors, as shown in Figure 72, I. Two groups of receptors were devised, prepared and exploited in recognization of halide anions in $CDCl_3$ and DMSO-d_6 solution. The electronic, solvents, and fluoro-substitution effects were investigated in detail. The affinities of receptors towards halide anions in $CDCl_3$ are found to be higher than in DMSO-d_6. In addition, the fluoro-substituted receptors were stronger binders than their nonfluoro-substituted analogues. The affinities of receptors towards halide anions decreased in the sequence of $Cl^- > Br^- > I^-$ in both $CDCl_3$ and DMSO-d_6. The presence of pentafluorophenyl group in anion receptors increased the possibility of participation of anion-π interactions in anion sensing and recognition in solution. This study supports the method of the tuning of affinities of receptors towards anions in solution by electronic, solvent, and fluoro-substituent effects.

Secondly, the new biphenyl-conjugated quinoline receptors for halide anions were designed and synthesized, as shown in Figure 72 II. Their binding behavior towards halide anions was studied in $CDCl_3$ and DMSO-d_6. Due to a combination of fluoro-substituted effects and lone-pair π interactions, two receptors showed different configurations in solid structures. Through the investigation of thermodynamic origin,

it was concluded that the binding process between the nonfluoro-substituted receptor in $CDCl_3$ was majorly enthalpically driven, while the binding process in DMSO-d_6 was both enthalpically and entropically driven.

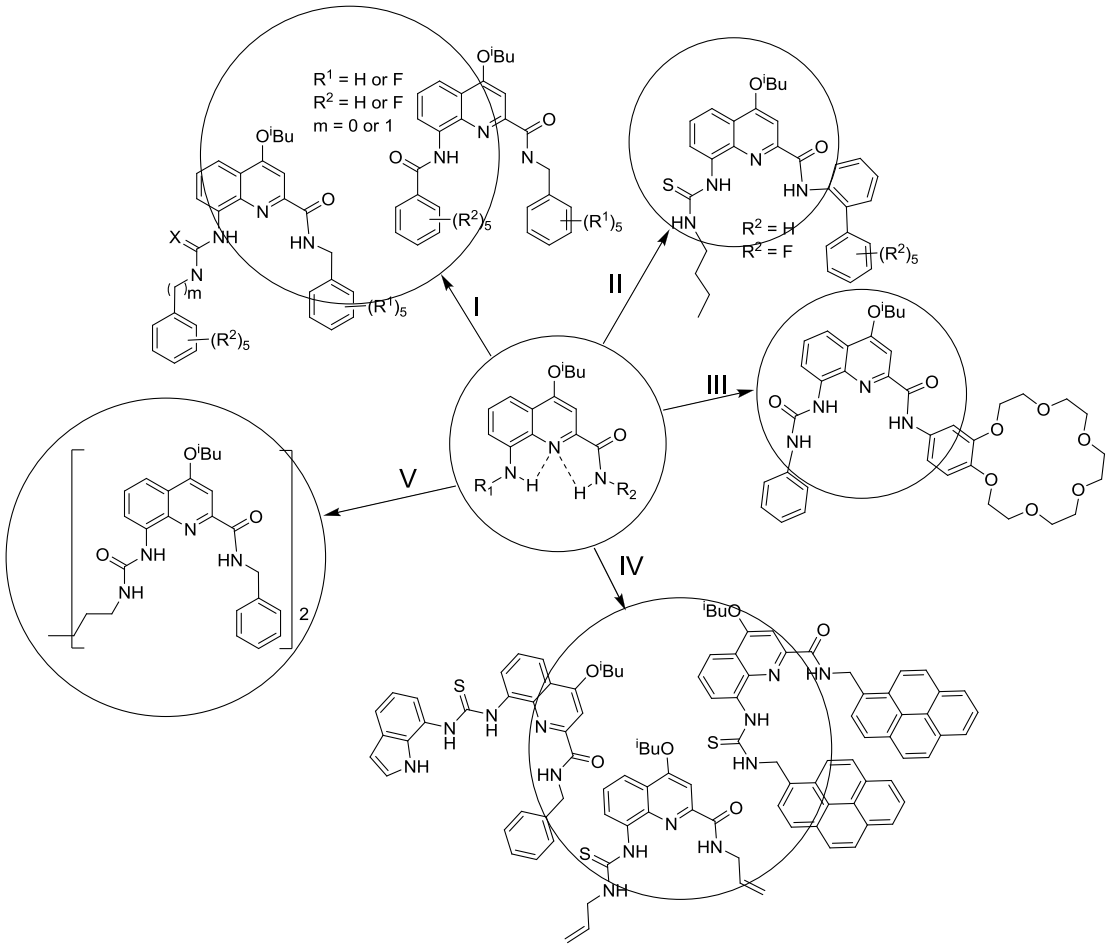


Figure 72 The schematic diagram of quinoline-based anion.

Thirdly, a novel quinoline-substituted crown ether was designed and prepared and its applications as a receptor towards anions and ion pairs were investigated in detail, as shown in Figure 72 III. The receptor showed moderate affinities towards halide anions in $CDCl_3$ solution. Due to the presence of both a cation-complexation site and an anion-binding moiety, the receptor functioned as a good ion pair receptor in different solvents and showed positive cooperativity effects. In addition, it was utilized repeatedly as a solubilizer of inorganic salts in organic phases, such as $CDCl_3$ and DMSO-d_6. This study intensifies the method that a straightforward combination of a common anion receptor and a well-studied cation-complexation moiety enables

the formation of ion pair receptors and solubilizers of salts in organic solvents.

Fourthly, different receptors have been obtained through derivation of quinoline backbones, as shown Figure 72 IV and V. Due to the presence of (thio)urea and amide groups, they are supposed to be good anion receptors towards halide anions and oxo-anions.

Fifthly, the quinoline backbones with different substituent species can belong to different crystal systems, for example, receptor **11** with nonfluoro-substituents belongs to monoclinic systems; while receptor **12** with fluoro-substituents belongs to triclinic systems; and unexpectedly, receptor **42** with one indolyl group instead of phenyl group belongs to orthorhombic. Moreover, it seems that the role of solvents is not so vital in controlling the crystal systems for these quinoline backones. Two crystals of receptor **24** were obtained from different solvents, e.g. DMSO and CH_2Cl_2/CH_3CN, and after elucidation, both samples belong to triclinic systems and prove very similar. This study potentiates the method that the crystal systems of a given structure in solid can be tuned through different functionalities.

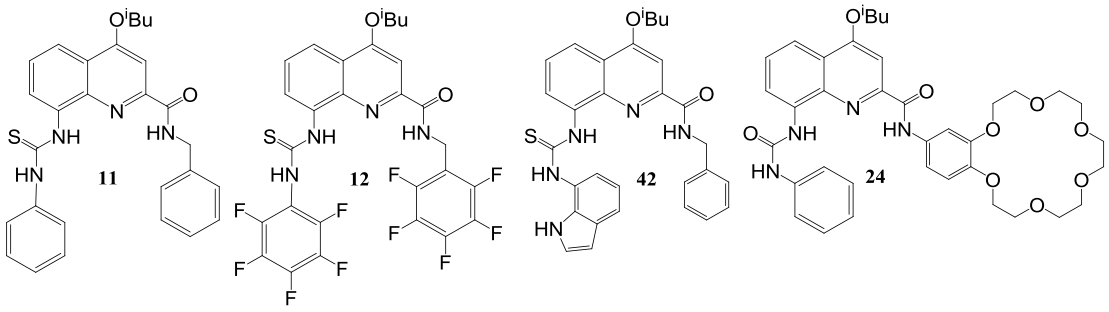


Figure 73 The chemical structures of 4 receptors.

Sixthly, various NH groups as hydrogen bond donors play a vital role in anion coordination, catalysis, and rotaxane-construction. This thesis showed various –NH-groups and offered a general order with the increasing ability as hydrogen bond donors. This sequence should offer valuable information for the design of anion receptors and catalysts and the construction of supramolecular architectures.

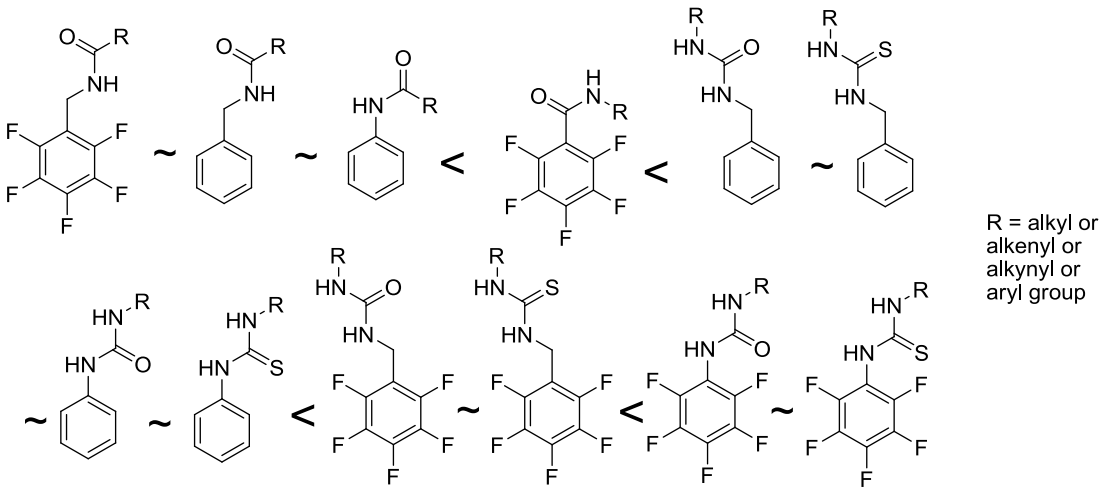
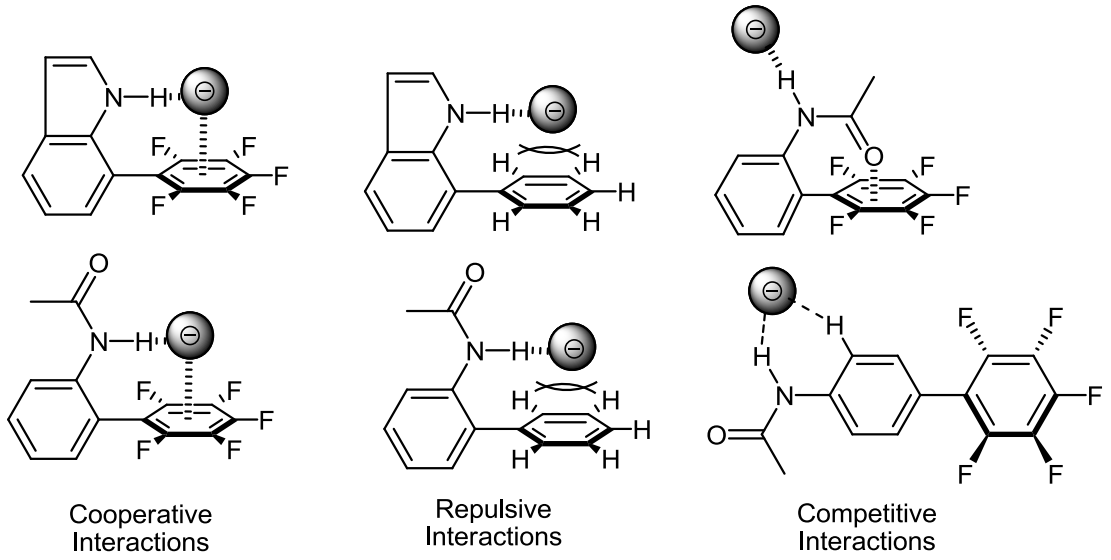


Figure 74 The general sequence of various NH-containing anion binding sites in solution.

8.2 Conclusions of Anion-π Interactions

The anion-π interactions are pretty weak in solution, so the study on this field normally is not easy to achieve. Especially, the study on anion-π interactions is often influenced by other non-covalent interactions, such as inter-/intramolecular lone-pair π contacts, electrostatic effects etc. By means of elaborate design and preparation, five receptors were utilized to associate anions in solution. The receptor containing mere one hydrogen bond donor and potential anion-π interactions showed the weakest binding affinities towards anions. The receptor containing only one hydrogen bond donor and potential anion-π interactions and lone-pair π contacts showed slightly stronger binding affinities towards anions. The receptor containing two hydrogen bond donors and potential anion-π interactions showed the strongest binding affinities towards anions. A novel binding backbone of incorporation of an amide N-H and a phenyl C-H was found and reported for the first time, as shown in Scheme 11.



Scheme 11 Three proposed binding modes for anions by studied receptors.

8.3 Perspectives

Owing to its interesting intra/inter molecular hydrogen bonding, 2-amido-8-aminoquinoline and its derivatives have been widely utilized on anion recognition and sensing, ion pair recognition, and construction of foldamers in supramolecular chemistry. Based on the study in this dissertation, the further study on this unique structure is proposed, as shown in Figure 75. Firstly, the macrocyle receptors based on quinoline is likely to be excellent receptors for anions due to the preorganization. Secondly, due to its two "hands", the quinoline can be exploited in the construction of different size macrocycles using appropriate anions as a template. Thirdly, the quinoline can be employed in catalysis science. Chiral (thio)urea derivatives as privileged chiral catalysts have been broadly used in accelerating reactions through stabilization of the anions by means of hydrogen bonding. As far as the scaffold is concerned, the chiral centre can be easily introduced into R group, the preorganized hydrogen cavity for stabilization of anionic guests and the crown ether for stabilization of cationic species. Finally, the quinoline is potential to be applied in supramolecular catalysis through introduction of catechol groups in form of self-assembly nanocages.

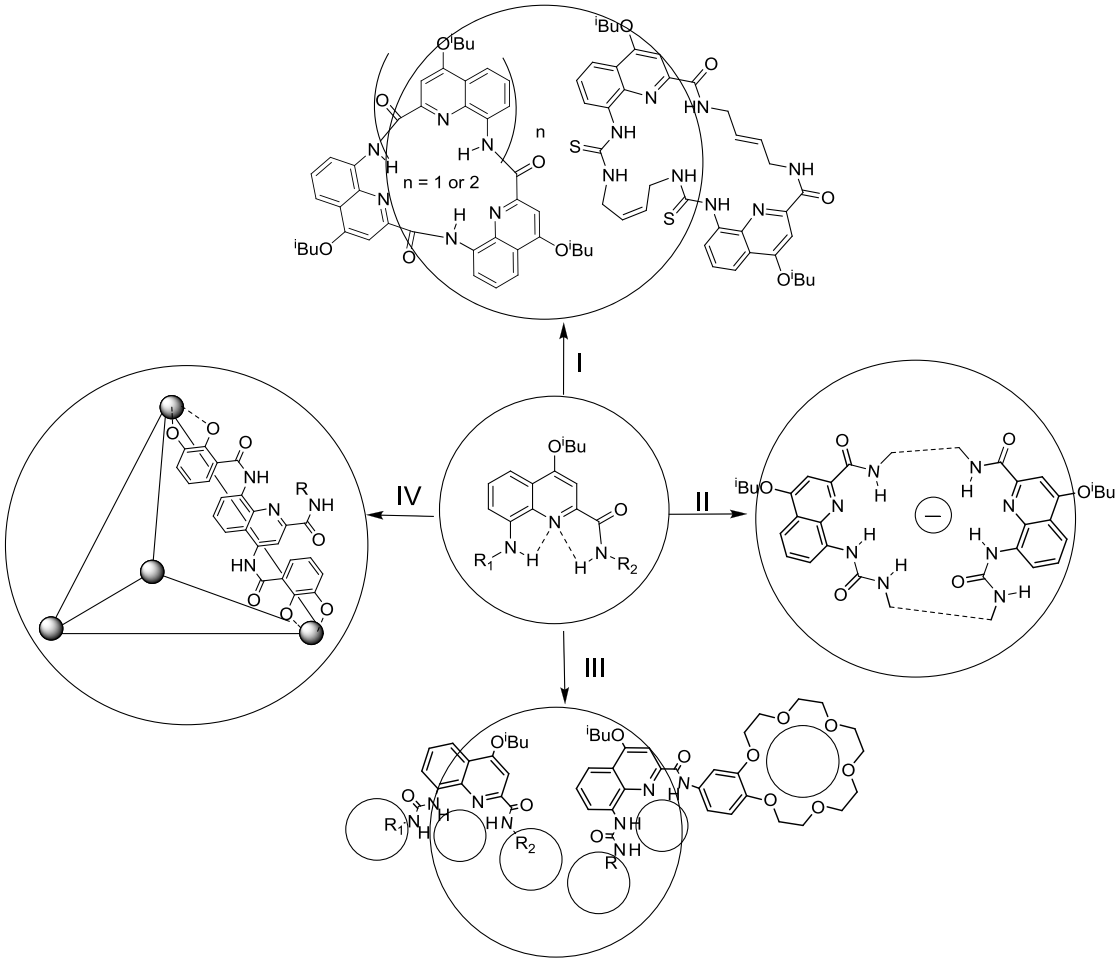


Figure 75 Further studies on quinoline-based anion receptors.

Chapter 9 Experimental Section

9.1 Chemical Reagents, Instruments and Typical Procedures

9.1.1 Chemical Reagents

Chemicals commercially available from Merck, Sigma Aldrich, Alfa Aesar, TCI, ABCR or Acros were used as received. All solvents were used after distillation without further purification, unless otherwise indicated. After stirring with CaH_2 overnight, dichloromethane or CH_3CN was distilled for use. THF were dried by filtration over activated alumina (basic) in a column. After stirring with Mg powder overnight, methanol was distilled for use. All reactions were carried out using pre-dried solvents and nitrogen atmosphere unless otherwise stated. All NMR spectra were recorded in deuterated chloroform ($CDCl_3$), deuterated acetonitrile (CD_3CN), deuterated methanol (CD_3OD) or deuterated dimethyl sulfoxide (DMSO-d_6)

9.1.2 Instruments

All NMR spectra were recorded by using a Varian Mercury 300, Varian 400 or Varian 600 spectrometer.

Mass spectra were measured by using EI (70 eV), CI (100 eV,methane) or ESI techniques on a Finnigan SSQ 7000 or Thermo Deca XP spectrometer.

Infrared spectra were obtained on a Perkin-Elmer FTIR spectrometer spectrum 100. The samples were measured in KBr (400-650 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 has been collected at 100 K on a Bruker D8 goniometer equipped with an APEX CCD detector using Mo Kα 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 [1] was used for integration and SADABS [2] for multi-scan absorption correction.The structures were solved with direct methods (SHELXS97) and refined by full-matrix least squares on F^2 (SHELXL97) [3]. Anisotropic displacement parameters were assigned to non-H atoms. H atoms bonded to N were localized in Difference Fourier maps; their positions were refined freely. (1) Bruker, 2003. SAINT+, Version 6.45; Bruker AXS Inc., Madison, Wisconsin, USA. (2) Sheldrick, G. M.; 2004.'SADABS, Program for Empirical Absorption Correction of Area Detector Data', University of Göttingen. (3) Sheldrick, G. M.; Acta Cryst., 2008, A64, 112.

9.1.3 Typical Procedures

9.1.3.1 Solid-liquid Extraction

Receptor **24** is soluble in appropriate deuterated solvents ($CDCl_3$ or DMSO-d_6). Insoluble guests (such as KCl, NaCl, NH_4Cl etc.) were added in excess as powders, and the NMR tubes were stirred 12 h at room temperature. After standing 1h, the NMR spectra were acquired.[126]

9.1.3.2 NMR Titration

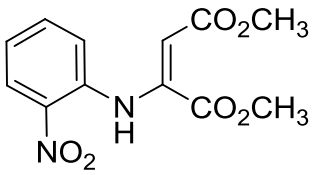
For binding constants calculated based on ^1H NMR and ^{19}F NMR titrations, chemical shift δ (ppm) are plotted against acceptor concentration (M).

9.1.3.3 Job Plots

Job plots were created using either ^1H NMR or ^{19}F NMR by plotting $|\Delta\delta\chi|$ against χ.

9.2 Syntheses and Characterization of Compounds

1.1. Synthesis of compound **1**[127]



To a solution of 2-nitroaniline (3.45 g, 0.025 mmol) in 150 mL of MeOH was added dimethyl acetylenedicarboxylate (3.90 g, 0.0275 mmol). After stirring at rt. for 18 h, the mixture was heated at reflux for 6 h and cooled, and then the resulting yellow solid were collected and washed with MeOH to yield 6.50 g of 2-[(2-nitrophenyl)amino]-2-butenedioic acid dimethyl ester **1**.

Yield: 6.50 g. (M = 280.2 g mol^{-1}, n = 0.023 mol, 92%).

Melting point: 133.1-134.2 ℃.

^{1}H NMR spectrum (400 MHz, $CDCl_3$): δ = 11.12 (s, 1 H), 8.16 – 8.13 (dd, 1 H), 7.48 – 7.44 (m, 1 H), 7.10 – 7.06 (m, 1 H), 6.78 – 6.75 (dd, 1 H), 5.84 (s, 1 H), 3.81 (s, 3 H), 3.75 (s, 3 H).

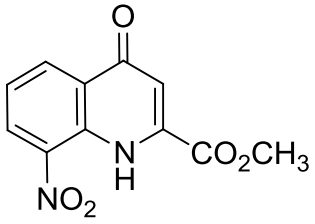
^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ = 167.96, 164.33, 143.47, 138.06, 136.86, 134.20, 126.20, 122.05, 120.38, 102.96, 53.06, 51.83.

Mass spectrum (CI): m/z (%) = 281.1 (99.51) $[M + H]^+$, 249.1 (100.00) $[M - CH_3O]^+$.

IR (KBr): 3270, 2951, 2114, 1732, 1676, 1600, 1502, 1434, 1386, 1335, 1279, 1210, 1158, 1027, 976, 850, 825, 776, 740, 690, 661 cm^{-1}.

Elemental analysis (%): $C_{12}H_{12}N_2O_6$ calcd. C 51.43, H 4.32, N 10.00; found C 51.44, H 4.48, N 10.07.

1.2. Synthesis of compound **2**[127].



A mixture of **1** (1.70 g, 6.06 mmol) and ca. 10 mL (20 g) of PPA was heated at 120 °C for 1 h. The mixture was cooled and poured into saturated Na_2CO_3 solution and the resulting yellow solid was collected through filtration to provide 0.76 g of 1,4-dihydro-8-nitro-4-oxo-2-quinoline carboxylic acid methyl ester **2**.

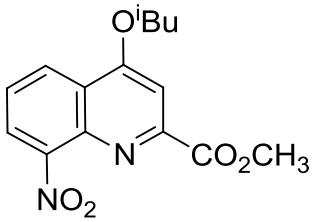
Yield: 0.76 g. (M = 248.2 g mol^{-1}, n = 3.06 mmol, 51%).

Melting point: 191-192 ℃.

Mass spectrum (CI): m/z (%) = 249.0 (100) $[M + H]^+$.

IR spectrum (KBr): 3334, 2981, 2717, 2319, 1723, 1599, 1499, 1456, 1369, 1272, 1165, 1017, 875, 783, 747, 707, 663 cm^{-1}.

1.3. Synthesis of compound **3**.[77c]



A mixture of **2** (2.0 g, 8.0 mmol), triphenylphosphine (2.25 g, 1.05 eq), 2-methyl-1-propanol (0.82 mL, 1.1 eq), and anhydrous THF under nitrogen gas stirring, was cooled down to 0 °C using ice/water bath. DIAD was added and the mixture was stirred at 0 °C for 30 min, then at room temperature overnight. The solvent was evaporated and the product was purified by flash chromatography (SiO_2) eluting with CH_2Cl_2 or recrystalization from CH_2Cl_2/CH_3OH to provide 2.07 g of methyl 4-isobutoxyl-8-nitroquinoline-2-carboxylate **3**.

Yield: 2.07 g. (M = 304.11 g mol^{-1}, n = 6.8 mol, 92%).

Melting point: 174-175 ℃.

^{1}H NMR spectrum (400 M, $CDCl_3$): δ = 8.43 – 8.40 (dd, 1 H), 8.05 – 8.03 (dd, 1 H), 7.59 (m, 2 H), 4.03, 4.02 (d, 2 H), 3.97 (s, 3 H), 2.24 (m, 1 H), 1.09 (d, 6 H) .

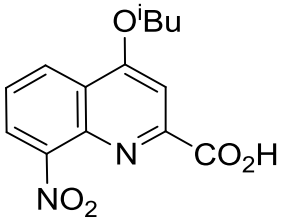
^{13}C NMR spectrum (101M, $CDCl_3$): δ = 165.66, 162.74, 151.29, 140.02, 126.31, 125.87, 125.06, 123.31, 102.18, 75.62, 53.36, 28.10, 19.16.

Mass spectrum (CI): m/z (%) = 275.0 (100.00), $[M - C_2H_5]^+$, 305.0 (100.00), $[M + H]^+$.

IR spectrum (KBr): 3069, 2966, 2882, 2324, 2049, 1910, 1718, 1587, 1529, 1440, 1361, 1267, 1119, 1011, 866, 785, 759, 667 cm^{-1}.

Elemental analysis (%): $C_{15}H_{16}N_2O_5$ Calcd: C, 59.21; H, 5.30; N, 9.21. Found: C, 59.16; H, 5.15, N, 9.15.

1.4. Synthesis of compound **4**.[77c]



The methyl ester **3** (150 mg, 0.49 mmol) was dissolved in a mixture of THF (20 mL) and methanol (10 mL), and KOH (100 mg, 1.79 mmol, 3.65 eq) was added, and the solution was stirred at ambient temperature for 20 h. The solution was neutralized using excess of AcOH and the solvents were evaporated. Dichloromethane was added to the residue and washed with water. The organic phases from extraction were combined, dried over $MgSO_4$, and the solvent was removed to provide a yellow solid.

Yield:0.128 g. (M = 290.27 g mol^{-1}, n = 0.44 mmol, 89%).

Melting point: 140-141 ℃.

^{1}H NMR spectrum (400 M, $CDCl_3$): δ = 8.49 – 8.47 (dd, 1 H), 8.17 – 8.15 (dd, 1 H), 7.67 (m, 2 H), 4.08, 4.06 (d, 2 H), 2.26 (m, 1 H), 1.10, 1.08 (d, 6 H).

^{13}C NMR spectrum (101M, $CDCl_3$): δ = 164.24, 163.55, 149.26, 127.06, 126.48,

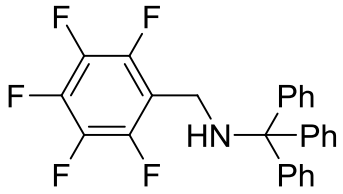
126.17, 123.68, 100.22, 76.20, 28.03, 19.10.

Mass spectrum (CI): m/z (%) = 291.0 (100.00), $[M + H]^+$; 319.1 (39.96), $[M + C_2H_5]^+$; 247.1 (72.48) $[M – C_3H_7]^+$.

IR spectrum (KBr): 3323, 3076, 2966, 1765, 1584, 1527, 1423, 1368, 1179, 1120, 1013, 873, 763, 675 cm^{-1}.

Elemental analysis (%): $C_{14}H_{14}N_2O_5$ Calcd: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.66; H, 4.74, N, 9.56.

1.5. Synthesis of compound **5**.[88]



To a solution of tritylamine (520 mg, 2.0 mmol) in DMF (5 mL) was added 2,3,4,5,6-pentafluorobenzyl bromide (260 mg, 1.0 mmol) and the resulting solution was stirred at room temperature for 1 h and monitored by TLC (hexane). The salt $TrNH_2$ ·HBr had precipitated from solution was removed by filtration. The filtrate was concentrated *in vacuo* and the crude residue was purified by silica gel flash column chromatography (hexane) to give N-trityl-2,3,4,5,6-pentafluorobenzyl amine **5** (403 mg, 92 %).

Yield: 403 mg. (M = 439.42 g mol^{-1}, n = 0.92 mol, 92%).

Melting point: 112-113 ℃.

^{1}H NMR spectrum (400 M, $CDCl_3$): δ= 7.53 – 7.50 (m, 6 H), 7.32 – 7.28 (m, 6 H), 7.23 - 7.19 (m, 3 H), 3.37 (s, 2 H).

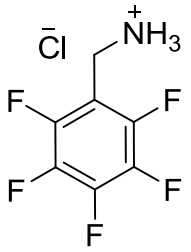
^{19}F NMR spectrum (376 M, $CDCl_3$): δ = 143.62 – 143.71 (dd, 2 F), 156.14 (t, 1 F), 162.34 (m, 2 F).

Mass spectrum (CI): m/z (%) = 243.3 (100.00), $[M – C_7H_4F_5N]^+$, 440.5 (74.67), $[M + H]^+$.

IR spectrum (KBr): 3326, 3062, 3028, 2881, 1657 1596, 1499, 1465, 1301, 1212, 1124, 1062, 1018, 968, 931, 899, 851, 773, 746, 702 cm^{-1}.

Elemental analysis (%): $C_{12}H_{12}N_2O_6$ Calcd: C, 71.07; H, 4.13; N, 3.19. Found: C, 70.89; H, 4.54, N, 3.09

1.6. Synthesis of compound **6**.[88]



5 (439 mg, 1.0 mmol) in a solution of 60% TFA in CH_2Cl_2 (v/v)(5 mL) was stirred for 10 min at room temperature, then CH_3OH (2 mL) was added. The solution

was stirred for 1 h and the solvent was evaporated *in vacuo*. A solution of concentrated HCl in CH_3OH (1:1, 10 mL) was added. The slurry was filtered and the solid washed with dry ether. The filtrate was concentrated *in vacuo* to afford 210 mg of 2,3,4,5,6-pentafluorobenzyl amine hydrochloride.

Yield: 210 mg. (M = 233.57 g mol^{-1}, n = 0.90 mol, 90%).

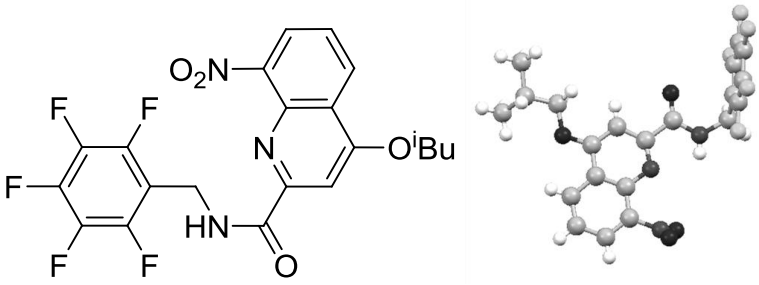
^{1}H NMR spectrum (400 MHz, CD_3OD): δ = 4.28 (s, 2H).

^{19}F NMR (276 MHz, CD_3OD): δ = -143.23 (m, 2 F), -154.52 (td, 1 F), -160.10 (m, 2 F).

IR spectrum (KBr): 2969, 2191, 1746, 1659, 1560, 1505, 1381, 1311, 1151, 1114, 982, 925, 886, 735 cm^{-1}.

Elemental analysis (%): $C_7H_5ClNF_5$, calcd. C 36.00, H 2.16, N 6.00; found C 36.36, H 2.43, N 5.90.

1.7. Synthesis of compound **7**.[128]



To an anhydrous CH_2Cl_2 (20 mL) solution of a mixture of **4** (290 mg, 1.0 mmol, 1.0 eq) and pentafluorobenzylamine hydrochloride (467 mg, 2.0 mmol, 2.0 eq) were successively added DIPEA (1.27 mL), HOBt (270 mg, 2 mmol, 2 eq), and EDC·HCl (383 mg, 2 mmol, 2 eq). The process was monitored by TLC. Upon completion after stirring for ca. 6 h under nitrogen at room temperature, the reaction mixture was washed with saturated aqueous NH_4Cl solution. The organic extract was dried over Na_2SO_4 and filtered off. Solvent was evaporated to dryness and the residue was purified on silica gel with dichloromethane or by recrystallization from dichloromethane/MeOH to allow isolation of 4-isobutoxy-8-nitroquinoline-2-carboxylic acid pentafluorobenzylamide **7** (422 mg) as a colorless solid.

Yield: 422 mg. (M = 469.36 g mol^{-1}, n = 0.90 mol, 90%).

Melting point: 153 ℃.

^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ = 8.54 (t, 1 H), 8.47 (dd, 1 H), 8.12 (dd, 1 H), 7.76 (s, 1 H), 7.63 (m, 1 H), 4.78 (d, 2 H), 4.08 (d, 2 H), 2.29 (m, 1 H), 1.14 (d, 6 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -142.49 (dd, 2 F), -154.64 (t, 1 F), -161.67 (m, 2 F).

^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ = 163.63, 163.30, 152.38, 147.64, 138.97, 126.72, 125.40, 125.24, 123.33, 99.91, 77.29, 76.97, 76.65, 75.78, 31.51, 28.01, 19.10.

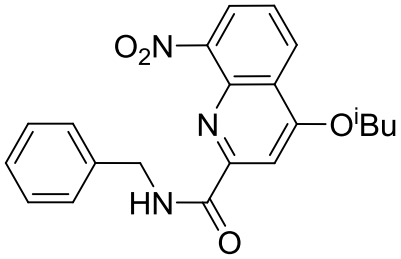
Mass spectrum (ESI): m/z (%) = 470.92 (100.00), $(M + H)^+$.

IR spectrum (KBr): 3397, 2960, 2878, 1690, 1591, 1498, 1362, 1144, 1120, 1011, 941, 868, 787, 758 cm^{-1}.

Elemental analysis (%): $C_{21}H_{16}N_3O_4F_5$, calcd. C 53.74, H 3.44, N 8.95; found C 53.96, H 3.36, N 8.95.

Crystallographic parameters for the structure determined: CCDC-906525, X-ray quality crystals were obtained from CH_3OH/CH_2Cl_2; $C_{21}H_{16}F_5N_3O_4$; *Mr* = 469.37; crystal size 0.23 × 0.15 × 0.10 mm^3; monoclinic; space group $P2_1/c$ (No.14); a = 5.2515(1) Å, b = 24.8800(5) Å, c = 15.5918(3) Å; β = 93.978 (1)°; V = 2032.27(7) $Å^3$; Z = 4; ρ_{cal} = 1.534 g cm^{-3}; μ = 0.137 mm^{-1}; $F(000)$ = 960; 12688 collected reflections (θ_{max} = 27.87°) of which 4750 were independent (R_{int} = 0.039); T_{max} = 0.9864; T_{min} = 0.9691; T = 223(2) K; full-matrix least-square on F^2 with 0 restraints and 303 parameters; GOF = 1.093; $R1$ = 0.0595($I > 2\sigma(I)$); $\omega R2$(all data) = 0.1389; peak/hole = 0.213/-0.199 e $Å^{-3}$.

1.8. Synthesis of compound **8**.



To an anhydrous CH_2Cl_2 (20 mL) solution of a mixture of **4** (290 mg, 1.0 mmol, 1.0 eq) and benzylamine (0.22 mL, 2.0 mmol, 2.0 eq) were successively added DIPEA (1.27 mL), HOBt (270 mg, 2 mmol, 2 eq), and EDC·HCl (383 mg, 2 mmol, 2 eq). The process was monitored by TLC. Upon completion after stirring for ca. 6 h under nitrogen at room temperature, the reaction mixture was washed with saturated aqueous NH_4Cl solution. The organic extract was dried over Na_2SO_4 and filtered off. Solvent was evaporated to dryness and the residue was purified on silica gel with dichloromethane or by recrystallization from dichloromethane/MeOH to allow isolation of the compound **8** (322 mg) as a yellow solid.

Yield: 322 mg. (M = 379.41 g mol^{-1}, n = 0.85 mol, 85%).

Melting point: 142 ℃.

^{1}H NMR spectrum (400 MHz, $CDCl_3$): δ = 8.54 (t, 1 H), 8.49 (dd, 1 H), 8.09 (dd, 1 H), 7.83 (s, 1 H), 7.61 (s, 1 H), 7.37 (m, 4 H), 7.28 (m, 1 H), 4.72 (d, 2 H), 4.13 (d, 2 H), 2.30 (m, 1 H), 1.15 (d, 6 H).

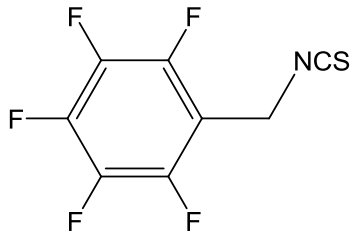
^{13}C NMR spectrum (100 MHz, $CDCl_3$): δ = 163.66, 163.20, 153.13, 147.70, 138.99, 137.98, 128.69, 127.55, 127.42, 126.67, 125.18, 125.03, 123.27, 100.07, 75.73, 43.57, 28.06, 19.14.

Mass spectrum (ESI): m/z (%) = 402.14352 (100) $[M + Na]^+$, 380.16183 (10) $[M + H]^+$.

IR spectrum (KBr): 3382, 3101, 2959, 2875, 1680, 1587, 1566, 1520, 1336, 1215, 1129, 1014, 865, 742, 696 cm^{-1}.

Elemental analysis (%): $C_{21}H_{21}N_3O_4$ calcd. C 66.48, H 5.58, N 11.08; found C 66.36, H 5.44, N 11.04.

1.9. Synthesis of compound **9**.



To an anhydrous CH_2Cl_2 (20 mL) were successively added **5** (150 mg, 0.64 mmol, 1.0 eq) and DIPEA (0.135 mL, 1.29 mmol, 2.0 eq) and the mixture was stirred under nitrogen atmosphere for 10 min. Then, TCP (179 mg, 0.644 mmol, 1.2 eq) was added to the mixture. After being stirred for 8 h under nitrogen atmosphere at room temperature, the solvent was evaporated to dryness, and the residue was chromatographed on silica gel with hexane as an eluent to allow isolation of **9** as a colorless oil, which was characterized by ^{1}H NMR, ^{19} NMR as well as mass spectrometry and used for next reaction without further characterization.

Yield: 130 mg. (M = 239.17 g mol^{-1}, n = 0.54 mol, 85%).

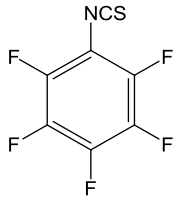
^{1}H NMR spectrum (300 M Hz, $CDCl_3$): δ = 4.76 (m, 2H).

^{19}F NMR spectrum (282 M Hz, $CDCl_3$): δ = -142.37 (m, 2 F), -151.57 (t,1 F), -160.29 (m, 2 F).

^{13}C NMR spectrum (75M Hz, $CDCl_3$): δ = 36.21.

Mass spectrum (EI): m/z (%) = 181.1 (100.00), $[C_7H_2F_5]^+$; 240.1 (49.79), $[M + H]^+$.

1.10. Synthesis of compound **10**.



To an anhydrous CH_2Cl_2 (20 mL) solution of pentafluoroaniline (183 mmol, 1.0 mml, 1.0 eq) was added DPTC (279 mg, 1.2 mmol, 1.2 eq). After being stirred for 8 h under nitrogen atmosphere at room temperature, the solvent was evaporated to dryness, and the residue was chromatographed on silica gel with hexane as an eluent to allow isolation of **10** as colorless oil, which was characterized by ^{1}H NMR, ^{19} NMR and mass spectrum and used for next reaction without further characterization.

Yield:174 mg. (M = 225.14 g mol^{-1}, n = 0.95 mol, 95%).

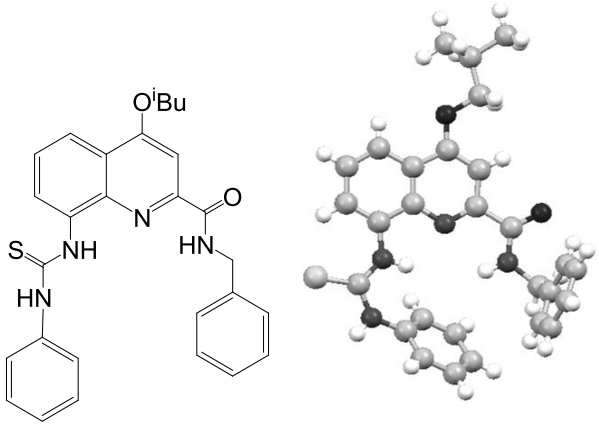
^{1}H NMR spectrum (300 M, $CDCl_3$): no signal.

^{19}F NMR spectrum (282 MHz, $CDCl_3$): δ = -145.34, -145.39 (d, 2F), -155.73, -155.80, -155.88 (t, 1F), -161.04, -161.12, -161.17 (m, 2F).

Mass spectrum (EI): m/z (%) = 57.3 (100.00), $[NCS]^+$; 225.2 (40.50), M^+.

1.11. Synthesis of compound **11**.

4-Isobutoxy-8-(phenylthioureido)quinoline-2-carboxylic acid benzylamide



A mixture of **8** (379 mg, 1.0 mmol, 1.0 equiv.) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C was stirred at room temperature under an atmosphere of hydrogen (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.

A solution of 4-isobutoxy-8-aminoquinoline-2-carboxylic acid benzylamide (1.0 mmol, 1.0 equiv.) and phenyl isothiocyanate (0.33mL, 3.0 mmol, 3.0 equiv.) in dichloromethane (30 mL) was heated at reflux overnight. After cooling to room temperature, the solvent was removed *in vacuo*. The residue was purified by recrystallization from dichloromethane/MeOH to allow isolation of a light yellow solid.

Yield: 344 mg (M = 484.61 g mol^{-1}, n = 0.71 mmol, 71 %).

Melting point: 194 ℃.

^{1}H NMR spectrum (600 MHz, $CDCl_3$): δ = 10.22 (s, 1 H), 9.48 (d, 1 H), 8.04 (s, 1 H), 7.89 (d, 1 H), 7.64 (s, 1 H), 7.52 (t, 1 H), 7.28 (m, 3 H), 7.20 (m, 5 H), 7.13 (d, 1 H), 7.04 (t, 1 H), 4.46 (d, 2 H), 3.96 (d, 2 H), 2.19 (m, 1 H), 1.04 (d, 6 H).

^{13}C NMR spectrum (150 MHz, $CDCl_3$): δ = 177.16, 164.32, 163.51, 149.38, 138.57, 138.13, 136.39, 134.33, 130.07, 128.61, 127.27, 127.24, 126.94, 126.79, 125.03, 122.05, 118.52, 116.89, 99.78, 75.37, 43.11, 28.10, 19.18.

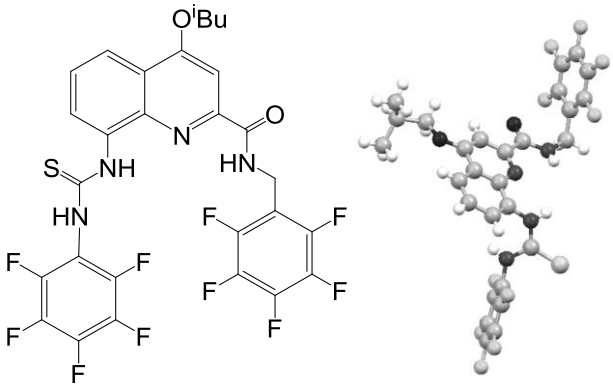
IR spectrum (KBr): 3403, 3281, 3222, 2955, 1664, 1528, 1346, 1227, 1160, 1051, 913, 861, 812, 755, 687 cm^{-1}.

Mass spectrum (ESI): m/z (%) = 507.18379 (100.00), $[M + Na]^+$, 485.20196 (90.00) $[C_{28}H_{29}N_4O_2S + H]^+$, 350.18738 (55.00) $[C_{21}H_{24}N_3O_2]^+$.

Elemental analysis (%): $C_{28}H_{28}N_4O_2S$ 0.5H_2O: calcd. C 68.13, H 5.92, N 11,35; found C 68.40, H 5.51, N 10.87.

Crystallographic parameters for the structure determined: CCDC-906526, X-ray quality crystals were obtained from MeOH/dichloromethane: $C_{28}H_{28}N_4O_2S$; *Mr* = 484.60; crystal size 0.27 × 0.13 × 0.05 mm^3; monoclinic; space group $P2_1/c$ (No.14); a = 8.0294(2) Å, b = 16.1218(4) Å, c = 19.8969(6) Å; β = 100.567 (1)°; V = 2531.94(12) Å^3; Z = 4; $\rho_{calcd.}$ = 1.271 g cm^{-3}; μ = 0.160 mm^{-1}; F(000) = 1024; 7226 collected reflections (θ_{max} = 25.00°) of which 4340 were independent (R_{int} = 0.0251); T_{max} = 0.9920; T_{min} = 0.9580; T = 223(2) K; full-matrix least-square on F^2 with 0 restraint and 327 parameters; GOF = 1.057; $R1$ = 0.0573($I > 2\sigma$(I)); $\omega R2$(all data) = 0.1356; peak/hole = 0.197/-0.196 eÅ^{-3}.

1.12. Synthesis of compound **12**.



The synthesis of **12** was done similar to that of **11**. The compound was purified by recrystallization from dichloromethane/MeOH to obtain a colorless solid.
Yield: 372 mg (M = 664.52 g mol^{-1}, n = 0.56 mmol, 56%).

M.p.: 167 ℃.

^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ = 9.49 (s, 1 H), 8.55 (d, 1 H), 8.45 (t, 1 H), 8.08 (s, 1 H), 7.82 (d, 1 H), 7.44 (m, 2 H), 4.80 (d, 2 H), 3.86 (d, 2 H), 2.19 (m, 1 H), 1.09 (d, 6 H).

^{19}F NMR spectrum (282 MHz, $CDCl_3$): δ = -142.72 (d, 2 F), -144.42 (d, 2 F), -154.08 (m, 1 F), -154.33 (t, 1 F), -161.56 (m, 2 F), -162.07 (d, 2 F).

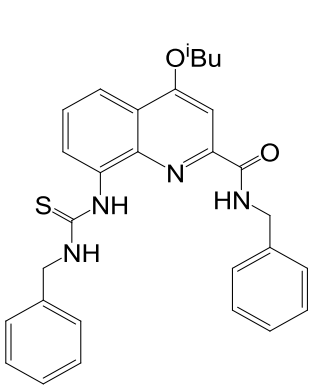
^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ = 181.17, 165.17, 163.37, 149.80, 139.44, 133.71, 126.84, 122.37, 121.37, 118.95, 99.34, 31.66, 28.16, 19.04.

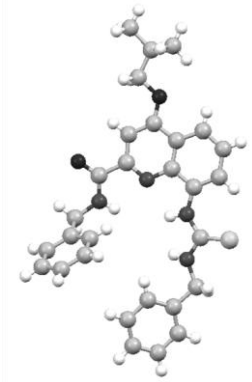
IR (KBr): 3369, 2949, 2234, 1713, 1611, 1502, 1464, 1324, 1197, 1134, 1099, 993, 842, 750 cm^{-1}. MS (ESI): m/z (%) = 665.58 (60) [M + H] $^+$, 440.85 (100) [$C_{21}H_{18}F_5N_3O_2$ + H] $^+$.

Elemental analysis (%): $C_{28}H_{18}F_{10}N_4O_2S$, calcd. C 50.61, H 2.73, N 8.43; found C 50.56, H 2.79, N 8.39.

Crystallographic parameters for the structure determined: X-ray quality crystals were obtained from chloroform: $C_{28}H_{18}N_4O_2SF_{10}$ $CHCl_3$; *Mr* = 783.89; crystal size 0.20 × 0.05 × 0.02 mm^3; triclinic; space group P-$_1$ (No.2); a = 10.3604(6) Å, b = 12.1417(7) Å, c = 13.7148(8) Å; β = 95.138(4)°; V = 1599.69(16) Å^3; Z = 2; $\rho_{calcd.}$ = 1.627 g cm^{-3}; μ = 4.074 mm^{-1}; F(000) = 788; 20060 collected reflections (θ_{max} = 25.00°) of which 5393 were independent (R_{int} = 0.058); T_{max} = 0.9230; T_{min} = 0.4960; T = 223(2) K; full-matrix least-square on F^2 with 466 restraints and 466 parameters; GOF = 1.006; R1 = 0.068($I > 2\sigma$(I)); ωR2(all data) = 0.2037; peak/hole = 0.87 /-0.59 eÅ^{-3}.

1.13. Synthesis of compound **13**.





The synthesis of **13** was as described for **11**. It was purified by recrystallization from dichloromethane/MeOH to allow isolation of the compound as a light yellow solid.

Yield: 339 mg (M = 498.64 g mol^{-1}, n = 0.68 mmol,68 %).

M.p.: 163 ℃.

^{1}H NMR (400 MHz, DMSO- d_6): δ = 9.16 (s, 1 H), 8.43 (s, 1 H), 8.18 (s, 1 H), 7.89 (dd, 1 H), 7.60 (s, 1 H), 7.43 (t, 1 H), 7.17 (m, 9 H), 6.77 (s, 1 H), 4.71 (d, 2 H), 4.52 (d, 1 H), 3.87 (d, 2 H), 2.16 (m, 1 H), 1.01 (d, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.86, 163.38, 149.45, 139.24, 137.62, 134.56, 128.64, 128.61, 127.80, 127.65, 127.44, 127.20, 126.93, 122.60, 119.82, 117.30, 99.41, 75.12, 49.05, 43.39, 28.06, 19.13.

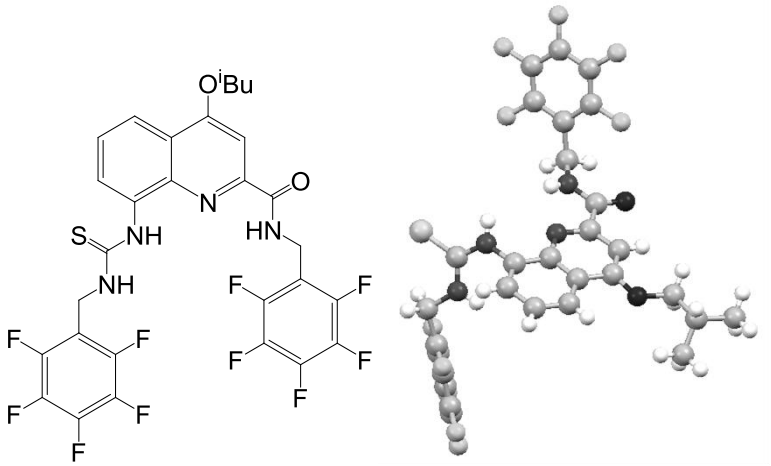
IR (KBr): 3289, 2084, 1647, 1544, 1460, 1423, 1362, 1330, 1250, 1228, 1180, 1143, 1041, 857, 724, 692 cm^{-1}.

MS (ESI): m/z (%) = 499.07 (99.68), $[M + Na]^+$, 350.20 (100.00) $[C_{21}H_{24}N_3O_2]^+$

Elemental analysis (%): $C_{29}H_{30}N_4O_{32}S$, calcd. C 69.85, H 6.06, N 11,24; found C 69.56, H 5.73, N 11.11.

X-ray quality crystals were obtained from MeOH/dichloromethane: CCDC-906527, $C_{29}H_{30}N_4O_2S$; *Mr* = 498.63; crystal size 0.37 × 0.10 × 0.06 mm^3; monoclinic; space group $P2_1/c$ (No.14); a = 8.2730(2) Å, b = 31.1994(4) Å, c = 20.2195(4) Å; β = 91.083(1)°; V = 5217.98(18) Å^3; Z = 8; $\rho_{calcd.}$ = 1.269 g cm^{-3}; μ = 0.158 mm^{-1}; F(000) = 2112; 16171 collected reflections (θ_{max} = 25.00°) of which 9048 were independent (R_{int} = 0.0491); T_{max} = 0.9906; T_{min} = 0.9440; T = 223(2) K; full-matrix least-square on F^2 with 0 restraint and 671 parameters; GOF = 1.049; $R1$ = 0.0677($I > 2\sigma(I)$); ω$R2$ (all data) = 0.1556; peak/hole = 0.215/-0.206 eÅ^{-3}.

1.14. Synthesis of compound **14**.



The synthesis of **14** was done similar to that of **11**. It was purified by recrystallization from dichloromethane/MeOH to allow isolation of the compound as a yellow solid.

Yield: 366 mg (M = 678.54 g mol^{-1}, n = 0.54 mmol,54 %).

M.p.: 196 ℃.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.99 (s, 1 H), 8.52 (t, 1 H), 8.03 (d, 2 H), 7.62 (s, 1 H), 7.53 (t, 1 H), 6.92 (t, 1 H), 4.96 (t, 2 H), 4.75 (d, 2 H), 3.99 (d, 2 H), 2.25 (m, 1 H), 1.12 (d, 6 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = -142.22 (dd, 2 F), -142.58 (dd, 2 F), -153.88 (t, 1 F), -154.52 (t, 1 F), -161.41 (m, 2 F), -161.67 (m, 2 F).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.31, 164.16, 163.53, 149.88, 147.21, 139.93, 133.81, 126.82, 123.05, 121.33, 119.02, 110.96, 99.63, 37.04, 31.56, 28.06, 19.12.

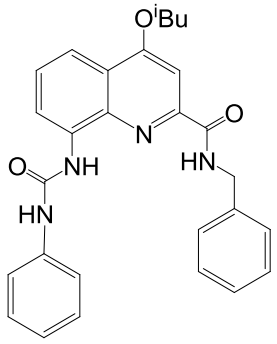
IR (KBr): 3320, 3175, 2963, 1664, 1506, 1417, 1311, 1212, 1121, 1026, 965, 924, 763 cm^{-1}.

MS (ESI): m/z (%) = 679.17 (100) $[M + H]^+$.

Elemental analysis (%): $C_{29}H_{20}F_{10}N_4O_2S$, calcd. C 51.33, H 2.97, N 8.26; found C 51.22, H 2.96, N 8.25.

X-ray quality crystals were obtained from MeOH/CH_2Cl_2: CCDC-906528, $C_{29}H_{20}F_{10}N_4O_2S$; *Mr* = 678.55; crystal size 0.27 × 0.13 × 0.10 mm^3; triclinic; space group *P*-1 (No.2); *a* = 10.3605(3) Å, *b* = 12.1967(4) Å, *c* = 13.2370(4) Å; α = 108.120(1)°, β = 108.706(2)°, γ = 99.221(3)°; *V* = 1441.59(8) Å^3; *Z* = 2; ρ_{cal} = 1.563 g cm^{-3}; μ = 0.213 mm^{-1}; *F*(000) = 688; 13439 collected reflections (θ_{max} = 25.00°) of which 5000 were independent (R_{int} = 0.036); T_{max} = 0.9790; T_{min} = 0.9447; *T* = 223(2) K; full-matrix least-square on F^2 with 7 restraint and 426 parameters; GOF = 1.068; *R*1 = 0.0589($I > 2\sigma$(I)); ωR2 (all data) = 0.1496; peak/hole = 1.019/-0.518 eÅ^{-3}.

1.15. Synthesis of compound **15**.



The synthesis of **15** was similar as the one of **11**. The compound was purified by recrystallization from dichloromethane/MeOH to allow isolation as yellow solid.

Yield: 314 mg (M =468.55 g mol^{-1}, n = 0.67 mmol,67 %).

M.p.: 126 ℃.

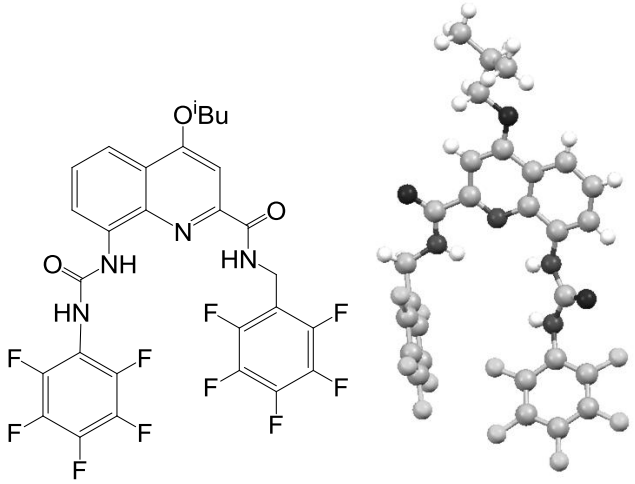
^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.66 (s, 1 H), 9.63 (t, 1 H), 9.27 (s, 1 H), 8.52 (dd, 1 H), 7.72 (dd, 1 H), 7.66 (s, 1 H), 7.57 (t, 1 H), 7.49 (m, 2 H), 7.32 (m, 7 H), 6.98 (t, 1 H), 4.67 (d, 2 H), 4.11 (d, 2 H), 2.19 (m, 1 H), 1.07 (d, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.46, 163.13, 152.67, 149.65, 139.64, 137.65, 136.50, 129.35, 128.84, 128.26, 127.62, 127.36, 118.95, 115.97, 113.68, 99.63, 75.08, 43.07, 28.09, 19.38. IR (KBr): 3324, 2964, 1646, 1523, 1416, 1313, 1198, 1071, 1001, 752, 690 cm^{-1}.

MS (ESI): m/z (%) = 491.20361(100) $[M + Na]^+$.

Elemental analysis (%): $C_{28}H_{28}N_4O_3$ $0.5H_2O$, calcd. C 70.42, H 6.12, N 11,73; found C 70.70, H 5.98, N 11.76.

1.16. Synthesis of compound **16**.



The synthesis of **16** proceeded similar to the one of **11**. The compound was purified by recrystallization from dichloromethane/MeOH to allow isolation as colorless solid.

Yield: 512 mg (M = 648.45 g mol^{-1}, n = 0.79 mmol,79 %).

M.p.: 241 ℃.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.96 (s, 1 H), 9.53 (t, 1 H), 9.12 (s, 1 H), 8.46 (dd, 1 H), 7.79 (dd, 1 H), 7.64 (m, 2 H), 4.78 (d, 2 H), 4.13, (d, 2 H) 2.21 (m, 1

H), 1.10 (d, 6 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = -142.41 (dd, 2 F), -146.17 (dd, 2 F), -156.11 (t, 1 F), -159.31 (t, 1 F), -163.20 (m, 2 F), -163.85 (m, 2 F).

IR (KBr): 3310, 2969, 1685, 1644, 1561, 1501, 1461, 1233, 1008, 980, 767, 745 cm^{-1}.

MS (ESI): m/z (%) = 649.00 (100) [M + H] $^{+}$.

Elemental analysis (%): $C_{28}H_{18}F_{10}N_4O_3 \cdot H_2O$, calcd. C 50.46, H 3.03, N 8.41; found C 50.71, H 3.19, N 8.57.

X-ray quality crystals were obtained from DMSO: CCDC-906529, $C_{28}H_{18}F_{10}N_4O_3$ $(CH_3)_2SO$; Mr = 726.59; crystal size 0.53 × 0.20 × 0.10 mm^3; monoclinic; space group $P2_1/n$ (No.14); a = 15.0156(3) Å, b = 9.5866(2) Å, c = 21.3804(5) Å; β = 92.722(1)°; V = 3074.21(11) Å^3; Z = 4; $\rho_{calcd.}$ = 1.570 g cm^{-3}; μ = 0.210 mm^{-1}; F(000) = 1480; 9631 collected reflections θ_{max} = 25.00°) of which 5343 were independent (R_{int} = 0.0373); T_{max} = 0.9793; T_{min} = 0.8968; T = 223(2) K; full-matrix least-square on F^2 with 68 restraint and 470 parameters; GOF = 1.059; $R1$ = 0.0630($I > 2\sigma$(I)); $\omega R2$ (all data) = 0.1451; peak/hole = 0.358/-0.386 eÅ^{-3}.

1.17. Synthesis of compound **17**.

A mixture of **7** (469 mg, 1.0 mmol, 1.0 equiv.) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C was stirred at room temperature under an atmosphere of hydrogen (20 bar) overnight. The solution was filtered through Celite and the filtrate was evaporated to dryness. The residue was used in the next step reaction without purification.

To a 100 mL round-bottomed flask equipped with a magnetic stirrer in N_2, the amine (ca. 439 mg, 1.0 mmol, 1.0 equiv.) was added. Subsequently, dried CH_3CN (40 mL) and triethylamine (0.33 mL) were successively added to the flask. After cooling the reaction to 0°C, pentafluorobenzoyl chloride (0.14 mL, 2.2 mmol, 2.2 equiv.) was slowly added dropwise *via* syringe. The suspension was allowed to reach room temperature and was stirred overnight. When the reaction finished, the solvent was evaporated and the residue was washed with saturated aqueous NH_4Cl solution. Then the organic extract was dried over Na_2SO_4 and filtered off from an insoluble fraction. The filtrate was evaporated to dryness, and the residue was purified by crystallization from MeOH/dichloromethane to allow isolation of **17** as a light yellow solid.

Yield: 456 mg (M = 633.44 g mol^{-1}, n = 0.72 mmol, ca. 72 %).

M.p.: 194 ℃.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.98 (s, 1H), 8.78 (dd, 1H), 8.15 (t, 1H), 7.95 (dd, 1H), 7.65 (s, 1H), 7.55 (t, 1H), 4.76 (d, 2H), 4.00 (d, 2H), 2.22 (m, 1H), 1.07 (d, 6H).

^{19}F NMR (376 MHz, $CDCl_3$): δ = -140.57 (d, 2 F), -143.54 (d, 2 F), -149.12 (m, 1 F), -154.29 (t, 1 F), -159.82 (m, 2 F), -161.65 (d, 2 F).

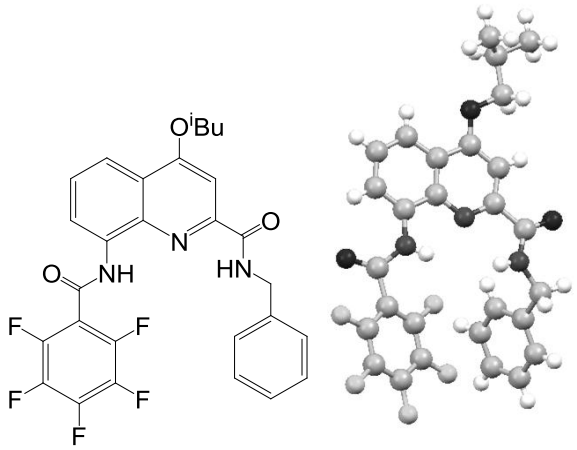
^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.03, 163.67, 155.10, 149.41, 133.00, 127.50, 122.04, 118.85, 117.60, 99.53, 75.52, 31.31, 28.06, 19.08.

IR (KBr): 3515, 3401, 2966, 1684, 1657, 1548, 1500, 1420, 1331, 1123, 1060, 1012, 950, 764 cm^{-1}.

MS (ESI): m/z (%) = 634.13 (100) $[M + H]^+$.

Elemental analysis (%): $C_{28}H_{17}F_{10}N_3O_3$, calcd. C 53.09, H 2.71, N 6.63; found C 53.38, H 2.87, N 6.18.

1.18. Synthesis of compound **18**.



The synthesis of **18** was similar to that of **17**. The compound was purified by re-crystallization from dichloromethane/MeOH to allow isolation as a light yellow solid.

Yield: 332 mg (M = 543.48 g mol^{-1}, n = 0.61 mmol,61%).

M.p.: 197 ℃.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.06 (s, 1 H), 8.83 (d, 1 H), 8.10 (s, 1 H), 8.02 (d, 1 H), 7.76 (s,1 H), 7.60 (t, 1H), 7.34 (m, 5H), 4.68 (d, 2H), 4.09 (d, 2H), 2.30 (m, 1H), 1.13 (d, 6H).

^{19}F NMR (564 MHz, $CDCl_3$): δ = -140.28 (dd, 2 F), 149.20 (t, 1 F), -159.29 (m, 2 F).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.04, 163.70, 154.99, 150.02, 137.82, 137.79, 133.08, 128.73, 127.69, 127.63, 127.40, 122.06, 118.79, 117.61, 99.71, 75.49, 43.86, 28.13, 19.18.

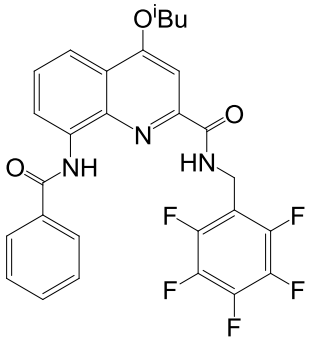
IR (KBr): 3780, 3443, 3328, 2919, 2852, 1689, 1539, 1383, 1221, 1040, 998, 756, 724 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 543.2 (95.59) $[M]^{\cdot+}$, 410.1 (100) $[C_{20}H_{15}F_5N_2O_2]^{\cdot+}$.

Elemental analysis (%): $C_{28}H_{22}F_5N_3O_3$, calcd. C 61.88, H 4.08, N 7.73; found C 61.99, H 4.23, N 7.79.

X-ray quality crystals were obtained from $MeOH/CH_2Cl_2$: CCDC-906530, $C_{28}H_{22}F_5N_3O_3$; *Mr* = 543.49; crystal size 0.30 × 0.13 × 0.06 mm^3; monoclinic; space group $P2_1/c$ (No.14); a = 16.1036(3) Å, b = 8.2664(2) Å, c = 19.9664(5) Å; β = 104.067(1)°; V = 2578.20(10) $Å^3$; Z = 4; $\rho_{calcd.}$ = 1.400 g cm^{-3}; μ = 0.116 mm^{-1}; F(000) = 1120; 10498 collected reflections (θ_{max} = 25.00°) of which 4389 were independent (R_{int} = 0.042); T_{max} = 0.9931; T_{min} = 0.9659; T = 223(2) K; full-matrix least-square on F^2 with 0 restraint and 360 parameters; GOF = 1.097; $R1$ = 0.0651($I > 2\sigma(I)$); $\omega R2$ (all data) = 0.1464; peak/hole = 0.216/-0.205 e$Å^{-3}$.

1.19. Synthesis of compound **19**.



The synthesis of **19** was similar to that of **17**. The compound was purified by re-crystallization from dichloromethan/MeOH to obtain a colorless solid.

Yield: 462 mg (M = 543.48 g mol^{-1}, n = 0.85 mmol, 85 %).

M.p.: 215 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.13 (s, 1 H), 8.90 (dd, 1 H), 8.19 (t, 1 H), 7.95 (m, 2 H), 7.88 (dd, 1 H), 7.64 (s, 1 H), 7.52 (m, 4 H), 4.78 (d, 2 H), 4.01(d, 2 H), 2.22(m, 1 H), 1.07(d, 6 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ = -143.02 (dd, 2 F), -154.02 (t, 1 F), -161.10 (m, 2 F).

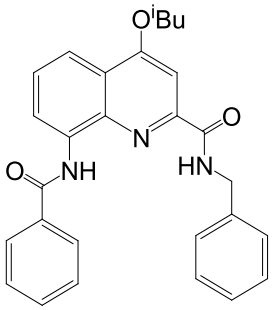
^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.31, 164.15, 163.69, 148.87, 138.01, 135.21, 134.18, 132.10, 128.96, 127.89, 126.91, 122.20, 117.92, 116.20, 99.35, 75.42, 31.26, 28.09, 19.16.

IR (KBr): 3380, 2975, 1660, 1528, 1501, 1417, 1328, 1259, 1017, 948, 761, 694 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 543.2 (100) $[M]^+$.

Elemental analysis (%): $C_{28}H_{22}F_5N_3O_3$, calcd. C 61.88, H 4.08, N 7,73; found C 61.47, H 3.77, N 7.65.

1.20. Synthesis of compound **20**.



The synthesis of **20** was performed similar to the one of **17**. The compound was purified by recrystallization from dichloromethane/MeOH to obtain a colorless solid.

Yield: 245 mg (M = 453.53 g mol^{-1}, n = 0.54 mmol, 54 %).

M.p.: 191 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.19 (s, 1 H), 8.87 (dd, 1 H), 8.01 (t, 1 H), 7.90 (dd, 1 H), 7.78 (dd, 2 H), 7.71 (s, 1 H), 7.54 (t, 1 H), 7.44 (m, 1 H), 7.36 (m, 5 H), 7.22 (t, 2 H), 4.70 (d, 2 H), 4.04 (d, 2 H), 2.24 (m, 1 H), 1.08 (d, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.03, 164.20, 163.70, 149.53, 138.02,

137.90, 135.06, 134.12, 131.82, 129.01, 128.89, 127.82, 127.69, 126.79, 117.68, 116.19, 99.46, 43.92, 28.16, 19.22.

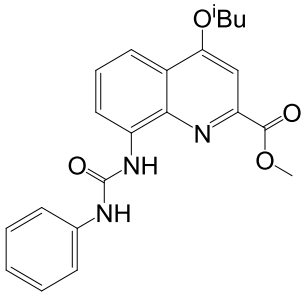
IR (KBr): 3379, 2971, 1673, 1650, 1532, 1421, 1331, 1229, 1028, 911, 761, 697 cm^{-1}.

MS (ESI): m/z (%) = 454.27 (100) $[M+H]^+$.

Elemental analysis (%): $C_{28}H_{27}F_5N_3O_3$ $0.5H_2O$, calcd. C 72.71, H 6.10, N 9.08; found C 73.04, H 5.85, N 9.08.

1.21. Synthesis of compound **21**.

Methyl 4-isobutoxy-8-(phenylureido)quinoline-2-carboxylate (21).



A mixture of **3** (304 mg, 1.0 mmol, 1.0 equiv.) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C (30 mg) was stirred at room temperature under an atmosphere of hydrogen (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.

A solution of methyl 4-isobutoxy-8-aminoquinoline-2-carboxylate (ca. 1.0 mmol, 1.0 equiv.) and phenyl isocyanate (0.33 mL, 3.0 mmol, 3.0 equiv.) in dichloromethane (30 mL) was stirred overnight. Then, the solvent was removed *in vacuo*. The residue was purified by recrystallization from dichloromethane/MeOH to allow isolation of a light yellow solid.

Yield: 169 mg (M = 393.44 g mol^{-1}, n = 0.43 mmol, 43 %).

M.p.: 198-200 ℃.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.54 (s, 1H), 8.68 (d, 1H), 7.80 (d, 1H), 7.57 (m, 2H), 7.52 (d, 2H), 7.48 (s, 1H), 7.35 (t, 2H), 7.11 (t, 1H), 4.04 (m, 5H), 2.31 (m, 1H), 1.16 (d, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 166.03, 163.02, 152.58, 145.90, 138.55, 136.35, 129.11, 128.74, 123.40, 122.15, 120.18, 116.00, 113.77, 100.99, 75.13, 53.00, 28.21, 19.25.

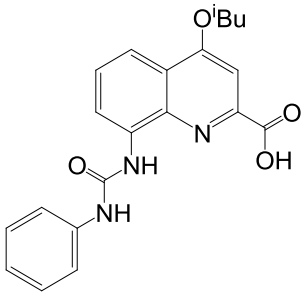
IR (KBr): 3441, 3345, 2959, 1706, 1603, 1525, 1442, 1417, 1388, 1358, 1315, 1277, 1232, 1193, 1069, 1017, 994, 852, 817, 787, 754, 690 cm^{-1}.

MS (CI): m/z (%) = 301.2 (100.00), $[C_{16}H_{17}N_2O_4]^+$, 394.2 (64.82) $[M + H]^+$, 275.2 (62.85) $[C_{15}H_{19}N_2O_3]^+$.

Elemental analysis (%): $C_{22}H_{23}N_3O_4$ H_2O, calcd. C 64.22, H 6.12, N 10.21; found C 64.17, H 5.89, N 9.76.

1.22. Synthesis of compound **22**.

4-isobutoxy-8-(phenylureido)quinoline-2- carboxylic acid (**22**).



The methyl ester **21** (787 mg, 2.0 mmol, 1.0 equiv.) was dissolved in a mixture of THF (100 mL) and methanol (50 mL). KOH (2.5 equiv.) was added, and the solution was stirred at room temperature overnight. The solution was neutralized using excess of AcOH. Then the solvents were evaporated and then dissolved in dichloromethane and washed with water, dried ($MgSO_4$) and evaporated to give a yellow solid which was characterized by ^{1}H NMR and MS and used without further purification.

Yield: 668 mg (M = 379.41 g mol^{-1}, n = 1.76 mmol, 88 %).

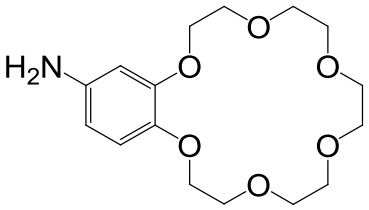
Melting points: 209-210 ℃

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.94 (s, 1H), 9.54 (s, 1H), 8.65 (d, 1H), 7.91 (dd, 1H), 7.80 (s, 1H), 7.67 (t, 1H), 7.25 (m, 2 H), 7.24 – 7.21 (m, 2H), 6.98 (m, 1H), 4.22 (d, 2H), 2.34 (m, 1H), 1.17 (d, 6H).

MS (ESI): m/z (%) = 380.16144 (100) $[M + H]^+$. MS (-c ESI): m/z (%) = 259.11346 (100) $[C_{14}H_{15}N_2O_3]^-$, 378.15274 (50) $[M-H]^-$.

1.23. Synthesis of compound **23**.

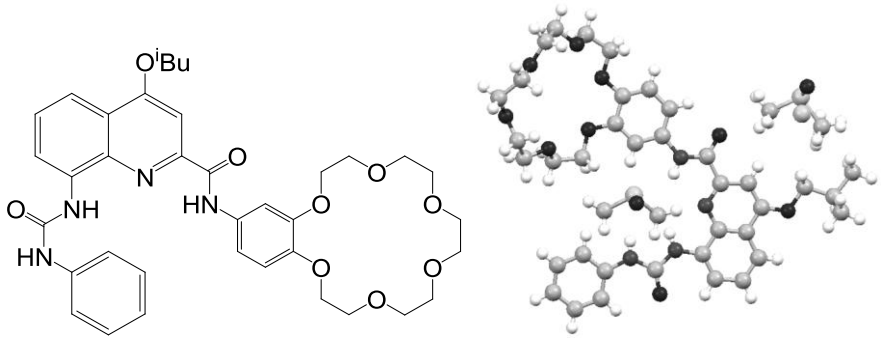
4-aminobenzo-18-crown-6



A mixture of 4-nitrobenzo-18-crown-6 (178 mg, 0.5 mmol, 1.0 equiv.) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C (30 mg) was stirred at room temperature under an atmosphere of hydrogen (20 bar) overnight. The solution was filtered through Celite and the filtrate was evaporated to dryness. The residue was used directly in the next coupling step.

1.24. Synthesis of compound **24**.

4-isobutoxy-8-(phenylureido)quinoline-2- carboxylic acid (6,7,9,10,12,13,15, 16,18,19-deca hydro -5,8,11,14,17,20-hexaoxabenzocyclooctadecen-2-yl)-amide.



To an anhydrous CH_2Cl_2 (20 mL) and CH_3CN (40 mL) solution of a mixture of quinoline acid **22** (189 mg, 0.5 mmol, 1.0 equiv.) and freshly hydrogenatively reduced 4-aminobenzo-18-crown-6 (0.5 mmol, 1 equiv.) were successively added DIPEA (0.75 equiv.) and HBTU (0.75 equiv.). The process was monitored by TLC. After stirring for 6 h under nitrogen at room temperature, the reaction mixture was washed with saturated aqueous NH_4Cl solution. The organic extract was dried over Na_2SO_4 and filtered off. Solvent was evaporated to dryness and the residue was purified on silica gel with dichloromethane/methanol (first 30/1, then 10/1, v/v) to allow isolation of the compound as a light yellow solid.

Yield: 189 mg (M = 688.77 g mol^{-1}, n = 0.27 mmol, 55 %).

M.p.: 225-227 ℃.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.70 (s, 1H), 9.20 (s, 1H), 8.57 (d, J = 7.5 Hz, 1H), 8.17 (s, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.61 (s, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.36 (d, J = 7.7 Hz, 2H), 7.21 (s, 1H), 7.16 (t, J = 7.5 Hz, 2H), 6.91 (t, J = 7.2 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 8.1 Hz, 1H), 3.96 (s, 2H), 3.90 (s, 2H), 3.83 (d, J = 3.3 Hz, 2H), 3.78 (d, J = 6.0 Hz, 2H), 3.72 (s, 4H), 3.69 – 3.65 (m, 6H), 3.63 (s, 4H), 2.15 (m, 1H), 1.01 (d, J = 6.6 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.15, 173.72, 164.18, 159.86, 159.62, 156.88, 149.21, 148.77, 146.18, 141.64, 139.82, 138.53, 134.44, 132.86, 131.23, 128.35, 125.51, 125.46, 124.89, 119.13, 109.55, 85.82, 81.52, 81.48, 81.42, 81.38, 81.31, 80.34, 80.18, 80.01, 79.52, 38.81, 29.86.

IR (KBr): 3532, 3262, 3127, 3070, 2875, 2292, 2108, 1990, 1957, 1693, 1600, 1524, 1600, 1524, 1443, 1392, 1355, 1262, 1202, 1113, 1062, 950, 887, 858, 809, 755, 694 cm^{-1}.

MS (+c ESI): m/z (%) = 711.29730 (100) $[M + Na]^+$. (-c ESI): m/z (%) = 723.26831 (100) $[M + H_2O+OH]^-$.

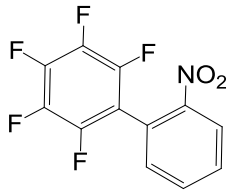
Elemental analysis (%): $C_{37}H_{44}N_4O_9$, calcd. C 64.52, H 6.44, N 8.13; found C 64.14, H 6.30, N 7.92.

X-ray quality crystals were obtained from DMSO: CCDC-929585, $C_{37}H_{44}N_4O_9$ 2(C_2H_6OS); Mr = 845.02; crystal size 0.24 × 0.09 × 0.04 mm^3; Triclinic; space group $P\bar{1}$; a = 11.9166(16) Å, b = 13.5384(18) Å, c = 13.9031(19) Å; β = 73.138(3)°; V = 2123.8(5) Å^3; Z = 2; $\rho_{calcd.}$ = 1.321 g cm^{-3}; μ = 0.19 mm^{-1}; F(000) = 900.0; 26044 collected reflections (θ_{max} = 26.570°) of which 8807 were independent (R_{int} = 0.069); T_{max} = 0.993; T_{min} = 0.956; T = 100 K; full-matrix least-square on F^2 with 7 restraint and 551 parameters; GOF = 1.050; $R1$ = 0.0552($I > 2\sigma$(I)); $\omega R2$ (all

data) = 0.1254; peak/hole = 0.57/-0.38 eÅ^{-3}.

1.25. Synthesis of compound **25**.

2,3,4,5,6-pentafluoro-2'-nitro-1,1'-biphenyl



To a two-neck round bottom flask equipped with a stirring bar under an atmosphere of nitrogen were successively added C_6F_5H (0.448 mL, 4.0 mmol), 2-nitrobenzoic acid (1.002 g, 6.0 mmol), Ag_2CO_3 (4.48 g, 12.0 mmol), $PdCl_2$ (142 mg, 0.8 mmol), PPh_3 (418 mg, 1.6 mmol) and DMSO (20 mL). The reaction mixture was stirred and heated at 130°C for 12 h, and then cooled to room temperature. The mixture was diluted with CH_2Cl_2 and filtered through Celite. The organic phase was washed with saturated NH_4Cl solution, dried with $MgSO_4$, filtered, and concentrated via *vacuo*. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/hexane = 1/1) to afford 500 mg of the product in 43% yield.

Yield: 500 mg (M = 289.16 g mol^{-1}, n = 1.73 mmol, 43%)

M.p. 82 – 83 ℃.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.24 (dd, 1 H), 7.77 (td, 1 H), 7.70 (m, 1 H), 7.45 (d, 1 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 148.38, 144.61, 142.97, 140.39, 138.55, 136.86, 133.63, 133.00, 130.85, 125.45, 121.49, 112.60.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -141.24, -141.25, -141.29, -141.31, (dd, 2 F), -153.34, -153.39, -153.45 (t, 1 F), -161.44, -161.46, -161.50, -161.52, -161.56, -161.58 (td, 2 F).

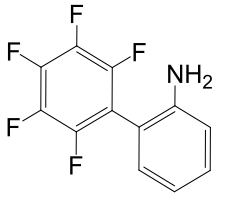
IR (KBr): 3105, 2868, 1656, 1574, 1491, 1439, 1347, 1092, 1055, 981, 839, 791, 729, 688.

MS (EI): m/z (%) = 289.1 (100.00), M^+.

Elemental analysis (%): $C_{12}H_4NF_5O_2$, calcd. C 49.84, H 1.39, N 4.84; found C 49.34, H 1.50, N 4.73.

1.26. Synthesis of compound **26a** and **26b**.

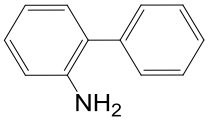
26a



A mixture of 2,3,4,5,6-pentafluoro-2'-nitro-1,1'-biphenyl (253 mg, 0.875 mmol) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C (30 mg) was stirred at room temperature under an atmosphere of hydrogen (20 bar) overnight. The solution was filtered through Celite and the filtrate was evaporated to dryness. The residue was used di-

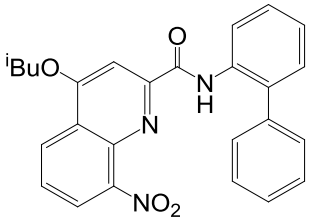
rectly in the next step.

26b



A mixture of 2-nitrobiphenyl (200 mg, 1.0 mmol) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C (30 mg) was stirred at room temperature under an atmosphere of hydrogen (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.

1.27. Synthesis of compound **27**.



To an anhydrous CH_2Cl_2 (20 mL) solution of a mixture of 4-isobutoxy-8-nitro quinoline-2-carboxylic acid **4** (290 mg, 1.0 mmol, 1.0 equiv.) and freshly prepared 2'-aminobiphenyl (1.0 mmol, 1.0 eq.) were successively added DIPEA (1.27 mL), HOBt (270 mg, 2.0 mmol, 2.0 eq.), and EDC·HCl (383 mg, 2.0 mmol, 2.0 eq.). The process was monitored by TLC. Upon completion after stirring for 6 h under nitrogen at room temperature, the reaction mixture was washed with saturated aqueous NH_4Cl solution. The organic extract was dried over Na_2SO_4 and filtered off. Solvent was evaporated to dryness and the residue was purified on silica gel with dichloromethane and hexane (1/1 v/v) or by recrystallization from dichloromethane/MeOH to allow isolation of the compound as a yellow solid.

Yield: 352 mg (M = 441.48 g mol^{-1}, n = 0.80 mmol, 80%).

M.p.: 168-170 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.20 (s, 1 H), 8.57, 8.56 (d, 1 H), 8.45, 8.44 (d, 1 H), 8.04, 8.02 (d, 1 H), 7.84 (s, 1 H), 7.57 (m, 3 H), 7.49 (t, 1 H), 7.45 (m, 3H), 7.33 (dd, 1H), 7.24 (m, 1H), 4.12, 4.11 (d, 2H), 2.29 (m, 1H), 1.13 (d, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.07, 172.24, 164.21, 158.47, 149.59, 148.46, 145.14, 144.37, 141.32, 140.03, 139.76, 139.00, 138.96, 137.24, 136.06, 135.97, 135.42, 134.05, 132.03, 110.71, 86.52, 38.85, 29.92, 10.75.

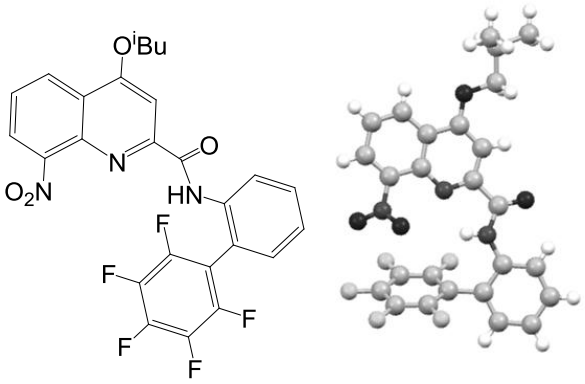
IR (KBr): 3328, 3064, 2971, 2881, 2326, 1897, 1677, 1579, 1523, 1355, 1268, 1207, 1103, 1014, 870, 750, 687 cm^{-1}.

MS (EI): m/z (%) = 441.3(100) $[M]^+$.

Elemental analysis (%): $C_{26}H_{23}N_3O_4 \cdot H_2O$, calcd. C 69.32., H 5.37, N 9.33; found C 69.87, H 4.82, N 9.24.

1.28. Synthesis of compound **28**.

4-Isobutoxy-8-nitroquinoline-2-carboxylic acid 2,3,4,5,6-pentafluoro-2'-biphenylamide



To an anhydrous CH_2Cl_2 (20 mL) solution of a mixture of 4-isobutoxy-8-nitroquinoline- 2-carboxylic acid 4 (254 mg, 0.875 mmol, 1.0 equiv.) and freshly prepared 2,3,4,5,6-pentafluoro-2'-aminobiphenyl (ca. 0.875 mmol, 1.0 eq.) were successively added DIPEA (0.5 mL), HOBt (236 mg, 1.75 mmol, 2.0 eq.), and EDC ·HCl (336 mg, 1.75 mmol, 2.0 eq.). The process was monitored by TLC. Upon completion after stirring for 6 h under nitrogen at room temperature, the reaction mixture was washed with saturated aqueous NH_4Cl solution. The organic extract was dried over Na_2SO_4 and filtered off. Solvent was evaporated to dryness and the residue was purified on silica gel with dichloromethane or by recrystallization from dichloromethane/MeOH to allow isolation of the compound as a colorless solid.

Yield: 409 mg (M = 531.43 g mol^{-1}, n = 0.77 mmol, 88 %).

M.p.: 204-206 ℃.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.98 (s, 1 H), 8.69, 8.68 (d, 1 H), 8.45, 8.43 (d, 1 H), 8.02, 8.00 (d, 1 H), 7.82 (s, 1 H), 7.60 (m, 2 H), 7.28 (m, 2 H), 4.12, 4.11 (d, 2 H), 2.29 (m, 1 H), 1.13, 1.12 (d, 6 H).

^{19}F NMR (564 MHz, $CDCl_3$): δ = -140.17, -140.18, -140.21, -140.22 (dd, 2F), -151.91, -151.95, -151.99 (t, 1F), -160.68, -160.69, -160.72, -160.73, -160.76, -160.77 (td, 2F).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.57, 161.15, 152.61, 147.63, 145.10, 143.44, 139.16, 138.51, 137.48, 136.17, 131.35, 130.70, 126.43, 125.54, 124.83, 124.58, 123.23, 121.09, 117.02, 110.97, 99.72, 75.85, 29.65, 28.05, 19.10.

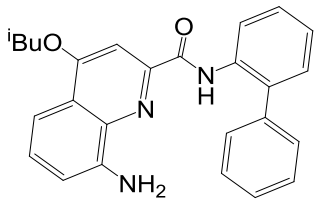
IR (KBr): 3748, 3289, 2974, 2327, 2111, 1691, 1583, 1523, 1497, 1352, 1102, 1058, 1017, 984, 858, 758, 710 cm^{-1}.

MS (CI): m/z (%) = 532.4 (100.00), $[M + H]^+$, 560.5 (12.62), $[M + C_2H_5]^+$.

Elemental analysis (%): $C_{26}H_{18}F_5N_3O_4$, calcd. C 58.76, H 3.41, N 7.91; found C 58.35, H 3.41, N 7.80.

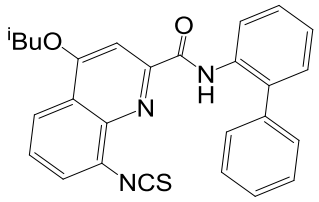
X-ray quality crystals were obtained from MeOH/dichloromethane: $C_{26}H_{18}F_5N_3O_4$; *Mr* = 531.43; crystal size 0.3 × 0.3 × 0.3 mm^3; Triclinic; space group *P*-1, *a* = 9.7294(19) Å, *b* = 10.317(2) Å, *c* = 12.072(2) Å; β = 86.237(8)°; *V* = 1166.0(4) Å^3; *Z* = 2; ρ_{cal} = 1.514 g cm^{-3}; μ = 1.547 mm^{-1}; *F*(000) = 544; 40159 collected reflections (θ_{max} = 66.9°) of which 23523 were independent (R_{int} = 0.061); T_{max} = 0.7530; T_{min} = 0.6235; *T* = 100 (2) K; full-matrix least-square on F^2 with 0 restraint and 416 parameters; GOF = 2.85; *R*1 = 0.061($I > 2\sigma(I)$); $\omega R2$(all data) = 0.036; peak/hole = 1.41/-1.21 e Å^{-3}.

1.29. Synthesis of compound **29**.



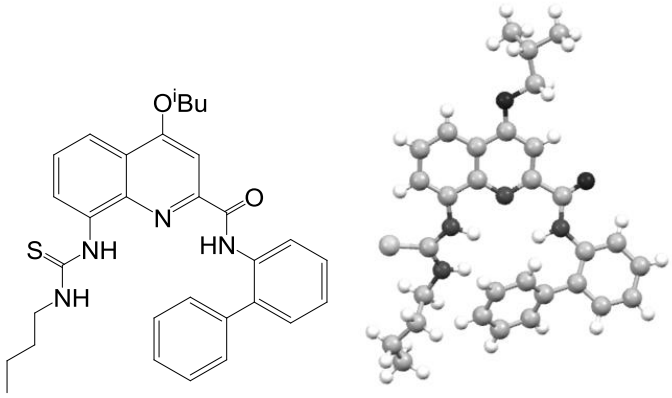
A mixture of **27** (162 mg, 0.367 mmol) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C (30 mg) was stirred at room temperature under an atmosphere of hydrogen (20 bar) overnight. The solution was filtered through Celite and the filtrate was evaporated to dryness. The residue was used directly in the next step.

1.30. Synthesis of compound **30**.



To an anhydrous CH_2Cl_2 (20 mL) solution of **29** (ca. 0.367 mmol, 1.0 eq) was added TCP (102 mg, 0.44 mmol, 1.2 eq). After being stirred for 8 h under nitrogen atmosphere at room temperature, the solvent was evaporated to dryness, and the residue was chromatographed on silica gel with hexane as eluents to allow isolation of **30** as colorless oil, which was used for next reaction without characterization.

1.31. Synthesis of compound **31**.



n-Butylamine (220 μL, 2.22 mmol, 6.0 eq) was added to a solution of **30** (ca. 0.367 mmol) in dry dichloromethane (15 mL) in a round flask filled with nitrogen. The mixture was stirred overnight and then the solvent was evaporated. The residue was chromatographed on silica gel with dichloromethane as an eluent to allow isolation of **31** as a light yellow solid.

Yield: 120 mg (M = 526.69 g mol^{-1}, n = 0.228 mmol, ca. 62%)

M.p.: 178-180 ℃.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.93 (s, 1 H), 8.82 (s, 1 H), 8.67 (s, 1 H), 8.34, 8.33 (d, 1 H), 7.64 (s, 1 H), 7.51 (m, 4 H), 7.41 (m, 3 H), 7.24 (m, 3 H), 6.98 (s, 1 H),

3.84 (d, 1 H), 3.69 (s, 2 H), 2.18 (m, 1 H), 1.71 (m, 2 H), 1.46 (m, 2 H), 1.10, 1.09 (d, 6 H), 0.97 (t, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 179.66, 163.18, 162.85, 149.69, 138.12, 134.85, 133.93, 132.56, 130.20, 129.17, 128.36, 128.07, 126.92, 124.91, 121.84, 121.09, 118.14, 115.89, 75.02, 44.49, 30.98, 28.09, 20.28, 19.15, 13.88.

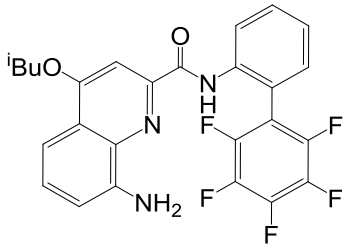
IR (KBr): 3306, 3060, 2959, 2871, 2116, 1665, 1577, 1529, 1452, 1356, 1316, 1259, 1178, 1126, 1031, 811, 753, 694 cm^{-1}.

MS (ESI): m/z (%) = 527.24854 (100.00), $[M + H]^+$.

Elemental analysis (%): $C_{31}H_{34}N_4O_2S$, calcd. C 70.69, H 6.51, N 10.64; found C 70.17, H 6.65, N 10.35.

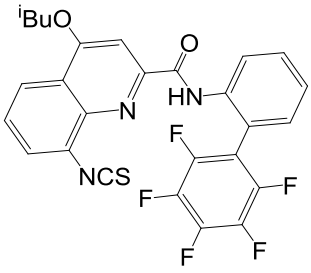
X-ray quality crystals were obtained from MeOH/dichloromethane: $C_{31}H_{34}N_4O_2S$; *Mr* = 526.68; crystal size 0.29 × 0.24 × 0.20 mm^3; Triclinic; space group *P*-1, *a* = 13.6960 (16) Å, *b* = 14.7436 (17) Å, *c* = 15.3268 (18) Å; β = 77.575 (2)°; *V* = 2756.3 (6) $Å^3$; *Z* = 4; ρ_{cal} = 1.269 g cm^{-3}; μ = 0.15 mm^{-1}; *F*(000) = 1120.0; 25303 collected reflections (θ_{max} = 26.59°) of which 11475 were independent (R_{int} = 0.058); T_{max} = 0.970; T_{min} = 0.957; *T* = 100 (2) K; full-matrix least-square on F^2 with 40 restraints and 666 parameters; GOF = 1.05; *R*1 = 0.087 ($I > 2\sigma(I)$); $\omega R2$(all data) = 0.254; peak/hole = 0.61/-0.65 e $Å^{-3}$.

1.32. Synthesis of compound **32**.



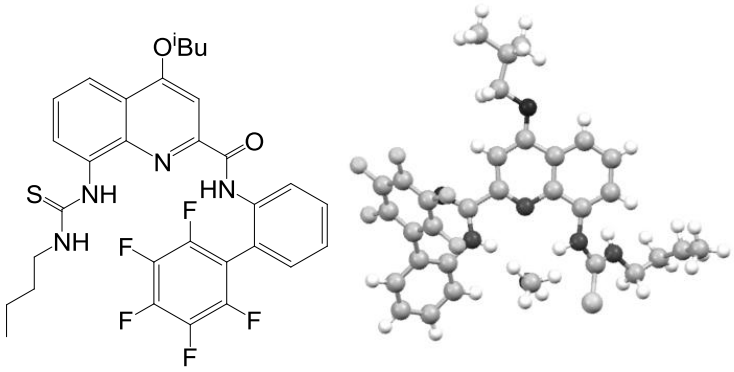
A mixture of **28** (118 mg, 0.222 mmol) dissolved in CH_2Cl_2 (15 mL) and 10% Pd/C (30 mg) was stirred at room temperature under an atmosphere of hydrogen (20 bar) overnight. The solution was filtered through Celite and the filtrate was evaporated to dryness. The residue was used directly in the next step.

1.33. Synthesis of compound **33**.



To an anhydrous CH_2Cl_2 (20 mL) solution of **29** (ca. 0.222 mmol, 1.0 eq) was added TCP (62 mg, 0.266 mmol, 1.2 eq). After being stirred for 8 h under nitrogen atmosphere at room temperature, the solvent was evaporated to dryness, and the residue was chromatographed on silica gel with hexane as an eluent to allow isolation of **33** as colorless oil, which was used for next reaction without characterization.

1.34. Synthesis of compound **34**.



n-Butylamine (110 μL, 1.11 mmol, 5.0 eq) was added to a solution of **30** (0.222 mmol, 1.0 eq) in dry dichloromethane (15 mL) in a round flask filled with nitrogen. The mixture was stirred overnight and then the solvent was evaporated. The residue was chromatographed on silica gel with dichloromethane as an eluent to allow isolation of **34** as a light yellow solid.

Yield: 87 mg (M = 616.64 g mol^{-1}, n = 0.141 mmol, ca. 44%)

M.p.: 138-140 ℃.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.74 (s, 1 H), 8.63 (s, 1 H), 8.06, 8.02 (m, 3 H), 7.71 (s, 1 H), 7.55 (m, 2 H), 7.37 (m, 2 H), 6.49 (s, 1 H), 4.06, 4.05 (d, 2 H), 3.65 (m, 2 H), 2.27 (m, 1 H), 1.61 (m, 2 H), 1.35 (m, 2 H), 1.13, 1.12 (d, 6 H), 0.93, 0.91, 0.90 (t, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 180.47, 163.77, 162.37, 150.08, 135.58, 134.19, 131.82, 130.55, 127.02, 125.97, 125.09, 120.05, 118.07, 99.78, 75.58, 30.88, 28.17, 20.18, 19.21.

IR (KBr): 3327, 3066, 2970, 2324, 2105, 1899, 1678, 1579, 1514, 1353, 1267, 1206, 1162, 1113, 1014, 870, 816, 748, 687 cm^{-1}.

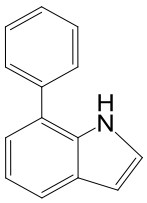
MS (ESI): m/z (%) = 57.5 (100.00), $[C_4H_9]^+$; 501.3 (35.23), $[C_{26}H_{20}F_5N_3O_2]^+$; 543.4 (14.70), $[C_{27}H_{18}F_5N_3O_2S]^+$, 616.5 (13.56), $[M]^+$.

Elemental analysis (%): $C_{31}H_{29}N_4F_5O_2S$ $0.5H_2O$, calcd. C 59.51, H 4.83, N 8.95; found C 59.44, H 4.37, N 8.71.

X-ray quality crystals were obtained from MeOH/dichloromethane: $C_{31}H_{29}N_4F_5O_2S$; *Mr* = 616.64; crystal size 0.272 × 0.335 × 0.806 mm^3; Triclinic; space group *P*-1, *a* = 8.1926 (9) Å, *b* = 13.4425 (16) Å, *c* = 16.253 (3) Å; β = 97.983 (3)°; *V* = 1575.4 (4) Å^3; *Z* = 2; ρ_{cal} = 1.367 g cm^{-3}; μ = 0.178 mm^{-1}; *F*(000) = 676; 83520 collected reflections (θ_{max} = 26.3°) of which 46227 were independent (R_{int} = 0.053); T_{max} = 0.7453; T_{min} = 0.5955; *T* = 100 (2) K; full-matrix least-square on F^2 with 40 restraints and 666 parameters; GOF = 5.17; *R*1 = 0.085 ($I > 2\sigma(I)$); $\omega R2$(all data) = 0.09; peak/hole = 2.47/-1.14 e Å^{-3}.

1.35. Synthesis of compound **35**.

7-phenyl-1H-indole (**35**) [116]



To a two-neck round bottom flask equipped with a stirring bar under an atmosphere of nitrogen in the presence of dry methanol were successively added potassium phenyltrifluoroborate (92 mg, 0.5 mmol), 7-bromo-1*H*-indole (98 mg, 0.5 mmol), K_2CO_3 (204 mg, 1.5 mmol), and $Pd(OAc)_2$ (10 mg, 0.045 mmol). The reaction mixture was stirred and heated at flux for 12 h, and then cooled to room temperature and diluted with water. The solvent was evaporated, washed with brine, extracted with CH_2Cl_2, and the organic extract was dried over $MgSO_4$. Solvents were evaporated to dryness and the residue was purified on silica gel with dichloromethane as an eluent. The product was provided as a pale yellow solid in 47% (45 mg, 0.23 mmol).

Yield: 45 mg (M = 193.24 g mol^{-1}, n = 0.23 mmol, 47%)

M.p.: 62 – 63 ℃.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.97 (s, 1H), 7.66 (m, 1H), 7.64 (m, 1H), 7.53 (m, 3H), 7.41 (m, 1H), 7.31 (t, 1H), 7.11 (m, 2H), 6.53 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.27, 133.72, 129.13, 128.26, 128.22, 127.39, 125.59, 124.31, 121.88, 120.30, 120.03.

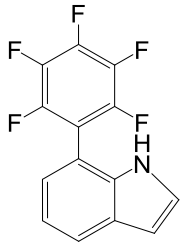
IR (KBr): 3437, 3045, 1594, 1481, 1413, 1335, 1076, 995, 800, 759, 706 cm^{-1}.

MS (EI): m/z (%) = 193.2 (100.00), M^+.

Elemental analysis (%): $C_{14}H_{11}N$, calcd. C 87.01, H 5.74, N 7.25; found C 86.66, H 5.58, N 7.12.

1.36. Synthesis of compound **36**.

7-(2,3,4,5,6-pentafluorophenyl)-1H-indole (**36**)[120]:



Vinylmagnesium bromide (3.34 mL, 2.34 mmol) was quickly added to a stirred freshly dried THF solution of 2,3,4,5,6-pentafluoro-2'-nitrobiphenyl (225 mg, 0.778 mmol) cooled to -40 °C (dry ice/acetonitrile), under nitrogen. The reaction mixture was stirred for 30 minutes and then poured into saturated aqueous NH_4Cl solution, extracted with ether and dried over anhydrous sodium sulphate. Solvent was evaporated to dryness and the residue was purified on silica gel with hexane/dichloromethane (v/v, 5/2) to allow isolation of the compound as a light brown yellow solid.

Yield: 176 mg (M = 283.20 g mol^{-1}, n = 0.622 mmol, 80%).

M.p.: 111 - 113 ℃.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.11 (s, 1 H), 7.75 - 7.69 (m, 1 H), 7.43,

7.42, 7.41(t, 1 H), 7.16 - 7.14 (d, 2 H), 6.56 - 6.55 (m, 1 H).

^{19}F NMR (282 MHz, DMSO-d_6): δ = -140.08, -140.10, -140.16, -140.19 (dd, 2 F), -157.00, -157.08, -157.15 (t, 1 F), -162.79, -162.82, -162.88, -162.90, -162.96, -162.98 (td, 2 F).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.81, 128.71, 124.74, 124.49, 122.52, 119.83, 103.32.

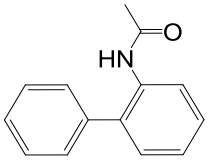
IR (KBr): 3424, 2125, 1650, 1489, 1430, 1334, 1087, 982, 855, 806, 723 cm^{-1}.

MS (EI): m/z (%) = 283.2 (100%) [M, $C_{14}H_6F_5N$]$^+$.

Elemental analysis (%): $C_{14}H_6F_5N$ (283.04), calcd. C 59.38, H 2.14, N 4.95; found: C 58.97, H 2.34, N 4.78.

1.37. Synthesis of compound **37**.

N-(biphenyl-2-yl)acetamide (**37**)



A mixture of 2-nitrobiphenyl (246 mg, 1.23 mmol) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C (30 mg) was stirred at room temperature under an atmosphere of hydrogen (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.

To a solution of 2-aminobiphenyl (ca. 1.23 mmol) in CH_2Cl_2 (25 mL) was added pyridine (0.15 mL) and acetyl chloride (0.105 mL) at 0 ℃ under nitrogen atmosphere. The reaction mixture was warmed to rt and stirred overnight. The solvent was removed *in vacuo*. The residue was washed with water, extracted with CH_2Cl_2, and purified on silica gel with dichloromethane/hexane (1/1) as an eluent. The product was provided as a yellow solid.

Yield: 204 mg (M = 211.26 g mol^{-1}, n = 0.97 mmol, ca. 79%)

M.p.: 120 – 121 ℃.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.27, 8.26 (d, 1H), 7.50, 7.49, 7.48 (t, 2H), 7.43, 7.42, 7.41 (t, 1H), 7.37 (m, 3H), 7.24 (m, 1H), 7.18 (t, 1H), 7.13 (s, 1H), 2.02 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.20, 138.14, 134.67, 132.15, 130.03, 129.22, 129.08, 128.41, 127.96, 124.34, 121.62, 24.60.

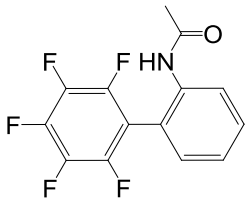
IR (KBr): 3283, 3028, 2321, 1962, 1656, 1530, 1433, 1369, 1298, 1006, 741, 699 cm^{-1}.

MS (CI): m/z (%) = 212.2(100.00), M$^+$, 240.2(13.31), [M + C_2H_5]$^+$, 169.1(16.83), $C_{12}H_{11}N^+$.

Elemantal analysis (%): $C_{14}H_{13}NO$, calcd. 79.59, H 6.20, N 6.63; found C 79.72, H 5.71, N 6.28.

1.38. Synthesis of compound **38**.

N-(2,3,4,5,6-pentafluorobiphenyl-2′-yl)acetamide (**38**)



The synthesis of **38** was performed similar to that of **37**. It was purified on silica gel with dichloromethane as an eluent. The product was provided as a solid in 83% (132 mg, 0.438mmol).

Yield: 132 mg (M = 301.21 g mol^{-1}, n = 0.438 mmol, ca. 83%)

M.p.: 184 – 185 ℃.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.39 (s, 1H), 7.60 (d, 1H), 7.47 (m, 1H), 7.33(m, 2H), 1.85(s, 3H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 168.64, 145.10, 143.64, 141.20, 138.28, 137.38, 136.75, 131.53, 130.55, 125.75, 125.50, 120.53, 114.04, 23.46.

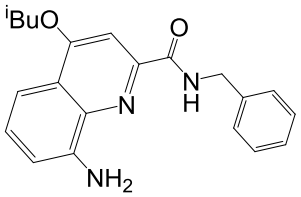
^{19}F NMR (376 MHz, DMSO-d_6): δ = -140.91, -140.93, -140.98, -141.00(dd, 2F), -156.65, -156.71, -156.77(t, 1F), -163.42, -163.44, -163.48, -163.50, -163.54, -163.56(td, 2F).

IR (KBr): 3249, 2997, 1663, 1495, 1450, 1292, 1059, 981, 862, 838, 753, 682 cm^{-1}.

MS (CI): m/z (%) = 302.1(100.00), $[M+H]^+$, 330.2(15.92). $[M + C_2H_5]^+$.

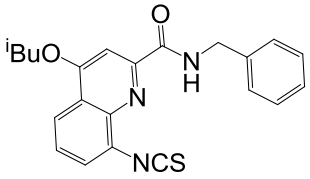
Elemental analysis (%): $C_{14}H_8F_5NO$, calcd. 55.82, H 2.68, N 4.65; found C 55.90, H 2.89, N 4.35.

1.39. Synthesis of compound **39**.



A mixture of **8** (230 mg, 0.61 mmol) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C (75 mg) was stirred at room temperature under an atmosphere of hydrogen (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.

1.40. Synthesis of compound **40**.

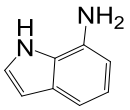


To an anhydrous CH_2Cl_2 (20 mL) solution of **39** (ca. 0.61 mmol, 1.0 eq) was added TCP (169 mg, 0.73 mmol, 1.2 eq). After being stirred for 8 h under nitrogen atmosphere at room temperature, the solvent was evaporated to dryness, and the residue was chromatographed on silica gel with hexane as an eluent to allow isolation of

40 as colorless oil, which was characterized with ^{1}H NMR and used for next reaction without characterization.

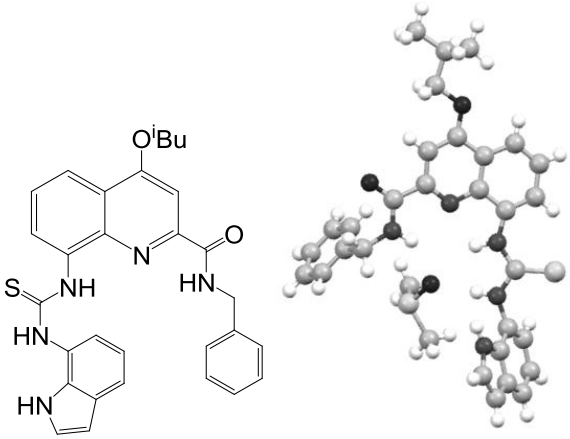
^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.80 (t, 1 H), 8.15, 8.15, 8.13, 8.12 (dd, 1 H), 7.78 (s, 1 H), 7.42 (m, 7 H), 4.73, 4.71 (d, 2 H), 4.11, 4.08 (d, 2 H), 2.29 (m, 1 H), 1.14, 1.12 (d, 6 H).

1.41. Synthesis of compound **41**.



A mixture of 7-nitroindole (99 mg, 0.61 mmol) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C (30 mg) was stirred at room temperature under an atmosphere of hydrogen (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.

1.42. Synthesis of compound **42**.



7-aminoindole **41** (ca. 0.61 mmol, 1.0 eq) was added to a solution of **40** (ca. 0.61 mmol) in dry dichloromethane (15 mL), in a round bottom flask filled with nitrogen. The mixture was stirred overnight and then the solvent was evaporated. The residue was chromatographed on silica gel with dichloromethane as an eluent to allow isolation of **42** as a light yellow solid.

Yield: 50 mg (M = 523.65 g mol^{-1}, n = 0.095 mmol, 16%)

M.p.: 168-169 ℃.

^{1}H NMR (600 MHz, DMSO-d_6) : δ = 11.17 (s, 1 H), 10.62 (s, 1 H), 10.42 (s, 1 H), 9.53, 9.52 (d, 1 H), 9.29 (w, 1 H), 7.86, 7.85 (d, 1 H), 7.70 (s, 1 H), 7.65, 7.63, 7.62 (t, 1 H), 7.48, 7.47 (s, 1 H), 7.32 (m, 5 H), 7.24, 7.23, 7.22 (t, 1 H), 7.17, 7.16 (d, 1 H), 7.02, 7.01, 6.99 (t, 1 H), 6.47, 6.47, 6.46 (t, 1 H), 4.65, 4.64 (d, 2 H), 4.14, 4.13 (d, 2 H), 2.20 (m, 1 H), 1.08, 1.07 (d, 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.

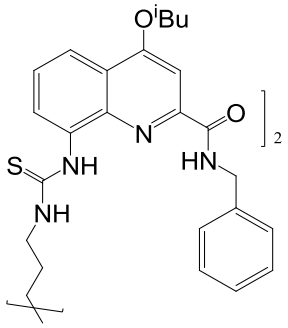
IR (KBr): 3405, 3263, 2962, 2031, 1668, 1535, 1422, 1345, 1218, 1163, 1057, 954, 860, 790, 727 cm^{-1}.

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), $[C_{22}H_{21}N_3O_2S]$.

Elemental analysis (%): $C_{30}H_{29}N_5O_2S$, calcd. C 68.81, H 5.58, N 13.37; found C 68.26, H 5.65, N 13.25.

X-ray quality crystals were obtained from DMSO: $C_{30}H_{29}N_5O_2S$ $(CH_3)SO$; *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; $\beta = 90^\circ$; *V* = 12382.3 (15) $Å^3$; *Z* = 16; ρ_{cal} = 1.291 g cm^{-3}; μ = 0.21 mm^{-1}; *F*(000) = 5088; 36864 collected reflections ($\theta_{max} = 22.2306^\circ$) 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 ($I > 2\sigma(I)$); $\omega R2$(all data) = 0.088; peak/hole = 0.21/-0.17 e $Å^{-3}$.

1.43. Synthesis of compound **43**.



1,6-diaminohexane (27 mg, 0.23 mmol, 1.0 eq) was added to a solution of **40** (ca. 0.46 mmol) in dry dichloromethane (15 mL), in a round flask filled with nitrogen. The mixture was stirred overnight and then the solvent was evaporated. The residue was recrystallized from methanol/dichloromethane (v/v 1/2) as to allow isolation of **43** as a light yellow solid.

Yield: 124 mg (M = 899.18 g mol^{-1}, n = 0.138 mmol, ca. 60%)

M.p. 219 – 221 ℃.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.29 (s, 2 H), 9.69 (s, 2 H), 9.16, 9.14 (dd, 2 H), 8.75 (s, 2 H), 7.84, 7.83, 7.81, 7.81 (dd, 2 H), 7.66 (s, 2 H), 7.62, 7.59, 7.59 (t, 2 H), 7.34 (m, 10 H), 4.65, 4.63 (d, 4 H), 4.16, 4.14 (d, 4 H), 3.54 (s, 4 H), 2.22 (m, 2 H), 1.60 (s, 4 H), 1.38 (m, 4 H), 1.10, 1.08 (d, 12 H).

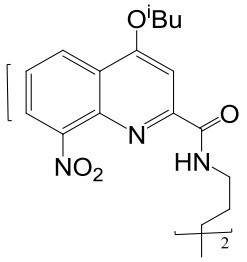
^{13}C NMR (151 MHz, DMSO-d_6): δ = 180.19, 164.38, 163.10, 149.88, 139.67, 138.78, 136.55, 128.71, 127.64, 127.30, 121.80, 119.10, 114.93, 99.64, 75.07, 43.80, 42.99, 28.67, 28.10, 26.64, 19.40.

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

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

Elemental analysis (%): $C_{50}H_{58}N_8O_4S_2 \cdot H_2O$, calcd. C 65.48, H 6.59, N 12.22; found C 65.03, H 6.45, N 12.15.

1.44. Synthesis of compound **44**.



A solution of the acid **4** (482 mg, 1.66 mmol, 1.0 eq) in excess $SOCl_2$ was heated to reflux for 3 h. The $SOCl_2$ was flushed using nitrogen 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 1,6-diaminohexane (77.1 mg, 0.66 mmol, 0.5 eq) and DIPEA (5.5 eq) in CH_2Cl_2 (10 mL) at 0 ℃. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed and the residue was purified by flash chromatography on silica gel eluting with $CH_2Cl_2/CH_3COOC_2H_5$ (15:1) to afford the pure product **44** as a light yellow solid.

Yield: 350 mg (M = 660.72 g mol^{-1}, n = 0.53 mmol, 80%).

Melting point: 202-204 ℃.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49, 8.49, 8.46, 8.46 (dd, 2 H), 8.26, 8.24, 8.22 (t, 2 H), 8.12, 8.12, 8.09, 8.09 (dd, 2 H), 7.80 (s, 2 H), 7.63, 7.61, 7.58 (t, 2 H), 4.13, 4.10 (d, 4 H), 3.53 (m, 4 H), 2.30 (m, 2 H), 1.71 (m, 4 H), 1.50 (, 4 H), 1.15, 1.12 (d, 12 H).

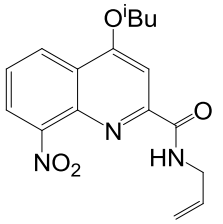
^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.49, 163.17, 153.38, 126.67, 125.03, 123.22, 99.97, 39.60, 29.47, 28.06, 26.61, 19.15.

IR (KBr): 3781, 3395, 3292, 2931, 2089, 1673, 1526, 1350, 1226, 1138, 1012, 870, 824, 749, 668 cm^{-1}.

MS (ESI): m/z (%) = 683.27277 (100.00), $[M + Na]^+$.

Elemental analysis (%): $C_{34}H_{40}N_6O_8$, calcd. C 61.81, H 6.10, N 12.72; found C 61.57, H 5.98, N 12.72.

1.45. Synthesis of compound **45**.



A solution of the acid **4** (250 mg, 0.86 mmol, 1.0 eq) in an excess of $SOCl_2$ was heated to reflux for 3 h. The $SOCl_2$ was flushed using nitrogen 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 3-aminopropene (0.128 mL, 1.72 mmol, 2.0 eq) and triethylamine (5.5 eq) in CH_2Cl_2 (10 mL) at 0 ℃. The reaction mixture was allowed to warm to room temperature 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 **45** as a light yellow solid.

Yield: 260 mg (M = 329.14 g mol^{-1}, n = 0.79 mmol, 92%).

Meilting point: 105-106 ℃.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51, 8.51, 8.48, 8.48 (dd, 1H), 8.30 (t, 1 H), 8.13, 8.13, 8.10, 8.10 (dd, 1 H), 7.81 (s, 1 H), 7.66, 7.63, 7.60 (t, 1 H), 5.97 (m, 1 H), 5.28 (m, 2 H), 4.13 (m, 4 H), 2.30 (m, 1 H), 1.15, 1.13 (d, 6 H).

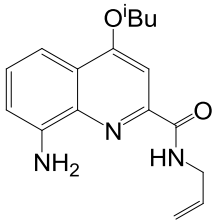
^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.46, 163.19, 153.13, 147.69, 138.91, 133.59, 126.65, 125.15, 124.95, 123.26, 116.46, 99.98, 91.88, 41.98, 28.06, 19.13.

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

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

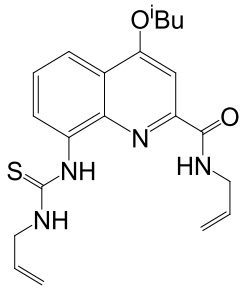
Elemental analysis (%): $C_{17}H_{19}N_3O_4$, calcd. C 62.00, H 5.81, N 12.76; found C 62.12, H 5.63, N 12.75.

1.46. Synthesis of compound **46**.



Iron powder (220 mg, 3.93 mmol, 13.0 eq) and concd. hydrochloric acid (ca. 14 mL) were added to a solution of nitroquinoline **45** (100 mg, 0.304 mmol, 1.0 eq) in EtOH (10 mL) and water (ca. 2 mL) and the mixture was heated to reflux for 90 min. After the mixture was cooled to room temperature, DCM was added to the mixture, and it was dried with $MgSO_4$. After filtration through Celite and evaporation of the solvent, the residue was used directly in the next step without further purification and characterization.

1.47. Synthesis of compound **47**.



3-Isothiocyanato-1-propene (0.090 mL, 0.912 mmol, 3.0 eq) was added to a solution of **46** (ca. 0.304 mmol, 1.0 eq) in dry DCM (15 mL)/EtOH (15 mL), in a round flask filled with nitrogen. 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/Ethyl acetate (15/1, v/v) to afford the pure product **47** as a light yellow solid.

Yield: 65 mg (M = 398.52 g mol^{-1}, n = 0.163 mmol, 54%)

M.p.: 177 – 178 ℃.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.30(s, 1 H), 9.27, 9.26, 9.25(t, 1 H), 9.20, 9.20, 9.18, 9.18(dd, 1 H), 8.88, 8.86, 8.85(t, 1 H), 7.82, 7.82, 7.80, 7.80(dd, 1 H), 7.62, (s, 1 H) 7.59, 7.57, 7.55(t, 1 H), 5.95(m, 2 H), 5.17(m, 4 H), 4.25, 4.24, 4.23(t, 2 H), 4.12, 4.11(d, 1 H), 4.05, 4.04, 4.02(t, 2 H), 2.19(m, 1 H), 1.07, 1.05(d, 6 H).

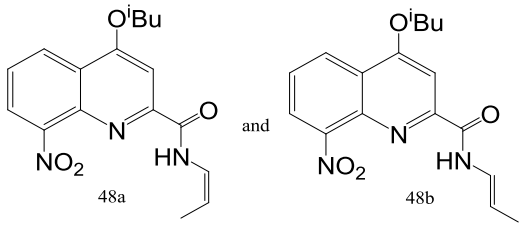
^{13}C NMR (151 MHz, $CDCl_3$): δ = 180.54, 164.17, 163.48, 150.25, 139.53, 134.20, 133.72, 132.80, 126.66, 122.81, 120.20, 117.97, 117.70, 116.73, 99.71, 75.36, 47.48, 42.12, 28.08, 19.13.

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

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), $[M]^+$.

Elemental analysis (%): $C_{21}H_{26}N_4O_2S$, calcd. C 63.29, H 6.58, N 14.06; found C 63.09, H 6.74, N 13.80.

1.48. Synthesis of compound **48**.



48a 48b

The 2nd generation Grubbs' catalyst (19 mg, 0.0228 mmol, 0.15 eq) was added to a solution of **45** (50 mg, 0.152 mmol, 1.0 eq) in dry DCM (15 mL) in a round flask filled with nitrogen. The mixture was stirred overnight, and then the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with CH_2Cl_2 to afford a mixture of **48a** and **48b** as a light yellow solid.

Yield: 20 mg (M = 329.35 g mol^{-1}, n = 0.0607 mmol, 40%)

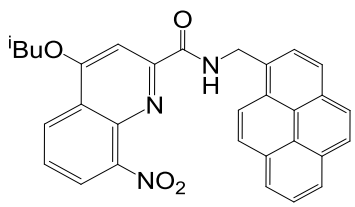
^{1}H NMR (300 MHz, $CDCl_3$) for **isomer 1**: δ = 10.02, 9.98 (d, 1H), 8.53, 8.53, 8.50, 8.50 (dd, 1H), 8.21, 8.21, 8.19, 8.18 (dd, 1H), 7.79 (s, 1H), 7.65 (m, 1H), 6.91 (m, 1H), 5.06(m, 1H), 4.14, 4.12(d, 2H), 2.31(m, 1H), 1.86, 1.86, 1.84, 1.83 (dd, 2H), 1.16, 1.14 (d, 6H).

For **isomer 2**: δ = 9.61, 9.57 (d, 1H), 8.51, 8.51, 8.48, 8.48 (dd, 1H), 8.15, 8.15, 8.12, 8.12 (dd, 1H), 7.79 (s, 1H), 7.62 (m, 1H), 6.91 (m, 1H), 5.55(m, 1H), 4.13, 4.11(d, 2H), 2.31(m, 1H), 1.81, 1.80, 1.78, 1.78 (dd, 2H), 1.16, 1.13 (d, 6H).

n (**isomer 1**) / n (i**somer 2**) = 3/2

MS (CI): m/z (%) = 330.4 (100.00), $[M + H]^+$; 358.3 (10.48), $[M + C_2H_5]^+$.

1.49. Synthesis of compound **49**.



To an anhydrous CH_2Cl_2 (20 mL) solution of a mixture of

4-isobutoxy-8-nitroquinoline-2-carboxylic acid **4** (232 mg, 0.8 mmol, 0.8 equiv.) and 1-Pyrenemethylamine hydrochloride (267 mg, 1.0 mmol, 1.0 eq.) were successively added DIPEA (0.5 mL), HOBt (135.13 mg, 1.0 mmol, 1.0 eq.), and EDC·HCl (191 mg, 1.0 mmol, 1.0 eq.). The process was monitored by TLC. Upon completion after stirring for 6 h under nitrogen at room temperature, the reaction mixture was washed with saturated aqueous NH_4Cl solution. The organic extract was dried over Na_2SO_4 and filtered off. Solvent was evaporated to dryness and the residue was purified by recrystallization from dichloromethane/MeOH (v/v 2/1) to allow isolation of the compound as a light yellow solid.

Yield: 300 mg (M = 503.18g mol^{-1}, n = 0.60 mmol,75 %).

M.p.: 210-212 ℃.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.75, 8.73, 8.71 (t, 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, 5.44 (d, 2 H), 4.15, 4.13 (d, 2 H), 2.31 (m, 1 H), 1.16, 1.13 (d, 6 H).

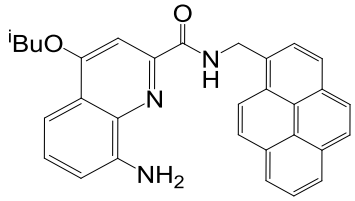
^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.32, 163.44, 163.20, 153.09, 147.58, 138.93, 131.26, 131.11, 130.93, 130.76, 128.84, 128.16, 127.39, 126.68, 126.55, 125.92, 125.23, 125.13, 124.91, 123.30, 122.71, 100.10, 41.78, 28.07, 19.14.

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

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), $[M]^+$

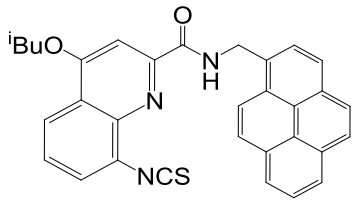
Elemental analysis (%): $C_{31}H_{25}O_4N_3$, calcd. C 73.94, H 5.00, N 8.34; found C 73.39, H 5.11, N 8.09.

1.50. Synthesis of compound **50**.



A mixture of **49** (85 mg, 0.169 mmol, 1.0 eq) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C (30 mg) was stirred at room temperature under an atmosphere of hydrogen (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.

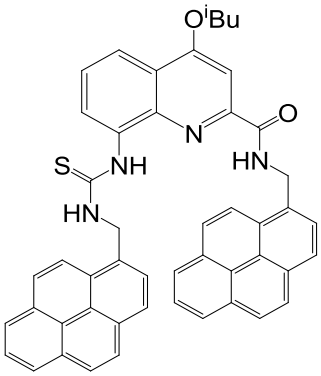
1.51. Synthesis of compound **51**.



To an anhydrous CH_2Cl_2 (20 mL) solution of **50** (ca. 0.169 mmol, 1.0 eq) was added TCP (43 mg, 0.186 mmol, 1.1 eq). After being stirred for 8 h under nitrogen atmosphere at room temperature, the solvent was evaporated to dryness, and the resi-

due was chromatographed on silica gel with hexane as an eluent to allow isolation of **51** as a yellow solid, which was used for next reaction without characterization.

1.52. Synthesis of compound **52**.



To an anhydrous CH_2Cl_2 (20 mL) solution of 1-Pyrenemethylamine hydrochloride (75 mg, 10.279 mmol, 1.5 eq.) were successively added DIPEA (0.5 mL), and **51** (ca. 0.169 mmol, 1.0 eq) in a round flask filled with nitrogen. The mixture was stirred overnight and then the solvent was evaporated. The residue was chromatographed on silica gel with dichloromethane as an eluent to allow isolation of **52** as a light yellow solid.

Yield: 63 mg (M = 746.92 g mol^{-1}, n = 0.084 mmol, ca. 50%)

M.p.: 186-188 ℃.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.49 (s, 1 H), 9.72 (t, 1 H), 9.33, 9.30 (d, 1 H), 9.21, 9.20, 9.18 (t, 1 H), 8.42, 8.39 (d, 2 H), 8.33, 8.30 (d, 1 H), 8.24 (m, 4 H), 8.08 (m, 8 H), 7.93 (m, 3 H), 7.84, 7.81 (d, 1 H), 7.66 (m, 2 H), 5.52, 5.51 (d, 2 H), 5.25, 5.23 (d, 2 H), 4.12, 4.10 (d, 2 H), 2.18 (m, 1 H), 1.08, 1.06 (d, 6 H).

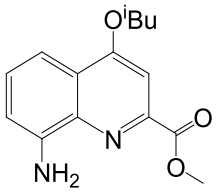
^{13}C NMR (151 MHz, DMSO-d_6): δ = 163.18, 138.91, 136.36, 136.32, 132.67, 131.99, 131.16, 130.74, 130.60, 130.42, 128.93, 128.34, 127.73, 127.43, 126.64, 125.87, 125.77, 125.69, 125.55, 125.20, 124.98, 123.60, 123.43, 121.85, 119.25, 115.37, 99.75, 75.15, 45.83, 28.09, 19.38.

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

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

Elemental analysis (%): $C_{49}H_{38}N_4O_2S$ 0.5H_2O, calcd. C 77.85, H 5.20, N 7.41; found C 77.83, H 4.85, N 7.24.

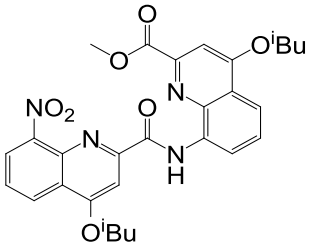
1.53. Synthesis of compound **53**.



A mixture of **3** (220 mg, 0.73 mmol, 1 equiv.) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C (30 mg) was stirred at room temperature under an atmosphere of hydrogen

(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.

1.54. Synthesis of compound **54**.



A solution of the acid **4** (220 mg, 0.73 mmol, 1.0 eq) in an excess of $SOCl_2$ was heated to reflux for 3 h. The $SOCl_2$ was flushed using nitrogen 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 **53** (ca. 0.73 mmol, 1.0 eq) and triethylamine (5.5 eq) in CH_2Cl_2 (10 mL) at 0 ℃. The reaction mixture was allowed to warm to room temperature 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 **54** as a light yellow solid.

Yield: 370 mg (M = 546.57 g mol^{-1}, n = 0.68 mmol, 93%).

Meilting point: 200-201 ℃.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.88 (s, 1 H), 9.11, 9.08 (d, 1 H), 8.55, 8.52 (d, 1 H), 8.21, 8.19 (d, 1 H), 8.04, 8.01 (d, 1 H), 7.96 (s, 1 H), 7.63 (m, 3 H), 4.23 (s, 3 H), 4.18, 4.16 (d, 2 H), 4.09, 4.07 (d, 2 H), 2.34 (m, 2 H), 1.17 (m, 12 H).

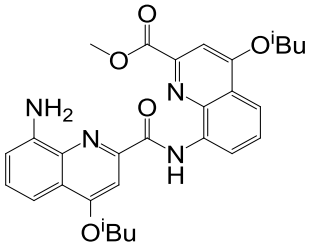
^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.51, 166.91, 163.21, 162.75, 162.48, 153.98, 148.34, 134.87, 127.81, 126.68, 125.40, 118.74, 116.69, 101.48, 100.24, 53.64, 28.19, 19.19.

IR (KBr): 3312, 2961, 1717, 1670, 1592, 1518, 1417, 1344, 1266, 1111, 1028, 911, 867, 826, 736, 671 cm^{-1}.

MS (ESI): m/z (%) = 547.41 (100.00), $[M + H]^+$.

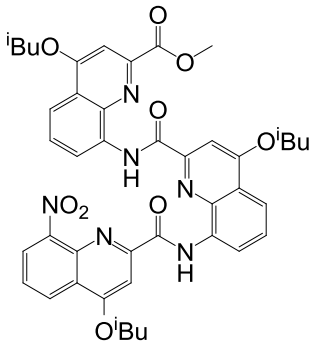
Elemental analysis (%): $C_{29}H_{30}N_4O_7$ 0.5 H_2O, calcd. C 62.69, H 5.62, N 10.08; found C 62.67, H 5.49, N 10.03.

1.55. Synthesis of compound **55**.



A mixture of **54** (128 mg, 0.24 mmol, 1.0 equiv.) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C (30 mg) was stirred at room temperature under an atmosphere of hydrogen (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.

1.56. Synthesis of compound **56**.



A solution of the acid **4** (70 mg, 0.24 mmol, 1.0 eq) in an excess of $SOCl_2$ was heated to reflux for 3 h. The $SOCl_2$ was flushed using nitrogen 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 **55** (ca. 0.24 mmol, 1.0 eq) and triethylamine (5.5 eq) in CH_2Cl_2 (10 mL) at 0 ℃. The reaction mixture was allowed to warm to room temperature 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 **56** as a light yellow solid.

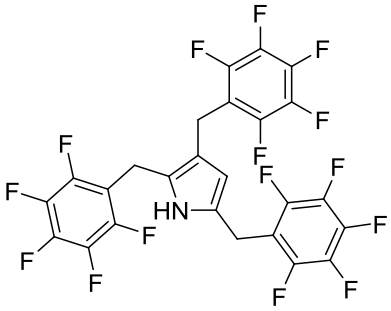
Yield: 75 mg (M = 788.84 g mol^{-1}, n = 0.095 mmol, 40%).

Meilting points:161-163 ℃.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.24, 12.21(d, 2 H), 9.02(m, 2 H), 8.49, 8.48, 8.46, 8.45(dd, 1 H), 8.07, 8.07, 8.05, 8.04(dd, 1 H), 7.92(m, 2 H), 7.84(s, 1 H), 7.70(m, 2 H), 7.57, 7.57, 7.54, 7.54(dd, 1 H), 7.38, 7.36, 7.33(t, 1 H), 6.76(s, 1 H), 4.13(m, 6 H), 3.47(s, 2 H), 2.35(m, 3 H), 1.17(m, 18 H).

MS (ESI): m/z (%) = 789.40 (100.00), $[M + H]^+$.

1.57. Synthesis of compound **57**.[124]



Pentafluorobenzyl bromide (1.5 mL, 2.61 g, 10 mmol, 5 eq.) was added to a mixture of pyrrole (0.140mL, 0.134 mg, 2.0 mmol, 1.0 eq.) and 1-*n*-butyl-3-methylimidazolium hexafluoroantimonate [bmim][SbF_6] (2.4 mL) in acetonitrile (0.6 mL). The mixture was stirred over 48 h at 80 ℃. The reaction mixture was extracted from ionic liquid phase with ether and filtered to remove the ionic liquid. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane to hexane:ethyl acetate, 5/1, v/v).

Yield: 35 mg (M = 607.31 g mol^{-1}, n = 0.058 mmol, 2.9%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (s, 1 H), 5.66 (s, 1 H), 4.02 (s, 2 H), 3.85 (s, 2 H), 3.79 (s, 2 H).

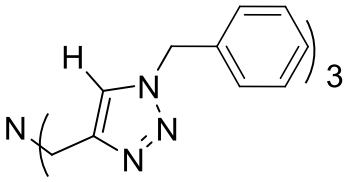
^{19}F NMR (282 MHz, $CDCl_3$): δ = -144.02 (m, 4 F), -144.28, -144.31, -144.36, -144.39 (dd, 2 F), -156.03, -156.10, -156.18 (t, 1 F), -156.31, -156.38, -156.45 (t, 1 F), -157.61, -157.68, -157.76 (t, 1 F), -161.30 (m, 2 F), -161.67 (m, 2 F), -162.48 (m, 2 F).

IR (KBr): 3457, 2923, 2068, 1655, 1499, 1299, 1420, 1120, 996, 958, 897, 805, 672 cm^{-1}.

MS (ESI): m/z (%) = 608.47 (100.00), $[M + H]^+$.

Elemental analysis (%): $C_{25}H_8NF_{15}$, calcd. C 49.44, H 1.33, N 2.31; found C 49.84, H 1.42, N 2.14.

1.58. Synthesis of compound **58**.



A mixture of sodium azide (855 mg, 13.1 mmol, 1.5 eq) and benzyl bromide (1500 mg, 8,77 mmol, 1.0 eq) in mixed acetone/water (v/v, 1:4) solution was stirred over night and monitored by TLC. Upon no benzyl bromide left in solution, the reaction solution was washed with water three times, dried with $MgSO_4$, and evaporated the solvent. It was used for next reaction without further purification.

To a mixture of freshly obtained benzyl azide (ca. 8.77 mmol) dissolved in mixed 15 mL DCM/H_2O (v/v, 1/1) were added tripropargylamine (0.414 mL, 383 mg, 2.92 mmol, 1.0 eq), $CuSO_4$ $5H_2O$ (36.5 mg, 0.146 mmol, 0.05 eq), and sodium ascorbate (86.4 mg, 0.439 mmol, 0.15 eq). The reaction mixture was vigorously stirred overnight at room temperature. The mixture was washed with water three times, and the organic phases were combined together and dried with $MgSO_4$. After evaporation of the solvent, the residue was purified by flash chromatography (silica gel). The eluents gradually changed from DCM to DCM/MeOH (19:1) to afford **58** as a light yellow solid.

Yield: 1105 mg (M = 530.63 g mol^{-1}, n = 2.08 mmol, 71%)

M.p.: 136 ℃.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (s, 3 H), 7.39 -7.22 (m, 15 H), 5.50 (s, 6 H), 3.70 (s, 6 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 144.2, 134.7, 129.1, 128.7, 128.0, 123.7, 54.1, 47.1.

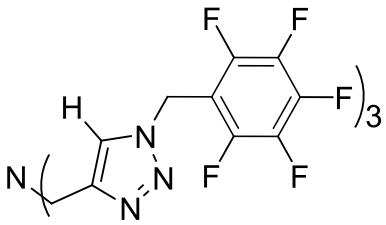
IR (KBr): 3869, 3295, 3111, 3061, 2937, 2827, 2761, 2323, 2088, 1954, 1743, 1587, 1549, 1496, 1453, 1327, 1214, 1169, 1125, 1087, 1046, 986, 929, 820, 755, 714 cm^{-1}.

MS (ESI): m/z (%) = 553.25336 (100.00), $[M + Na]^+$., 531.27197 (75.00), $[M + H]^+$.

Elemental analysis (%): $C_{30}H_{30}N_{10}$ $0.5H_2O$, calcd. C 66.77, H 5.79, N 25.96;

found C 66.83, H 5.80, N 25.55.

1.59. Synthesis of compound **59**.



A mixture of a 0.50-molar sodium azide solution in DMSO (10.8 mL, 281 mg, 5.40 mmol, 1.2 eq) and pentafluorobenzyl bromide (0.679 mL, 1174 mg, 4.50 mmol, 1.0 eq) was stirred for 30 min and monitored by TLC. Upon no pentafluorobenzyl bromide left in solution with the light orange solution turning to milky white, the reaction solution was used for the next reaction without further purification or characterization.

To the freshly obtained solution of pentafluorobenzyl azide (ca. 4.50 mmol) in DMSO were successively added tripropargylamine (164 mg, 1.25 mmol, 1.0 eq), CuBr (17.9 mg, 0.125 mmol, 0.10eq), and TEA (ca. 17μL, 12.6 mg, 125 μmol, 0.10 eq). Subsequently, ca. 10 mL of water and DCM each were added to the solution. The mixture was vigorously stirred for 30 min. Upon no pentafluorobenzyl azide left in solution, the reaction was stopped. After water-wash three times, the organic phase was combined together, dried over $MgSO_4$. After evaporation of solvents, the residue was purified by flash column chromatography (silica gel). Eluents changed gradually from DCM to DCM:MeOH (v/v, 19/1) to allow isolation of **59** as a light solid.

Yield: 602.7 mg (M = 800.48 g mol^{-1}, n = 0.753 mmol, 60%)

M.p.: 145 ℃.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (s, 3 H), 5.62 (s, 6 H), 3.74 (s, 6 H).

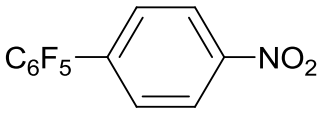
^{13}C NMR (151 MHz, DMSO-d_6): δ = 147.2, 144.3, 143.9, 136.1, 123.6, 108.2, 46.9, 40.8.

IR (KBr): 3129, 2973, 2846, 2652, 2164, 2101, 1987, 1739, 1659, 1588, 1502, 1437, 1373, 1311, 1219, 1181, 1127, 1024, 968, 917, 801, 719, 682 cm^{-1}.

MS (ESI): m/z (%) = 823.10664 (100.00), $[M + Na]^+$., 801.12685 (46.00), $[M + H]^+$.

Elemental analysis (%): $C_{30}H_{15}N_{10}F_{15}$, calcd. C 45.01, H 1.89, N 17.50; found C 45.22, H 2.17, N 17.31.

1.60. Synthesis of compound **60**



To a septum-capped 25 mL two-necked flask were added $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.05 eq), PPh_3 (26.2 mg, 0.1 mmol, 0.1 eq), Ag_2CO_3 (207 mg, 0.75 mmol, 0.75 eq), 1-iodo-4-nitrobenzene (249.0 mg, 1.0 mmol, 1.0 eq) and pentafluorobenzene (0.168 mL, 252 mg, 1.5 mmol, 1.5 eq) under nitrogen atmosphere. Subsequently,

deionized water (degased) (2 mL) was added into the mixture, and the mixture was warmed to 70 ℃, and stirred for 24 h. The reaction mixture was cooled to room temperature, and CH_2Cl_2 was added. The mixture was filtered through Celite and the filtrate was washed with water. The organic phase was dried with Na_2SO_4 and purified with chromatograph (silica gel, 10:1, hexane/DCM) to provide the target compound, which was characterized by NMR without further characterization and used directly for next reaction.

Yield: 248 mg (M = 289.16 g mol^{-1}, n = 0.858 mmol, 86%)

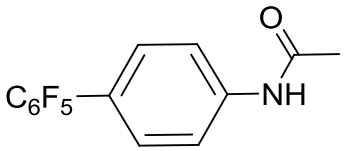
M.p.:94 -95 ℃.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.37 (d, 2 H), 7.64 (d, 2 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 131.28, 123.89.

^{19}F NMR (564 MHz, DMSO-d_6): δ = -142.51 (dd, 2 F), -152.46 (t, 1 F), -160.77 (td, 2 F).

1.61. Synthesis of compound **61**.



A mixture of **60** (100 mg, 0.50 mmol) dissolved in CH_2Cl_2 (20 mL) and 10% Pd/C (30 mg) was stirred at room temperature under an atmosphere of hydrogen (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.

To a solution of freshly obtained 2,3,4,5,6-pentafluoro-4′-aminobiphenyl (ca. 0.50 mmol) in CH_2Cl_2 (25 mL) was added pyridine (0.15 mL) and acetyl chloride (0.078 mL, 1.1 mmol, 3 eq) at 0 ℃ under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred overnight. The solvent was removed *in vacuo*. The residue was washed with water, extracted with CH_2Cl_2, and purified on silica gel with dichloromethane/hexane (1/1) as an eluent. The product was provided as a yellow solid in 83% (125 mg, 0.41 mmol).

Yield:125 mg (M = 301.21 g mol^{-1}, n = 0.0.41 mmol, 83%)

M.p.: 196 – 198 ℃.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.63 (d, 2 H), 7.39 (d, 2 H), 7.30 (s, 1 H), 2.21 (s, 3 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 168.33, 130.89, 119.64, 24.71.

^{19}F NMR (564 MHz, DMSO-d_6): δ = -143.39 (dd, 2 F), -155.79 (t, 1 F), -162.27 (td, 2 F).

MS (ESI): m/z (%) = 324.04224 (100.00), $[M + Na]^+$.

IR (KBr): 3834, 3370, 2927, 2314, 2082, 1658, 1602, 1490, 1344, 1198, 1105, 1061, 981, 834, 730, 688 cm^{-1}.

Elemental analysis (%): $C_{14}H_8F_5NO$, calcd. 55.82, H 2.68, N 4.65; found C 56.00, H 2.51, N 4.51.

Chapter 10 References

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Appendix

Appendix 1: Curriculum Vitae of Zhanhu Sun

Appendix2: List of Publications

Appendix 3: Acknowledgements

Curriculum Vitae of Zhanhu Sun

Personal information:

Name: Zhanhu Sun

Date of Birth: August, 06. 1981

Gender: Male

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Eudcation:

Ph. D, **Organic Chemistry**, (Expected Sep. 2013), RWTH Aachen University, Aachen, Germany. Advisor: Prof. Markus Albrecht

Master of Science, **Physical Chemistry**, June 2010, Nankai University, Tianjin, China. GPA: 88/100 Ranking (1^{st}/25) Advisor: Prof.Yu Liu and Prof. Heng-Yi Zhang

Bachelor of Science, **Chemistry**, June 2007, Langfang Teachers' College, Langfang, China GPA: 84/100.

List of Publications

a) Journal Articles

1) **Zhan-Hu**, **Sun**; Markus, Albrecht; Roland Fröhlich. *Eur. J. Org. Chem*. **2013**. *2013*, 3254-3262. Tuning the halide affinity of quinoline based anion receptors.

2) **Zhan-Hu**, **Sun**; Fang-Fang, Pan; Markus, Albrecht; Gerhard Raabe. *Eur. J. Org. Chem*. **2013**, DOI: 10.1002/ejoc.201301032. Salt-solubilization and ion pair recognition through quinoline-based crown ether.

b) Poster Presentations

1) **Zhanhu, Sun;** Markus, Albrecht; Roland Fröhlich. Quinoline-based Anion Receptors. *Templates in Chemistry - Progress and Perspectives*, Bonn/Germany, 22nd/23rd. September **2011**.

2) **Zhanhu, Sun;** Markus, Albrecht; Roland Fröhlich. Amide-functionalized Quinoline Derivatives as Receptors for Anions. *Symposium on Cooperative Effects in Chemistry* , Münster/Germany, 4th. May **2012**.

3) **Zhan-Hu**, **Sun**; Markus, Albrecht; Gerhard Raabe. Salt-solubilization and ion pairs recognition through quinoline-based crown ether. *The* 5. *New Year's Symposium*, Aachen/Germany, 11th. January **2013**.

4) **Zhan-Hu, Sun;** Fang-Fang, Pan; Gerhard, Raabe; Markus, Albrecht. Quinoline-base Receptors Decorated with Biphenyl towards Anions. *The 2nd German Symposium in Supramolecular Chemistry SupraChem 2013*, Münster/Germany, 14th/15th. Feb. **2013**.

c) Oral Presentations

1) *G4-Treffen 2012* (Albrecht/Schalley/Lützen/Engeser), Oberwesel/Germany, 11th/13th. Sep. **2012**. "*Salts and Ion Pairs Recognition through Quino-*

line-based Crown Ether"

2) *AGOCS 2013* (Aachen-Groningen Organic Chemistry Symposium), Aachen/Germany, 13th. June **2013**. "*Salt-solubilization and ion pair recognition by a quinoline- substituted crown ether"*

3) *G4-Treffen 2013* (Albrecht/Schalley/Lützen/Engeser), Freie Uni. Berlin/Berlin/Germany, 21th/23th. Aug. **2013**. "*Investigation of Competitive Interactions in Anion Binding: NH-, CH-, anion-p and lone-pair π Supported NH-anion Interactions.*"

d) Selective Conferences Attended

1) *Cortona Week – Natural Sciences and the Wholeness of Life*, Cortona/Italy, (ETH Zürich organized) 10.-17. Sep. **2011**.

2) *Templates in Chemistry - Progress and Perspectives*, Bonn/Germany, 22nd/23rd. Sep. **2011**.

3) *A Symposium on Cooperative Effects in Chemistry* , Münster/Germany, 4th. May **2012**.

4) *The 2nd German Symposium in Supramolecular Chemistry--SupraChem 2013,* Münster/Germany, 14th/15th. Feb. **2013**.

5) *Symposium Celebrating 125 Years of Angewandte Chemie*, Berlin/Germany, 12th, March. **2013**.

6) *The 2013 SciFinder® Future Leaders in Chemistry program*. (Selected to attend in Sep. 2013). Part 1: *246th ACS National Meeting & Exposition*, Indianapolis, Indiana/the United States, September 7-11, **2013**; part 2: *CAS Campus*, Columbus, Ohio/the United States, September 12-14, **2013**.

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