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Highly Selective Recognition of α-Chiral Primary Organoammonium Ions by C_3-Symmetric Peptide Receptors

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A straightforward synthesis of C_3-symmetric, imidazole-containing, macrocyclic peptides with different binding arms is presented. The chirality of the backbone and the selection of adequate receptor arms make these systems highly selective receptors for α-chiral primary organoammonium ions. Furthermore, the receptors have the ability to discriminate between enantiomeric guests with selectivity ratios of up to 87:13. The binding constants and the selectivity ratios were estimated by standard ^{1}H NMR titration techniques in $CDCl_3$.

Introduction

Enantiomeric recognition is an essential process in living organisms as well as in artificial systems and involves the discrimination of one enantiomer of the guest from the other by a chiral host. It is important from various viewpoints, such as enzyme-substrate interactions,[1] the resolution of enantiomers in chemical processes, and asymmetric catalysis.[2] Therefore, the design and synthesis of new chiral systems for the selective recognition of small molecules is one of the most challenging topics in the fields of catalysis,[3,4] separation science,[5,6] and the design of enzyme mimetics.[7–9]

Chiral or protonated amines are frequently used as guests in chiral recognition as they are basic building blocks of biologically active molecules. The enantioselective discrimination of such molecules is crucial because it is known that several representatives of this group have essential biological properties, which are completely different from those of their enantiomers.[10]

Since Cram et al. synthesized crown ethers, which were the first enantioselective receptors for primary organoammonium salts,[11,12] a great number of chiral artificial receptors have been developed and studied.[10] Presently, crown ether derivatives showing C_1 or C_2 symmetry prevail as receptors for primary organoammonium salts,[13–15] and there are only a few examples of enantioselective receptors for chiral ammonium ions with C_3 symmetry.[16,17] A recent example of a C_1-symmetric receptor is the macrocycle **1**, which provides in chloroform a selectivity ratio of 2.50 for the perchlorate salt of (*R*)-α-phenylethylamine (K_a = 33000 M^{-1}) vs. the perchlorate salt of (*S*)-α-phenylethylamine (K_a = 13000 M^{-1}, Figure 1).[14] The C_2-symmetric macrocycle **2** shows a selectivity ratio in acetonitrile of 3.65 for the perchlorate salt of (*R*)-α-(1-naphthyl)ethylamine (K_a = 7753 M^{-1}) vs. the perchlorate salt of (*S*)-α-(1-naphthyl)-ethylamine (K_a = 2123 M^{-1}).[15]

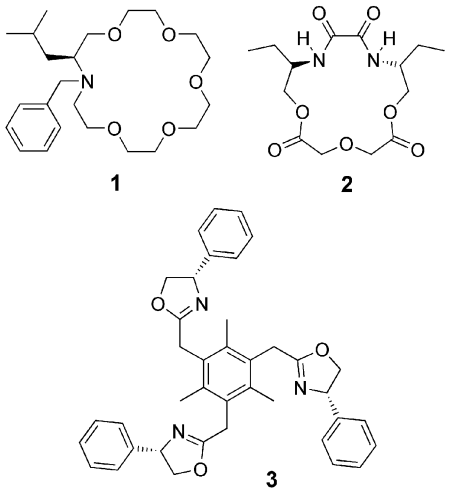

Figure 1. Receptors for the enantiomeric recognition of chiral ammonium ions.

The question of whether or not C_3- or D_3-symmetric systems are able to act as receptors for chiral recognition has been controversial for a long time,[18] and Ahn et al. were the first to succeed in synthesizing a C_3-symmetric receptor (**3**), which shows selectivity ratios of up to 71:29 in chloroform in the field of enantiomeric discrimination.[17] This receptor type is built by coupling the chiral binding arms to the achiral backbone in such a way that they can organize themselves around a potential guest in a predetermined ar-

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rangement. To obtain sufficient stereoinduction, the chiral elements and the donor groups have to be arranged closely to each other (Figure 2).

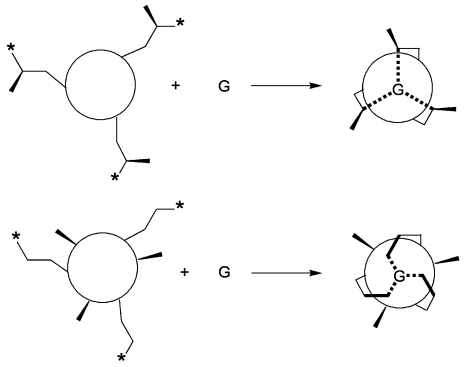


Figure 2. Schematic description of the enantiomeric discrimination of C_3-symmetric receptors with chiral binding arms (top) or a chiral scaffold (below).

An alternative design of three-armed, C_3-symmetric receptors for enantiomeric discrimination is the use of chiral scaffolds to which achiral binding arms can be coupled. Here, the scaffold not only serves as a spacer but also preorganizes the conformation of the binding arms, thus leading to an enantioselective discrimination of chiral guests. The advantage of such an approach is the straightforward synthesis starting from only one chiral platform; different receptors possessing diverse recognition sites can be prepared by simply attaching achiral arms to the chiral scaffold.

Since pseudopeptidic macrocycles are important molecules due to their interesting applications in catalysis,[19] biomedicine,[20] and materials science,[21] our intention was to use this concept to develop efficient C_3-symmetric receptors for the enantiomeric discrimination of chiral ammonium ions. As appropriate scaffolds, we employed our recently developed, macrocyclic, azole-containing cyclopeptides, which have already been used for the control of axial and planar chirality[22,23] and for chirality transfer in C_3-symmetric metal complexes.[24,25] As arms of the new receptors, we chose nitrogen-containing aromatic heterocycles, as they have basic units for the recognition of ammonium ions and are rigid and bulky and, therefore, able to transfer the chiral information of the scaffold to the active binding site, thereby making an enantioselective discrimination possible. Herein, we report the synthesis of receptors **4**–**6** (Figure 3) and the analysis of their binding properties and selectivities vis-à-vis α-chiral primary organoammonium salts in $CDCl_3$ using ^1H NMR titration techniques.

Results and Discussion

Synthesis of the Receptors

The syntheses of the macrocyclic receptors **4**–**6** are shown in Scheme 1 and Scheme 2. The final step for all three receptors is essentially the same: we attached the three arms bearing the recognition groups to the known scaffold **17**[26] by a simple *N*-alkylation with the corresponding halogenomethyl compounds, the latter being available in a few steps from commercially available heterocycles (Scheme 1). In the case of the 1-(chloromethyl)-1*H*-benzimidazole (**9**), the synthesis starts from benzimidazole (**7**), which we transformed into the 1-hydroxymethyl derivative **8** by reaction with formaldehyde in THF at room temp.[27] After we recrystallized it from ethanol and water, we directly suspended alcohol **8** in chloroform and treated it with thionyl chloride for 3 h to give the chloromethyl hydrochloride **9** in an almost quantitative yield with a small amount of impurities, which could not be removed.

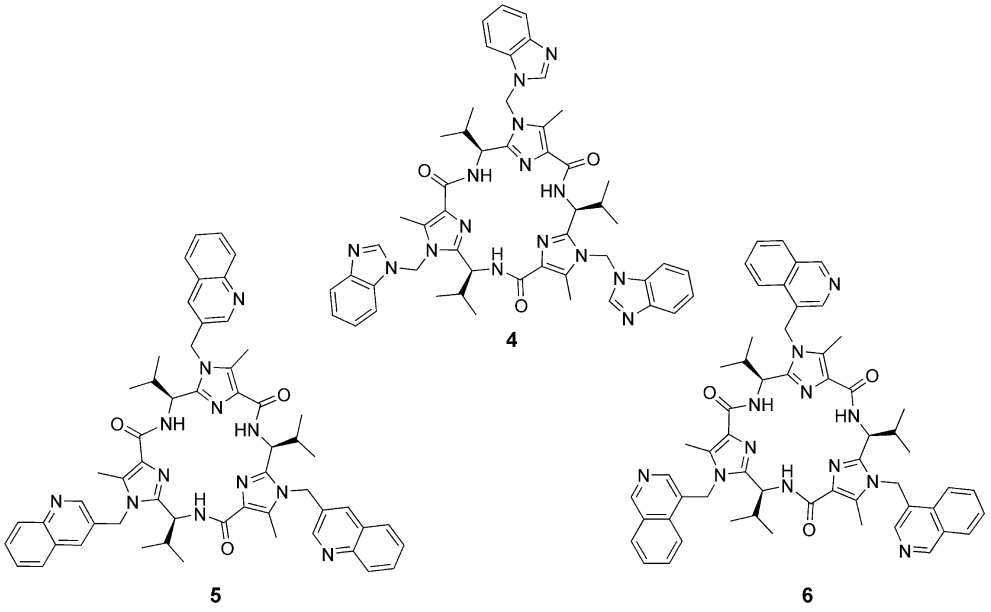
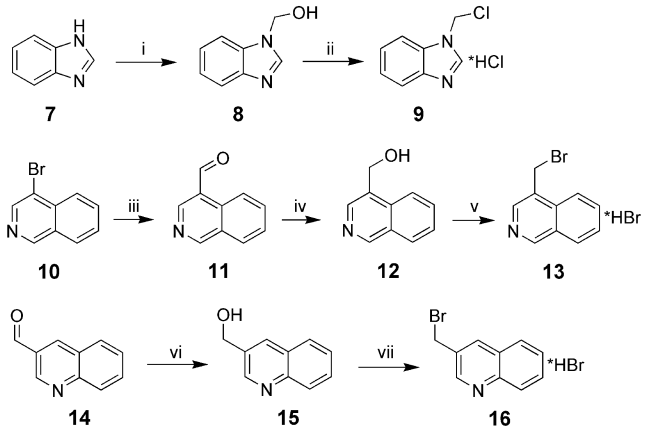
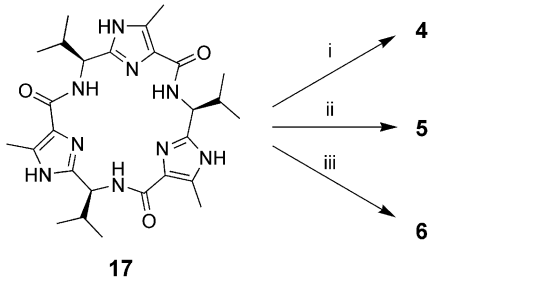


Figure 3. Structures of C_3-symmetric macrocyclic receptors.



Scheme 1. Synthesis of the receptor arms **9**, **13** and **16**: i) HCHO, THF, room temp., 85%; ii) $SOCl_2$, $CHCl_3$, room temp., 98%; iii) *n*BuLi; DMF, H^+/H_2O, THF, –78 °C, 63%; iv) $NaBH_4$, H_2O/AcOH, EtOH, room temp., 69%; v) HBr, AcOH, reflux, 88%; vi) $NaBH_4$, H_2O/AcOH, EtOH, room temp., 92%; vii) HBr, AcOH, reflux, 82%.



Scheme 2. Synthesis of receptor **4**–**6**: i) 1-(chloromethyl)-1*H*-benzimidazole hydrochloride (**9**), NaH, DMF, room temp., 48%; ii) 3-(bromomethyl)quinoline hydrobromide (**16**), Cs_2CO_3, CH_3CN, reflux, 31%; iii) 4-(bromomethyl)isoquinoline hydrobromide (**13**), NaH, DMF, room temp., 20%.

For the synthesis of the isoquinoline derivative **13**, we started from commercially available 4-bromoisoquinoline (**10**). In the first step, we prepared the carbaldehyde **11** by a metal-halide substitution followed by formylation with DMF. We isolated the desired 4-isoquinolinecarbaldehyde (**11**) after chromatography in a yield of 63%. The reduction of the aldehyde group with sodium borohydride gave the corresponding alcohol **12** in good yield.[28] The best way to transform the alcohol **12** into the bromide turned out to be the use of hydrogen bromide in acetic acid. After 2 h of refluxing in acetic acid and the addition of ether, we obtained the hydrobromide of 4-(bromomethyl)isoquinoline (**13**) in a good yield.

We performed the synthesis of 3-(bromomethyl)quinoline hydrobromide (**16**) in an analogous manner. The starting compound was the commercially available 3-quinolinecarbaldehyde (**14**). The reduction with sodium borohydride yielded the alcohol **15** (92%), which we treated with hydrogen bromide in acetic acid to give the hydrobromide of 3-(bromomethyl)quinoline (**16**).

Subsequently, we attached the halogenomethyl compounds **9**, **13**, and **16** to the scaffold **17** (Scheme 2). For the alkylation, we used sodium hydride as the base in DMF, as these were the most efficient conditions for the alkylation of peptidic imidazole units.[29] After reaction times of 24 h and more, we were able to isolate the receptors **4** and **6** in yields of 48% and 20%, respectively. Besides the threefold alkylated scaffold, we also found less-substituted macrocycles. All attempts to enhance the alkylation rate by increasing the reaction times and/or increasing the equivalents of the receptor arms, failed. However, it was possible to transform the isolated, less-substituted derivatives into the desired scaffolds **4** and **6** by a subsequent alkylation reaction, thus increasing the overall yield.

The synthesis of the quinoline receptor **5** under the above-referenced conditions did not succeed, and we could only isolate less-substituted products. However, changing the base, the solvent and the reaction procedure brought about the desired result; we refluxed scaffold **17** in acetonitrile for 3 h together with cesium carbonate, and then added 3-(bromomethyl)quinoline hydrobromide (**13**) at reflux. These conditions gave the desired receptor **5** in a yield of 31% and a small amount of the less-substituted derivatives.

Selective Cation Binding

As NMR spectroscopy is one of the most effective tools in studying host-guest supramolecular chemistry, we applied standard ^{1}H NMR titration experiments to investigate the stability of the complexes of the receptors **4**–**6** with different chiral primary ammonium cations. Upon the addition of guest molecules to the ligands, the signals in the ^{1}H NMR spectra migrated upfield or downfield due to the interactions between the hydrogen-bond donor and acceptor. From how the shifts changed with the added guest, conclusions can be drawn as to which individual protons are involved in the interaction, as well as the extent to which they participate.[30,31] As solvent, we used $CDCl_3$, as we expected the values for K_a to be not too high. Very polar solvents like DMSO or methanol strongly compete for the binding sites of the ligands and make the determination of the binding constants impossible. Nevertheless, in some cases, we had to add 2% of methanol because of the low solubility of the guests. We used a constant host concentration (1×10^{-3} M) for the measurements and increased the concentration of the cations, which were used as their perchlorate salts, from 0.1 to 5 equiv. During the titration, we observed significant shifts of the aromatic protons next to the nitrogen in the receptor arms, which indicated strong hydrogen-bonding interactions for these nitrogens. Furthermore, the spectra showed a fast equilibrium between free and complexed forms of the ligands, proved by the continuous displacement of the proton chemical shifts. Standard nonlinear analysis of the chemical shift data delivered the 1:1 binding constants for the receptors **4**–**6**, and these are summarized in Tables 1 and 2. To confirm the 1:1 stoichiometry, we constructed an exemplary Job Plot of the

complexation of receptor **6** and the perchlorate salt of (*R*)-α-benzylethylamine (Figure 4). For an adequate comparison of the binding constants, we used only the shifts of the aromatic proton in the receptor arm, which was bound to the carbon atom between the nitrogen atom and the atom carrying the methylene bridge, for the calculation of K_a. In almost all cases, these chemical shifts were the maximally shifted ones. In general, complex formation led to an upfield shift of the observed protons, which can be explained by the aromatic ring current. In the course of complex formation, the observed protons protruded into an area above the imidazole planes, and this behavior caused the upfield shift of these protons.

Table 1. Binding constants K_a (M^{-1}) for the formation of 1:1 complexes of **4**–**6** with the perchlorates of (*R*)- and (*S*)-α-phenylethylamine in $CDCl_3$ at 298 K.[a]

Entry	Guest	**4**	**5**	**6**
1	(*R*)-**PEA**	<1	200 (± 30)	30000 (± 11000)[b]
2	(*S*)-**PEA**	<1	480 (± 60)	4500 (± 590)

[a] The association constants K_a (M^{-1}) were measured using ^1H NMR spectroscopic titrations. [b] A host concentration of 2.5×10^{-4} M was used for titration studies, because of the high binding constant.

Table 2. Binding constants (K_a [M^{-1}]), maximum observed chemical shifts ($\Delta\delta_{max}$), Gibbs free energy changes ($-\Delta G^0$), selectivity coefficients, and differences of the Gibbs free energy changes ($\Delta\Delta G^0$) for the formation of 1:1 complexes of **5** and **6** with different perchlorate salts of α-chiral primary organoammonium ions in $CDCl_3$ at 298 K.[a]

Guest	K_a	$\Delta\delta_{max}$	Selectivity coefficients	$-\Delta G^0$ [kJ mol^{-1}]	$\Delta\Delta G^0$ [b] [kJ mol^{-1}]
5*(*R*)-**PEA**	200 (± 40)	0.03	2.4	13.1	–2.2
5*(*S*)-**PEA**	480 (± 70)	0.06		15.3	
5*(*R*)-**PAM**	16000 (± 4900)	0.01	8.4	24	5.3
5*(*S*)-**PAM**	1900 (± 500)	0.02		18.7	
5*(*R*)-**BA**	130 (± 40)	0.01	7.2	12.1	–4.9
5*(*S*)-**BA**	940 (± 240)	0.01		17	
5*(*R*)-**NEA**[c]	–[d]	–[d]	–	–	–
5*(*S*)-**NEA**[c]	–[d]	–[d]		–	
5*(*R*)-**BEA**	560 (± 210)	0.01	1.0	15.7	0.1
5*(*S*)-**BEA**	540 (± 50)	0.05		15.6	
5*(*R*)-**AH**	360 (± 70)	0.01	3.6	14.6	3.2
5*(*S*)-**AH**	100 (± 20)	0.02		11.4	
6*(*R*)-**PEA**	30000 (± 11000)[e]	0.25	6.7	25.5	4.7
6*(*S*)-**PEA**	4500 (± 590)	0.30		20.8	
6*(*R*)-**PAM**	2000 (± 240)	0.22	1.8	18.8	1.5
6*(*S*)-**PAM**	1100 (± 270)	0.22		17.4	
6*(*R*)-**BA**	1600 (± 260)	0.17	1.5	18.3	–1.0
6*(*S*)-**BA**	2400 (± 930)	0.20		19.3	
6*(*R*)-**NEA**[c]	1000 (± 180)	0.06	1.6	17.1	1.2
6*(*S*)-**NEA**[c]	610 (± 110)	0.06		15.9	
6*(*R*)-**BEA**	6600 (± 1600)	0.30	2.1	21.8	1.8
6*(*S*)-**BEA**	3200 (± 450)	0.28		20	
6*(*R*)-**AH**	9700 (± 3100)	0.13	4.0	22.7	3.5
6*(*S*)-**AH**	2400 (± 710)	0.16		19.3	

[a] The association constants K_a (M^{-1}) were measured using ^1H NMR spectroscopic titrations. [b] $\Delta\Delta G^0 = [-\Delta G^0_{(R)}] - [-\Delta G^0_{(S)}]$. [c] The measurements were performed in $CDCl_3$/2% CD_3OD. [d] The value of $\Delta\delta_{max}$ was too low for reasonable calculations of K_a. [e] A host concentration of 2.5×10^{-4} M was used for titration studies because of the high binding constant.

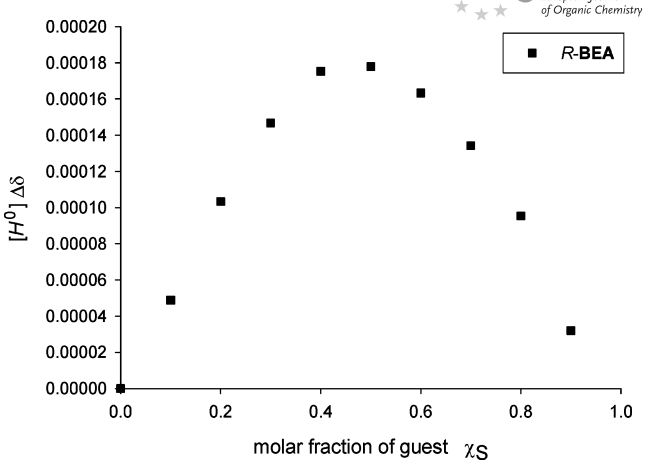


Figure 4. Job plot titration for the complexation of receptor **6** and the perchlorate salt of (*R*)-α-benzylethylamine in $CDCl_3$.

Initially, we determined the binding constants of receptor **4**–**6** with the perchlorate salts of (*R*)- and (*S*)-α-phenylethylamine [(*R*)-**PEA** and (*S*)-**PEA**], as these cations are commonly used standard guests for the chiral recognition of ammonium ions and in most cases give the best results.[15–17,32] The addition of (*R*)-**PEA** or (*S*)-**PEA**, respectively, to benzimidazole receptor **4** resulted in an upfield shift of the proton of approximately 0.10 ppm. The obtained titration curves showed a pseudolinear progression, and thus, we obtained binding constants smaller than 1 M^{-1}. Obviously, receptor **4** was not able to arrange the basic nitrogens of the benzimidazole units is such a way that a stable complex was formed.

For the quinoline receptor **5**, we calculated similar values for both enantiomers [200 M^{-1} for (*R*)-**PEA** and 480 M^{-1} for (*S*)-**PEA**]. These values were still quite low, but nevertheless, there was a slight selectivity in favor of (*S*)-**PEA**. The maximum shifts after adding 5 equiv. of the guests were 0.03 ppm and 0.06 ppm, respectively and, thus, quite small (Figure 5).

The determination of K_a for isoquinoline receptor **6** with (*R*)-**PEA** and (*S*)-**PEA** showed that this receptor fulfilled our expectations. In both cases, we observed large shifts of around 0.30 ppm when we added the guests to the receptor, and we determined binding constants of 4500 M^{-1} for (*S*)-**PEA** and 30000 M^{-1} for (*R*)-**PEA**. The obtained titration curve for **6**/(*R*)-**PEA** showed that after adding approximately 1.5 equiv. of the guest, the curve faded into a plateau, and a saturation of the host began to arise (Figure 5). These data show that by synthesizing the isoquinoline receptor **6**, it was possible to generate a C_3-symmetric receptor with a good selectivity ratio of 87:13 for (*R*)-**PEA**.

These results encouraged us to perform more titrations with receptors **5** and **6** in order to examine their behavior vis-à-vis other guests. A significant challenge was to find adequate molecules that can be easily and purely transformed into their perchlorate salts and are completely soluble in $CDCl_3$ or in $CDCl_3$/2% CD_3OD. We found the perchlorate salts listed in Figure 6 to fulfill these requirements and, thus, used them to perform additional measurements.

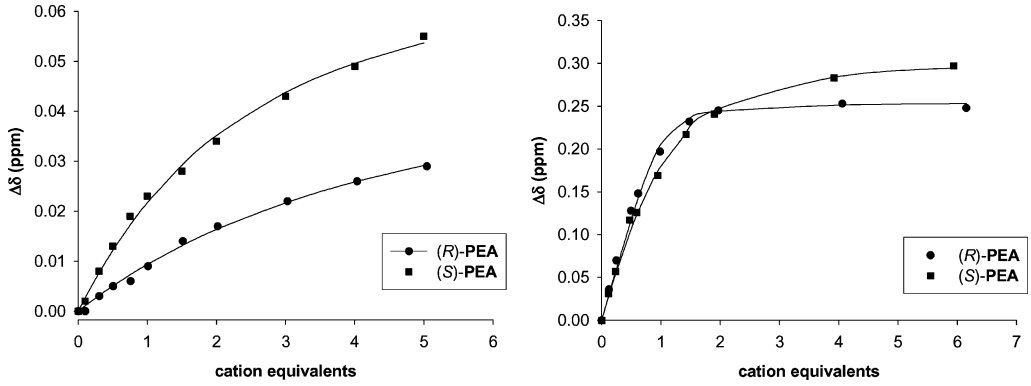


Figure 5. ^{1}H NMR titration curves for the complexation of **5** (left) and **6** (right) with (*R*)-**PEA** and (*S*)-**PEA** in $CDCl_3$.

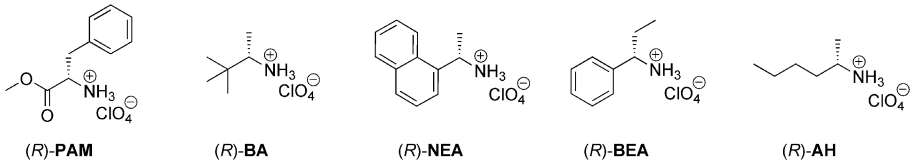


Figure 6. (*R*) enantiomers of the α-chiral primary organoammonium ions used as guests for ^{1}H NMR titrations.

The comparison of the data for quinoline receptor **5** showed that the maximum chemical shifts of the observed protons were in general quite small. They ranged between 0.01 ppm and 0.05 ppm, and the obtained binding constants for these complexes resembled the results of the measurement with (*R*)-**PEA** and (*S*)-**PEA**. It was not possible to get binding constants for the titration with (*R*)-**NEA** and (*S*)-**NEA** due to the minimal and inconstant shifts of the signals. We determined quite small constants for the complexes **5***(*R*)-**AH** and **5***(*S*)-**AH** with values of 360 M^{-1} and 100 M^{-1}, respectively. Thus, we found a selectivity with a coefficient of 3.6 for the (*R*) enantiomer. The progression of the titration curves did not show any sharp crossover into a plateau, which also indicates small binding constants (Figure 7). We found moderate values for K_a, but essentially no enantioselective discrimination for the complexes **5***(*R*)-**BEA** (560 M^{-1}) and **5***(*S*)-**BEA** (540 M^{-1}).

In contrast, we determined high enantioselectivities for the complexes of **5** with (*R*)-**BA** vs. (*S*)-**BA** and for the complexes of **5** with (*R*)-**PAM** vs. (*S*)-**PAM**. These selectivities were even better than those found for the complex of receptor **6** with (*R*)-**PEA** and (*S*)-**PEA**. However, the binding constants are substantially smaller. The binding constants were 130 M^{-1} for **5***(*R*)-**BA** and 940 M^{-1} for **5***(*S*)-**BA**, which implied that (*S*)-**BA** was bound 7.0 times better than the (*R*) enantiomer. The titrations of (*R*)-**PAM** und (*S*)-**PAM** with **5** resulted in values for K_a of 16000 M^{-1} and 1900 M^{-1}, respectively, and thus, we observed a high selectivity ratio of 90:10. As expected, the titration curve showed that after the addition of approximately 2 equiv. of the guests, the curves faded into a plateau, which indicated a saturation of the host (Figure 7). Nevertheless, we note that the values and the selectivity coefficients calculated for the complexation of the ammonium ions with quinoline receptor **5** must be taken with caution as these values derived from rather small $\Delta\delta_{max}$ values.

The comparison of the data for isoquinoline receptor **6** showed that for this receptor, after the addition of 5 equiv. of the guest, the maximum shifts of the protons and the obtained binding constants were generally ten times larger

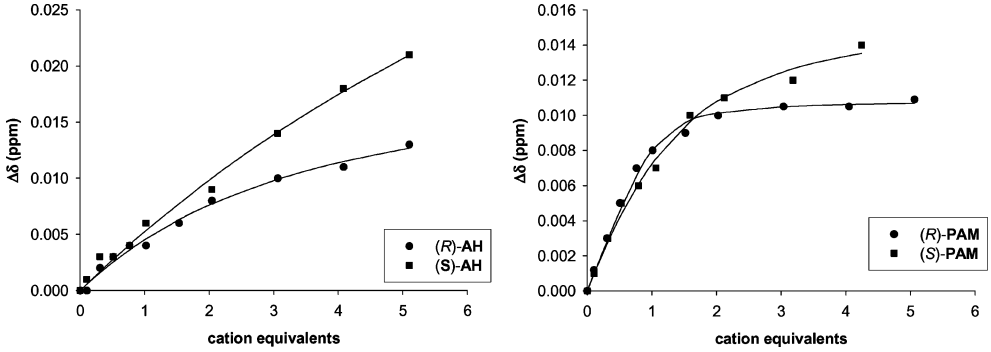


Figure 7. ^{1}H NMR titration curves for the complexation of **5** with (*R*)-**AH** and (*S*)-**AH** (left) and (*R*)-**PAM** and (*S*)-**PAM** (right) in $CDCl_3$.

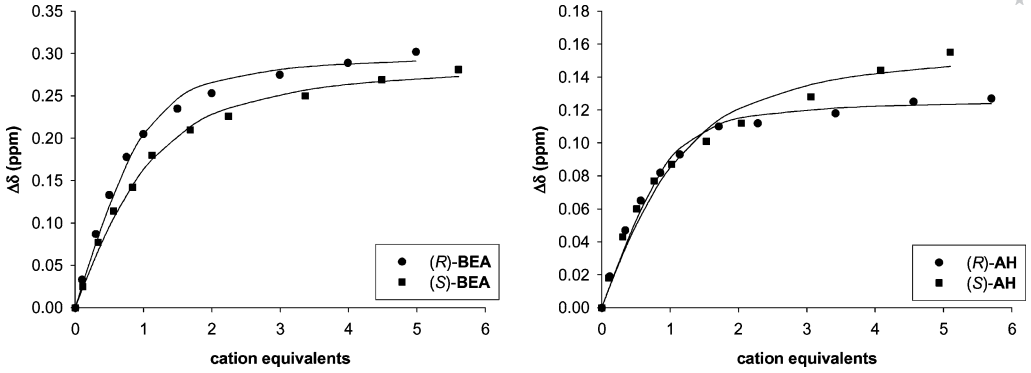


Figure 8. ^{1}H NMR titration curves for the complexation of **6** with (*R*)-**BEA** and (*S*)-**BEA** (left) and (*R*)-**AH** and (*S*)-**AH** (right) in $CDCl_3$.

than the corresponding values for receptor **5**. The maximum shifts ranged between 0.06 ppm and 0.30 ppm and the evaluated binding constants ranged between 610 M^{-1} for **6***(*S*)-**NEA** and 30000 M^{-1} for the complex with (*R*)-**PEA**. We found the smallest binding constants for (*R*)-**NEA** and (*S*)-**NEA** (1000 M^{-1} and 610 M^{-1}, respectively), (*R*)- and (*S*)-**PAM** (2000 M^{-1} and 1100 M^{-1}, respectively), and (*R*)- and (*S*)-**BA** (1600 M^{-1} and 2400 M^{-1}, respectively). With a coefficient of 1.5 to 1.8, the selectivities for these guests were quite small. We found a comparable small selectivity with a coefficient of 2.1, but with much higher binding constants, for **6***(*R*)-**BEA** (6600 M^{-1}) and **6***(*S*)-**BEA** (3200 M^{-1}). We obtained even better values for K_a of 9700 M^{-1} and 2400 M^{-1} and a selectivity ratio of 80:20 in favor of the (*R*) enantiomer for **6***(*R*)-**AH** and **6***(*S*)-**AH**. By comparing the titration curves it can be seen that for both complexes of the (*R*) enantiomers, the fading into a plateau after the addition of 2 equiv. of the guests was much sharper than it was for the (*S*) enantiomers, in accordance with the higher binding constants of the complexes of the (*R*) enantiomers (Figure 8).

A comparison of all the results shows that both receptors (**5** and **6**) are very sensitive to small changes in the guest molecules. Yet, the substitution of the methyl group in α-phenylethylamine (**PEA**) by the ethyl group in α-ethylbenzylamine (**BEA**) reduced the binding constants for receptor **6** drastically. Interestingly, the receptors showed contrary behavior regarding the different ammonium ions. In the case of receptor **5**, we found the largest binding constant for the complex with (*R*)-**PAM**, and the affinity of **5** for (*R*)-**PEA** was one of the lowest measured. For receptor **6**, the opposite was true. We detected the largest binding constant for the complex **6***(*R*)-**PEA**, whereas we found one of the lowest affinities for the complex **6***(*R*)-**PAM**. Furthermore, it is notable that quinoline receptor **5** generally delivered smaller binding constants.

The enantioselectivity of complex formation for receptors **5** and **6** cannot be explained with the model of Moberg for C_3-symmetric receptors.[16e] A possible explanation for the enantioselectivity should, however, be deducible from the conformation of the complexes. For this purpose, we calculated the molecular structures of the energetically preferred conformers of **6***(*R*)-**PEA** and **6***(*S*)-**PEA** using density functional theory (DFT).[33] These complexes were chosen because α-phenylethylamine is the guest with the lowest number of possible conformers, and the selectivity ratio of 87:13 for **6***(*R*)-**PEA** vs. **6***(*S*)-**PEA** is the highest one found for this guest. We used the recently published M05–2X functional because this can predict correctly the medium-range correlation energies,[34] which are supposed to be the most important interaction for the selectivity. We calculated the energy difference between the diastereomers to be 6.6 kJ mol^{-1} in favor of **6***(*R*)-**PEA**, in accordance with the NMR titration experiments (Figure 9). The selectivity can probably be explained by correlation energies between the aromatic unit of the guest and the aromatic ring of one of the isoquinoline units. In order to maximize these interactions, the distance between the α-carbon of the guest and the isoquinoline unit that interacts with the benzene unit becomes shorter at the expense of the distances between the α-carbon and the other isoquinoline units. In the complex **6***(*R*)-**PEA**, we calculated the distance between the α-carbon of the guest and the nitrogen of the isoquinoline unit that interacts with the benzene unit to be 3.57 Å. In case of **6***(*S*)-**PEA**, we found a value of 3.61 Å. Here the shortening of this distance leads to a shortening of the distance between the methyl group and the isoquinoline unit next to it and, thus, increases the repulsive interactions between the methyl group and the isoquinoline unit. In the case of **6***(*R*)-**PEA**, the repulsive interaction between the methyl group and the isoquinoline unit is weaker as these groups

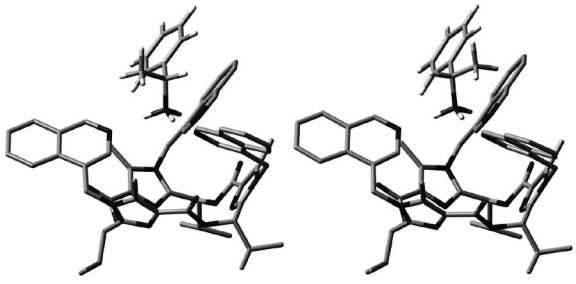


Figure 9. Molecular structures of the energetically preferred conformers of **6***(*R*)-**PEA** (left) and **6***(*S*)-**PEA** (right) calculated by using M05–2X/6-31G*; all hydrogens except those of the guest are omitted for clarity.

do not point toward each other but, due to the helix-like orientation of the isoquinoline units, are oriented in the same direction.

Conclusions

In summary, we were able to synthesize receptors **4**–**6** in a few steps and investigate their binding ability towards α-chiral primary organoammonium ions by using ^{1}H NMR titration techniques in $CDCl_3$. We could show that the choice of adequate aromatic receptor arms is of utmost importance for the affinity and especially for the selectivity of the receptor. Hence, depending on the receptor arms, we found binding constants for the complexes with α-chiral primary organoammonium ions range from less than 1 up to 30000 M^{-1}. The receptors **5** and **6** showed contrary selectivities toward those organoammonium ions bound most strongly. Furthermore, we found that both receptors have the ability to discriminate between enantiomeric guests with selectivity ratios of up to 87:13.

Experimental Section

General Remarks: All chemicals were reagent grade and used as purchased. All moisture-sensitive reactions were performed under an inert atmosphere of argon using distilled anhydrous solvents. Reactions were monitored by TLC analysis using silica gel 60 F_{254} thin layer plates. Flash chromatography was carried out with silica gel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were measured with Bruker Avance DMX 300 and Avance DRX 500 spectrometers. All chemical shifts (δ) are given in ppm relative to TMS. The spectra were referenced to the deuterated solvents indicated in brackets in the analytical data. HRMS spectra were recorded with a Bruker BioTOF III Instrument. IR spectra were measured with a Varian 3100 FT-IR Excalibur Series spectrometer. UV/Vis absorption spectra were obtained with a Varian Cary 300 Bio instrument.

Abbreviations: DCM: dichloromethane, DMF: *N*,*N*-dimethylformamide, Val: valine.

1-(Hydroxymethyl)benzimidazole (8): Benzimidazole (**7**, 2.00 g, 16.93 mmol) was dissolved in THF (50 mL) followed by the slow addition of formaldehyde (37% in H_2O, 1.37 g, 16.93 mmol). The solution was stirred for an additional 1 h, and then the solvent was removed. The residue was recrystallized from EtOH/H_2O to give 2.12 g (84.5%) of the desired product (**8**) as a white solid. ^{1}H NMR (500 MHz, CD_3OD): δ = 8.14 (s, 1 H, imidazole C*H*), 7.60 [dd, $^3J_{H,H}$ = 3.2, $^3J_{H,H}$ = 5.7 Hz, 2 H, H_{ar}], 7.25 (dd, $^3J_{H,H}$ = 3.2, $^3J_{H,H}$ = 6.1 Hz, 2 H, H_{ar}), 4.65 (s, 2 H, CH_2) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 144.5 (q, C_{ar}), 142.5 (t, imidazole C*H*), 134.4 (q, C_{ar}), 124.5 (t, C_{ar}), 123.8 (t, C_{ar}), 120.1 (t, C_{ar}), 111.9 (t, C_{ar}), 69.1 (s, CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3138, 3100, 2945, 2855, 2720, 2543, 1784, 1616, 1497, 1459, 1399, 1274, 1217, 1198, 1092, 1070, 898, 743 cm^{-1}. UV/Vis (MeOH, $c = 1.10 \times 10^{-4}$ mmol/mL): λ (logε) = 244 (3.67), 272 (3.64), 279 (3.64) nm. ESI-HRMS: *m*/*z* calcd. for $C_8H_8N_2O$ [M + H]$^+$ 149.0720; found 149.0718.

1-(Chloromethyl)-1*H*-benzimidazole Hydrochloride (9): 1-(Hydroxymethyl)benzimidazole (**8**, 0.50 g, 3.37 mmol) was suspended in chloroform (10 mL) under Ar followed by the slow addition of thionyl chloride (1.81 g, 15.19 mmol). Stirring was continued for another 2 d. The solvent was then evaporated, and the residue was dried under high vacuum to give 684 mg (100.0%) of the hydrochloride **9**, which was used without further purification for the next step. ^{1}H NMR (500 MHz, CD_3OD): δ = 9.81 (s, 1 H, imidazole C*H*), 8.10–8.08 (m, 1 H, H_{ar}), 7.95–7.93 (m, 1 H, H_{ar}), 7.79–7.73 (m, 2 H, H_{ar}), 6.54 (s, 2 H, CH_2) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 143.4 (t, imidazole *C*H), 132.4 (q, C_{ar}), 131.5 (q, C_{ar}), 129.0 (t, C_{ar}), 128.7 (t, C_{ar}), 116.4 (t, C_{ar}), 114.5 (t, C_{ar}), 53.9 (s, *C*H_2) ppm. IR (KBr): $\tilde{\nu}$ = 3097, 3013, 2965, 1613, 1548, 1499, 1448, 1376, 1311, 1201, 1089, 823, 754, 719 cm^{-1}. UV/Vis (MeOH, $c = 9.60 \times 10^{-4}$ mmol/mL): λ (logε) = 218 (3.79) nm. ESI-HRMS: *m*/*z* calcd. for $C_8H_7ClN_2$ [M + H]$^+$ 167.0371; found 167.0593, calcd. for $C_8H_7ClN_2$ [M + Na]$^+$ 189.0190; found 189.0339.

4-Isoquinolinecarbaldehyde (11): To a solution of 4-bromoisoquinoline (2.00 g, 9.61 mmol) in THF under Ar at –78 °C a solution of *n*-butyllithium (1.6 M in *n*-hexane, 4.49 g, 10.57 mmol) was added slowly. The resulting mixture was stirred for an additional 1 h at –78 °C, and then DMF (1.41 g, 19.23 mmol) was added slowly. Stirring was continued for another 40 min, and then the reaction mixture was poured into aqueous $NaHCO_3$ (5%, 100 mL) and stirred vigorously. Afterwards, the layers were separated, and the aqueous phase was extracted with DCM (3 × 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated, and the residue was subjected to column chromatography on silica gel (DCM/EtOAc, 3:1) to give 908 mg (62.5%) of **11** as a white solid. TLC: R_f = 0.38 (DCM/EtOAc, 3:1, silica). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.39 (s, 1 H, OC*H*), 9.42 (s, 1 H, H_{ar}), 9.20 (dd, $^3J_{H,H}$ = 0.9, $^3J_{H,H}$ = 8.7 Hz, 1 H, H_{ar}), 8.94 (s, 1 H, H_{ar}), 8.08 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, H_{ar}), 7.91 (ddd, $^3J_{H,H}$ = 1.4, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 8.5 Hz, 1 H, H_{ar}), 7.74 (ddd, $^3J_{H,H}$ = 1.1, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 8.1 Hz, 1 H, H_{ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.0 (t, OC*H*), 158.5 (t, C_{ar}), 153.1 (t, C_{ar}), 133.7 (q, C_{ar}), 128.6 (t, C_{ar}), 128.6 (q, C_{ar}), 128.5 (t, C_{ar}), 125.0 (q, C_{ar}), 124.6 (t, C_{ar}), 124.6 (t, C_{ar}) ppm. IR (KBr): $\tilde{\nu}$ = 3422, 2957, 2858, 2765, 1695, 1620, 1568, 1501, 1373, 1231, 1151, 1068, 901, 781, 763, 717, 663, 632 cm^{-1}. UV/Vis (MeOH, $c = 2.85 \times 10^{-5}$ mmol/mL): λ (logε) = 447.5 (5.37), 419.0 (4.51) nm. ESI-HRMS: *m*/*z* calcd. for $C_{10}H_7NO$ [M + H]$^+$ 158.0600; found 158.0607.

4-(Hydroxymethyl)isoquinoline (12): To a solution of carbaldehyde **11** (908 mg, 5.77 mmol) in EtOH (130 mL), $NaBH_4$ (219 mg, 5.78 mmol) was added in portions, and the mixture was stirred for 45 min. Water (50 mL) was added, and after 20 min of additional stirring, AcOH (1.98 mL, 34.66 mmol) was added slowly. The solution was extracted with DCM (60 mL), and the layers were separated. The organic layer was washed with a saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (1 × 20 mL), dried with $MgSO_4$ and concentrated, and the residue was subjected to column chromatography on silica gel (DCM/EtOAc/MeOH, 75:25:5 → 75:25:11) to give 631 mg (68.5%) of **12** as a white solid. TLC: R_f = 0.18 (DCM/EtOAc/MeOH, 75:25:5, silica). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.06 (s, 1 H, H_{ar}), 8.37 (s, 1 H, H_{ar}), 8.13 (dd, $^3J_{H,H}$ = 0.6, $^3J_{H,H}$ = 8.5 Hz, 1 H, H_{ar}), 7.93 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, H_{ar}), 7.73 (ddd, $^3J_{H,H}$ = 1.3, $^3J_{H,H}$ = 6.9, $^3J_{H,H}$ = 8.5 Hz, 1 H, H_{ar}), 7.61 (ddd, $^3J_{H,H}$ = 1.3, $^3J_{H,H}$ = 6.9, $^3J_{H,H}$ = 8.5 Hz, 1 H, H_{ar}), 5.07 (s, 2 H, CH_2), 3.80–3.38 (br. s, 1 H, OH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.9 (t, C_{ar}), 141.6 (t, C_{ar}), 134.4 (q, C_{ar}), 131.0 (t, C_{ar}), 130.1 (q, C_{ar}), 128.5 (q, C_{ar}), 128.3 (t, C_{ar}), 127.4 (t, C_{ar}), 123.4 (t, C_{ar}), 61.1 (s, *C*H_2) ppm. IR (KBr): $\tilde{\nu}$ = 3174, 3061, 2870, 2835, 2685, 1624, 1592, 1570, 1504, 1392, 1151, 1085, 1013, 895, 875, 775, 745, 634 cm^{-1}. UV/Vis (MeOH, $c = 3.52 \times 10^{-5}$ mmol/mL): λ (logε) = 337.5 (3.84), 346.0 (3.23) nm. ESI-HRMS: *m*/*z* calcd. for $C_{10}H_9NO$ [M + H]$^+$ 160.0757; found 160.0771.

4-(Bromomethyl)isoquinoline Hydrobromide (13): 4-(Hydroxymethyl)isoquinoline (**12**, 400 mg, 2.51 mmol) was dissolved in AcOH (10 mL). A solution of HBr (33% in AcOH, 16 mL) was added, and the mixture was refluxed for 2 h. Et_2O (50 mL) was then added, whereupon the product precipitated as a grey solid. The product was filtered, washed with Et_2O, and dried in vacuo to give 671 mg (88.0%) of **13**, which was used without further purification for the next step. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.85 (s, 1 H, H_{ar}), 8.88 (s, 1 H, H_{ar}), 8.56 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, H_{ar}), 8.46 (dd, $^3J_{H,H}$ = 0.7, $^3J_{H,H}$ = 8.4 Hz, 1 H, H_{ar}), 8.29 (ddd, $^3J_{H,H}$ = 1.3, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 8.5 Hz, 1 H, H_{ar}), 8.03 (ddd, $^3J_{H,H}$ = 1.0, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 8.1 Hz, 1 H, H_{ar}) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 146.7 (t, C_{ar}), 137.4 (t, C_{ar}), 136.5 (q, C_{ar}), 131.3 (t, C_{ar}), 130.8 (q, C_{ar}), 130.5 (t, C_{ar}), 126.7 (t, C_{ar}), 124.2 (q, C_{ar}), 123.9 (t, C_{ar}), 39.5 (s, CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3052, 3003, 2609, 2560, 2027, 1872, 1639, 1611, 1371, 1223, 859, 783, 756, 710 cm^{-1}. UV/Vis (MeOH, $c = 2.00 \times 10^{-5}$ mmol/mL): λ (logε) = 319 (3.57) nm. ESI-HRMS: *m*/*z* calcd. for $C_{10}H_8BrN$ [M + H]$^+$ 221.9918; found 221.9916.

3-(Hydroxymethyl)quinoline (15): To a solution of carbaldehyde **14** (1000 mg, 6.36 mmol) in EtOH (200 mL), $NaBH_4$ (241 mg, 6.36 mmol) was added in portions, and the mixture was stirred for 45 min. Water (50 mL) was added, and after 20 min of additional stirring, AcOH (2.18 mL, 38.18 mmol) was added slowly. The solution was then extracted with DCM (60 mL), and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (1 × 20 mL), dried with $MgSO_4$ and concentrated, and the residue was subjected to column chromatography on silica gel (DCM/EtOAc/MeOH, 75:25:5 → 75:25:11) to give 934 mg (92.3%) of **15** as a white solid. ^{1}H NMR (500 MHz, CD_3OD): δ = 8.85 (d, $^4J_{H,H}$ = 2.1 Hz, 1 H, H_{ar}), 8.28 (d, $^4J_{H,H}$ = 1.0 Hz, 1 H, H_{ar}), 8.01 (dd, $^4J_{H,H}$ = 1.3, $^3J_{H,H}$ = 7.7 Hz, 1 H, H_{ar}), 7.92 (dd, $^4J_{H,H}$ = 1.3, $^3J_{H,H}$ = 8.2 Hz, 1 H, H_{ar}), 7.74 (ddd, $^4J_{H,H}$ = 1.4, $^3J_{H,H}$ = 6.9, $^3J_{H,H}$ = 8.4 Hz, 1 H, H_{ar}), 7.60 (ddd, $^4J_{H,H}$ = 1.1, $^3J_{H,H}$ = 6.9, $^3J_{H,H}$ = 8.1 Hz, 1 H, H_{ar}), 4.89 (s, 2 H, CH_2) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 151.2 (t, C_{Ar}), 147.9 (q, C_{ar}), 136.3 (q, C_{ar}), 135.9 (t, C_{ar}), 131.0 (t, C_{ar}), 129.7 (q, C_{ar}), 129.3 (t, C_{ar}), 128.9 (t, C_{ar}), 128.4 (t, C_{ar}), 62.9 (s, CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3218, 3062, 2922, 2862, 1576, 1499, 1031, 785, 749 cm^{-1}. UV/Vis (MeOH, $c = 2.00 \times 10^{-5}$ mmol/mL): λ (logε) = 225 (4.56), 310 (3.42) nm. ESI-HRMS: *m*/*z* calcd. for $C_{10}H_9NO$ [M + H]$^+$ 160.0757; found 160.0765.

3-(Bromomethyl)quinoline Hydrobromide (16): 4-(Hydroxymethyl)-isoquinoline (**15**, 1.14 g, 7.14 mmol) was dissolved in AcOH (30 mL). A solution of HBr (33% in AcOH, 45 mL) was added, and the mixture was refluxed for 2 h. Et_2O (150 mL) was then added, whereupon the product precipitated as a white solid. The product was filtered, washed with Et_2O, and dried in vacuo to give 1.77 g (81.8%) of **16**, which was used without further purification for the next step. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.36 (d, $^4J_{H,H}$ = 1.9 Hz, 1 H, H_{ar}), 9.16 (d, $^4J_{H,H}$ = 0.53 Hz, 1 H, H_{ar}), 8.40 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, H_{ar}), 8.30 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H, H_{ar}), 8.14 (ddd, $^4J_{H,H}$ = 1.3, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 8.5 Hz, 1 H, H_{ar}), 7.97 (ddd, $^4J_{H,H}$ = 0.9, $^3J_{H,H}$ = 7.1, $^3J_{H,H}$ = 8.1 Hz, 1 H, H_{ar}), 4.88 (s, 2 H, CH_2) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 144.5 (t, C_{ar}), 142.8 (t, C_{ar}), 137.1 (q, C_{ar}), 136.6 (q, C_{ar}), 134.1 (t, C_{ar}), 129.9 (t, C_{ar}), 129.0 (t, C_{ar}), 128.3 (q, C_{ar}), 120.6 (t, C_{ar}), 59.7 (s, CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3064, 2006, 2959, 2875, 2559, 2518, 2361, 1999, 1564, 1281, 1231, 889, 772 cm^{-1}. UV/Vis (MeOH, $c = 2.00 \times 10^{-5}$ mmol/mL): λ (logε) = 232 (4.68), 313 (4.41) nm. ESI-HRMS: *m*/*z* calcd. for $C_{10}H_8BrN$ [M + H]$^+$ 221.9918; found 221.9918.

Benzimidazole Receptor 4: Scaffold **17** (20 mg, 0.04 mmol) and 1-(chloromethyl)-1*H*-benzimidazole hydrochloride (**9**, 45 mg, 0.22 mmol) were dissolved in DMF at 0 °C under Ar. To this solution, NaH (60% dispersion in mineral oil, 19 mg, 0.45 mmol) was added slowly, and the mixture was stirred at this temperature for additional 30 min. The solution was then warmed to room temp. and stirred for another 24 h. The next day, EtOAc (100 mL) was added, and the organic layer was washed with water (1 × 20 mL) and brine (3 × 20 mL), dried with $MgSO_4$ and concentrated, and the residue was subjected to column chromatography on silica gel (DCM/MeOH, 100:2 → 100:12) to give 18 mg (47.5%) of **4** as a slightly yellow solid. TLC: R_f = 0.15 (DCM/MeOH, 10:1, silica). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05 (d, $^3J_{H,H}$ = 10.0 Hz, 3 H, N*H*CO), 8.02 (s, 3 H, H_{ar}), 7.83–7.80 (m, 3 H, H_{ar}), 7.52–7.49 (m, 3 H, H_{ar}), 7.36–7.30 (m, 6 H, H_{ar}), 6.37 (d, $^3J_{H,H}$ = 14.6 Hz, 3 H, CH_2), 6.13 (d, $^3J_{H,H}$ = 14.6 Hz, 3 H, CH_2), 5.11 (dd, $^3J_{H,H}$ = 7.9, $^3J_{H,H}$ = 10.0 Hz, 3 H, Val α-C*H*), 2.62 (s, 9 H, imidazole CH_3), 2.02–1.93 (m, 3 H, Val β-C*H*), 0.99 (d, $^3J_{H,H}$ = 6.7 Hz, 9 H, Val CH_3), 0.51 (d, $^3J_{H,H}$ = 6.7 Hz, 9 H, Val CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.6 (q, *C*ONH), 149.1 (q, imidazole *C*-5), 143.7 (q, C_{ar}), 141.7 (t, C_{ar}), 132.8 (q, imidazole *C*-3), 131.4 (q, C_{ar}), 131.1 (q, imidazole *C*-2), 124.4 (t, C_{ar}), 123.4 (t, C_{ar}), 121.2 (t, C_{ar}), 109.6 (t, C_{ar}), 52.0 (t, Val α-*C*H), 50.3 (s, *C*H$_2$), 33.8 (t, Val β-*C*H), 19.2 (p, Val *C*H$_3$), 18.5 (p, Val *C*H$_3$), 10.2 (p, imidazole *C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3382, 2961, 2952, 1653, 1597, 1500, 1457, 1283, 1210, 740 cm^{-1}. UV/Vis (MeOH, $c = 2.00 \times 10^{-5}$ mmol/mL): λ (logε) = 274 (sh, 3.99) nm. ESI-HRMS: *m*/*z* calcd. for $C_{51}H_{57}N_{15}O_3$ [M + H]$^+$ 928.4842; found 928.4930, calcd. for $C_{51}H_{57}N_{15}O_3$ [M + Na]$^+$ 950.4661; found 950.4733.

Quinoline Receptor 5: Scaffold **17** (75 mg, 0.14 mmol) and 3-(bromomethyl)quinoline hydrobromide (**16**, 254 mg, 0.84 mmol) were dissolved in absolute CH_3CN under Ar. To this solution, $CsCO_3$ (682 mg, 2.09 mmol) was added, and the mixture was refluxed for 5 h whilst stirring. The solution was then cooled to room temp., and stirring was continued for an additional 48 h. The solvent was removed, and the residue was dissolved in DCM (150 mL). The organic layer was washed with water (2 × 30 mL) and saturated aqueous $NaHCO_3$ (1 × 30 mL), dried with $MgSO_4$ and concentrated, and the residue was subjected to column chromatography on silica gel (DCM/MeOH, 100:1 → 100:10) to give 42 mg (31.4%) of **5** as a yellow solid. TLC: R_f = 0.33 (DCM/MeOH, 10:1, silica). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.78 (d, $^4J_{H,H}$ = 2.3 Hz, 3 H, H_{ar}), 8.51 (d, $^3J_{H,H}$ = 9.4 Hz, 3 H, N*H*CO), 8.07 (d, $^3J_{H,H}$ = 8.4 Hz, 3 H, H_{ar}), 7.70–7.63 (m, 9 H, H_{ar}), 7.44 (ddd, $^4J_{H,H}$ = 1.0, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 8.1 Hz, 3 H, H_{ar}), 5.41 (d, $^3J_{H,H}$ = 17.3 Hz, 3 H, CH_2), 5.29 (d, $^3J_{H,H}$ = 17.2 Hz, 3 H, CH_2), 5.27 (dd, $^3J_{H,H}$ = 5.5, $^3J_{H,H}$ = 9.3 Hz, 3 H, Val α-C*H*), 2.44 (s, 9 H, imidazole CH_3), 2.13–2.05 (m, 3 H, Val β-C*H*), 1.07 (d, $^3J_{H,H}$ = 6.7 Hz, 9 H, Val CH_3), 1.00 (d, $^3J_{H,H}$ = 6.8 Hz, 9 H, Val CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.2 (q, *C*ONH), 148.7 (t, C_{ar}), 148.0 (q, imidazole *C*-5), 147.6 (q, C_{ar}), 133.4 (t, C_{ar}), 132.2 (q, imidazole *C*-3), 130.7 (q, imidazole *C*-2), 130.1 (t, C_{ar}), 129.4 (t, C_{ar}), 128.3 (q, C_{ar}), 127.9 (t, C_{ar}), 127.8 (q, C_{ar}), 127.4 (t, C_{ar}), 50.0 (t, Val α-*C*H), 45.1 (s, *C*H$_2$), 34.9 (t, Val β-*C*H), 20.1 (p, Val *C*H$_3$), 17.7 (p, Val *C*H$_3$), 10.1 (p, imidazole *C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3382, 2960, 2919, 2845, 1652, 1593, 1497, 1462, 1422, 1372, 1326, 1222, 787, 752 cm^{-1}. UV/Vis (MeOH, $c = 2.00 \times 10^{-5}$ mmol/mL): λ (logε) = 310 (3.93) nm. ESI-HRMS: *m*/*z* calcd. for $C_{57}H_{60}N_{12}O_3$ [M + H]$^+$ 961.4984; found 961.5012, calcd. for $C_{57}H_{60}N_{12}O_3$ [M + Na]$^+$ 983.4804; found 983.4850.

Isoquinoline Receptor 6: Scaffold **17** (50 mg, 0.09 mmol) and 4-(bromomethyl)isoquinoline hydrobromide (**13**, 169 mg, 0.56 mmol) were dissolved in DMF at 0 °C under Ar. To this solution, NaH

(60% dispersion in mineral oil, 48 mg, 1.12 mmol) was added slowly, and the mixture was stirred at this temperature for an additional 30 min. The solution was then warmed to room temp. and stirred for another 24 h. The next day, EtOAc (100 mL) was added, and the organic layer was washed with water (1 × 20 mL) and brine (3 × 20 mL), dried with $MgSO_4$ and concentrated, and the residue was subjected to column chromatography on silica gel (DCM/MeOH, 100:1 → 100:10) to give 18 mg (20.0%) of **6** as a yellowish-brown solid. TLC: R_f = 0.27 (DCM/MeOH, 10:1, silica). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.22 (s, 3 H, H_{ar}), 8.56 (d, $^3J_{H,H}$ = 9.2 Hz, 3 H, N*H*CO), 8.07 (d, $^3J_{H,H}$ = 8.0 Hz, 3 H, H_{ar}), 7.98 (d, $^3J_{H,H}$ = 8.5 Hz, 3 H, H_{ar}), 7.86 (ddd, $^4J_{H,H}$ = 1.1, $^3J_{H,H}$ = 7.1, $^3J_{H,H}$ = 8.3 Hz, 3 H, H_{ar}), 7.75–7.67 (m, 9 H, H_{ar}), 5.65 (d, $^3J_{H,H}$ = 17.7 Hz, 3 H, CH_2), 5.53 (d, $^3J_{H,H}$ = 17.6 Hz, 3 H, CH_2), 5.23 (dd, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ = 9.2 Hz, 3 H, Val α-C*H*), 2.43 (s, 9 H, imidazole CH_3), 2.06–1.94 (m, 3 H, Val β-C*H*), 1.03 (d, $^3J_{H,H}$ = 6.8 Hz, 9 H, Val CH_3), 0.95 (d, $^3J_{H,H}$ = 6.8 Hz, 9 H, Val CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.4 (q, *C*ONH), 153.4 (t, C_{ar}), 147.6 (q, imidazole *C*-5), 139.9 (t, C_{ar}), 132.8 (q, imidazole *C*-3), 132.6 (q, C_{ar}), 131.7 (t, C_{ar}), 130.6 (q, imidazole *C*-2), 129.0 (t, C_{ar}), 128.1 (q, C_{ar}), 128.0 (t, C_{ar}), 124.5 (q, C_{ar}), 121.4 (t, C_{ar}), 49.8 (t, Val α-*C*H), 43.1 (s, *C*H$_2$), 34.7 (t, Val β-*C*H), 20.2 (p, Val *C*H$_3$), 17.4 (p, Val *C*H$_3$), 9.9 (p, imidazole *C*H$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3382, 2959, 2919, 2850, 1717, 1656, 1591, 1505, 1462, 1260, 1093, 1020, 780, 751 cm^{-1}. UV/Vis (MeOH, $c = 2.00 \times 10^{-5}$ mmol/mL): λ (logε) = 316 (3.93) nm. ESI-HRMS: *m*/*z* calcd. for $C_{57}H_{60}N_{12}O_3$ [M + H]$^+$ 961.4984; found 961.4992, calcd. for $C_{57}H_{60}N_{12}O_3$ [M + Na]$^+$ 983.4804; found 983.4813.

Perchlorate Salts (General Procedure): The primary amine was dissolved in Et_2O or, if not soluble therein, in MeOH. Perchloric acid (1 equiv., 70% in H_2O) was added, and the solution was stirred for 15 min. In some cases, the perchlorate salts precipitated; otherwise, the solvent was removed, and the residue was dried under high vacuum to give the desired product as a white salt.

^{1}H NMR Titrations: All salts and ligands were pre-dried under high vacuum and then kept under argon. $CDCl_3$ of 99.8% isotopic purity, from Sigma–Aldrich, was used as purchased. For the titration experiments, a Bruker Avance DMX 300 (^{1}H: 300 MHz) was used. The NMR titrations were repeated 2–3 times.

Stock solutions of the host molecule being studied were prepared in $CDCl_3$ at a final concentration of 1.00×10^{-3} mmol/mL. Stock solutions of the ammonium ions were prepared by dissolving approximately 10 equiv. of the perchlorate salts in 2 mL of the host stock solution. From these solutions, 10–500 μL portions were again diluted with the host stock solution up to 1 mL to prepare the samples measured. The shifts of the proton signals were monitored, and 10 data points were recorded. The association constants were calculated from changes in the chemical shifts of the protons between the nitrogen and the linkage of the receptor arm to the scaffold. Nonlinear curve fitting for a simple 1:1 binding model was carried out with the SIGMAPLOT program.

For the Job Plot titrations, stock solutions of the host molecule and the respective guest molecules were prepared in $CDCl_3$ at a final concentration of 1.9×10^{-3} mmol/mL. From the host solution, 100–1000 μL were transferred into an NMR tube, and the tube was filled with the guest solution up to 1 mL so that the sum of the host and guest concentration was constant in each probe. The samples were measured, and afterwards, analyzed by plotting the molar fraction of guest (X_G) as a function of $[H_0] \times \Delta\delta$.[35] The Plots themselves were generated using SIGMAPLOT 9.0.

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