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An ion pair receptor facilitating the extraction of chloride salt from the aqueous to the organic phase†

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A new multitopic salt receptor based on an L-ornithine scaffold was synthesized using a simple approach; this receptor consists of a crown ether based cation and two squaramide anion binding domains. The binding properties of this receptor were measured spectrophotometrically, in acetonitrile solution. A comparative binding study of reference receptors enabled the evaluation of the role of particular binding domains in salt binding. The collected data revealed a stronger contribution of the anion binding domain located in the side chain of amino acid than the α-supported one. The cooperative action of these two binding domains is needed to strongly associate salts. Receptor **1** was found to be able to extract chloride salt from the aqueous to the organic phase.

Introduction

Amino acids are convenient building blocks for the preparation of anion receptors. Numerous cyclic and open chain receptors prepared from amino acids or containing amino acid units have been proposed and shown to effectively bind anions.[1,2] Apart from their use in recognizing achiral anions, the chiral nature of amino acids has been used for the construction of molecular receptors that are able to discriminate enantiomers.[3] In particular, such receptors have been broadly investigated for the chiral recognition of protected amino acids.

More recently, we reported that amino acids are also an excellent platform for the construction of receptors that are able to simultaneously bind anions and cations.[4] Introducing crown ether units using the carboxylic acid function and transforming the amino function into the corresponding thiourea led to receptors that were able to bind ion pairs more strongly than anions (TBA salts). The enhancement of anion binding in the presence of sodium cations was attributed to the cooperative binding of cation and anions. The sodium cations are bound to the crown ethers and interaction with lone pairs of the sulfur atom in the thiourea function increases the acidity and their ability to form stronger complexes. This enhancement in ion pair binding is even more pronounced when the thiourea anion binding site is replaced by a urea function.[5] In this case, the hard sodium cation was found to interact more strongly with the hard urea than with the soft thiourea function. Furthermore, we found that in the case of amino acid based ion pair receptors such as ornithine or lysine, the presence of an additional amine function can be engaged to introduce another anion binding site into the receptor structure.[6] This finding resulted in more effective ion pair recognition by harnessing a double cooperative effect: enhancement of anion binding in the presence of cations and the simultaneous action of two anion binding domains. Finally, we demonstrated that incorporation of such ion pairs in a polymeric chain led to materials that were able to extract ion pairs from the aqueous to the organic phase.[4a] Nevertheless, none of the proposed receptors alone were able to behave in the same manner and could be used in such extraction. Thus we concluded that stronger binding domains should be substituted into the ornithine based receptor structure. We envisioned that the use of two properly oriented squaramide anion binding domains with the ability to act cooperatively and a crown ether cation binding domain in the ornithine scaffold may lead to strong ion pair receptors that are able to extract salts from aqueous solutions. Unlike the urea or thiourea anion binding sites, the squaramide function is known to form much stronger complexes with anions, therefore this expectation seemed promising.[7]

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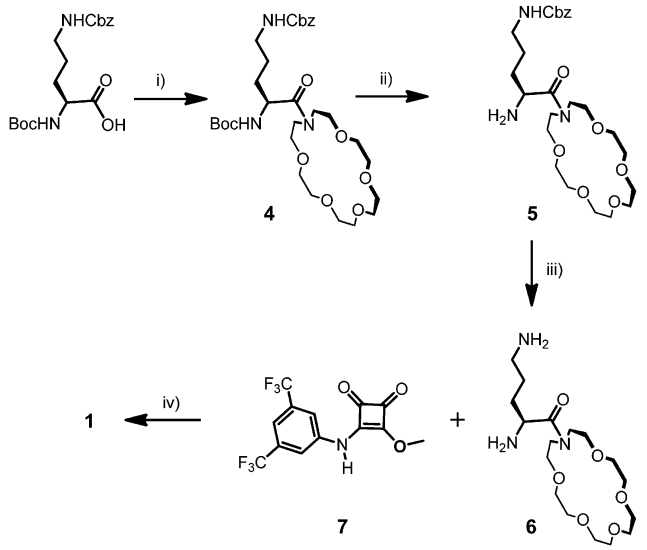
† Electronic supplementary information (ESI) available: Spectroscopic data for all new compounds, UV-Vis and ^{1}H NMR measurements (Job plots, dilution curves, binding isotherms), and extraction experiment data. CCDC 1478326. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6nj01482h

Results and discussion

Receptor synthesis

In order to test this hypothesis, we designed and synthesized squaramide based ion pair receptors in four steps starting from



Scheme 1 Synthesis of receptor **1**. *Reagents and conditions*: (i) DCC, 1-aza-18-crown-6, CH_2Cl_2, 0 °C to r.t., 92%; (ii) TFA-CH_2Cl_2 (1 : 1), r.t., then $NaHCO_3$; (iii) H_2, Pd/C, MeOH-THF, r.t., quantitative; and (iv) *N*,*N*-diisopropylethylamine, MeOH, r.t., 69%.

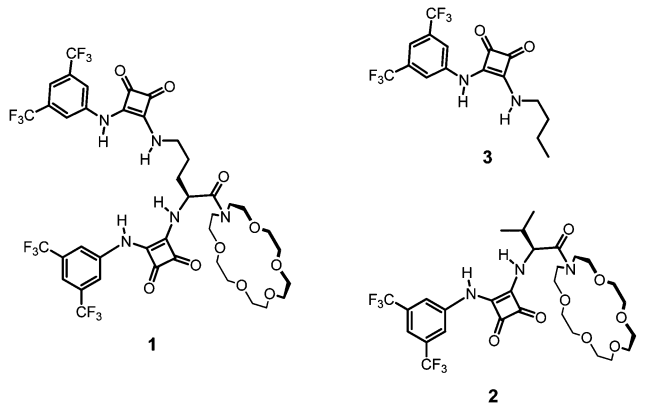


Fig. 1 The structures of the investigated receptors **1–3**.

the commercially available Nα-Boc-Nδ-Cbz-L-ornithine (Scheme 1). The ion pair receptor is easily affordable because the synthetic protocol presented here requires only one chromatographic purification in the first step, after introducing a crown ether unit into the ornithine scaffold. The Boc protection is then cleaved in a trifluoroacetic acid mediated reaction and the corresponding amine **5** can be simply purified using extraction. Finally, after quantitative Cbz deprotection and reaction of the resultant diamine **6** with two equivalents of squaramide **7** in the presence of *N*,*N*-diisopropylethylamine, precipitation of receptor **1** occurred (Fig. 1). Filtration and washing the precipitate with methanol furnished an ornithine based ion pair receptor possessing two squaramide anion binding domains and one cation binding domain in overall good yield.

Anion and ion pair binding studies

The binding ability of receptor **1** towards selected anions (added as TBA salts) and ion pairs (titration with TBA salts in the presence of sodium perchlorate) was investigated spectrophotometrically in acetonitrile solution. To prove that self-association of receptor **1** in the investigated concentration range does not occur, a dilution study experiment was first performed. Job plot analysis showed that receptor **1** forms complexes with anions in 1 : 1 stoichiometry. Receptor **1** was found to form very strong complexes with investigated anions in the arrangement order $Br^- < NO_2^- < PhCOO^- < Cl^- < CH_3COO^-$ (Table 1).

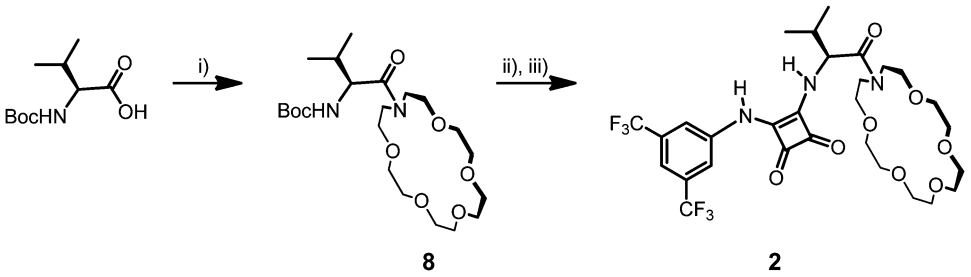
Table 1 Association constants (K_a) for interactions between receptor **1** and selected anions in the absence or presence of one equivalent of sodium perchlorate[a]

	1	**1** + 1 eq. Na^+
Br^-	5.37×10^4	5.12×10^4
NO_2^-	1.04×10^5	1.07×10^5
Cl^-	1.62×10^6	1.58×10^6
$PhCOO^-$	6.31×10^5	6.30×10^5
CH_3COO^-	2.95×10^6	2.90×10^6

[a] UV-Vis, solvent CH_3CN, temperature 293 K, $[\mathbf{1}] = 1.75 \times 10^{-5}$ M, anions added as TBA salts [TBAX] ~2 mM, M^{-1}, sodium added as $NaClO_4$, errors < 10%.

Strikingly, the chloride anion is bound to the receptor very strongly, even more so than the Y-shaped benzoate anion. We concluded that this strong chloride anion association might be attributed to the good fitting of this anion to the receptor **1** binding cavity. Furthermore, we found that in all cases, in the presence of sodium cations no enhancement in anion binding was observed. This may suggest such strong formation of hydrogen bonds of both squaramide functions that the cooperativity originating from the simultaneous binding of cations and anions, as previously reported for amino acid based receptors, is here negligible.

To verify this assumption, L-valine based reference receptor **2** possessing one squaramide anion binding domain was synthesized and tested towards chloride anions (Scheme 2 and Table 2). Indeed, receptor **2** is able to bind chloride anions more strongly in the presence of one equivalent of sodium cations (added as $NaClO_4$) than in the presence of tetrabutylammonium cations. Specifically, receptor **2** associated with chloride anions with a stability constant of 3.23×10^4 M^{-1}, while in the presence of sodium cations an enhancement of more than one and a half times was observed (Table 2). More importantly, receptor **2** is able to form complexes with chloride anions two orders of magnitude more weakly than receptor **1** possessing two anion binding sites. Based on these results we presumed that the squaramide anion binding domain located on the δ-position of ornithine based receptor **1** makes a greater contribution to the formation of the complexes than the α-supported anion binding domain. Therefore, the next reference receptor **3** (part of the structure of receptor **1**) was synthesized and tested towards chloride anions. Indeed, the homotopic receptor **3** associated chloride anions one magnitude of order more strongly than L-valine based reference receptor **2** ($K_{Cl^-} = 2.17 \times 10^5$ M^{-1} for receptor **3**), but still one magnitude of order more weakly than the double-supported receptor **1**. Thus we found that despite the moderate to strong abilities to form chloride complexes shown by receptors **2** and **3**, the use of two anion binding sites in receptor **1**



Scheme 2 Synthesis of receptor **2**. *Reagents and conditions*: (i) DCC, 1-aza-18-crown-6, CH_2Cl_2, 0 °C to r.t., 85%; (ii) TFA-CH_2Cl_2 (1 : 1), r.t.; and (iii) squaramide **7**, *N*,*N*-diisopropylethylamine, MeOH, r.t., 62%.

Table 2 Comparison of association constants (K_a) for interactions between receptors **1–3** and chloride anions in the absence or presence of one equivalent of sodium perchlorate[a]

	1	2	3
TBACl	1.62×10^6	3.23×10^4	2.17×10^5
NaCl[b]	1.58×10^6	5.25×10^4	2.06×10^5

[a] UV-Vis, solvent CH_3CN, temperature 293 K, [1] = 1.75×10^{-5} M, [2] = 3.96×10^{-5} M, [3] = 2.92×10^{-5} M, M^{-1}, errors < 10%. [b] Added as a mixture of TBACl and one equivalent of sodium perchlorate.

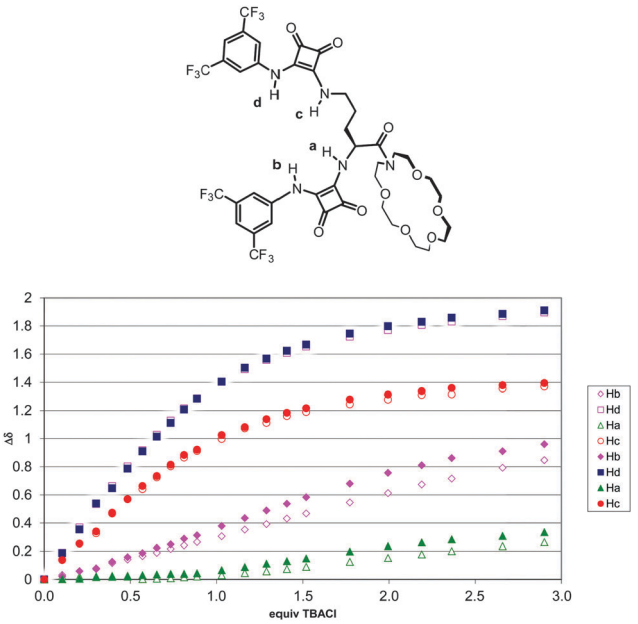


Fig. 2 ^{1}H NMR titrations of receptor **1** with TBACl in the presence of 1 equiv. of $NaClO_4$. Profiles based on the chemical shift ($\Delta\delta$) of squaramide protons. Open symbols refer to titration in the absence of sodium cations; full symbols refer to titration in the presence of sodium cations.

allows even stronger complexes to be created. This is clear evidence for the not only simultaneous but cooperative action of two, properly oriented anion binding sites in receptor **1**'s structure.[8]

To gain more insight into the binding mode of receptor **1**, ^{1}H NMR titration experiments were conducted. It should be noted that receptor **1** is insufficiently soluble in acetonitrile for this experiment to be carried out in pure solvent, thus a mixture of 10% DMSO-d_6 in CD_3CN was used. To carefully track the changes upon titration and distinguish between the signals from the α- and δ-supported domains of each squaramide NH, 2D NMR analysis was first conducted. This experiment showed that the NHs that belong to the α-supported anion binding domain were shifted upfield relative to the squaramide protons assigned to the binding domain located in the side chain of the amino acid. Analysis of the binding isotherms obtained upon titration of receptor **1** with chloride anions in the presence and absence of sodium cations supports a few conclusions. First, contrary to UV-vis measurements done in acetonitrile, the ^{1}H NMR titration data are better fitted to a 1 : 2 model. In the presence of DMSO-d_6 a decrease in the ability to form [**1**·Cl^-] complexes was observed, and the stability constant so obtained revealed that receptor **1** binds the chloride anion with stability constants of $K_{11} = 2.80 \times 10^3$ M^{-1} and $K_{12} = 60$ M^{-1}. Secondly, as for the anion binding domains in molecular receptors **2** and **3**, in the case of receptor **1** there is a clear difference in participation in anion binding by the α- and δ-supported anion binding sites. In particular, subsequent addition of tetrabutylammonium chloride to a solution of receptor **1** caused considerable chemical shifts in the ^{1}H NMR spectrum of the signals corresponding to both protons of the δ-supported anion binding domain. This indicates the formation of strong hydrogen bonds between anions and that domain. On the other hand the changes in chemical shifts were less pronounced for protons assigned to the α-supported anion binding domain, which suggests a lesser participation of this domain in the binding event. It was also found that in the presence of one equivalent of sodium perchlorate, receptor **1** binds the chloride anion more strongly ($K_{11} = 4.06 \times 10^3$ M^{-1} and $K_{12} = 3.76 \times 10^2$ M^{-1}) than in the presence of tetrabutylammonium cations (Fig. 2).

X-Ray analysis

Additional support for this rationalization of the binding event by receptor **1** comes from solid state measurements. Despite making several attempts to crystallize complexes of **1** with salts, we were unable to obtain crystals suitable for X-ray measurements. Nevertheless, we were able to crystallize receptor **1** by exposure of dimethylsulfoxide solution of **1** to atmospheric moisture. The crystal structure so obtained showed no intramolecular hydrogen bonds between receptor **1** units (Fig. 3). In the absence of anions the squaramide NHs form strong hydrogen

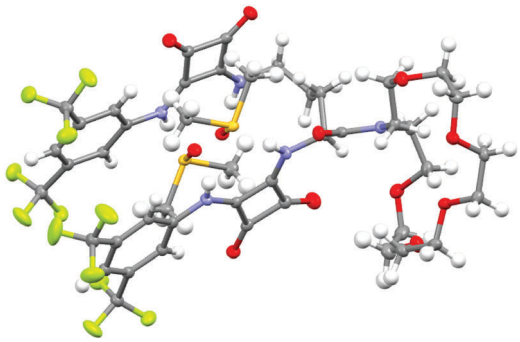


Fig. 3 X-Ray crystal structure of receptor **1**.

bonds with residual DMSO, which corresponds to an average N–O distance of 2.97 Å. Interestingly the α- and δ-supported anion binding domains are situated in parallel but the NHs are directed against each other. Presumably, the opposite arrangement of these domains may facilitate anion binding through the simultaneous action of both anion binding sites, while only spacing of these domains is needed.

Extraction and transport study

Given that receptor **1** is able to interact so strongly with chloride anions, we decided to test it in the extraction of chloride salt from the aqueous to the organic phase. Toluidine blue dye containing the chloride counteranion was selected to track the visual effects, and a suspension of **1** in a mixture of 20% *n*-butanol in chloroform was used as an extractant. Treatment of an aqueous solution of toluidine blue (2 ml, 5×10^{-5} M) with 2 ml of suspension containing 1, 10 and 50 equivalents of **1** resulted in a colored organic phase as well as clarification of the organic solution (Fig. 4). The observed color changes intensified gradually with increasing content of receptor **1** in the organic phase, while no color change was observed for reference experiments relying on the extraction of dye solution with a mixture of *n*-butanol and chloroform (Fig. 4). Analysis of the aqueous phases using UV-vis spectroscopy was chosen for quantification of these results. We found that with increasing amount of receptor **1** in the organic phase, an increased drop in dye concentration in the aqueous phase was observed. In particular, when 1, 10 and 50 equivalents of receptor **1** were used in extraction experiments, a 20%, 30% and 68% drop in dye concentration in the aqueous phase was observed, respectively. A 15% drop in dye concentration was also observed in the reference experiment.

Given that no color change in the organic phase was observed during the test experiment, we concluded that this drop in dye concentration in the test experiment originated from the extraction of *n*-butanol to the aqueous phase and its dilution. Therefore, the results obtained for the extraction of toluidine blue using increasing amounts of receptor **1** should be analyzed carefully, taking into account the dilution of the aqueous phase with extracted *n*-butanol. Addition of tetrabutylammonium chloride to the biphasic mixture after extraction caused partial back extraction of the dye from the organic to the aqueous phase. Moreover we found that neither reference receptors **2** and **3**, nor 15-crown-5 is able to effectively extract toluidine blue from the aqueous to the organic phase (Fig. 5). When 50 equivalents of receptors **2**, **3** or 15-crown-5 were used in extraction experiments the organic phases were only slightly colored and 15–18% drop in dye concentration (similar to the reference experiment) in the aqueous phase was observed.

Encouraged by these results, we decided to use receptor **1** in the extraction of a salt consisting of two hard ions, namely sodium chloride. Therefore, we conducted analogous experiments and extracted 2 ml of 5×10^{-5} M solution of sodium chloride with 2 ml containing 10 and 100 equivalents of receptor **1** in an *n*-butanol and chloroform mixture. Only in the case of 10 equivalents of receptor **1** clarification of the organic solution was observed, and this experiment was further analyzed. The sodium content in the aqueous phase was monitored using atomic absorption spectrometry (AAS). Unfortunately, we found that the sodium content in both aqueous phases (referenced and after extraction with receptor **1** solution) contained the same amount of sodium cations. Specifically, there was no drop in the concentration of sodium chloride in the aqueous phase with respect to the reference experiment. Moreover the AAS

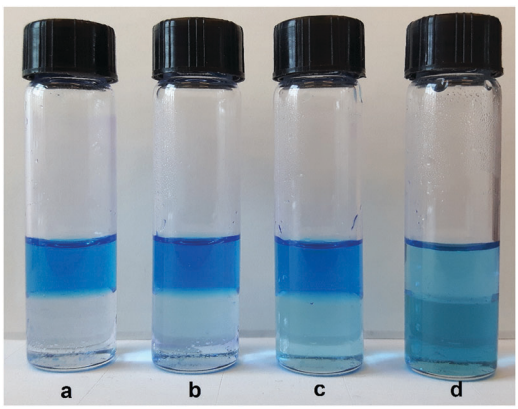


Fig. 4 Extraction of aqueous solution of toluidine blue (top layers) with: (a) 20% *n*-butanol in chloroform, (b) 1 equiv. of receptor **1** in the organic phase, (c) 10 equiv. of receptor **1** in the organic phase, (d) 100 equiv. of receptor **1** in the organic phase (bottom layers).

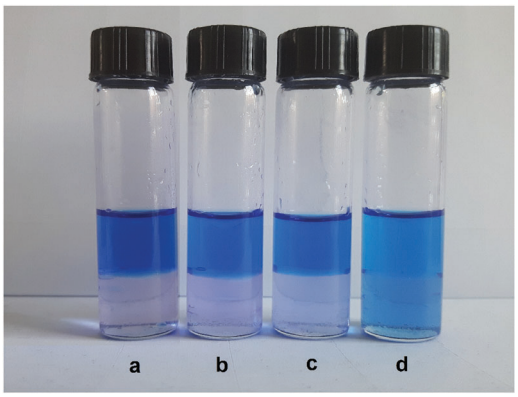


Fig. 5 Extraction of aqueous solution of toluidine blue (top layers) with a solution of 20% *n*-butanol in chloroform containing 50 equivalents of: (a) 15-crown-5; (b) receptor **2**; (c) receptor **3**; and (d) receptor **1** (bottom layers).

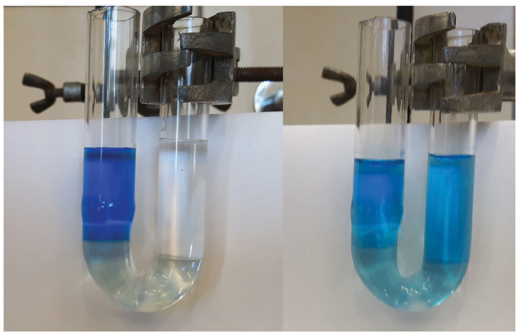


Fig. 6 Bulk liquid membrane transport experiment. Left: Initial state, right: after 48 h.

experiment confirmed the dilution of the aqueous phase with *n*-butanol after extraction, because atomization of the sample taken from the aqueous phase of referenced extraction was higher than in the case of stock solution.

Finally we decided to use receptor **1** in a bulk liquid membrane transport experiment (Fig. 6). Initially, the source phase consisted of 3 ml of 5×10^{-5} aqueous toluidine blue solution and 3 ml of the 20% *n*-butanol in chloroform mixture; the liquid membrane contained 10 equivalents of receptor **1**. The dye concentration in the receiving phase was determined by UV-Vis measurements and it was found that after 48 h the dye concentration in both source and receiving phases was the same. As expected, as in the case of the extraction experiments, the transport study failed when a salt consisting of two hard ions was used. Thus the extraction and transport experiments demonstrate that receptor **1** is capable of extracting and transporting chloride salts from the aqueous solution. Nevertheless, these experiments could be performed only when chloride salts containing soft countercations were used.

Conclusions

Summing up, we have synthesized, using a simple approach, ion pair receptor **1** consisting of two squaramide anion binding domains and one crown ether based cation binding site. Based on UV-vis and ^{1}H NMR measurements we have shown that receptor **1** is able to form strong complexes with the salts investigated. Two reference receptors (parts of receptor 1) were synthesized and tested to better understand the influence of particular binding sites in receptor **1** structure on salt binding. We have found that the anion binding domain located in the side chain of amino acid makes a greater contribution to salt binding than the α-supported one. Moreover, we found that simultaneous action of these two domains is responsible for cooperative anion binding. The strong ability of receptor **1** to bind chloride salts was used in extraction and transport experiments. We have shown that receptor **1** is able to extract chloride salts from aqueous to organic phase. However, these experiments could be performed only when chloride salts containing soft countercations were used. Therefore, our future efforts will focus on synthesizing copolymers containing receptor **1** analogs allowing them to extract and transport hard ions from aqueous to organic phase effectively.

Experimental section

Compounds **4**, **5** and **7** were prepared according to the procedure found in the literature.[4,9] Other reagents and chemicals were of reagent grade quality and purchased commercially. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 or 500 MHz. ^{1}H NMR chemical shifts δ are reported in ppm referenced to the residual solvent signal (DMSO-d_6 or $CDCl_3$). UV-Vis titrations were performed in acetonitrile using a Thermo Spectronic Unicam UV500 spectrophotometer. High resolution mass spectra (HRMS) were measured on a Quattro LC Micromass unit using the ESI technique. Binding constants Ka were calculated using HypSpec or HypNmr 2008 software.

Preparation of receptor 1

To the degassed solution of **5** (1.02 g, 2 mmol) in 50 ml of THF–MeOH (1 : 4) catalytic amounts of 10% Pd/C were added. The reaction mixture was kept under a H_2 atmosphere (balloon pressure) at room temperature overnight. The catalyst was removed by filtration through a pad of Celite and washed with MeOH. The filtrate was concentrated under reduced pressure to give the crude product in quantitative yield (754 mg). The diamine **6** was used in the next step without further purification.

HRMS (ESI): calcd for $C_{17}H_{35}N_3O_6Na$ $[M + Na]^+$: 400.2424, found: 400.2430.

To a solution of diamine **6** (113 mg, 0.3 mmol) in 2 ml of MeOH, *N*,*N*-diisopropylethylamine (180 μl, 1 mmol) and squaramide 7 (330 mg, 0.97 mmol) were added. After stirring overnight at room temperature, the precipitate was filtered off, washed twice with methanol and dried *in vacuo* to give a white solid (205 mg) in 69% yield.

HRMS (ESI): calcd for $C_{41}H_{41}F_{12}N_5O_{10}Na$ $[M + Na]^+$: 1014.2560, found: 1014.2540.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.44 (s, 1H), 10.08 (s, 1H), 8.30–8.40 (m, 1H), 7.90 (d, J = 8.2 Hz, 5H), 7.78 (s, 1H), 7.51 (s, 2H), 5.28 (s, 1H), 3.86–3.40 (m, 26H), 1.98–1.74 (m, 2H), 1.70–1.52 (m, 2H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 184.77, 184.38, 180.47, 170.09, 169.73, 168.30, 162.77, 162.51, 140.97, 131.57, 131.30, 131.04, 130.78, 126.31, 124.14, 121.97, 119.80, 117.63, 114.43, 70.33, 70.00, 69.98, 69.92, 69.89, 69.70, 68.74, 68.25, 52.79, 48.41, 46.23, 43.31, 30.69, 25.48.

Preparation of compound 8

To a solution of *N*-(*tert*-butoxycarbonyl)-L-valine (1.0 g, 4.60 mmol) and 1,3-dicyclohexylocarbodiimide (1.04 g, 5.07 mmol) in 20 ml of dry dichloromethane, 1-aza-18-crown-6 (1.22 g, 4.64 mmol) at 0 °C (ice bath) was added. The reaction mixture was stirred for 30 min and then left at room temperature overnight. The precipitate was filtered off, washed with dichloromethane and the filtrate was evaporated. The residue was purified by silica gel column chromatography (5% methanol in chloroform) to give the title product as a colorless oil (1.80 g, 85% yield).

HRMS (ESI): calcd for $C_{22}H_{42}N_2O_8Na$ $[M + Na]^+$: 485.2839, found: 485.2857.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.24 (d, J = 9.5 Hz, 1H), 4.47 (dd, J = 9.2, 6.3 Hz, 1H), 3.91–3.42 (m, 24H), 2.08–1.88 (m, 1H), 1.45 (s, 9H), 0.95 (dd, J = 14.9, 6.8 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.42, 155.55, 79.17, 70.74, 70.70, 70.59, 70.55, 70.38, 69.60, 69.52, 54.88, 48.63, 46.92, 31.90, 28.28, 19.53, 17.31.

Preparation of receptor 2

Compound **8** (1 g, 2.16 mmol) was dissolved in 30 ml of dichloromethane and 5 ml of trifluoroacetic acid was added. The reaction mixture was stirred at room temperature until the starting material was consumed (TLC monitoring). The mixture was then treated with saturated and solid $NaHCO_3$ to neutralize trifluoroacetic acid. The biphasic mixture was then separated and the organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained amine was used in the next step without further purification.

HRMS (ESI): calcd for $C_{17}H_{34}N_2O_6Na$ $[M + Na]^+$: 385.2315, found: 385.2321.

To a solution of the aforementioned amine (204 mg, 0.56 mmol) in 2 ml of MeOH, *N*,*N*-diisopropylethylamine (110 μl, 0.62 mmol) and squaramide **7** (275 mg, 0.81 mmol) were added. After stirring overnight at room temperature, the reaction mixture was concentrated and the residue was purified by silica gel column chromatography (5% methanol in chloroform) to give receptor **2** as a white oil (232 mg, 62% yield).

HRMS (ESI): calcd for $C_{29}H_{37}F_6N_3O_8Na$ $[M + Na]^+$: 692.2383, found: 692.2391.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.24 (d, J = 9.7 Hz, 1H), 8.09 (s, 2H), 7.68 (s, 1H), 5.07 (dd, J = 9.5, 6.1 Hz, 1H), 3.76–3.40 (m, 24H), 2.08 (m, 1H), 0.92 (t, J = 7.2 Hz, 6H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 184.16, 180.38, 170.19, 168.99, 162.38, 141.15, 131.76, 131.49, 131.23, 130.97, 126.41, 124.24, 122.08, 119.91, 117.98, 114.75, 70.22, 70.01, 70.00, 69.97, 69.92, 69.87, 69.76, 68.71, 68.28, 57.82, 48.32, 46.35, 32.08, 18.85, 16.88.

Preparation of receptor 3

To the suspension of squaramide **7** (502 mg, 1.48 mmol) in 10 ml of MeOH, *n*-butylamine (160 μl, 1.62 mmol) was added. After stirring overnight at room temperature, the precipitate was filtered off, washed twice with methanol and dried *in vacuo* to give a white solid (490 mg) in 87% yield.

HRMS (ESI): calcd for $C_{16}H_{14}F_6N_2O_2Na$ $[M + Na]^+$: 403.0857, found: 403.0870.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.01 (s, 2H), 7.70 (s, 1H), 7.62 (s, 1H), 3.54–3.72 (m, 2H), 1.65–1.46 (m, 2H), 1.36 (dq, J = 14.3, 7.2 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 184.76, 180.28, 169.77, 162.23, 141.16, 131.49, 131.23, 130.97, 126.42, 124.25, 122.08, 119.91, 117.85, 114.50, 43.56, 32.55, 19.01, 13.42.

X-ray measurements

The crystallographic data for receptor **1** have been deposited with the Cambridge Crystallographic Data Center as Supplementary Publication No. CCDC 1478326.

Receptor **1** was crystallized by slow diffusion of H_2O into DMSO solution of **1**. The X-ray measurement of receptor **1** was performed at 100(2) K on a Bruker D8 Venture Photon100 CMOS diffractometer equipped with a TRIUMPH monochromator and a MoKα fine focus sealed tube (λ = 0.71073 Å). A total of 2890 frames were collected using the Bruker APEX2 program.[10] The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm.[11] The integration of the data using a triclinic unit cell yielded a total of 40 481 reflections to a maximum θ angle of 26.00° (0.81 Å resolution), of which 10 005 were independent (average redundancy 4.046, completeness = 100.0%, R_{int} = 1.91%, R_{sig} = 1.74%) and 9686 (96.81%) were greater than $2\sigma(F^2)$. The final cell constants a = 8.8305(17) Å, b = 9.1614(18) Å, c = 16.760(3) Å, α = 75.104(5)°, β = 81.510(5)°, γ = 77.835(5)°, V = 1274.6(4) Å^3 are based upon the refinement of the *XYZ*-centroids of 9916 reflections above 20 $\sigma(I)$ with 4.678° < 2θ < 52.21°. Data were corrected for absorption effects using the multi-scan method (SADABS).[12] The ratio of minimum to maximum apparent transmission was 0.958. The calculated minimum and maximum transmission coefficients (based on crystal size) were 0.8870 and 0.9750.

The structure was solved and refined using the SHELXTL software package using the space group $P1$, with Z = 1 for the formula unit $C_{45}H_{53}F_{12}N_5O_{12}S_2$ and the Flack parameter equal to 0.088(14).[13,14] The final anisotropic full-matrix least-squares refinement on F^2 with 705 variables converged at R_1 = 2.33%, for the observed data and wR_2 = 5.59% for all data. The goodness-of-fit was 1.039. The largest peak in the final difference electron density synthesis was 0.253 e$^-$ Å^{-3} and the largest hole was −0.169 e$^-$ Å^{-3} with an RMS deviation of 0.034 e$^-$ Å^{-3}. On the basis of the final model, the calculated density was 1.496 g cm^{-3} and F(000), 594 e$^-$.

All non-hydrogen atoms were refined anisotropically. Most of the hydrogen atoms were placed in calculated positions and refined within the riding model. Coordinates of hydrogen atoms engaged in hydrogen bonds were refined together with their isotropic temperature parameters. The temperature factors of the constrained hydrogen atoms were not refined and were set to either 1.2 or 1.5 times larger than $U_{eq.}$ of the corresponding heavy atom. The atomic scattering factors were taken from the International Tables.[15]

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