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Cooperative ion pair recognition by multitopic L-ornithine based salt receptors.

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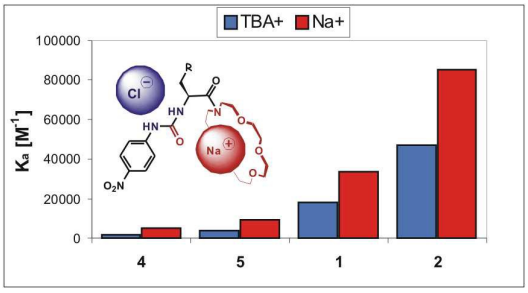
Graphical Abstract:



TOC Sentence: Development of L-ornithine based multitopic receptors allowed to obtain an effective and selective salt receptor.

Abstract: The L-ornithine scaffold was used to develop molecular receptors with improved efficacy in ion pair binding. With two appropriately oriented strong anion binding domains (urea and (thio)urea groups) and one cation binding group (crown ether moiety), these receptors exhibit effective association to the sodium salts of selected anions. We show that the simultaneous action of the two anion binding domains, reinforced by cation coordination, is responsible for the binding strength of receptors **1** and **2**. The binding constants for the anions and sodium salt complexes of these receptors were determined using spectrophotometric and ^{1}H NMR titration measurements. Besides carboxylate ions, in the presence of sodium cations all the selected anions associate to receptors **1** and **2** in a positive cooperative manner. The strongest cooperative binding was observed for the association of sodium chloride to receptor **2**, supported with urea and thiourea anion binding domains (K_a= 85 500 M^{-1}). Lacking two strong anion binding domains, receptors **4** and **5** can only interact with sodium chloride much more weakly (K_a= 5 100 and 8 900 M^{-1}, respectively).

INTRODUCTION

The natural tendency of oppositely charged ions to associate in ion pairs led us to consider the combination of cation and anion recognition motives into a single molecular receptor to simultaneously bind a cation and anion in the form of an ion pair (solvent, ligand-separated, or contact ion pair). The resulting heteroditopic molecular receptor-ion pair complex is electrically neutral and therefore proves advantageous in salt solubilization, extraction, and membrane transport

applications.[1] Moreover, through electrostatic or allosteric effects the complexation of the first ion can increase the receptor's affinity for the second ion.[2] This positive cooperative effect is especially important for anion recognition, as anions usually coordinate more weakly than cations to molecular receptors.[3] To maximize the positive cooperativity of ions binding, the geometry of the heteroditopic receptor must be optimized so that the anion and cation binding sites are located in spatial proximity. This creates difficulties in the design and synthesis of ion pair receptors, and therefore the number of effective heteroditopic receptors remains limited. Many of the reported receptors have a multi-macrocyclic structure, and their synthesis is usually low yielding and requires the application of high-dilution techniques.[4] Due to the "closed" structure of these receptors it is difficult to introduce an additional structural element, such as a new binding domain, chromophore or increased solubility/lipophilicity function into the system. Furthermore, fine-tuning the structure, and concurrently the binding properties, of many heteroditopic receptors (not only multi-macrocyclic) is very problematic. Therefore, synthesis of heterotopic receptors that can effectively recognize ion pairs and are concurrently prone to structural modification is an important area of interest.

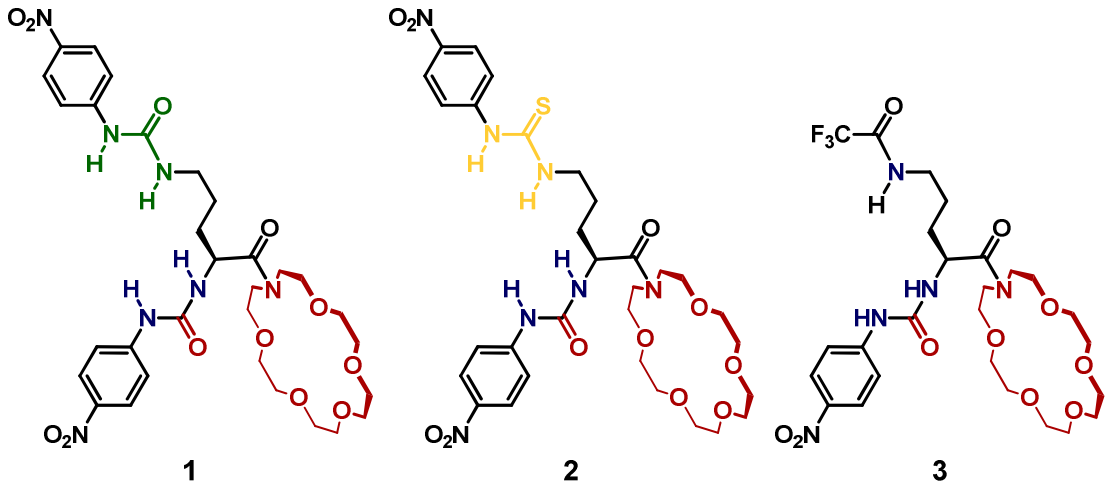


Fig. 1 The structure of amino acid based salt receptors.

We recently reported a heterotopic molecular receptor **3** that is easy to prepare and modify, has an "open" structure, yet displays high positive cooperativity between anion and cation recognition.[5] This receptor is based on L-ornithine molecular scaffold and consists of aza-18-crown-6 (cation binding domain), a nitrophenylurea group (main anion and supporting the cation binding domain) and a trifluoroacetamide group (supporting the anion binding domain). In the course of our detailed studies on this type of receptor, we have established that a urea group attached to the amino acid α-position serves not only as an anion binding domain, but also provides an additional binding site

(oxygen lone pairs) for cation recognition.[6] We also have found that an amide group placed at δ-carbon contributes to the anion recognition and is crucial to high cooperation in anion binding. Thus, to increase the contribution of the amino acid side arm located H-bond donor group to anion recognition, we prepared receptors **1** and **2** containing a urea or thiourea group, respectively, at δ-position. This strategy seems to be the obvious way to boost the strength of anion recognition, as one of the main principles in the design of molecular receptors is to multiply the non-covalent interactions.[7] On the other hand, this strategy may pose some unexpected problems.[8] First, mainly due to preorganization problems, introducing an additional binding group to a receptor does not always increase its binding affinity. Secondly, if the two (or more) binding sites substantially differ in H-bonding donor abilities, one group may dominate the recognition process and greatly diminish the contribution of other groups. Lastly, binding sites with H-bond donors and acceptors (amide, urea, thiourea groups) may interact with each other by means of inter/intra-molecular hydrogen bonds. Therefore to address these questions, we report here the solution binding studies of anion and salt recognition of receptors **1** and **2** containing two strong anion-binding domains and a cation-binding domain (Fig. 1).

RESULTS AND DISCUSSION

Receptors **1** and **2** were prepared in five steps starting with commercially available Nα-Boc-Nδ-Cbz-L-ornithine by the sequential substitution of amino acid functional groups with aza-18-crown-6, and nitrophenyl-urea or -thiourea moieties. The binding abilities of **1** and **2** toward anions and salts were investigated spectrophotometrically in an acetronitrile solution. As thiourea and, especially, the urea group are known for their tendencies to form inter- and/or intra-molecular hydrogen bonds, dilution studies were carried out in a concentration range of 4-30 μM and showed no evidence for self-association.

UV-Vis Binding Studies.

Upon the addition of anions (as tetra-*n*-butylammonium salts, TBA) to ~23 μM solutions of **1** or **2**, the band centered at 337 nm undergoes a distinct red-shift up to 351 nm. This shift is attributed to the hydrogen bond formation between the anions and the (thio)ureas NH groups. The presence of two sharp isosbestic points at 265 and 340 nm implies that only two species coexist at the equilibrium point. The 1:1 binding stoichiometry was also verified by a Job plot analysis. Importantly, no additional absorption band is observed at a longer wavelength, which would indicate anion-induced deprotonation of one of the (thio)ureas NH hydrogen atoms.[9] The only

exception is the deprotonation of the thiourea group of **2** by strongly basic acetate anions. The association constants calculated by the nonlinear regression analysis of the binding isotherms are presented in Table 1.[10]

Table 1 Association constants (K_a) for interactions between receptors **1** and **2** and selected anions in the absence or presence of one equivalent of sodium cations[a]

	Receptor 1			Receptor 2		
	TBA^+	**Na^+**	**K_{Na}/K_{TBA}**	**TBA^+**	**Na^+**	**K_{Na}/K_{TBA}**
NO_2^-	3 800	7 800	2,05	7 200	18 500	1,82
Br^-	3 400	5 100	1,5	3 700	4 700	1,27
Cl^-	18 200/	33 500	1,84	46 800	85 500	2,57
$PhCOO^-$	460 000	161 000	0,35	$1{,}19 \cdot 10^6$	526 000	0,44
Ac^-	$3{,}5 \cdot 10^6$	280 000	-	deprotonation	deprotonation	-

[a] UV-Vis, solvent CH_3CN, temperature 293 K, [**1**] = 2.58×10^{-5} M, [**2**] = 2.35×10^{-5} M, anions added as TBA salts [TBAX] ~2 mM; M^{-1}, Except of Ac^- errors < 10%.

Table 1 (rows 2 and 4) reveals that receptors **1** and **2** exhibit a preference for Y-shaped, basic carboxylate anions which is typical for anion receptors possessing a single (thio)urea group.[8a] As can be seen from the table, compound **2**, containing urea and thiourea groups, binds anions stronger than its bis-urea counterpart. This effect can be attributed to the stronger H-bond donor ability of the thiourea group compared to the urea group based on its pKa values (pKa = 21.1 and 26.9, respectively in DMSO).[11]

Our previous studies on cation recognition of the family of heterotopic receptors based on an L-ornithine platform, including compound **3**, revealed that these receptors strongly bind sodium cation, whereas other cations are bound much more weakly.[5,6] Therefore, the affinity of receptors **1** and **2** towards selected anions in the presence of one equivalent of a sodium cation has been examined. Table 1 (rows 3 and 6) reveals two different trends. In the presence of sodium cations, the association constants of the strongly coordinated anions such as benzoate and acetate decrease considerably (negative cooperation). This can be explained in terms of the formation of strong ion-pairs outside the receptor. On the other hand, the association constants of anions that TBA salts bind to receptor **1** or **2** less strongly are greatly enhanced in the presence of cobound Na^+ cations. The largest positive cooperativity factor (i.e. K_{Na}/K_{TBA}), is observed for the simultaneous binding of sodium and chloride ions by receptor **2**. However, the enhancement of chloride and nitrite anion

association to receptor **1** is also significant. The coordination of sodium cation to receptors **1** and **2** not only changes the association constant values but also alter the selectivity of anion recognition. Specifically, the combination of negative and positive cooperative effects causes receptors **1** and **2** to be much less selective for carboxylates in favor of chloride.

In order to verify aforementioned assumption that both receptors **1** and **2** associate to sodium salts in the most cooperative manner the chloride binding in the presence of potassium and ammonium cations were also examined. The resulting association constants of receptor **1** and **2** complexes of selected chloride salts are summarized in Table 2. Inspection of those data revealed that both receptors associate to chloride anion stronger in the presence of sodium cation than in the presence of potassium or ammonium cation. This effect is especially pronounced in case of receptor **2**.

Table 2 Association constants (K_a) for interactions between receptors **1** and **2** and chloride anion in the absence or presence of one equivalent of selected cations[a]

C^+	Receptor 1		Receptor 2	
	Cl^-	K_{C+}/K_{TBA+}	Cl^-	K_{C+}/K_{TBA+}
TBA^+	18 200	-	46 800	-
Na^+	33 500	1.84	85 500	2.57
K^+	27 500	1.51	53 700	1.14
NH_4^+	20 000	1.10	40 750	0.87

[a] UV-Vis, solvent CH_3CN, temperature 293 K, [**1**] = 2.58×10^{-5} M, [**2**] = 2.35×10^{-5} M, anions added as TBA salts [TBAX] ~2 mM; M^{-1}, Errors < 10%.

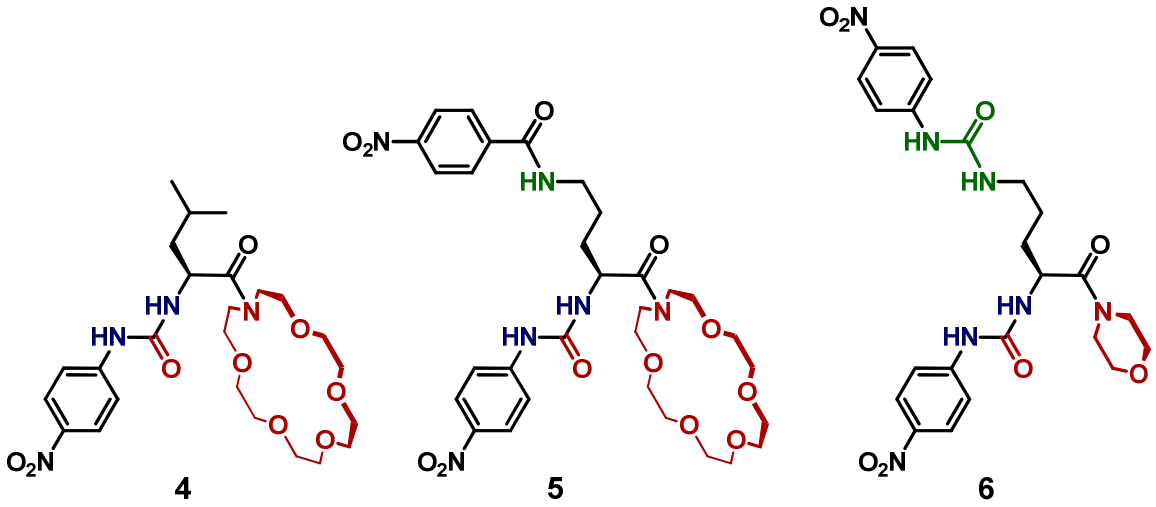


Fig. 2 The structure of reference salt receptors **4**, **5** and **6**.

To test the cooperation of both anion binding sites in anion and salt recognition, UV-Vis titration of the leucine based receptor (**4**) lacking the (thio)urea group attached to δ-carbon was performed (Fig. 2). As expected, the leucine-based receptor associates with the chloride anion relatively weakly, with association constants of 1700 M^{-1}. Thus the presence of an additional urea binding domain in receptor **1** resulted in an almost 11-fold enhancement, while receptor **2,** containing the thiourea moiety, could bind the chloride anion with 25-fold greater strength. In the presence of one equivalent of the sodium cation, this receptor binds the chloride anion with association constants of 5100 M^{-1} whereas receptor **1** and **2** bind the chloride anion 6.6 and 16.7 times more strongly, respectively.

To verify the hypothesis that both δ-(thio)urea NH's play an important role in anion recognition, a reference receptor **5** containing 4-nitrobenzamide instead of 4-nitrophenylurea moiety was tested (Fig. 2). The absence of one hydrogen donor bond in receptor **5** in comparison to receptors **1** and **2** caused a significant decrease in anion and salt binding. Specifically, the chloride anion and its sodium salt are bound to receptor **5** with association constants of 3900 and 8900 M^{-1}, respectively.

Finally, the binding properties of receptor **6** possessing anion binding domains only were investigated. It was demonstrated that replacement of crown ether moiety with morpholine unit resulted in loss of salt binding cooperativity of receptor **6**. Specifically, the chloride anion is bound to this receptor more weakly in the presence of sodium cations (K_a= 25100 and 28200 M^{-1}, respectively). Thus it was confirmed that presence of cation binding domain is essential for cooperative salt binding.

Taken together, the spectroscopic titration data of compounds **1**-**5** demonstrates that the number and strength of hydrogen bond donors located on the amino acid side arm is essential for effective ion binding, as is clearly seen in Fig. 3.

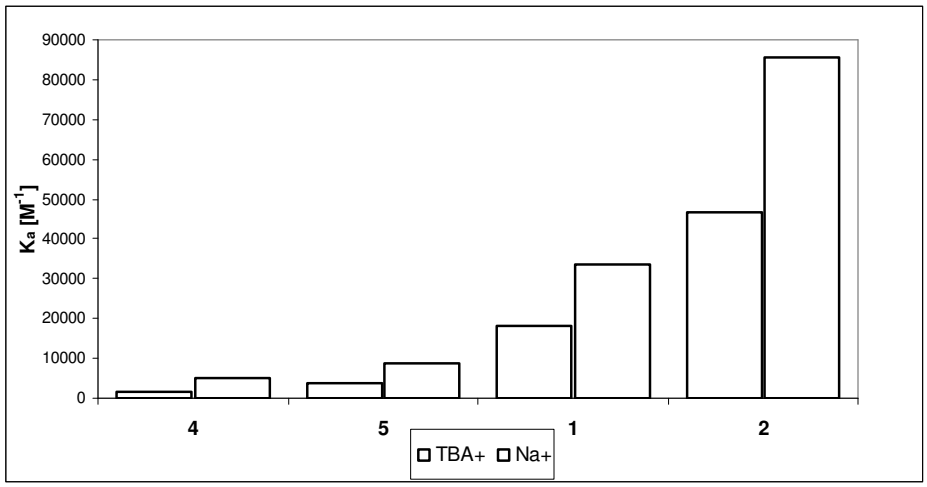
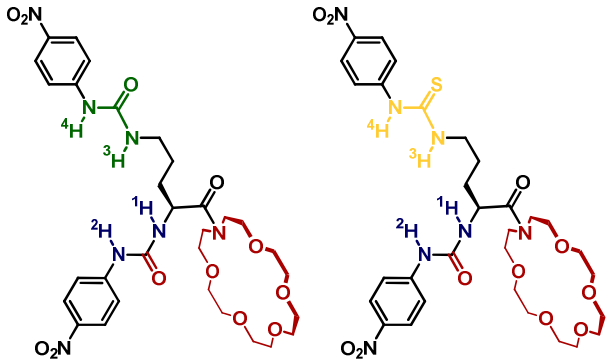


Fig. 3 Comparison of association constants for interactions of receptors **1,2,4,5** with chloride anion in the absence or presence of one equivalent of Na^+.

NMR Binding Studies.

To gain more insights into the anion and salt binding mode, NMR studies of **1** and **2** in CD_3CN were undertaken. First, the affinity of receptor **1** for sodium cations was established. The addition of sodium perchlorate to a 3.4 mM solution of **1** caused downfield shift of the crown ether protons. The association constant of [**1**·**Na**$^+$] complex was calculated to be 15 200 M^{-1}. Then ^{1}H NMR anion binding studies were undertaken. Upon the addition of TBABr, large downfield shifts in all four NH protons were observed (Table 3), which indicate the formation of strong hydrogen bonds between anions and receptors **1** and **2**.[12] These anion induced shifts ($\Delta\delta$) were largest for the NH protons attached to aromatic rings and smaller for NH connected to aliphatic carbons, reflecting the difference in the H-bond donor ability of both protons. Interestingly, complexation-induced shifts in both urea groups of **1** are almost identical, suggesting comparable participation of these groups in anion recognition. In the case of receptor **2**, the thiourea group NH proton shifts are larger than the urea groups, but not to an extent that would suggest the domination of the thiourea group in anion recognition.

Table 3 Association constants (K_a) for interactions of receptors **1** and **2** with bromide anions in the absence or presence of one equivalent of sodium cations[a]



1 2

		^{1}H	^{2}H	^{3}H	^{4}H	K_a
Receptor 1	**TBABr**	0.78	1.84	1.10	1.84	1445
	NaBr	1.23	2.18	1.31	2.02	2454
	δ_{Na}-δ_{TBA}	0.45	0.34	0.21	0.18	
Receptor 2	**TBABr**	0.86	1.68	1.32	2.17	2754
	NaBr	1.33	2.03	1.57	2.32	6156
	δ_{Na}-δ_{TBA}	0.47	0.35	0.25	0.15	

[a] ^{1}H NMR, solvent CD_3CN, temperature 293 K, [**1**] = 2.57 mM, [**2**] = 2.66 mM, [TBABr] =60 mM; M^{-1}, Errors < 10%.

The addition of anions to receptors **1** and **2** pretreated with one equivalent of $NaPF_6$ causes thio(urea) NH downfield shifts that are even larger than those in the absence of the cation evidence for stronger anion binding. The most pronounced anion-induced chemical shift differences (δ_{Na}-δ_{TBA}) in the absence and presence of the sodium cation were observed for both the ^{1}H and ^{2}H protons of the urea group attached to the α-carbon. Interestingly, the changes in the ^{3}H and ^{4}H protons of the urea group attached to the δ-carbon are less pronounced. This may suggest that sodium cation complexation directly influences the α-attached urea group.

These results are in accordance with our previous studies, which revealed that enhancement in salt binding can be rationalized in terms of the complexation of sodium cation to crown ether moiety and lone pairs of urea oxygen atoms.[5,6a,13] Sodium cation coordination to urea oxygen increases the acidity of the urea NH's and fixes the nitrophenylurea moiety orientation, and exposes the NH groups to enable better cooperation with a second (thio)urea function.

The association constants calculated from the ^{1}H NMR data obtained from the titrations of **1** and **2** with a bromide anion in the absence and presence of sodium cation are presented in Table 2.

Similarly to the UV-Vis studies, the NMR titrations revealed that receptor **1** associates to bromide anion more weakly than receptor **2**. In the presence of the sodium cation, bromide complexation is stronger for both receptors, thus demonstrating cooperative salt binding.

The association constants calculated with the NMR titrations allowed direct comparison of receptors **1** and **2** with the previously reported receptor **3**. Receptor **3** equipped with trifluoroacetamide group binds the bromide anion almost four and seven times more weakly than receptors **1** and **2**, respectively. In the presence of the sodium cation, receptor **1** binds bromide anion slightly more weakly than receptor **3** (3450 M^{-1}), while receptor **2**, with the thiourea group, associates to bromide almost two times more strongly. Interestingly, receptor **3** displays a cooperativity factor K_{Na+}/K_{TBA+} =8.8, while receptors **1** and **2** bind sodium salts in a less cooperative manner, namely K_{Na+}/K_{TBA+} =1.7 and 2.2, respectively. We have therefore demonstrated that effective ion pair association can be achieved in two different manners. For receptors possessing one strong and one relatively weak anion binding group, the sodium complexation greatly increases anion and consequently salt recognition. On the other hand, effective salt coordination can be achieved by the cooperative action of strong anion binding groups, and cation and anion cooperation can be less significant.

CONCLUSIONS

In summary, we have found that the L-ornithine scaffold can be used for the construction of molecular receptors bearing three recognition sites, including cation binding and two strong anion binding domains. Spectrophotometric and ^{1}H NMR titration measurements enabled us to determine the association constants for the anions and sodium salts complexes of these receptors. Based on these data, we found that two appropriately oriented (thio)urea groups act in a concerted fashion, leading to strong anion binding, and in consequence salt binding. We have also shown that the (thio)urea group at δ-position is necessary for strong anion binding, as judged from comparative studies of receptor **5**.

Our previous study showed that strong salt recognition can result from high cooperation of cation and anion binding. This study supports the idea that construction of effective ion-pair receptors can be achieved by means of a combination of strong anion coordination at the cost of smaller cation and anion binding cooperativity. This approach led us to prepare molecular receptors that strongly interact with ion pairs.

EXPERIMENTAL SECTION

Receptors **1**, **2** and **5** were prepared according to the previously reported procedure for receptors **3** and **4**.[5,6] Other reagents and chemicals were of reagent grade quality and purchased commercially. ^{1}H and ^{13}C NMR spectra, as well as titration experiments, were recorded on a Bruker 300 MHz spectrometer. ^{1}H NMR chemical shifts δ are reported in ppm referenced to the protonated residual solvent signal (CD_3CN). UV-Vis titrations were performed using a Thermo Spectronic Unicam UV500 Spectrophotometer.

Receptor **1**.

HRMS (ESI): calcd for $C_{31}H_{43}N_7O_{12}Na$ $[M+ Na]^+$: 728.2867, found: 728.2861.

^{1}HNMR (300 MHz, CD_3CN) δ: 1.55-1.90 (m, 4H), 3.15 -3.27 (m, 2H), 3.46-3.85 (m, 24H), 4.65-4.85 (m, 1H), 6.19 (t, 1H, *J*=6 Hz), 6.52 (d, 1H, *J*=9 Hz), 7.48 (d, 2H, *J*=9 Hz), 7.58 (d, 2H, *J*=9 Hz), 7.97 (d, 2H, *J*=9 Hz), 8.03 (d, 2H, *J*=9 Hz), 8.67 (s, 1H), 8.76 (s, 1H).

^{13}CNMR (75 MHz, CD_3CN) δ: 26.77, 30.26, 39.97, 47.79, 49.57, 51.09, 70.11, 70.64, 70.70, 70.77, 70.87, 70.97, 71.30, 117.92, 118.14, 125.70, 125.89, 142.20, 143.41, 147.25, 147.89, 155.68, 155.89, 174.43.

Receptor **2**.

HRMS (ESI): calcd for $C_{31}H_{43}N_7O_{11}Na$ $[M+ Na]^+$: 744.2693, found: 744.2660.

^{1}HNMR (300 MHz, CD_3CN) δ: 1.60-1.90 (m, 4H), 3.40-3.85 (m, 26H), 4.77-4.89 (m, 1H), 6.55 (d, 1H, *J*=9 Hz), 7.31 (m, 1H), 7.43 (d, 2H, *J*=9 Hz), 7.71 (d, 2H, *J*=9 Hz), 7.98 (d, 2H, *J*=9 Hz), 8.09 (d, 2H, *J*=9 Hz), 8.22 (s, 1H), 8.78 (bs, 1H).

^{13}CNMR (75 MHz, CD_3CN) δ: 25.78, 31.62, 45.46, 48.47, 50.19, 51.09, 70.03, 70.79, 71.50, 71.54, 71.65, 71.74, 71.79, 122.81, 125.79, 126.19, 142.95, 147.00, 147.61, 155.76, 174.86, 181.97.

Receptor **5**.

HRMS (ESI): calcd for $C_{31}H_{42}N_6O_{12}Na$ $[M+ Na]^+$: 713.2758, found: 713.2783.

^{1}HNMR (300 MHz, CD_3CN) δ: 1.60-1.85 (m, 4H), 3.35-3.45 (m, 2H), 3.45-3.60 (m, 19H), 3.65-3.79 (m, 5H), 4.77-4.89 (m, 1H), 6.56 (d, 1H, *J*=9 Hz), 7.43 (d, 2H, *J*=9 Hz), 7.57 (m, 1H), 7.90-7.85 (m, 4H), 8.15-8.24 (m, 3H).

^{13}CNMR (75 MHz, CD_3CN) δ: 26.04, 31.30, 40.47, 47.92, 49.57, 50.59, 61.48, 70.26, 71.01, 71.10, 71.15, 71.22, 71.27, 71.32, 118.13, 124.45, 125.71, 129.30, 141.32, 142.44, 147.22, 150.38, 155.17, 166.29, 174.39.

Receptor **6**.

HRMS (ESI): calcd for $C_{23}H_{26}N_7O_8$ $[M-H]^-$: 528.1843, found: 528.1841.

^{1}HNMR (300 MHz, CD_3CN) δ: 1.55-1.85 (m, 4H), 3.20-3.30 (m, 2H), 3.05-3.25 (m, 8H), 4.75-4.90 (m, 15H), 5.62 (t, 1H, *J*=6 Hz), 6.48 (d, 1H, *J*=7.8 Hz), 7.43 (d, 2H, *J*=6 Hz), 7.57 (d, 2H, *J*=7.2 Hz), 7.86 (s, 1H), 7.99 (d, 2H, *J*=7.2 Hz), 8.08 (d, 2H, *J*=7.2 Hz), 8.16 (s, 1H).

^{13}CNMR (125 MHz, CD_3CN) δ: 26.66, 30.52, 40.19, 43.58, 47.06, 50.43, 67.35, 67.40, 118.16, 118.38, 125.79, 125.97, 142.53, 142.79, 147.27, 147.61, 155.29, 155.82, 172.74.

Supporting Information. Spectroscopic data for all new compounds, as well as experimental procedures for binding studies.

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