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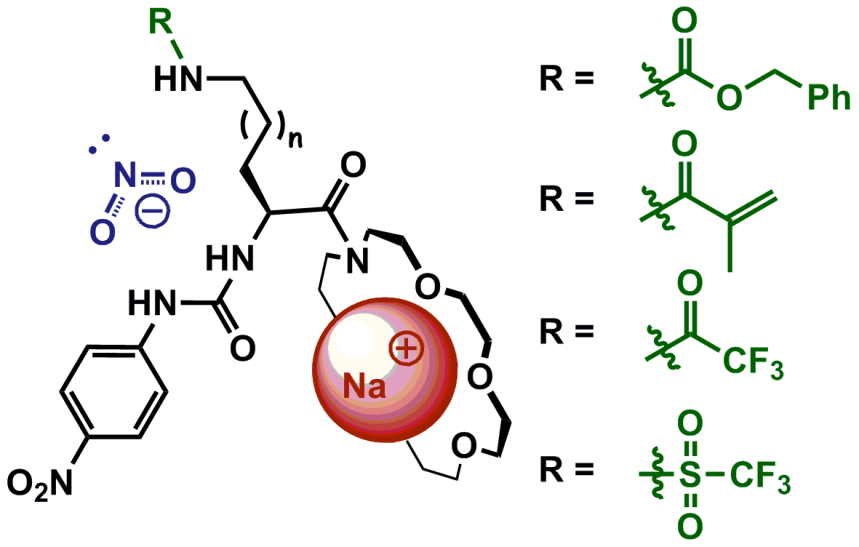
Systematic development of the geometric and electronic properties of the amino acid based salt receptors lead to very effective and selective **$NaNO_2$** receptor.

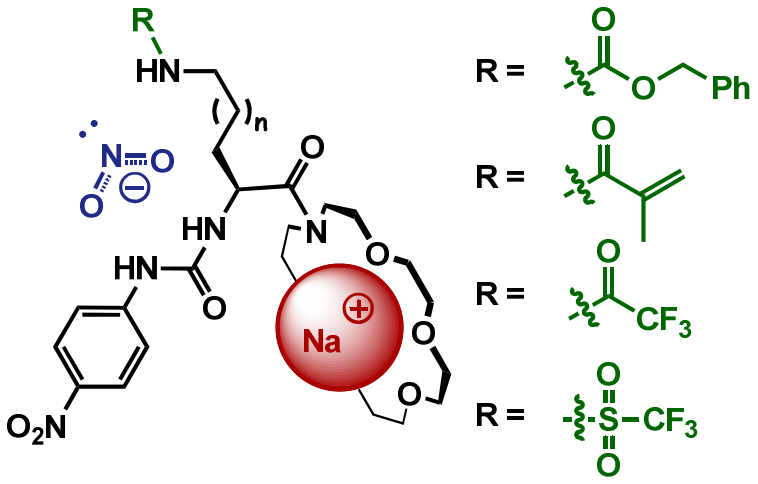


Boosting the salt recognition abilities of L-ornithine based multitopic molecular receptors by harnessing a double cooperative effect

*Piotr Piątek, Marcin Karbarz, Jan Romański**

Department of Chemistry, University of Warsaw, Pasteura 1, 02-093 Warsaw, Poland

Graphical Abstract:



ABSTRACT: A family of L-ornithine based salt receptors **1a-f** was synthesized, bearing a cation binding site and multiple anion binding sites (nitrophenylurea and amide groups) that may simultaneously associate with a single anion. The variation in H-bond donor abilities of one of these anion binding sites has relatively little influence on NO_2^- anion binding when the anion is

accompanied by a noncoordinating TBA cation. However, in the presence of sodium cation which strongly coordinates with the cation binding domain of **1a-f**, the increased H-bond donor abilities of the anion binding group results in a significant enhancement of NO_2^- anion binding. A direct correlation between the anion binding site H-bond donor tendencies and the binding cooperation of sodium cation and nitrite anion was also observed. Cation complexation fixes the nitrophenylurea moiety orientation and exposes that domain to bind anions. This cation and anion cooperation induces a second cooperative effect, namely the simultaneous association of a single anion to both urea and amide binding groups. Receptor **1d** was found to be highly selective for $NaNO_2$ over sodium bromide and nitrate. A transport experiment using a bulky liquid membrane showed that this receptor can effectively transport $NaNO_2$ from aqueous through organic phase.

INTRODUCTION

In both cation and anion binding by monotopic molecular receptors, the complexed ion is accompanied by a counterion. Thus for a receptor to associate with a target ion, it must compete with the counterion. To overcome this problem, so-called noncompeting counterions are often used in laboratory applications. However, in many real-life applications, the luxury of noncompetitive counterions is not available, and hence inter-ion competition can be significant. The only way to eliminate this problem is through the simultaneous binding of both anion and cation, i.e. salt binding.[1] This can be achieved using heteroditopic receptors to simultaneously bind the anion and the cation.[2] A potential advantage to be gained by covalently linking the anion and the cation binding sites is the possibility of positive binding cooperativity, which enhances the selectivity and efficacy of ionic species recognition.[3] Moreover, the complexation of both ions by a ditopic receptor enhances salt lipophilicity, thus facilitating its solubilization,

extraction and membrane transport.[4] However, in spite of their potential applications in various fields, the number of such ion pair receptors remains limited. Among other factors, this is due to the difficulties associated with the synthesis of heteroditopic receptors, which obviously must consist of at least two properly oriented (located) heterotopic binding regions. Moreover, many of the most effective salt receptors have multi-macrocyclic structure and their synthesis requires the application of high-dilution techniques.[3a-c, 3g-h, 4a,5] Therefore, fine-tuning of the structure, and concurrently the binding properties, of many heteroditopic receptors is very problematic. Furthermore, due to the "closed" structure of these receptors it is difficult to introduce an additional structural element into the system, such as a new binding domain, chromophore/fluorophore or increased solubility/lipophilicity function. Therefore the synthesis of multitopic receptors that can effectively recognize ion pairs and are concurrently prone to structural modification is an important area of interest.

Recently, we reported on the synthesis and binding of heteroditopic salt receptor based on L-ornithine scaffold.[6] This receptor consists of aza-18-crown-6 (cation binding domain) and nitrophenylthiourea (anion binding domain) appended to the carboxylic and α-amino groups of L-ornithine, respectively. Moreover, the ornithine δ-amino group was converted to a metacrylamide function and used for the preparation of copolymers containing the receptor. Further study revealed that this receptor is susceptible to structural changes that alternate its binding propensity. For example, we found that replacing the soft sulfur atom of the nitrophenylthiourea binding domain with a hard oxygen atom (receptor **1c**) reinforced Na^+ cation binding, which affected anion and salt binding.[7] In particular, this modification resulted in decreased anion binding strength, although immensely increased salt binding strength and selectivity towards $NaNO_2$ were observed. Detailed solution binding studies supported by

molecular modeling revealed that urea C=O group coordination to the crown ether complexed sodium cation is responsible for the reinforcement of anion binding to urea NH protons. Moreover, we noticed that the metacrylamide group located on the side arm of the receptor **1c** provides an additional binding domain for anion recognition and we showed that the strength of anion and salt binding is decreased when this group is not present. Based on this observation we envisioned that introducing a stronger H-bond donor group to the L-ornithine side arm should increase the anion and consequently salt association strength. Thus, here we report a study concerning the influence of such receptor side arm modifications on anion and salt binding effectiveness. For the receptor found to be the most effective, we also describe a detailed binding study and preliminary extraction and membrane transport experiments.

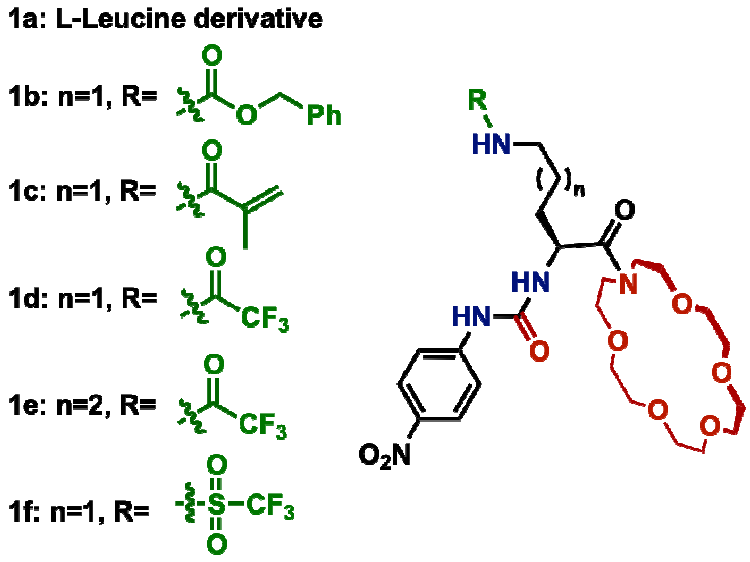
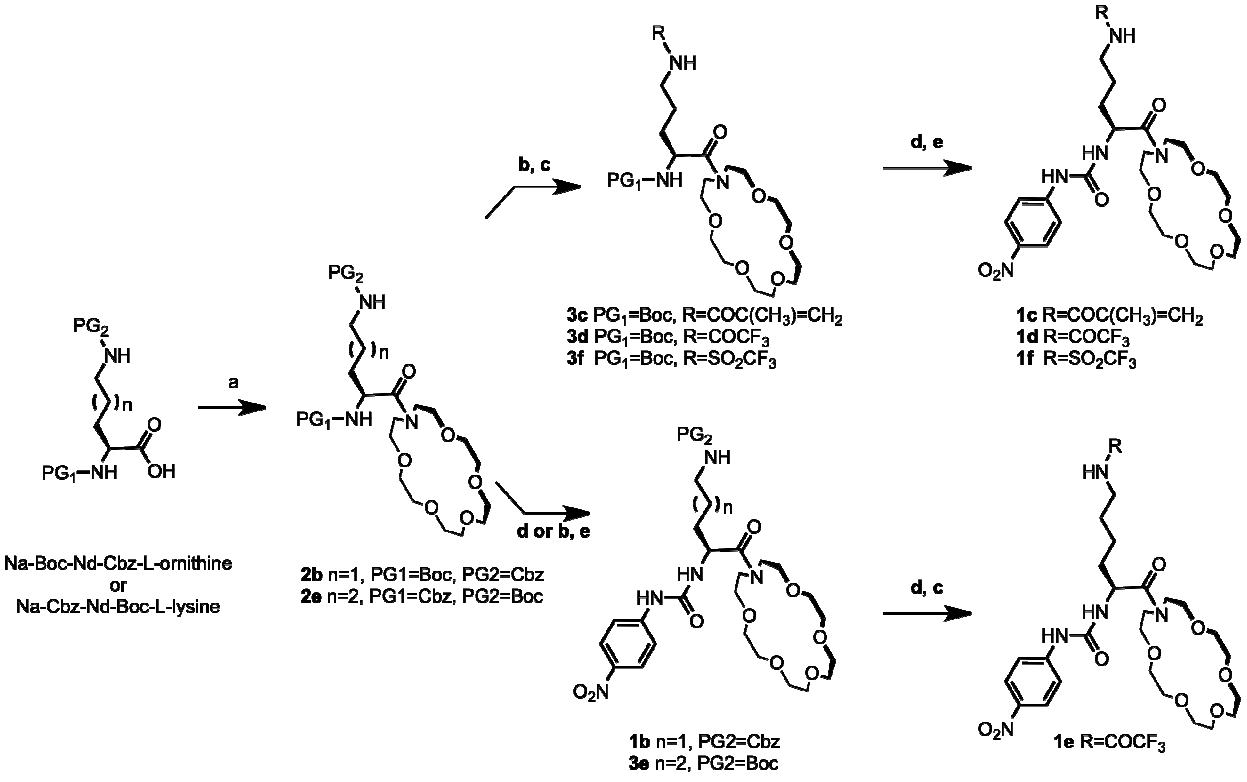


Fig. 1 The structure of amino acid based salt receptors.

RESULTS AND DISCUSSION

Receptors **1b-f** (Scheme 1 and Fig. 1) were prepared starting from commercially available Nα-Boc-Nδ-Cbz-L-ornithine or Nα-Cbz-Nγ-Boc-L-lysine. The DCC-promoted coupling of starting

compounds with aza-18-crown-6 lead to crown ether functionalized amino acids **2b** and **2e** with ~90% yield. Subsequent deprotection of Cbz group of ornithine derivative **2b** and acylation of δ-amine function gave compounds **3c**, **3d** and **3f**. Finally, TFA-promoted cleavage of Boc group followed by acylation of resulting amines with 4-nitrophenylisocyanate afforded receptors **1c**, **1d** and **1f**. The L-lysine based receptor **1e** was prepared from compound **2e** by deprotection of Nα-Boc group, acylation with 4-nitrophenylisocyanate and subsequent deprotection of side arm amine group and its acylation with trifluoroacetyl anhydride. Receptor **1a**, lacking an additional binding domain, was prepared in analogous manner starting from N-Boc-L-leucine.



Scheme 1 Synthesis of receptors **1b-f**. *Reagents and conditions:* a) DCC, 1-aza-18-crown-6, CH_2Cl_2, 0˚C to r.t., 91-92%; b) H_2, Pd/C, MeOH-THF, r.t., quantitative; c) **3c:** methacryloyl chloride, Et_3N, CH_2Cl_2, 0˚C to r.t., 50%; **1e** and **3d:** trifluoroacetyl anhydride, Et_3N, CH_2Cl_2, 0˚C to r.t., 73 and 72%; **3f:** trifluoromethanesulfonyl chloride, Et_3N, CH_2Cl_2, 0˚C to r.t., 91%; d)

TFA- CH_2Cl_2 (1:1), r.t., quantitative; e) 4-nitrophenyl isocyanate, Et_3N, THF, **1c:** 75%, **1d:** 60%, **1f:** 72%, **3e**: 81%.

Since the previously reported receptor **1c** is highly selective for sodium nitrite, we decided to screen the binding ability of receptors **1a-f** for nitrite anion and its sodium salt. The binding experiments were conducted in CD_3CN using ^1H NMR titration technique. The addition of tetra-*n*-butylammonium (TBA) nitrite to a 2.6 mM solution of receptor or receptor containing one equivalent of $NaPF_6$ caused nonlinear downfield shifts of both urea protons and amide proton located on the aminoacid side arm, if applicable. The association constants calculated by nonlinear regression analysis of the binding isotherms are presented in Table 1.

Table 1 Association constants (K_a) for interactions of receptors **1a-f** with NO_2^- in the absence or presence of one equivalent of sodium cations[a]

	δ_{NH}Amide	$TBANO_2$	1eq$NaPF_6$ $TBANO_2$	K_{Na}/K_{TBA}
1a	-	790	4 170	5.3
1b	5.7	795	4 250	5.3
1c	6.7	1 180	7 590	6.4
1d	7.6	1 450	19 000	13.1
1e	7.6	1 400	8 300	5.9
1f	7.9	-	-	-

[a] ^1H NMR, solvent CD_3CN, temperature 293 K, [**1**] = 2.6 mM, [$NaPF_6$] = 2.6 mM, [$TBANO_2$] <20 mM; M^{-1}, Errors < 10%.

The receptors listed in Table 1 are arranged in order of increasing H-bond donor ability of the side arm group, as estimated on the basis of amide-NH chemical shift of the free receptors (Table

1, Column 2 and Fig. 2).[8] As shown in Table 1, the L-leucine based receptor **1a**, without an additional anion binding domain, and receptor **1b**, possessing weak H-bond donor HNCbz function, associate to nitrite anion only moderately. Increasing the hydrogen bond donor ability of the side arm group by introducing metacrylamide **1c** or even trifluoroacetyl **1d** group did cause an enhancement in $TBANO_2$ association, but this increase was not great, at not quite twofold. Unfortunately, the most acidic trifluoromethanesulfonamide group is readily deprotonated by an NO_2^- anion, thus **1f** cannot be used for anion and salt binding studies.

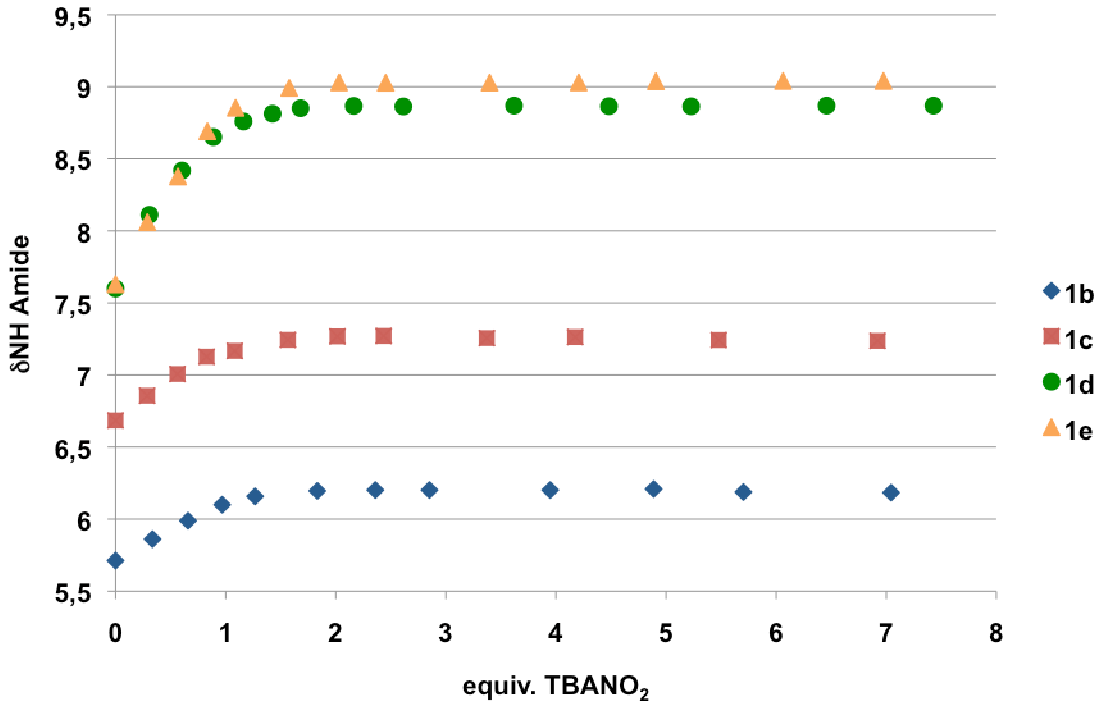


Fig. 2 ^{1}H NMR titrations of receptors **1b-e** with $TBANO_2$ in the presence of 1 equivalent of $NaPF_6$. Profiles based on the chemical shift (δ, ppm) of amide protons.

There is a much more distinct increase in binding strength with amplified H-bond donor ability of the side arm domain when the nitrite anion associates with **1**•Na^+ complexes generated by the addition of one equivalent of $NaPF_6$ to the receptor solution. Specifically, while sodium

complexes of receptors **1a** and **1b** bound NO_2^- with association constants of approximately 4200 M^{-1}, the association exhibited by **1c**•Na^+ is almost two times stronger, whereas the trifluoroacetyl derivative **1d**•Na^+ was found to bind nitrite with the remarkable association constant value of 19 000 M^{-1}. Therefore, increasing the H-bond donor ability of the side arm anion-binding group results in 4.5 times stronger binding of $NaNO_2$ salt.

Since the electronic effects of the side arm group of **1** play a very significant role in salt recognition, we decided to investigate how effects associated with the geometrical features of the binding cavity influence $NaNO_2$ binding. Therefore, we prepared L-lysine based receptor **1e** with increased distance between the urea and trifluoroacetamide groups. Interestingly, we found that this modification did not influence the strength of $TBANO_2$ binding, although $NaNO_2$ binding is greatly diminished compared to receptor **1d**. These results make it clear that a proper combination of electronic and geometric factors is necessary for effective recognition of ion pairs.

Positive cooperation (i.e. an enhancement of anion binding due to the presence of a cation) can be clearly seen for all the receptors studied, **1a-d** (Table 1, Column 5). The association constants for nitrite binding in the presence of sodium cation considerably increase compared to the association constants for nitrite anion accompanied by non-coordinating TBA cation. The highest cooperativity factor was found for receptor **1d**, whose association to nitrite is over 13 times stronger in the presence of sodium cation. Moreover, inspection of Table 1 revealed that cooperativity in salt binding correlates well with the H- bond donor tendency of amide located on the aminoacid side arm. Given that increased H-bond donor tendency has a relatively small impact on anion binding but a significant influence on anion binding in the presence of sodium cation, we tentatively attributed this phenomenon to cooperative effects.

The cooperativity between sodium and nitrate recognition of receptors **1a-d** could be ascribed to coordination of the urea oxygen atom to the crown ether complexed cation. In particular, the coordination of the urea oxygen atom to Na^+ reduces the electron density of the urea group, which is reflected in the blue shift charge transfer band as well as downfield shift of the urea N–H protons.[7] We assume that this coordination not only increases the acidity of the urea NHs but also fixes the nitrophenylurea moiety orientation and exposes that domain to bind anions together with amide function (Fig. 3). In consequence, cation and anion cooperation induces a second cooperative effect, namely simultaneous cooperation of both anion binding domains in complexation of a single ion.

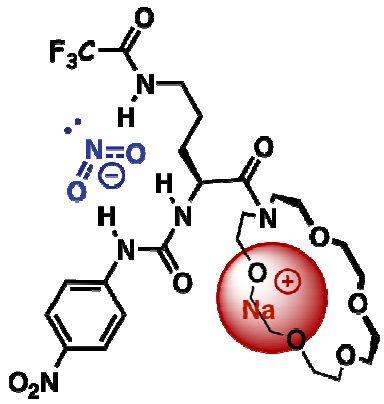


Fig. 3 A tentative sketch of the binding mode in the **1d**•$NaNO_2$ complex.

After screening the receptors' binding affinity for NO_2^- anion and $NaNO_2$ salt, the most effective receptor **1d** was further explored in detail. First, its affinity for K^+, NH_4^+ and Na^+ cation in the presence of the non-coordinating PF_6^- anion was established. The addition of cations to a 2.6 mM solution of **1d** caused nonlinear downfield shifts of the crown ether protons. The association constants calculated by nonlinear regression analysis of the binding isotherms revealed that both NH_4^+ and K^+ cations coordinated with the receptor only moderately, with association constant values of K_a = 420 and 740 M^{-1}, respectively. As for the previously reported

receptor **1c**, the association constant for Na^+ was found to be higher than 5×10^4, which precluded quantitative K_a determination.[9] Nevertheless, these experiments proved the high selectivity of receptor **1d** for sodium cation recognition. Therefore, the ion-pair binding experiments were carried out in the presence of sodium cation.

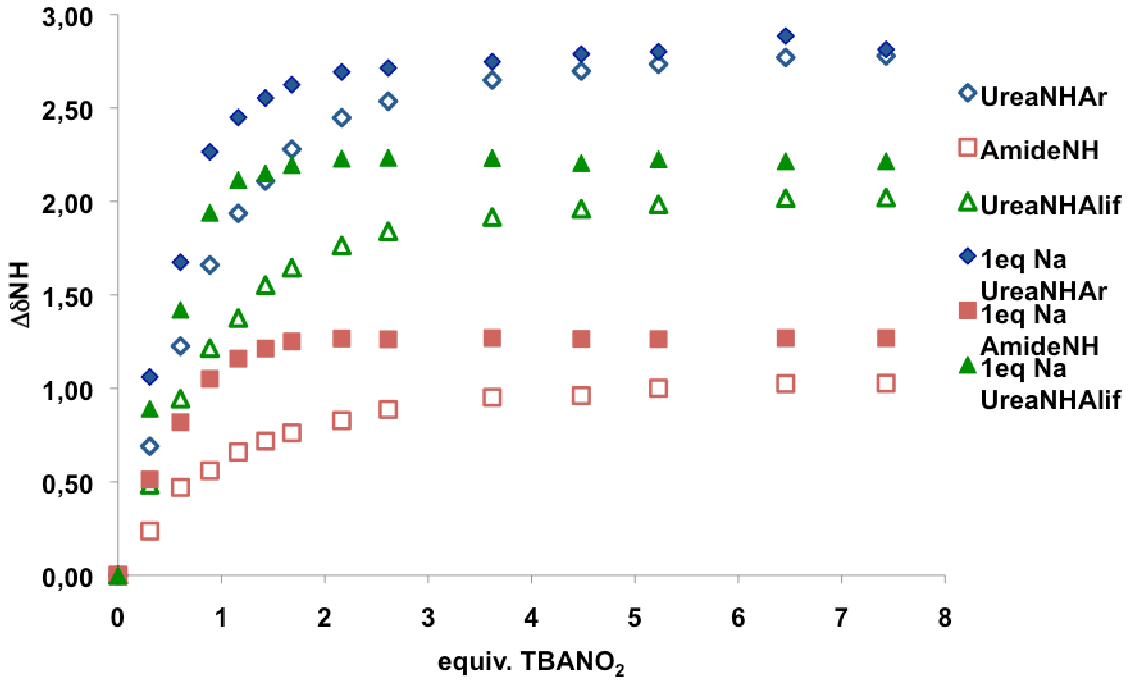


Fig. 4 ^{1}H NMR titration of receptors **1d** with $TBANO_2$ in the presence and absence of 1 equivalent of $NaPF_6$. Open symbols refer to the titration in the absence of sodium cation, full symbols refer to the titration in the presence of sodium cation.

The affinity of receptor **1d** towards selected anions and its sodium salts was then examined. Anion addition to **1d** solution caused nonlinear downfield shifts of both urea NH protons and amide proton located on the side arm of the receptor. (Fig. 4) Analyzing the complexation induced shifts of all three NH protons of **1d** using the curve fitting program HypNMR enabled the association constants listed in Table 2 to be calculated.

Table 2 Association constants (K_a) for interactions of receptor **1d** with anions in the absence or presence of 1 equivalent of sodium cations[a]

	TBA^+	Na^+	K_{Na}/K_{TBA}
F^-	-[b]	-[b]	-
Cl^-	3 100	-[c]	-
Br^-	390	3 450	8.8
NO_2^-	1 450	19 000	13.1
NO_3^-	150	1 250	8.2

[a] ^1H NMR, solvent CD_3CN, temperature 293 K, [**1d**] = 2.6 mM, [$NaPF_6$] = 2.6 mM, anions added as TBA salts [TBAX] ~20 mM; M^{-1}, Errors < 10%, [b] Receptor deprotonation [c] Precipitation

As Table 2 shows, receptor **1d** associates moderately with TBA salts of chloride and nitrite and weakly with bromide and nitrate anions, whereas fluoride anion causes receptor deprotonation. Like for nitrite anion (see Table 2), the association constants values for other anions are only slightly higher for receptor **1d** than for receptor **1c**.[7] For example, nitrate is bound to receptors **1c** and **1d** with association constants 110 and 150 M^{-1}, respectively. These results further corroborate the findings from NO_2^- binding studies of receptors **1a-e** that even considerable enhancement of the H-bond donor ability of the amide group did not cause a significant increase in anion binding strength. Interestingly, the same trend is observed for anion binding in the presence of sodium cation, with the notable exception of nitrite anion. For example, sodium

nitrate is bound to receptors **1c** and **1d** with association constants 850 and 1250 M^{-1}, respectively.[7]

However, the binding ability of the side-arm group has a significant impact on the salt binding selectivity. Specifically, the highest ion pair binding cooperativity was found for sodium nitrite, with a cooperativity factor of 13.1. The cooperativity factors for bromide and nitrate anions in the presence of hard sodium cation are similar for receptors **1d** and **1c**. In consequence, the introduction of a strong H-bond donor group into the side arm of receptor **1d** not only causes great enhancement of $NaNO_2$ binding strength but also makes receptor **1d** more selective towards this salt. This result can be attributed to the both spatial and electronic demand of the binding domains of the receptor. Specifically, we assume that the urea group mainly controls the geometry of the complexed anion, and it is well established that this group preferentially binds Y-shaped coplanar anions like nitrate or nitrite. Moreover, nitrite anion has the strongest H-bond accepting ability among the anions studied, which can be determined on the basis of its conjugated acid pK_a value.

To test whether receptor **1d** could be used to effect $NaNO_2$ extraction, preliminary extraction and membrane transport studies were carried out. Specifically, complete solid/liquid salt extraction studies were undertaken using solutions of **1d** in $CDCl_3$ layered over powdered inorganic salts. Based on N-H proton chemical shifts of salt saturated **1d** solutions, the relative content of **1d**•salt complexes in the organic phase could be estimated.[10]

Table 3 Solid/liquid extraction experiments data.[a)]

	δ_{NH}Urea	δ_{NH}Urea	δ_{NH}Amide	**1d**•salt [%][b)]
1d	8.30	7.76	6.93	-

NH_4NO_2	8.88	7.95	7.03	-
KNO_2	9.05	8.07	7.29	-
$NaNO_2$	9.86	8.65	7.83	47.2
NaBr	9.74	8.27	7.60	30.1
$NaNO_3$	9.23	8.18	7.34	40.5
NaCl	8.66	7.93	7.08	26.3

[a] ^{1}H NMR, solvent $CDCl_3$, temperature 293 K, [**1d**] = 3.2 mM; [b] determined by sodium content using atomic emission spectroscopy

The data collected in **Table 3** revealed that under interfacial conditions the selectivity towards cations of selected nitrite salts is in agreement with solution studies, namely $NH_4^+ < K^+ < Na^+$. Moreover the predisposition of **1d** to preferentially bind nitrite over Cl^-, Br^-, NO_3^- was also confirmed. This result is further corroborated by the quantitative determination of sodium cation concentration in the organic phase using atomic emission spectroscopy. These studies are in agreement with NMR experiments, although lower selectivity between nitrite and nitrate anions is observed.

The ability of receptor **1d** to extract and transport of $NaNO_2$ from aqueous solutions was also tested. A 1.5 M solution of $NaNO_2$ in deionized water was layered onto a 14 mM solution of **1d** in $CDCl_3$. The two layers were thoroughly mixed and then separated. The ^{1}H NMR spectrum of the organic phase revealed that NH signals are shifted only slightly. Using atomic emission spectroscopy we demonstrated that **1d** is able to transfer sodium cations into chloroform with an extraction efficiency of 3.1%. Encouraged by that result, we carried out a bulky liquid membrane transport experiment.[4e, 11] Initially, the source phase consisted of 2 ml of 1M aqueous $NaNO_2$ - solution and the 3 ml of chloroformic liquid membrane contained receptor **1d** at 40 mM. The salt concentration in the receiving phase was determined by conductomertic measurements and the initial flux was calculated to be 2.26×10^{-6} mol×($m^{-2}\times s^{-1}$). Thus extraction and transport

experiments demonstrate that receptor **1d** is capable of transporting $NaNO_2$ from solid state and more importantly from aqueous solution.

CONCLUSION:

In conclusion we have found that L-ornithine can be used as a convenient molecular platform for the construction of salt receptors. This platform allows for the introduction of cation and anion binding domains and possesses an additional amine group located on the side arm. This functional group can be modified for specific purposes, and in this study we employed it to introduce various anion binding groups with increased H-bond donor abilities. Although enhancement of the H-bond donor ability of the amide group has a relatively small influence on anion binding strength, this function plays an important role in the salt binding process. We showed that the increased H-bond donor abilities of an additional anion binding group correlated well with enhanced $NaNO_2$ binding strength. A similar correlation between amide group acidities and ion binding cooperation is also observed. Therefore, we assume that cation complexation fixes the nitrophenylurea moiety orientation and exposes that domain for anion binding. This cation and anion cooperation induces a second cooperative effect, namely simultaneous association of a single anion to both urea and amide binding groups. The highest cooperativity effect is observed for trifluoroacetamide equipped receptor **1d**, which interacts with $NaNO_2$ with the association constant of 19 000 M^{-1}. Furthermore, receptor **1d** was found to be highly selective for $NaNO_2$ over sodium bromide and nitrate salts. Receptor **1d** proved to be able to extract solid sodium salts of nitrite, nitrate, bromide and chloride into organic solution, exhibiting selectivity for $NaNO_2$ similar to that seen in solution studies. Finally, a transport experiment using bulky liquid membrane showed that receptor **1d** can effectively transport $NaNO_2$ from aqueous through organic phase. Thus we have demonstrated that systematic

development of the structure and electronic properties of the binding domains of molecular receptors may lead to a very effective and selective salt receptor.

EXPERIMENTAL SECTION

Compounds **1a**, **1c** and **2b** were prepared according to the procedure found in the literature.[6,7] Other reagents and chemicals were of reagent grade quality and purchased commercially. ^{1}H and ^{13}C NMR spectra as well as titrations experiments were recorded on a 200 MHz spectrometer. ^{1}H NMR chemical shifts δ are reported in ppm referenced to the tetramethylsilane ($CDCl_3$) or protonated residual solvent signal (CD_3CN).

Compound 2e. To a solution of N_α-Cbz-N_ε-Boc-L-lysine (549 mg, 1.44 mmol) and 1,3-dicyclohexylocarbodiimide (326 mg, 1.58 mmol) in 20 ml of dry dichloromethane, 1-aza-18-crown-6 (380 mg, 1.44 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 solvent was evaporated. The residue was purified by silica gel column chromatography (2% methanol in chloroform) to give the title product as a colorless oil (820 mg, 91% yield).

HRMS (ESI): calcd for $C_{31}H_{51}N_3O_{10}Na$ $[M+ Na]^+$: 648.3472, found: 648.3458.

^{1}HNMR (200 MHz, $CDCl_3$) δ: 1.28-1.51 (m, 9H+2H), 1.57-1.79 (m, 2H), 1.80-2.08 (m, 2H), 3.02-3.19 (m, 2H), 3.45-3.85 (m, 24H), 4.61-4.85 (m, 1H+1H), 5.09 (s, 2H), 5.62 (d, 1H, *J*=8.6 Hz), 7.31-7.39 (m, 5H).

^{13}CNMR (50 MHz, $CDCl_3$) δ: 22.61, 28.63, 29.80, 33.56, 40.40, 47.08, 49.02, 50.81, 66.97, 69.64, 69.83, 70.61, 70.76, 70.86, 71.09, 79.21, 128.22, 128.68, 136.59, 156.16, 172.43.

Compound 3d. To the degassed solution of **2b** (4.88 g, 7.99 mmol) in 100 ml of THF/MeOH (1:4) catalytic amounts of 10% Pd/C were added. The reaction mixture was kept under 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 (3.81 g). The amine was used in the next step without further purification. To the solution of amine (2.29 g, 4.8 mmol) in 100 ml of dry dichloromethane, triethylamine (870 µl, 6.24 mmol) was added. The reaction mixture was cooled under argon atmosphere (0 °C, ice bath) and trifluoroacetyl anhydride (734 µl, 5.28 mmol) was added dropwise. After stirring overnight at room temperature, the reaction mixture was diluted with water. The water layer was separated and extracted with dichloromethane (2x). The organic layers were collected and washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% methanol in chloroform) to give compound **3d**as a colorless oil (1.79 g, 72% yield).

HRMS (ESI): calcd for $C_{24}H_{42}F_3N_3O_9Na$ $[M+Na]^+$: 596.2771, found: 596.2766.

^{1}HNMR (200 MHz, $CDCl_3$) δ: 1.43 (s, 9H), 1.50-1.85 (m, 4H), 3.30-3.50 (m, 2H), 3.50-3.85 (m, 24H), 4.72 (bs, 1H), 5.35-5.45 (m, 1H), 7.60 (bs, 1H).

^{13}CNMR (50 MHz, $CDCl_3$) δ: 24.09, 28.51, 31.76, 40.12, 47.16, 49.31, 49.75, 69.51, 69.57, 70.49, 70.73, 70.89, 71.19, 80.06, 172.54.

Compound 3e. To the degassed solution of **2e** (820 mg, 1.32 mmol) in 30 ml of THF/MeOH (1:4) catalytic amounts of 10% Pd/C were added. The reaction mixture was kept under 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 (648 mg). The amine was used in next step without further purification. To the solution of amine (610 mg, 1.24 mmol) in 20 ml of dry THF, the 4-nitrophenyl isocyanate (230 mg, 1.4 mmol) was added. After stirring overnight at room temperature, the reaction mixture was concentrated and purified by silica gel column chromatography (2% methanol in chloroform) to give compound **3e** as a pale-yellow oil (660 mg, 81% yield).

HRMS (ESI): calcd for $C_{30}H_{49}N_5O_{11}Na$ $[M+ Na]^+$: 678.3326, found: 678.3344.

^{1}HNMR (200 MHz, $CDCl_3$) δ: 1.26-1.79 (m, 9H+6H), 2.97-3.16 (m, 2H), 3.55-3.94 (m, 24H), 4.85 (bs, 1H+1H), 6.96 (bs, 1H), 7.39 (d, 2H, *J*=9.2 Hz), 7.97 (d, 2H, *J*=9 Hz), 8.35 (s, 1H).

^{13}CNMR (50 MHz, $CDCl_3$) δ: 23.09, 28.63, 29.94, 33.06, 40.20, 47.79, 49.57, 49.88, 69.14, 69.78, 70.86, 71.08, 79.39, 117.69, 125.13, 141.91, 146.05, 154.80, 156.34, 175.00.

Compound 3f. To the degassed solution of **2b** (4.88 g, 7.99 mmol) in 100 ml of THF/MeOH (1:4) catalytic amounts of 10% Pd/C were added. The reaction mixture was kept under 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 (3.81 g). The amine was used in the next step without further purification. To the amine solution (500 mg, 1.05 mmol) in 40 ml of dry dichloromethane, the triethylamine (160 µl, 1.15 mmol) was added. The reaction mixture was cooled under argon atmosphere (0 °C, ice bath) and trifluoromethanesulfonyl chloride (111 µl, 1.05 mmol) was added. After stirring overnight at room temperature, the reaction mixture was diluted with water. Water layer was separated and extracted with dichloromethane (2x). The organic layers were collected, dried over $MgSO_4$, filtered, and concentrated under reduced

pressure. The residue was purified by silica gel column chromatography (5% methanol in chloroform) to give compound **3f** as a colorless oil (580 mg, 91% yield).

HRMS (ESI): calcd for $C_{23}H_{45}N_3O_{10}SNa$ $[M+ Na]^+$: 578.2723, found: 578.2730.

^{1}HNMR (200 MHz, $CDCl_3$) δ: 1.43 (s, 9H), 1.59-1.83 (m, 4H), 3.19 -3.40 (m, 2H), 3.55-4.05 (m, 24H), 4.65-4.84 (m, 1H), 5.47 (d, 1H, *J*=8.8 Hz), 7.33 (d, 1H, *J*=6.2 Hz).

^{13}CNMR (50 MHz, $CDCl_3$) δ: 20.26, 25.25, 28.53, 30.85, 44.04, 47.11, 49.51, 69.36, 69.45, 70.35, 70.51, 70.66, 77.44, 80.06, 123.30, 155.79, 172.57.

Receptor 1b. Compound **2b** (500 mg, 0.817 mmol) was dissolved in 10 ml of dichloromethane and 2.5 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 neutralized with saturated $NaHCO_3$. The water layer was separated and extracted with dichloromethane (2x). The organic layers were collected and washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The obtained amine (395 mg, 95% yield) was used in the next step without further purification. To the solution of amine (395 mg, 0.773 mmol) in 20 ml of dry THF, the 4-nitrophenyl isocyanate (126 mg, 0.773 mmol) was added. After stirring overnight at room temperature, the reaction mixture was concentrated and purified by silica gel column chromatography (2% methanol in chloroform) to give receptor **1b** as a pale-yellow oil (381 mg, 73% yield).

HRMS (ESI): calcd for $C_{32}H_{45}N_5O_{11}Na$ $[M+ Na]^+$: 698.3013, found: 698.2982.

^{1}HNMR (200 MHz, CD_3CN) δ: 1.40-1.80 (m, 4H), 3.00-3.20 (m, 2H), 3.40-3.80 (m, 24H), 4.75-4.85 (m, 1H), 5.02 (s, 2H), 5.75-5.85 (m, 1H), 6.39 (d, 1H, *J*=8.2 Hz), 7.20-7.40 (bs, 5H), 7.46 (d, 2H, *J*=12.4 Hz), 8.02 (d, 2H, *J*=9.4 Hz), 8.06 (s, 1H).

^{13}CNMR (50 MHz, CD_3CN) δ: 26.65, 31.08, 41.35, 47.97, 49.67, 50.62, 66.83, 69.59, 70.40, 71.14, 71.23, 71.28, 71.35, 71.45, 125.88, 128.76, 128.90, 129.51, 147.42, 155.19, 174.37.

Receptor 1d. Compound **3d** (1.4 g, 2.44 mmol) was dissolved in 50 ml of dichloromethane and 10 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 evaporated *in vacuo* to yield the crude product as trifluoroacetate salt in quantitative yield (1.3 g). The ammonium salt was used in the next step without further purification. To the solution of ammonium salt (1.3 g, 2.44 mmol) in 50 ml of dry THF under argon atmosphere, the triethylamine (850 μl, 6.1 mmol) and 4-nitrophenyl isocyanate (400 mg, 2.44 mmol) were added. After stirring overnight at room temperature, the reaction mixture was concentrated and the residue was partitioned between dichloromethane and water. Water layer was separated and extracted with dichloromethane (2x). The organic layers were collected and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (5% methanol in chloroform) to give receptor **1d** as a pale-yellow oil (860 mg, 60% yield).

HRMS (ESI): calcd for $C_{26}H_{38}F_3N_5O_{10}Na$ $[M+ Na]^+$: 660.2468, found: 660.2454.

^{1}HNMR (200 MHz, $CDCl_3$) δ: 1.62-1.95 (m, 4H), 3.25-3.47 (m, 2H), 3.50-4.12 (m, 24H), 5.04 (bs, 1H), 7.05 (bs, 1H), 7.47 (d, 2H, *J*=9 Hz), 7.81 (bs, 1H), 8.05 (d, 2H, *J*= 9.2 Hz), 8.37 (s, 1H).

^{13}CNMR (50 MHz, $CDCl_3$) δ: 25.07, 31.28, 39.98, 47.92, 49.41, 49.94, 68.84, 69.61, 70.72, 70.82, 71.19, 117.79, 125.19, 142.05, 145.92, 154.70, 174.67.

Receptor 1e. Compound **3e** (660 mg, 1.01 mmol) was dissolved in 10 ml of dichloromethane and 2 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 evaporated *in vacuo* to yield the crude product as trifluoroacetate salt in quantitative yield (675 mg). The ammonium salt was used in the next step without further purification. Next, to the solution of amine (675 mg, 1.01 mmol) in 20 ml of dry dichloromethane, the triethylamine (349 µl , 2.5 mmol) was added. The reaction mixture was cooled under argon atmosphere (0 °C, ice bath) and trifluoroacetyl anhydride (167 µl, 1.2 mmol) was added dropwise. After stirring overnight at room temperature, the reaction mixture was diluted with water. Water layer was separated and extracted with dichloromethane (2x). The organic layers were collected and washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% methanol in chloroform) to give receptor **1e** as a pale-yellow oil (480 mg, 73% yield).

HRMS (ESI): calcd for $C_{27}H_{40}F_3N_5O_{10}Na$ $[M+ Na]^+$: 674.2625, found: 674.2637.

^{1}HNMR (200 MHz, $CDCl_3$) δ: 1.36-1.87 (m, 6H), 3.26 -3.40 (m, 2H), 3.50-4.05 (m, 24H), 4.96 (bs, 1H), 7.02 (bd, 1H), 7.29 (bt, 1H), 7.42 (d, 2H, *J*=9 Hz), 78.02 (d, 2H, *J*=9.4 Hz), 8.33 (s, 1H).

^{13}CNMR (50 MHz, $CDCl_3$) δ: 22.83, 28.58, 33.11, 39.82, 47.78, 49.53, 49.73, 68.96, 69.67, 70.66, 70.81, 70.89, 71.16, 117.76, 125.55, 142.01, 145.94, 154.82, 157.40, 158.13, 174.87.

Receptor 1f. Compound **3f** (488 mg, 0.8 mmol) was dissolved in 20 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 evaporated *in*

vacuo to yield the crude product as trifluoroacetate salt in quantitative yield (498 mg). The ammonium salt was used in the next step without further purification. Next, to the solution of ammonium salt (498 mg, 0.8 mmol) in 50 ml of dry THF under argon atmosphere, the triethylamine (279 µl, 2 mmol) and 4-nitrophenyl isocyanate (131 mg, 2.44 mmol) were added. After stirring overnight at room temperature, the reaction mixture was concentrated and the residue was partitioned between dichloromethane and water. The water layer was separated and extracted with dichloromethane (2x). The organic layers were collected and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (2% methanol in chloroform) to give receptor **1f** as a pale-yellow oil (390 mg, 72% yield).

HRMS (ESI): calcd for $C_{25}H_{38}F_3N_5O_{11}SNa$ $[M+ Na]^+$: 696.2138, found: 696.2144.

^{1}HNMR (200 MHz, $CDCl_3$) δ: 1.63-2.05 (m, 4H), 3.22 -3.43 (m, 2H), 3.45-4.10 (m, 24H), 5.02 (bs, 1H), 7.11 (bd, 1H, *J*=7 Hz), 7.31 (bt, 1H), 7.42 (d, 2H, *J*=9 Hz), 8.03 (d, 2H, J=9 Hz), 8.27 (s, 1H).

^{13}CNMR (50 MHz, $CDCl_3$) δ: 26.10, 30.16, 43.98, 47.85, 50.07, 68.96, 70.48, 70.69, 71.12, 117.87, 125.12, 142.09, 145.73, 154.88, 174.63.

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

Corresponding Author

* E-mail: jarom@chem.uw.edu.pl

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