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Synthetic receptors for neutral nitro derivatives

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ABSTRACT

Different arylurea-based receptors with similar substitution pattern and one guanidine-based receptor were synthesised and studied concerning their binding capability towards the title functional group; specific binding of neutral nitro groups is revealed with relatively high binding constants in DMSO ranging from 470 to 1370 M^{-1} for urea and 730–990 M^{-1} for guanidine-based binding partners.

The utilisation of host–guest chemistry for a target is a well-established area of research and currently directed towards tailor-made receptors to bind suitable substrates in polar and non-polar solvents, respectively. A large number of receptors have been described in particular for the selective binding of anionic fragments.[1] Oxoanionic substrates such as carboxylic acids and carboxylates are important functional groups in biological and in self-assembled supramolecular systems.[2] Several binding receptors in particular for both simple and complex carboxylic compounds have been developed, in non-polar as well as in polar solvents.[3] Aryl(thio)urea derivatives build up bifurcate hydrogen donor–acceptor interactions, and therefore they are used as excellent neutral receptors for these oxoanions.[4,5] Moreover, urea and thiourea can act as an organocatalyst to activate the alkylation of aromatic compounds with nitroalkenes via the bidentate hydrogen bonding.[6] Various guanidium salts have also been successfully employed for the molecular recognition of carboxylates (amino acids) or phosphates (nucleotides).[7,8] Recently, guanidinocarbonyl pyrrole receptors were described as well, which displayed high affinities for carboxylates due to the combination of the electrostatic interaction and the binding via a bidentate hydrogen bonding.[3,9,10]

The neutral nitro group is one of the isosters of the mono-anionic carboxylate because of structural similarity.[3,11] Therefore, this group should be able to build up hydrogen donor–acceptor networks based on the nitro-urea and nitro-guanidine interactions. The combination of multiple weak interactions like in carboxylate-receptor systems leads to high binding affinities in polar solvent systems.[9] Many synthetic receptors have been constructed for mono-anionic carboxylate moieties, but surprisingly there are only few examples of synthetic receptors for the recognition of its isosteric anions, for example, phosphates, sulfonates groups and only one for the specific molecular recognition of the neutral nitro group.[10] However, there is one previous report that revealed the interaction between the nitro anions compound (nitronate) via hydrogen bond with the 1,3-dimethylthiourea by weak binding (K_a = 120 M^{-1}), but quite strong binding with bicyclic guanidinium (K_a = 3200 M^{-1}) in DMSO.[12] For this reason, we designed chromogenic receptor units and provided an assessment of their relative affinity in polar or non-polar solvent systems. We applied two strategies to the design of the receptors: one was based on aryl(thio)urea derivatives with increasing electron-deficient aryl moieties (**1**–**3**). In a second approach, we employed the zwitterionic guanidinium derivative **4,** which has never been used for the neutral nitro group recognition. As before, the urea moiety is a capable host for oxoanions,[11] and the binding can be tuned up by increasing the acidity of the hydrogen bond donor site by using strong withdrawing substituents on the aromatic ring and/or by substitution of the oxygen atom by a sulfur atom in the urea unit. Therefore, the thiourea derivatives were designed and synthesised to use as receptors for this purpose.

Herein, we report on the synthesis and binding characteristics of the nitro moiety of new unsymmetrically substituted aromatic (thio)urea derivatives, which were obtained by condensation of the corresponding aryl iso- and thioisocyanates with 4-vinylaniline in a single reaction step. These aryl(thio)urea-based receptors yield in chromogenic systems which are used as a signalling unit for the binding events. Compounds **1** and **4** were synthesised as described earlier,[9,13] and the novel compounds **2** and **3** were prepared in analogy with moderate to good yields (Fig. 1).

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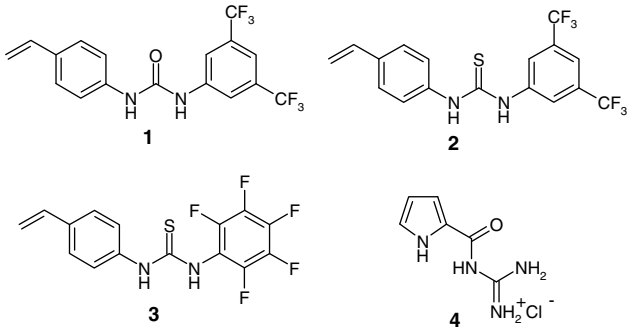


Figure 1. Structures of aryl(thio)urea—**1**, **2**, **3** and guanidine 4 based receptors used in the study.

Fluorescence spectroscopy has been utilised for the assessment of the association constants (K_a) of the nitro derivatives **5** and **6** (nitrofurantoin) with aryl(thio)ureas (**1**–**3**) and the guanidium pyrrole **4** in DMSO and $CHCl_3$. Fluorescence spectroscopy benefits from the strong quenching by the nitro group while binding to the chromophoric receptor (Scheme 1), and it is more sensitive than other spectroscopical methods in this case.[14] Newly synthesised substrate **7** was used in this study as a reference compound, because of its structural similarities with **6**; instead of the nitro group it bears a carboxylate group in order to compare the binding interactions with the receptors relative to the nitro compounds **5** and **6** (Fig. 2).

As shown in Figure 3, addition of substrate **5** to a solution of receptor **3** in DMSO caused significant quenching of the fluorescence intensity of receptor **3**, which is accompanied by a bathochromic shift from 373 nm to 404 nm of the emission. In addition to **5**, nitrofurantoin **6** acted as a similar quencher by decreasing the intensity of the fluorescence emission of all receptors. All association constants that were listed in Table 1 were calculated using Stern–Volmer plots of fluorescence titration data. Furthermore, NMR studies were used to reveal more detailed structural information about the nitro-receptor binding. The ^1H NMR experiments confirmed the proposed formation of a bidentate hydrogen-bound complex between nitro group and (thio)urea moieties. Our presumed interactions of nitro-urea/guanidine using nitrobenzylbromide **5** as a model compound are shown in Scheme 1. It demonstrates the binding pattern with two parallel hydrogen bonds in addition to the electrostatic attraction. As depicted in Figure 4, the ^1H NMR spectra exhibit upfield shifts of the urea NH proton resonances (~0.5 ppm) after adding substrate **5** to receptor **1** solution. This indicates the existence of interactions between oxygen atoms of the nitro group and the protons of the urea moiety. The changes of chemical shifts are due to the negative charge that is transferred onto the receptor framework after the hydrogen-bonding interaction with oxoanion.[4,5] Accordingly, but minor

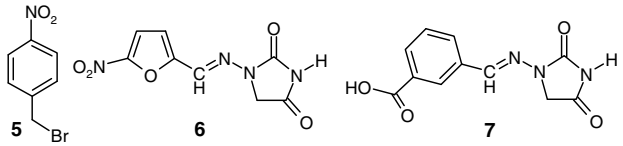


Figure 2. Substrates used in the binding studies; 4-nitrobenzylbromide **5**, *N*-(5-nitro-2-furfurylidene)-1-aminohydantoin **6** and 3-carboxybenzyl-1-methineamino-2,4-imidazolidinedione **7**.

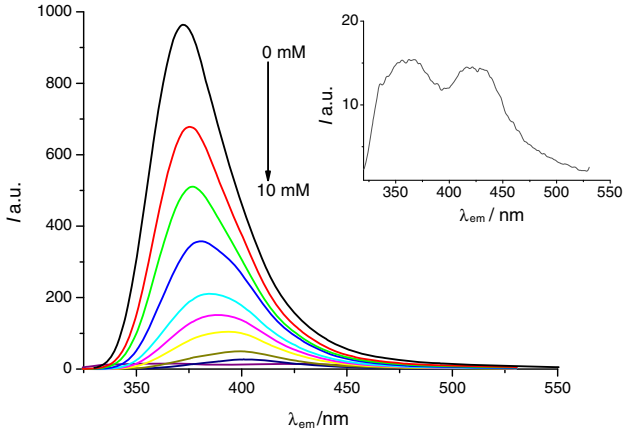


Figure 3. Fluorescence emission spectra obtained by titration of receptor **3** (1 mM) with substrate **5** (0 (top), 0.5, 1, 2, 3, 4, 5, 7.5, 10 mM (bottom)) in DMSO. Inset: emission spectrum of **5** (1 mM) (λ_{ex} = 310 nm).

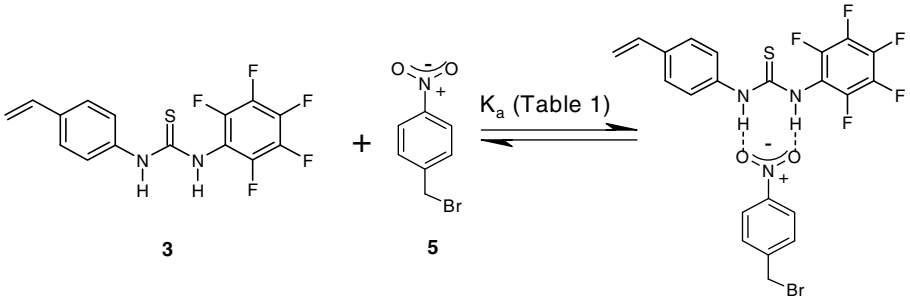
Table 1
Association constants (K_a/M^{-1}) of receptors with various substrates and solution[a]

Entry	5/DMSO	5/$CHCl_3$	6/DMSO	7/DMSO
1	470 ± 21	270 ± 6	1370 ± 55	1470 ± 89
2	1560 ± 112	480 ± 17	450 ± 33	470 ± 44
3	440[b]	950 ± 38	280 ± 18	430 ± 36
4	730 ± 43	n.s.	990 ± 38	640 ± 37

[a] Determined by fluorescence titration of 1 mM receptor with substrate from 0 to 10 mM at 25 °C in DMSO or $CHCl_3$.
[b] $K_s + K_d \cong$ association constant from static + dynamic case (n.s = not soluble).

changes of chemical shifts of the proton urea NH resonances were observed after the assembly of aryl(thio)urea **3** and guanidine **4** based receptors with nitro compounds **5** and **6**. Furthermore, the complexation by hydrogen bonds of a simple guanidinium derivative with nitroalkane was previously reported by X-ray crystal structure.[15]

Surprisingly, the nitro group of nitrofurantoin **6** or nitrobenzylbromide **5** has good binding affinities in (relatively)



Scheme 1.

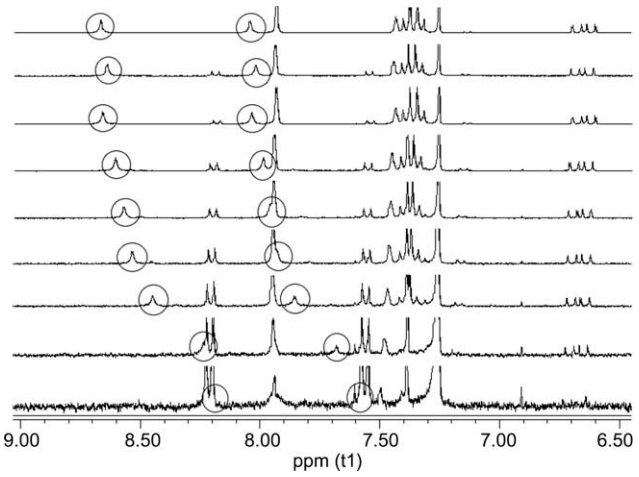
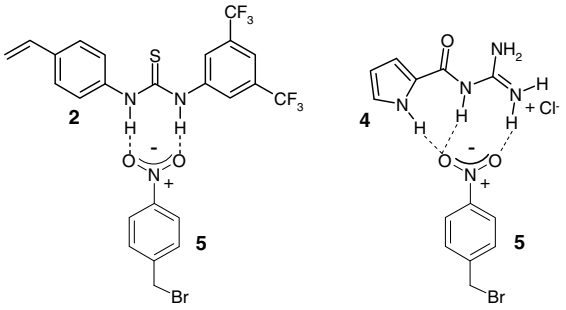


Figure 4. ^{1}H NMR titration of a 1 mM solution of receptor **1** with 0–10 mM (top to bottom) solution of substrate **5** in $CDCl_3$ and circles indicate the shift of urea proton resonances.

non-polar and polar solvents to both receptors unit classes with some K_a values larger than 10^3 M^{-1}. These results are in contrast to a previous report where no evidence of binding of nitrobenzene to unsymmetrically substituted urea derivatives was detected in either $CDCl_3$ or DMSO, whereas in CCl_4 was bound very weakly ($K_a \approx 180\ M^{-1}$).[11] This observation can be explained by the relatively poor hydrogen-bonding ability, which is due to the low pK_a value of the neutral nitro group.

It increases in the order **1** < **2** < **3** in both non-polar solvent ($CHCl_3$) and non-protic polar solvent (DMSO) because of it is compensated by the higher acidity of the urea receptors. Moreover, this is caused by a higher acidity of thiourea derivatives (pK_a = 21.0) than the corresponding urea derivatives (pK_a = 26.9).[4] The pK_a can be amplified by introducing electron-withdrawing substituents at the aryl moiety. These findings are in agreement with previous reports on carboxylate–urea interactions proving again that on varying the substitution of monourea systems, the K_a values in DMSO increase dramatically.[4,16,17] Titration experiments in DMSO were carried out because of solubility reasons, which revealed from the association constants that the binding of nitro substrates **5** and **6** was slightly weaker to most receptors than carboxylate **7**. We further assessed the complexation properties of carboxylate **7**, because of its structural and electronical similarities to **6**. Moreover, this study demonstrated that all substrates were bound more efficiently to urea hosts in the highly polar solvent DMSO with a decreasing binding in the order **1** > **2** > **3**. The high electron deficiency in **2** and **3** of the urea moiety leads to a competition of binding between the DMSO and the substrate. Thus, the solvation of the hydrogen bond acceptor sites were occupied results in the disruption of the complex.[4,5,18] These findings were supported by ^{1}H NMR titration of receptor **3** with substrate **5** in DMSO, which is reflected by very small upfield shift of the thiourea NH proton resonances (~0.01 ppm) (Fig. S16). A X-ray crystal structure of urea compound with DMSO[19] supports the solvation of solvent to the receptor and the formation of a dimer of the urea receptor in DMSO that lead to the competition and interruption of binding between receptor and substrate.[19] From this, we can draw the conclusion that there are less interactions between oxygen atoms of nitro group and the protons of the thiourea moiety as compared to **1** + **5**, where urea NH proton resonances were shifted 0.5 ppm (Fig. 4.). In addition, the Stern–Volmer plot of the fluorescence quenching of receptor **3** by substrate **5** in DMSO shows a non-linear correlation, which is associated with static and dynamic quenching mechanism[20] (Fig. S15). Therefore, the tendency of the



Scheme 2.

association constants of the aryl(thio)urea moiety and substrates in DMSO is in the order decreasing from **1** > **2** > **3** unlike in $CHCl_3$. Thus, the urea derivative **1** has the highest affinity for both nitro substrates **5** and **6** with K_a = 470 ± 21 and 1370 ± 55 M^{-1} in DMSO, respectively. But the insolubility of the receptor **4** as well as substrates **6** and **7** required the use of a non-protic polar solvent like DMSO.

Analogous binding studies of guanidine-based receptor **4** show similarly remarkable recognition of **5**, 6 and **7** in the range of 640–990 M^{-1} in DMSO (Table 1). These high K_a values can be explained by multiple hydrogen-bonding interactions paired with ionic interactions, which further gains in binding energy (Scheme 2) compared to the corresponding urea systems. Moreover, in host **4,** the H-bond donor sites are in very close proximity, which result in a less effective solvation than when widely spaced. The proposed multiple bonding structure of the host–guest complex was supported by the downfield shifts (~0.1 ppm) of all four NH proton resonances of the guanidine receptor (Fig. S17). In addition, the binding efficiency of the two receptors unit classes with nitro compounds **5** and **6** gave associations constants in range of 470–730 M^{-1} and 280–1370 M^{-1} in DMSO, respectively, which are a 2- to 9-fold increase in stability compared to the previous report.[11]

In summary, we have shown that different urea-based synthetic receptors can be utilised for the recognition of neutral nitro group derivatives and that manipulation of the electronical properties of the urea derivatives leads to high binding in highly competitive solvents like DMSO. The urea derivative receptor **1** and guanidinium receptor **4** are superior candidates with high affinity to nitro groups. The association constants of the two receptor unit classes with nitro compounds in DMSO are increased by one order of magnitude compared to previous report.[11] Moreover, the study revealed that the competition of the solvent during the binding process cannot be neglected, which makes the development of the receptors with high pK_a values unnecessary while working in DMSO. In accomplishment, most of receptors show slightly higher binding to the substrates in aqueous solvent system, DMSO, mimicking biological system and leading to a large range of applications in molecular imprinting process or biosensors.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.015.

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