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New bis-urea cross-linking monomers as effective oxyanion receptors

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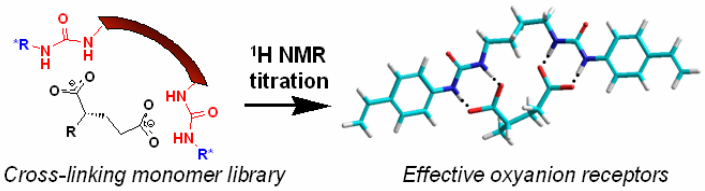
Abstract



A library of new polymerizable functional cross-linking monomers designed for complexation with the oxyanionic moiety of the chemotherapeutic drug methotrexate (MTX). The ^{1}H NMR binding study of a variety of synthetic receptors and the compilation of the obtained results lead to the identification of monomers combining interactive functionality and a cross-linking format, specific binding receptors for dicarboxylate-containing drugs.

Robust molecular recognition elements with antibody-like ability to bind and discriminate between molecules or other structures can today be synthesized using molecular imprinting techniques.[i,ii] Over the years, molecular imprinting of polymer matrixes has become a widely used approach to generate macromolecular receptors for target molecules.[iii] The non-covalent approach involves complexation in a solution of target molecules (templates) with functional monomers through supramolecular interaction, followed by a polymerization reaction with an excess of cross-linkers.[iv] Removal of the templates leaves behind specific recognition sites that are complementary to the template in terms of its shape, size and functionality in the polymer network. The use of molecularly imprinted polymers (MIPs) carries many applications in several areas.[v] An important analytical application is the use of MIPs as chromatographic devices for separating chemically similar molecules.[vi] They are also exploited in the field of organic synthesis for their catalytic and enantio-selective potential[vii] and as substitute for biological target receptors in dynamic combinatorial chemistry.[viii] Drug discovery by dynamic combinatorial chemistry[ix], classically involves the assembly of building blocks in the presence of a target receptor or enzyme that creates a driving force favoring the formation of the best-binding constituent.[x] The presence of a targeted enzyme in the synthetic reaction mixture results in greater amounts of efficient inhibitors (target-accelerated synthesis)[xi] or shifts the synthetic equilibrium (dynamic combinatorial libraries, DCC)[xii] by binding tightly the strongest target binders. However, the biological receptors used in this approach are usually only stable over a small temperature range and in a specific media. Organic solvents, temperature, pH, exposition to light-waves and oxidative environments are among the conditions that must be carefully taken into consideration when using a biological receptor. These soft conditions restrict the field of usable functional reactants and obtainable products. The use of MIPs as a substitute for biological target receptors could allow a

broader range of conditions for the DCC technique. MIPs are stable even at extreme temperatures and at pH where natural enzymes would degrade.[xiii] Their use in combinatorial chemistry would surpass the limits encountered so far. To tailor MIPs with homogeneous cavities crafted for maximizing recognition towards a specific type of chemical structure, we initiated a procedure of systematic template-moiety/receptor complexation analysis. Our approach involves a synthesis/binding study of a variety of receptors towards a specific ligand moiety. The obtained results allow us to select of hit-receptors possessing the best associations from the initial set of receptors. Compilation of data for various ligand moiety leads to the creation of broad libraries of polymerizable moiety-specific binding receptors available for the imprinting of drugs or other important compounds.

Herein, we present a specific example of target-molecule which will lead to information about dicarboxylate containing molecules. We report the synthesis of a library of new polymerizable functional monomers designed for imprinting the chemotherapeutic drug methotrexate (MTX) shown in Figure 1.

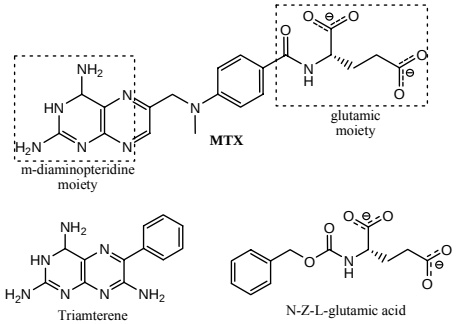


Figure 1. Structures of the target imprint drug (MTX) and of the two sub-structural models used in the binding tests.

Further, we describe the measurement of their relative affinities towards a MTX substructure template to identify specific properties that come to play in the creation of MTX-imprinted polyme The design of the library of novel functional monomers was based on a selection of three featuresthat are relevant for the creation of selective MIPs. First is the choice of bis-ureated binding functionalities, which exhibit strong affinity for dicarboxylate moieties.[xiv] The second feature is the selection of polymerizable end groups. We chose methacrylate functions, commonly used cross-linking chemical systems reknown for providing materials with good thermal stability.[xv] In all the monomers we designed, the methacrylate group is placed two carbons away from the H-bond donating ureas in order to prevent destabilization of the template/monomer complex during the polymerization process. The final feature is to design species with enhanced affinity for the MTX template by synthesizing a variety of selected di-(ureidoethylenemethacrylate) compounds, all differing by the chemical nature of their central spacer. As can be seen in Figure 2, the spacers we used in their length, rigidity, polarity and space filling. Subsequent study and comparison of the strengths of the monomer-template interactions makes possible the selection of "hit-monomers" possessing higher complexation affinity than other monomers. This lead to the identification of potent binding receptors for the MTX dicarboxylate moiety and also to the design of modifications to receptors for improving affinity. Weakly complexing receptors can be redirected for tests on other more suited moieties.

The monomers were synthesized in one-pot reactions by *N*-hydro-*C*-alkylamino additions of a diamine on the appropriate isocyanate. ^{1}H NMR titrations were performed with the monomers **1** to **10** using the substructural model bis(TBA)-*N*-Z-L-glutamate as the guest compound. The complexation-induced chemical shift (CIS) of the urea protons of receptors **1** to **10** were monitored. Addition of increasing amounts of bis(TBA)-*N*-Z-L-glutamate (0-10 equiv) to DMSO-d_6 solutions of the functional receptors allowed titration (Figures 3 and 4) from which we extracted the monomer/template interaction information (Table I). All titration data did fit well to 1:1 binding isotherms.[xvi] The competitive solvent DMSO-d_6 prevented self-association of monomer and/or guest to occur in these systems. The monomers

that gave rise to the weakest CIS are thoses harboring the shortest spacer, *i.e.* receptors **1** and **2**. Although their outer pair of N—H---O hydrogen bond with the carboxylate group of the guest do give rise to significant CIS (1.71 ppm and 1.70 ppm respectively), it is not unexpected to observe a weaker association of the inner proton considering that their respective spacers do not permit an ideal face-to-face positioning with the propylenedicarboxylic substrate.

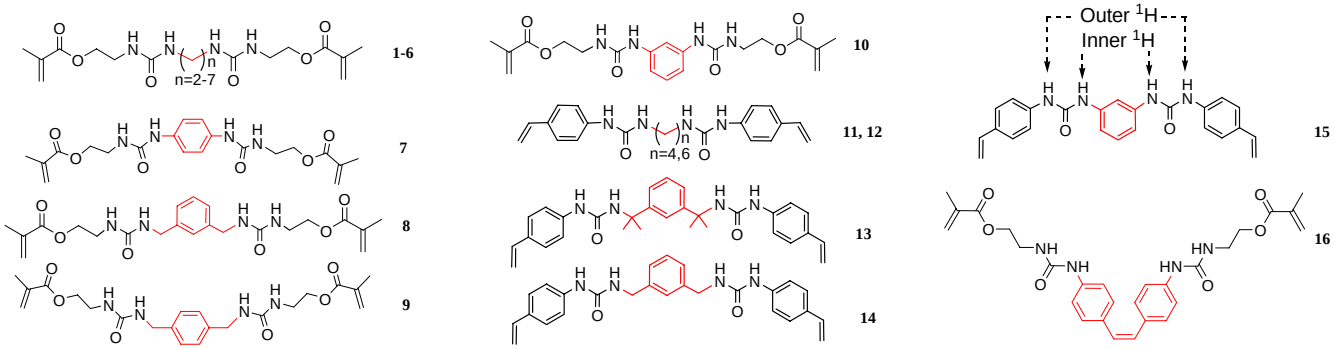


Figure 2. Library of novel polymerizable bis(ureidoethylenemethacrylate) receptors **1-10** designed for improved imprinting of methotrexate and modified receptors **11-16** based on the initial design of spacers.

Table I. Extrapolated Maximum Chemical Shifts (Δδ max)[a]

Receptor (-R-)	Δδ max, ppm	
	Inner ^{1}H	Outer ^{1}H
di(ureidoethylenemethacrylate)		
1 (ethylene)	1.42	1.71
2 (propylene)	1.64	1.70
3 (butylene)	1.76	2.01
4 (pentylene)	1.74	1.91
5 (hexamethylene)	1.76	1.99
6 (heptylene)	1.74	1.98
7 (*p*-phenylene)	2.74	3.28
8 (*m*-xylylene)	1.74	1.88
9 (*p*-xylylene)	1.96	2.30
10 (*m*-phenylene)	2.00	2.35
16 (stilbene)	3.27	3.59
di(ureidostyrene)		
11 (butylene)	2.42	2.66
12 (hexamethylene)	2.76	2.89
13 (*m*-bis(methylethylbenzene)	2.30	2.74
14 (*m*-xylylene)	3.04	2.95
15 (*m*-phenylene)	2.84	3.18

[a] The host concentration was 4 mM for entries **1-15** and 1mM for **16**, the solvent was DMSO-d_6

The other linear aliphatic monomers **3** to **6,** with butylene to heptylene spacers gave similar hydrogen-bonding interactions and led to more intense hydrogen bonding shifts. This aliphatic group of spacers presents the attribute of being flexible and devoid of steric congestion, which gives them the advantage of being adaptable for fitting to the substrate before rigidification into a polymerized structure. Monomers **7** to **10** of the set of functionalized receptors carried more rigid, polar and/or sterical filling properties not present in the six first cases. Surprisingly the *p*-phenylene monomer **7** gave rise to the most intense binding and a very good fit to a 1:1 binding isotherm, although we did not anticipate this

monomer-*N*-Z-glutamate stoichiometry because of the convex-curved nature of the monomer (Figure 2). We anticipated flexible linear monomers with capacity to bend over the dicarboxylic glutarate moiety (like receptors **3** to **7**) or more rigid concave-shaped monomers (receptors **8** to **10**) to satisfy the criteria of face-to-face 1:1 complementarity.

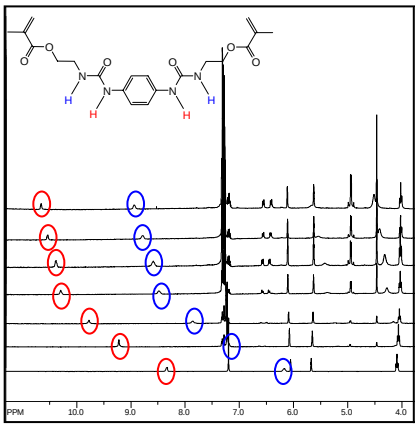


Figure 3. ^{1}H NMR spectra obtained for the complexation of receptor **7** with *N*-Z-glutamic acid.

A reasonable interpretation of the result is formation of 2:2 or 6:6 binding suprastructures. The *p*-xylylene type receptor **9** interacted strongly with the dicarboxy moiety in a 1:1 binding manner as already demonstrated.[xvii] The monomer/guest association in such a case was due to the length and shape of the spacer between the ureas on the receptors allowing suitable complementarity.[xviii] Receptor **8** showed lower ^{1}H shift upon titration likely due to the bulky nature of the *m*-xylylene. Receptor **10**, the most rigid and inflexible compound of the list is an informative example to consider in this monomer assembling study for two reasons: 1) although the inner protons are located in α-position of an electron-withdrawing aromatic ring making them much more acidic, their binding does not result in CIS as high as the outer protons due to inappropriate spacer length 2) the electron-withdrawing nature of the urea substituent (including the spacer itself) increases the acidity of the urea protons and, hence, compensates for the length by increasing the magnitude of association. Globally, monomers **3** to **6** showed effective binding strength although the aliphatic nature of their spacers did not allow binding as intense as monomers **7** to **10** containing phenylene or xylylene spacers. Receptors **1** and **2** appear to be too short and hence not well-suited ti binding bis(TBA)-*N*-Z-glutamate.

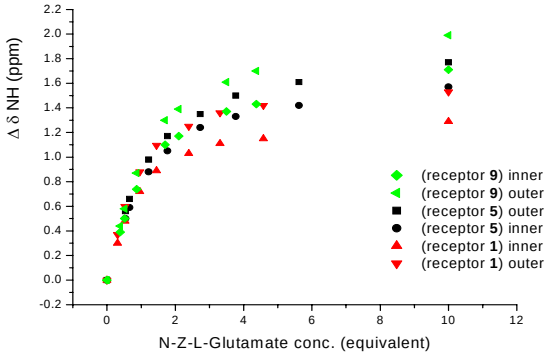


Figure 4. Chemical shifts of the inner and outer urea protons of the functionalized receptors **1**, **5** and **9** as a function of *N*-Z-L-glutamate guest compound concentration in DMSO-d_6.

The new receptors represent an assortment of units to choose from for crafting polymers with the desired properties. Among these properties, the various solubility, structural and electronic compatibility of the monomers increase their value as MIP conception agents to make them match in various co-monomer/solvent/substrate environments. The new cross-linking receptors could in addition offer the possibility to control the porosity and rigidity of the polymeric matrixes to be prepared. The strategy for monomer design has been previously investigated to combine interactive monomer functionality with a cross-linking format, giving as a result noncovalent molecularly imprinted polymers

(MIPs) with improved performance.[4] This strategy was explored under the premise that more functionality could be introduced without suffering performance losses due to reduced cross-linking. The results obtained from ^{1}H chemical shift studies of receptors **1-10** in binding bis(TBA)-*N*-Z-glutamate allowed the design of to the initial receptors. We created receptors **11** and **12** (Figure 2**)**, styrene-analogues of the flexible aliphatic receptors **3** and **5** in order to benefit from the spacer's nature while increasing the acidity of the urea protons. We also created monomers **13** and **14** which are modified versions of the *m*-xylylene receptor **8**, a rigid and very acidic m-phenylene receptor **15,** as well as **16** , a receptor that offers both the characteristics of possessing polymerizable units that are separated from the binding ureas and to possess enhanced acidic urea protons (Figure 2). In addition, the stilbene nature of **16** provides it with a controllable conformational change achievable by external stimulation such as UV-irradiation This last feature makes it a very attractive compound for use in polymer matrixes with switchable-recognition cavities, a use that is especially interesting since there were only few reports concerning photo-switchable receptor for molecules. In all cases, the CIS were increased compared to the ones of the original receptors versions. Hence, although some receptors from the second set lack the two carbons long spacing between the polymerizable-extremity and the H-binding urea found in the initial set, the greater H-bonding magnitude could compensate the potential thermodynamic complex-instability encountered during the polymerization process. Interestingly, the m-xylylene monomer **14** showed more CIS magnitude than its tetramethyl-substituted analogue **13**, espacially as to the inner ^{1}Hs where the difference of magnitude is notable. Altough they share the same skeletal architecture and length between the ureas, the presence of the methyl groups may twist the conformation of receptor **13**, not allowing it to get the well-matched conformation. The stilbene receptor **16** demonstrated CIS greater than those obtained for any of the other 15 compounds developed. On the basis of those results and considering the stilbene features discussed above, we are looking forward to use **16** as an interesting compound in MIP preparations to come. An important factor to consider in order to reduce the problem of receptor's non-specificity for their target-moiety encountered in molecular imprinting is to design monomers exhibiting from weak to non-existent attraction for the other moiety of the template. As receptors **1-16** were designed to complex the dicarboxylate part of MTX, we also evaluated the H-binding affinity of our monomers towards the diaminopteridine group as can be seen in Figure 5. The comparison of the chemical shifts of the receptor's urea protons as a function of *N*-Z-L-Glutamate conc. vs. triamterene conc. clearly shows the specificity of the bis-ureated receptor for the dicarboxylate moiety over the diaminopteridine one, both of which are present on an MTX template.

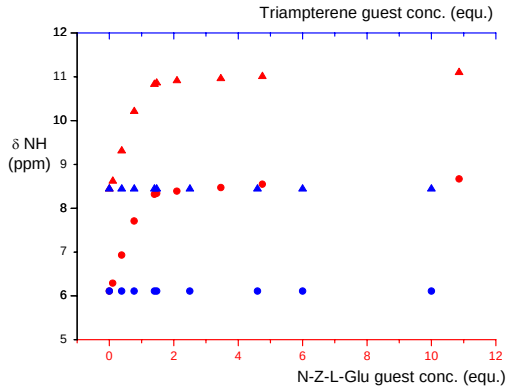


Figure 5. Chemical shifts of the inner (▲) and outer (●) urea protons of receptor **12** as a function of N-Z-L- Glu conc. (red) and triamteren conc. (blue) showing the specificity of the bis-ureated receptors for the dicarboxylic moiety of the MTX drug.

In conclusion, we have developed a family of new cross-linking agents that are readily co-polymerizable under mild conditions. The functionalized bis-ureated receptors **1** to **16** whose assemble properties on a substructural model of the chemotherapeutic drug MTX were investigated, offer a variety of monomers for use in MIP applications. Given that a large range of biologically important

molecules contain oxyanion functionality, the monomers may be selected for tests on other imprinting molecules. The choice of monomer for the creation of MIPs is an important feature and may depend on several factors including the desired porosity of the polymeric matrix, compatibility and solubility in solvent systems, binding magnitude of the molded cavities or necessity to generate or remove π-bindings/Van der Waals and other interactions type occurrence. All these factors and others which can be controlled by proper monomer selection, require access to a vast library of functionalized units in order to create the desired material properties. The new 16 compounds may be applied for the creation of MIPs used in chromatography technology and analytical chemistry or into the field of catalysis where the formation of imprint's analogues by dynamic combinatorial chemistry would be the ultimate achievement. In future work, the result of these studies will serve to build a correlation between the monomers H-bonding interaction upon complexation and the retention in HPLC columns of the monomers-based MIPs. The presented methodology is under development and might lead to creation of new MIPs with specific, catalytically active imprinted sites for several drugs.

Experimental Section.

Materials and Methods. All materials were of reagent grade. Ethylene diamine, , butylene diamine, pentylenediamine, hexamethylenediamine, heptamethylenediamine, *p*-phenylenediamine, *m*-phenylenediamine, *p*-xylylenediamine, *m*-xylylenediamine, 1,3-bis(1-isocyanato-1-methylethyl)benzene, 1,3-phenylene diisocyanate, *m*-xylylene diioscyanate, 2-isocyanatoethyl methacrylate (98%), 4,4'-diaminostilbene dihydrochloride (95%), 4-aminostyrene, 1,6-diisocyanato hexane, 1,4-diisocyanato butane, ethylene glycol dimethacrylate (EDMA), methyl methacrylate (MM), *N*-*Z*-L-glutamic acid, triampterene, DMSO-d_6 and 1 M methanolic tetrabutylammonium hydroxide were obtained from the Aldrich Chemical Co. and used as received without further purification. Propylene diamine was purchased from Fluka. N,N'-Azo-bis-(2,4-dimethyl)valeronitrile (ABDV) was purchased from Wako (Japan) and stored over appropriate freezing temperatures. Anhydrous solvents, tetrahydrofuran, p-dioxane, acetonitrile, petroleum ether, DMSO, DMF, pyridine and MeOH were purchased from EMD and were reagent grade or higher.

All ^{1}H NMR spectra were obtained using a Bruker Advance AMX 300 spectrometer at 300 MHz, and all ^{13}C NMR spectra were obtained using a Bruker Advance AV 400 spectrometer at 400 MHz. Differential scanning calorimetry analyses for the co-polymerization studies were collected using a DSC Mettler FP85 calorimeter. Solid state ^{13}C NMR spectra for the co-polymerization studies were obtained using a Bruker Avance 600 WB. Melting points were determined on a

Synthesis of bis(ureidoethylenemethacrylate) receptors 1-10. **General Procedure.** To a stirred solution of the desired diamine (20 mmol) in anhydrous tetrahydrofuran if not otherwise mentioned (70mL) under an inert atmosphere was added 2-isocyanatoethyl methacrylate (50 mmol) dropwise as a solution in dry THF (20mL). The solution was allowed to stir at room temperature overnight under a stream of nitrogen and then the solvent was evaporated under reduced pressure. The resulting solid residue was recrystallized or washed with several volumes of the mentioned solvent. The solid was dried under high vacuum.

1,2-bis(ureidoethylenemethacrylate) ethylene (1). Yield (washed six times in acetonitrile/p-dioxane): 75%. ^{1}H NMR (DMSO-d_6) δ: 1.85 (s, 6H), 2.97 (t, J = 2.5 Hz, 4H), 3.24 (m, 4H), 4.01 (t, J = 5.6 Hz, 4H), 5,66 (s, 2H), 5.99 (t, 2H), 6.03 (s, 2H), 6.06 (t, 2H)

1,3-bis(ureidoethylenemethacrylate) propylene (2). Yield (recrystallized in acetonitrile). ^{1}H NMR (DMSO-d_6) δ: 1.40 (m, 2H), 1.86 (s, 6H) 2.95 (q, J = 6.5 Hz, 4H), 3.25 dd, J = 6.8 Hz, 4H), 4.02 (t, J = 5.5 Hz, 4H), 5,67 (t, J=1.6 Hz, 2H), 5.94 (t, J = 5.8 Hz, 2H), 6.01 (t, J = 5.5 Hz, 2H), 6.04 (s, 2H)

1,4-bis(ureidoethylenemethacrylate) butylene (3). Yield (acetonitrile): 55%. ^{1}H NMR (DMSO-d_6) δ: 1.29 (m, 4H), 1.85 (t, 6H), 2.93 (q, *J* = 5.7 Hz, 4H), 3.24 (q, *J* = 5.8 Hz, 4H), 4.01 (t, *J* = 5.7 Hz, 4H), 5,66 (t, *J* = 1.6 Hz, 2H), 5.89 (t, *J* = 3.4 Hz, 2H), 5.93 (t, *J* = 3.5 Hz, 2H), 6.03 (s, 2H)

1,5-bis(ureidoethylenemethacrylate) pentylene (4). Yield (acetonitrile/THF): 55%. ^{1}H NMR (DMSO-d6) δ: 1.18 (m, 2H), 1.30 (tt, *J* = 7.0 Hz, 4H), 1.85 (s, 6H), 2.92 (q, *J* = 6.6 Hz, 4H), 3.24 (q, *J* = 5.7 Hz, 4H), 4.02 (t, *J* = 5.6 Hz, 4H), 5,66 (s, 2H), 5.90 (t, *J* = 5.6 Hz, 4H), 6.03 (s, 2H)

1,6-bis(ureidoethylenemethacrylate) hexamethylene (5). Yield (petroleum ether): 77%. ^{1}H NMR (DMSO-d_6) δ: 1.18-1.22 (m, 4H), 1.26-1.32 (m, 4H), 1.85 (s, 6H), 2.92 (dt, *J* = 6.4 Hz, 4H), 3.22 (dt, *J* = 5.7 Hz, 4H), 4.01 (t, *J* = 5.6 Hz, 4H), 5,66 (s, 2H), 5.90 (t, *J* = 5.8 Hz, 4H), 6.03 (s, 2H)

1,7-bis(ureidoethylenemethacrylate) heptylene (6). Yield (petroleum ether): 61%. ^{1}H NMR (DMSO-d6) δ: 1.19 (m, 6H), 1.28 (tt, *J*=7.0Hz, 4H), 1.85 (s, 6H), 2.91 (dt, *J* = 6.1 Hz, 4H), 3.22 (dt, *J* = 5.6 Hz, 4H), 4.00 (t, *J* = 6.0 Hz, 4H), 5,64 (s, 2H), 5.89 (t, *J* = 5.4 Hz, 2H), 6.03 (s, 2H)

p-phenylene-bis(ureidoethylenemethacrylate) (7). Yield (acetonitrile/p-dioxane): 72%. ^{1}H NMR (DMSO-d_6) δ: 1.86 (s, 6H), 4.09 (t, *J* = 5.4 Hz, 4 H), 5.67 (s, 2H), 6.05 (s, 2H), 6.18 (s, 2H), 7.20 (s, 2H), 8.33 (s, 2H)

m-xylylene-bis(ureidoethylenemethacrylate) (8). Yield (acetonitrile/p-dioxane): 64%. ^{1}H NMR (DMSO-d_6) δ: 1.85 (s, 6H), 3.27 (t, *J* = 5.6 Hz, 4H), 4.04 (t, *J* = 5.6 Hz, 4 H), 4.15 (d, *J* = 5.9 Hz, 2H), 5.66 (s, 2H) 6.03 (s, 2H), 6.06 (t, *J* = 5.8 Hz, 2H), 6.41 (t, *J* = 5.9 Hz, 2H), 7.05-7.07 (m, 3H), 7.18-7.23 (m, 1H)

p-xylylene-bis(ureidoethylenemethacrylate) (9). Yield (washed six times in acetonitrile): 73%, m.p. X,X ^{o}C. ^{1}H NMR (DMSO-d_6) δ: 1.85 (s,6H), 3.25 (t, *J* = 5.7 Hz, 4H), 4.04 (t, *J* = 5.5 Hz, 4H) 4.14 (d, *J* = 6.0 Hz, 2H), 5.65 (s,2H), 6.02 (s, 2H), 6.06 (t, *J* = 8.4 Hz, 2H), 7.13 (s, 4H)

m-phenylene-bis(ureidoethylenemethacrylate) (10). Yield (recrystalized in acetonitrile): 65%. ^{1}H NMR (DMSO-d_6) δ: 1.87 (s, 6H), 3.36 (t, *J* = 5.5 Hz, 4H), 4.10 (t, *J* = 5.4 Hz, 4H), 5.67 (s, 2H), 6.05 (s, 2H), 6.18 (t, 2H), 6.92-6.99 (m, 3H), 7.45 (s, 1H), 8.48 (s, 2H)

Synthesis of bis(ureiodostyrene) receptors 11-15. General Procedure. To a stirred solution of the desired diisocyanate (20 mmol) in anhydrous tetrahydrofuran if not otherwise mentioned (50mL) under an inert atmosphere was added 4-aminostyrene (50mmol) dropwise as a solution in dry THF (20mL). The solution was allowed to stir at room temperature overnight under a stream of nitrogen and then the solvent was evaporated under reduced pressure. The resulting solid residue was recrystallized or washed with several volumes of the mentioned solvent. The solid was dried under high vacuum.

butylenedi(ureidostyrene) (11). Yield (washed four times with toluene/acetonitrile/petroleum ether): 62%. ^{1}H NMR (DMSO-d_6) δ: 1.42 (t, 4H), 3.06-3.08 (m, 4H), 5.06 (d, *J* = 10.8 Hz, 2H) 5.62 (dd, *J* = 16.0 Hz, *J* = 1.5 Hz, 2H), 6.14 (t, *J* = 5.5 Hz, 2H), 6.59(dd, *J* = 17.6 Hz, *J* = 10.9 Hz, 2H), 7.27-7.35 (m, 8H), 8.45 (s, 2H)

hexamethylenedi(ureidostyrene) (12). Yield (acetonitrile/p-dioxane): 85%. ^{1}H NMR (DMSO-d_6) δ: 1.28 (t, 4H), 1.39 (t, *J* = 6.12 Hz, 4H) 3.05 (dd, *J* = 6.1 Hz, 4H) 5.06 (d, *J* = 11.1 Hz, 2H), 5.62 (d, *J* = 17.6 Hz, 2H), 6.11 (t, *J* = 5.6 Hz, 2H) 6.59 (dd, *J* = 10.9 Hz, *J* = 6.7 Hz, 2H) 7.27-7.35 (m, 8H) 8.44 (s, 2H)

***m*-bis(methylethylbenzene)di(ureidostyrene) (13).** Yield (washed with acetonitrile/p-dioxane): 82%. ^{1}H NMR (DMSO-d_6) δ: 1.56 (s, 12H), 5.05 (dd, *J* = 0.9 Hz, *J* = 10.9 Hz, 2H), 5.61 (dd, *J* = 1 Hz, *J* =

17.7 Hz, 2H), 6.53 (s, 2H), 6.60 (dd, *J* = 7.8 Hz, *J* = 3.3 Hz, 2H) 7.21-7.29 (m, 3H), 7.42 (s, 1H), 8.46 (s, 2H).

***m*-xylylenedi(ureidostyrene) (14).** Yield (washed six times in acetonitrile): 70%. ^{1}H NMR (DMSO-d_6) δ: 4.26 (dd, *J* = 6 Hz, *J* = 22.2 Hz, 4H), 5.07 (dd, *J* = 0.9 Hz, *J* = 10.8 Hz, 2H), 5.63 (dd, *J* = 1.0 Hz, *J* = 17.7 Hz, 2H), 6.59 (t, *J* = 10.8 Hz, 2H), 6.63 (d, *J* = 11.1 Hz, 2H), 6.99-7.36 (m, 6H) 8.6 (s, 2H)

***m*-phenylenedi(ureidostyrene) (15).** Yield (washed six times in acetonitrile): 68%. ^{1}H NMR (DMSO-d_6) δ:5.11 (dd, *J* = 8.7 Hz, *J* = 10.9 Hz, 2H), 5.68 (dd, *J* = 1 Hz, *J* = 17.6 Hz, 2H), 6.64 (dd, *J* = 11.1 Hz, *J* = 17.7 Hz, 2H), 7.03-7.12 (m, 3H), 7.35-7.43 (m, 8H), 7.65 (s, 1H), 8.65 (s, 2H), 9.70 (s, 2H)

Synthesis of bis(ureidoethylenemethacrylate)stilbene receptors 16. To a pyridine solution (30 mL) of 4,4'-diaminostilbene dihydrochloride (20mmol) was added 20mmol of NaH/60%-in mineral oil. The reaction mixture was gently stirred until no gas release was observed. The reaction mixture was filtrated to remove the NaCl deposit. To the crude pyridine mixture was then added a solution of 2-isocyanatoethyl methacrylate (50mmol) in dry THF (50mL) under an inert atmosphere. The solution was allowed to stir at room temperature over a period of 24 hrs and the solvent was then evaporated under reduced pressure. The resulting solid residue was washed six times in Acetonitrile. The white solid was dried under high vacuum. Yield: 65%. ^{1}H NMR (DMSO-d_6) d: 1.86 (s, 6H), 3.39 (dt, *J* = 6.0 Hz, *J* = 5.0 Hz, 4H), 4.11 (t, *J* = 5.2 Hz, 4H), 5.68 (s, 2H), 6.06 (s, 2H), 6.28 (t, *J* = 5.8 Hz, 2H), 6.97 (s, 2H), 7.34-7.41 (m, 8H), 8.62 (s, 2H)

Synthesis of Bis-tetrabutylammonium-*N*-*Z*-L-glutamate.
N-*Z*-L-Glutamic acid (4 mmol) was dissolved in methanol (70 mL) and 1 M methanolic tetrabutylammonium hydroxide (8 mmol) was added in one portion. The solution was stirred at ambient temperature for 1 h, and then the solvent was removed in vacuo. The oily residue was dried under high vacuum pump at 75 °C for a period of 18 hrs. and wasn't any further purified.

^{1}H NMR Titrations
Proton NMR spectroscopy-based titration studies were carried out using a Bruker Avance AMX 300 spectrometer at 300 MHz. The receptor solutions were titrated by adding known quantities of a concentrated solution of the bis(TBA) *N*-*Z*-L-Glutamate anions. Increasing the concentration of anion in the host-guest mixture solution induced a clear downfield shift in the NH peak of the receptor's ureas. Fitting the observed data points to a 1:1 binding profile, using *Microcal Origin 6.0*, gave the extrapolated complex induced chemical shifts.

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