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ORIGINAL PAPER

Synthesis and binding properties of guanidinium biscarboxylates

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Abstract The ammonium ion binding site of the enzyme glutaminase HisF inspired us to design guanidinium biscarboxylates as potential self-organized ionophores in molecular recognition. The syntheses of the title compounds based on aliphatic and aromatic building blocks, along with a general method for the preparation of δ-aminoethoxyacetic acids, are presented in this work. Investigation of the binding properties of the title compounds in dimethyl sulfoxide (DMSO) and methanol solution revealed no ammonium ion affinity, but interaction of the guanidinium moiety with acetate ions.

Keywords Guanidinium · Unnatural amino acid · Recognition · Ligand · Pyrrole

Introduction

Ionophores find applications in many fields of chemistry (examples for recognition with selective ligands [1–5], examples for chemosensors [6–12], selective ligands in guest transport [13–17]), and medical diagnostics (selective ligands general in analytic applications [18–23], examples for ion-selective electrodes [24–31], examples for optodes [32–38]). Their pre-organization is of key importance for achieving high binding affinity and selectivity, as supramolecular binding enthalpies are typically small and unfavorable entropic effects of binding should be minimized [43–47]. The classical approach is the use of macrocycles, such as crown ethers, but clefts [48–53], tripods [54–57], or tweezers [58] can be valuable alternatives. Tweezers are pincer-like molecules carrying two side-arms arranged in the form of a forceps, which can complement a particular guest by specific interactions. Many different examples such as **1** (for example [59, 60]), **2** [61, 62], **3** [63], **4** [64, 65], or **5** [66] with a rigid core and flexible side-arms are known (Fig. 1). Such clefts or tweezer-type molecules have been used for recognition of carboxylate [67–69], guanidinium [70], and metal ions [71], amino acids [72–74], and ion pairs [75].

In the bottom region of the enzyme glutaminase subunit HisF, two glutamic acids and one arginine side-chain functionalities form hydrogen bonds to the ammonium ion of a lysine side-chain in the center of a stabilizing $\alpha\beta$-eight barrel [76]. (An ammonium ion tunnel with gate mechanism is postulated as the mechanism of action of the enzyme: ammonium ions may replace the lysine residue and are coordinated by the carboxylate ions. Rebinding of the lysine residue moves the ammonium ion into the inner part of the enzyme to be transported to the HisG enzyme subunit.) Inspired by this, we derived a guanidinium biscarboxylate **6** as a minimal tweezer-type structure for potential ammonium ion binding. Intramolecular hydrogen bonds should pre-organize the structure and expose the carboxylate groups in close proximity as a potential cation binding site. Molecular modeling (DFT, BLYP6-G-31*) confirmed that the structure is a stable conformer in the gas phase (Fig. 2).

Unnatural amino acids such as **7** are suitable starting materials for synthesis of **6** (Scheme 1). The parent

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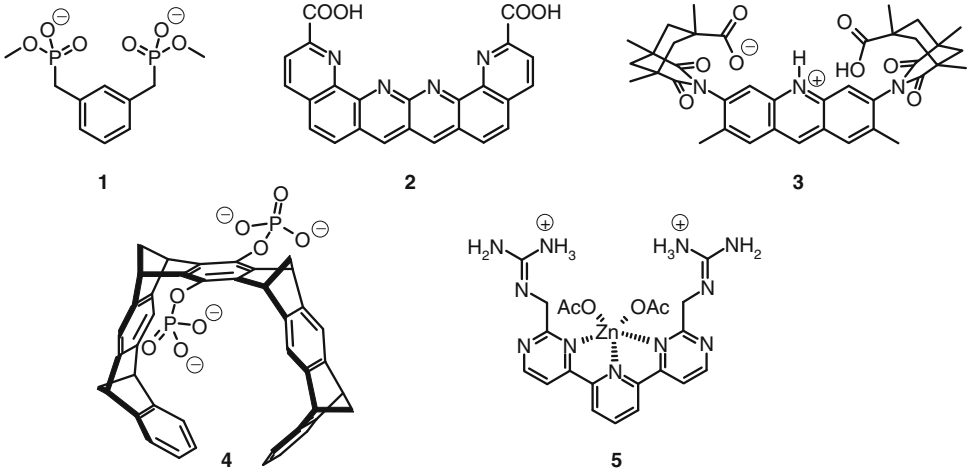
Fig. 1 Examples of bifunctional synthetic receptors with tweezers or cleft structures



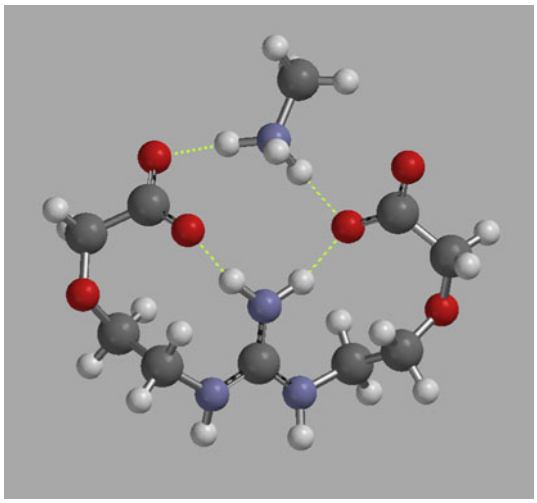
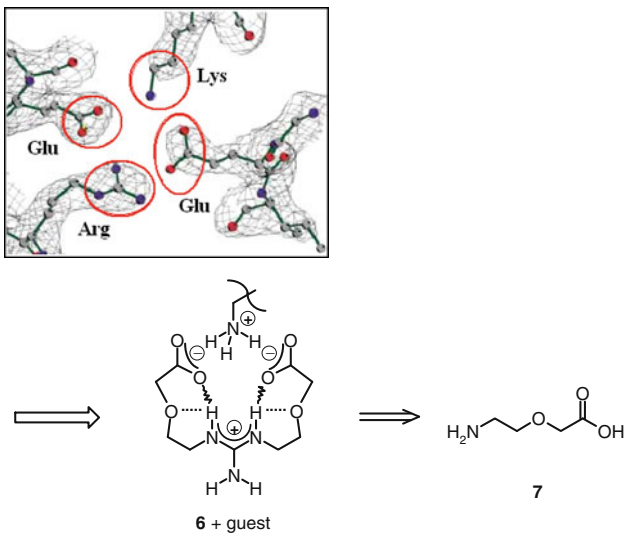


Fig. 2 Optimized geometry of compound **6** in the presence of a methylammonium ion (DFT, BYPL6-G-31*)



Scheme 1

aminoethoxyacetic acid [77, 78] is commercially available, but substituted derivatives have not been reported. We describe the preparation of derivatives of **7** and their conversion into **6**. The ammonium and acetate ion binding ability of **6** and a derivative were investigated by nuclear magnetic resonance (NMR) and emission titration.

Results and discussion

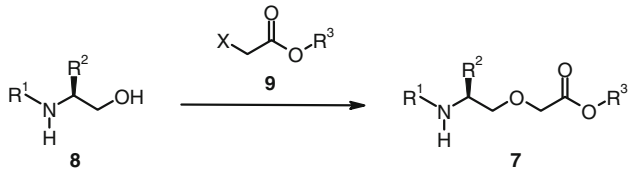
Synthesis

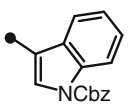
N-protected 1,2-amino alcohols **8** were prepared by standard conditions and used as starting materials. Substituted amino alcohols **8** were prepared by reduction of the corresponding amino acid methyl esters [79] with sodium boranate in dry tetrahydrofuran (THF) [80]. The indole moiety of tryptophanol was protected by Cbz chloride in dichloromethane in the presence of powdered sodium hydroxide and 10 mol% Bu_4NHSO_4 under dry conditions to give the protected indole in 92% yield [81]. The Cbz group avoids the formation of side-products. The synthesis using bromoacetic esters **9** proceeds in moderate to good yields, and the copper-mediated decomposition of azoesters [82–84] is a feasible alternative route to prepare derivatives of **7**. (NaH as base or the phase-transfer catalytic conversions were most successful. *t*-BuOK as base gives lower yields between 20% and 30%. For the copper(I)-mediated azoester reaction and the substituted amino alcohols, yields around 30% were observed. NaH is not compatible with Cbz protection, as hydrogen developed by the base cleaves the protection group, leading to a reduced yield and a more tedious workup.) Table 1 summarizes the results.

Deprotection by standard conditions gave the corresponding products in excellent yields (Scheme 2).

The amino esters were used to prepare 1,3-disubstituted guanidines in a two-step procedure via Cbz-protected

Table 1 Reaction partners and yields for preparation of δ-amino-ethoxyacetic acid esters



Entry	Amino alcohol **8**		Acetic ester **9**		Conditions	Yield of **7**/%	
	R^1	R^2	R^3	X			
1	Boc	H	tBu	Br	[a]	**7a**	83
2	Boc	H	Et	Br	[b]	**7b**	59
3	Boc	H	Et	N_2	[c]	**7b**	78
4	Cbz	H	tBu	Br	[a]	**7c**	87
5	Cbz	H	Et	N_2	[c]	**7d**	61
6	Boc		tBu	Br	[a]	**7e**	77
7	Boc		Et	Br	[b]	**7f**	52
8	Boc		tBu	Br	[a]	**7g**	89
9	Boc		Et	Br	[b]	**7h**	50
10	Boc		tBu	Br	[a]	**7i**	63

[a] Bu4 $N^+HSO_4^-$, Dichloromethane (DCM), H_2O, NaOH, RT, overnight

[b] NaH, THF (dry), RT, 3 h

[c] $Cu(OTf)_2$, PhHN–NH_2, Tetramethylethylenediamine (TMEDA), DCM (dry, degassed), N_2, 0 °C → RT, 8 h

thioureas. Benzyloxycarbonyl isothiocyanate (Cbz–NCS) [85–87] and ethoxycarbonyl isothiocyanate [88, 89] have been widely used for thiourea synthesis [90]. Cbz–NCS (**11**) [91] was used in our case, as the reaction to yield a thiourea proceeds rapidly and in high yield [92]. Representative examples of amino esters **10** which were converted by **11** into the corresponding Cbz–thioureas in good to excellent yields are summarized in Table 2.

Pyrrole (entry 8, Table 2) rigidifies the structure of the target receptor and can provide an additional hydrogen bond on each side-arm [93–99]. Pyridine derivatives (entry 9, Table 2) have been used in tweezer structures [100–104]. The rigid aromatic ring in combination with a metasubstituent may induce good pre-organization of binding sites in the final ligand.

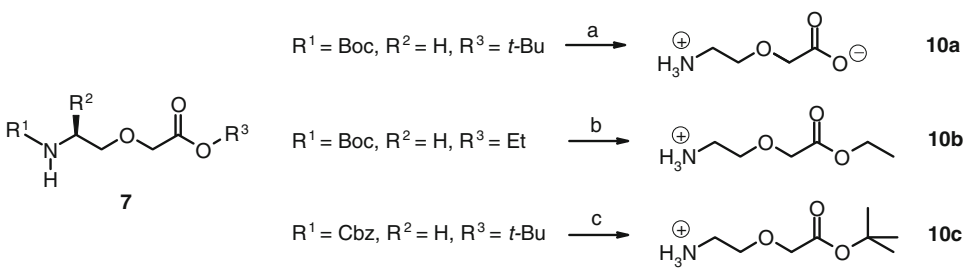
The next conversion step to the symmetric Cbz–guanidine moiety uses the esters to facilitate the product purification. The reaction can be performed in DMF, with NEt_3 as base, using either mercury(II) chloride or 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide (EDC) as an activating agent for thiourea, observing good yields. All conversions and their corresponding yields are given in Table 3. Thiourea **16** cannot be converted into the corresponding twofold substituted thiourea, yielding, by intramolecular reaction, the cyclic guanidine **21** as the only product (Kilburn et al. observed this with a similar amide compound (see also [105, 106]).

The Cbz protecting group was removed by hydrogenation using 10% Pd on charcoal at 30 bar of hydrogen pressure. The guanidinium esters (**22a/b** and **23**) are isolated as their hexafluorophosphate salts. Basic or acidic ester cleavage gives the deprotected tweezers **6** and **24** in excellent overall yields (Scheme 3).

Recognition properties of the tweezer receptors

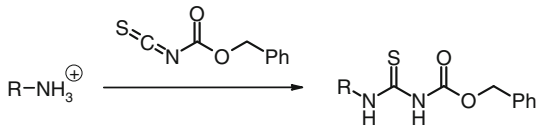
Carboxy guanidinium tweezers exist as zwitterionic structures over a wide range of pH. The pK_A values of their guanidinium functionality are 12 and 11.5 for **6** and **24**, respectively, in good agreement with the value for the arginine side-chain ($pK_A = 12.5$) [107]. The carboxylic acids in **6** show a pK_A value of 3.5, the carboxy groups in **24** of 4 (for pK_A determination experiments see the supporting information). The large differences in pK_A values between ammonium salt guest molecules and the

Scheme 2



a) MeOH, THF, or acetone, HCl 1N, RT, 5 h, quant.; b) DCM, Trifluoroacetic acid (TFA), or HCl in Et_2O, RT, 2-4 h, 93-98%; c) MeOH, HOAc, 10 bar H_2, Pd/C, RT, overnight, 94%

Table 2 Conversion of amines **10** with **11** into the corresponding Cbz–isothioureas **12–16**



10 **11** **12-16**

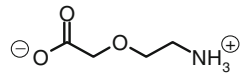
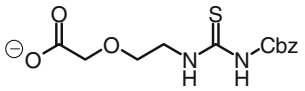
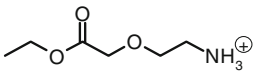
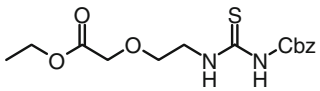
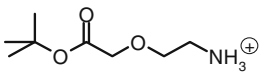
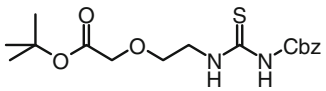
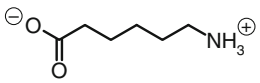
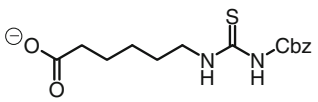
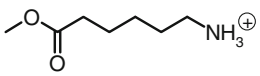
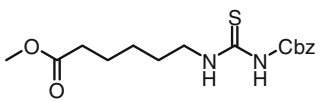
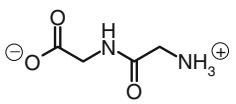
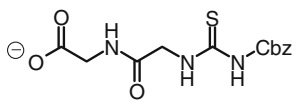
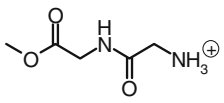
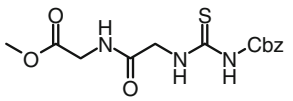
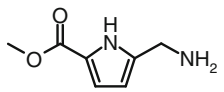
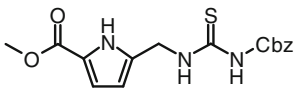
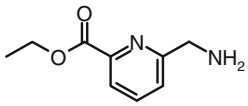
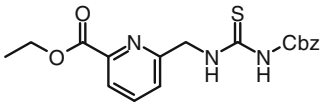
Entry	Amine	Conditions	Cbz–thiourea	Yield/%
1	 **10a**	[a]	 **12a**	84
2	 **10b**	[b], 2 h	 **12b**	91
3	 **10c**	[b], 2 h	 **12c**	89
4	 **10d**	[a]	 **13a**	81
5	 **10e**	[b], 2 h	 **13b**	83
6	 **10f**	[a]	 **14a**	78
7	 **10g**	[b], 3 h	 **14b**	84

Table 2 continued

Entry	Amine	Conditions	Cbz–thiourea	Yield/%
8	 **10h**	[b], 2 h	 **15**	92
9	 **10i**	[b], 2 h	 **16**	81

[a] Dioxane, H_2O, NaOH, Cbz–NCS, 12 h, RT

[b] DCM, NEt_3, Cbz–NCS, 2–3 h, RT

guanidinium carboxylate hosts exclude significant intramolecular proton transfer in water or DMSO.

Compounds **15**, **20**, **23**, and **24** show absorption maxima in methanol at 270 nm and emit upon excitation at 340 nm with quantum yield of about $\phi = 0.1$. [All quantum yields determined with quinine disulfate in 1 N H_2SO_4 as the reference compound ($\phi = 0.546$)]. The absorption and emission properties are only marginally affected by the protection groups (Fig. 3).

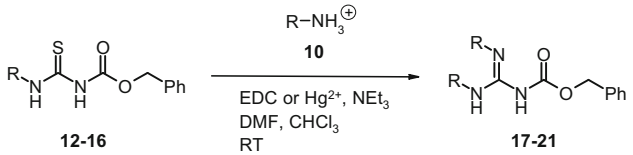
The binding of compounds **6** and **24** to *n*-butylammonium chloride and to tetrabutylammonium acetate were investigated by NMR and emission titrations. Figure 4 shows the chemically induced shift for the NMR titration of **24** with tetrabutylammonium acetate in DMSO (left) and the emission titration with a Job plot analysis in methanol (right). Nonlinear fitting of the titration data gives a binding constant of $K = 1{,}780$ dm^3/mol (1,540 dm^3/mol for compound **6**) from the NMR data and of $K = 2{,}320$ dm^3/mol from the emission data. The addition of *n*-butylammonium chloride does not result in significant changes in resonance or emission properties under the experimental conditions. The same applies to the addition of excess sodium or potassium ions. This indicates that in solution an interaction with the acetate anion occurs, but no binding of the ammonium ion as predicted from the gas-phase calculations. The emission titrations were extended in MeOH:H_2O 4:1 to the amino acids glycine, β-alanine, and gamma-aminobutyric acid (GABA). The acetate ion binding was determined as $K = 1{,}220$ dm^3/mol under these conditions, while the affinity of all amino acids was significantly lower at $K = 200$–250 dm^3/mol (see supporting info for titration data).

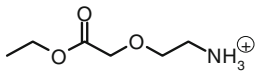
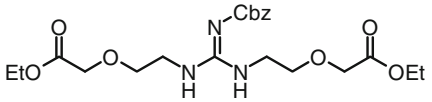
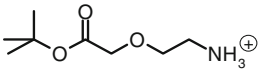
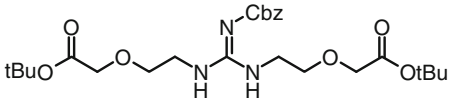
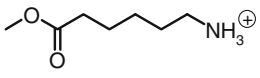
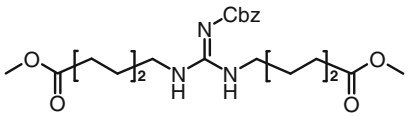
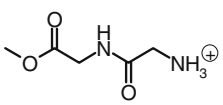
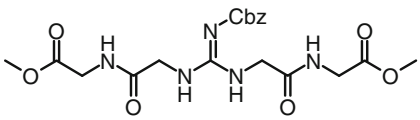
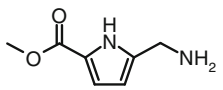
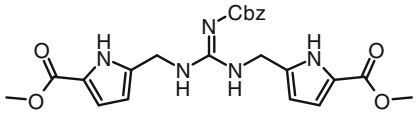
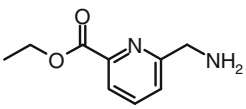
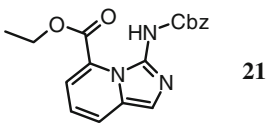
Ester **23** was investigated for comparison by emission titration with tetrabutylammonium acetate in methanol and methanol/water (4:1 v/v) and by NMR titration in DMSO. Binding constants of $K = 1.1 \times 10^4$ dm^3/mol in methanol and of $K = 4.2 \times 10^3$ dm^3/mol in methanol/water 4:1 were observed. The stoichiometry of all binding processes is 1:1 as determined by Job plot analysis. NMR titration in DMSO gave a binding constant of $K = 1.3 \times 10^3$ dm^3/mol, which is in good agreement with literature values for tetrabutylammonium acetate binding by alkyl-guanidines [108].

Conclusions

Symmetrically substituted biscarboxy guanidinium salts are accessible from unnatural glycol-δ-amino acids. While gas-phase calculations predicted intramolecular guanidinium–carboxylate interactions leading to a possible ammonium ion binding site with similar structure as observed in the glutaminase subunit HisF, measurements in DMSO and methanol revealed intermolecular binding between the guanidinium moiety and added acetate ions. No interaction with *n*-butylammonium ions could be detected in these solvents. Compounds **6** and **24** are, in contrast to the protein's ammonium ion binding site, very flexible in their structure and are not pre-organized. The formation of the calculated aggregate with an ammonium ion is energetically favored in the absence of stabilizing solvents due to charge neutralization. However, in solution the significant loss in entropy upon aggregate formation may be energetically prohibitive and can only be overcome in more rigid and suitably pre-organized receptor structures.

Table 3 Preparation of 1,3-symmetrically disubstituted guanidines

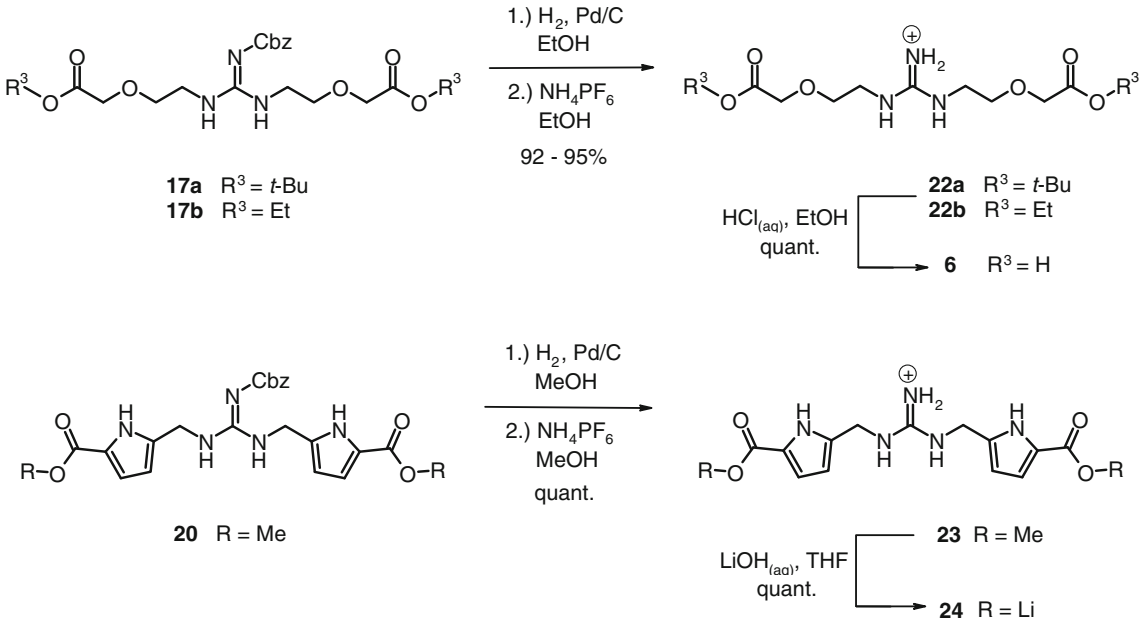


Entry	Amine	Cbz–thiourea	Cbz–guanidine	Yield/%
1	 **10b**	**12b**	 **17b**	73
2	 **10c**	**12c**	 **17a**	78
3	 **10e**	**13b**	 **18**	78
4	 **10g**	**14b**	 **19**	76
5	 **10h**	**15**	 **20**	87
6	 **10i**	**16**	 **21**	66

DMF, $CHCl_3$, NEt_3, EDC or $HgCl_2$, RT, overnight

Experimental

Analytical characterization of the synthesized compounds was done by common methods. Melting points were determined on Büchi SMP or a Lambda Photometrics OptiMelt MPA 100. Infrared (IR) spectra were recorded with a Bio-Rad FT-IR Excalibur FTS 3000. Ultraviolet (UV) spectra were recorded on a Cary 50 BIO spectrometer with temperature control at 25 °C. Electrospray mass spectra were performed on a Finnigan MAT TSQ 7000 ESI spectrometer. Other mass spectra were recorded on Varian CH-5 (EI), Finnigan MAT 95 (CI; FAB and FD). Xenon



Scheme 3

served as the ionization gas for fast-atom bombardment (FAB).

NMR spectra were recorded on Bruker Avance 600 (^{1}H: 600.1 MHz, ^{13}C: 150.1 MHz), Bruker Avance 400 (^{1}H: 400.1 MHz, ^{13}C: 100.6 MHz), or Bruker Avance 300 (^{1}H: 300.1 MHz, ^{13}C: 75.5 MHz) at 300 K. Characterization of the signals: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet; dd, double doublet; dt, double triplet; ddd, double double doublet. Integration was determined as the relative number of atoms, and the coupling constants are given in Hertz (Hz). The multiplicity of the carbon atoms is given as (+) = CH_3 or CH, (−) = CH_2 and (Cquat) for quaternary carbon atoms. Structural assignments are based on distortionless enhanced polarization transfer (DEPT) and correlation spectroscopy (COSY) experiments where applicable. Error of reported values: chemical shift: 0.01 ppm for ^{1}H NMR, 0.1 ppm for ^{13}C NMR, and 0.1 Hz for coupling constants. The solvent used is reported for each spectrum.

Analytical thin-layer chromatography (TLC) plates (silica gel 60 F254) and silica gel 60 (70–230 or 230–400 mesh) were used for chromatographic separations. Visualization of the spots was by UV light and/or staining with phosphomolybdate or ninhydrine, both in ethanol. DMF, CH_3CN, $CHCl_3$, THF, and Et_2O were dried by standard procedures and stored over molecular sieves. PE refers to petroleum ether with a boiling range of 70–90 °C; EA refers to ethyl acetate. All other solvents and chemicals were of reagent grade and used without further purification.

All test substances were of pro analysis grade, checked by NMR or HPLC, and used as purchased without further purification. The solvents for fluorescence measurements were from special spectroscopic purity purchased from Acros or Baker or Uvasol from Merck. Millipore water (18 MΩ, Milli Q Plus) was used; the 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffer was of according purity, suitable for biochemical optical screenings. If not otherwise specified, tetraethylammonium hydroxide or 0.1 M hydrochloric acid, both of analytical grade, were used to adjust the pH in the titrations and screenings.

1-*N*-Boc-ethanolamine and 1-*N*-Cbz–ethanolamine are commercially available. *N*-Boc-L-leucine methyl ester [79], *N*-Boc-L-tryptophane methyl ester [79], *N*-Boc-L-phenylalanine methyl ester [79], 3-[2-(*N*-Boc-amino)ethoxy] propionic acid ethyl ester [109], glycylglycine methyl ester hydrochloride [79], 2,6-pyridinedicarboxylic acid ethyl ester [79], 5-[(*N*-Boc-amino)-(4-methylphenylsulfonyl)methyl]-pyrrole-2-carboxylic acid methyl ester [110–112], 5-[(*N*-Boc-amino)methyl] pyrrole-2-carboxylic acid methyl ester [110–112], and 5-(aminomethyl)pyrrole-2-carboxylic acid methyl ester [110–112] were prepared according to known procedures.

General procedure 1 (GP 1): reduction of Boc-amino acids with $NaBH_4$ [113]

The corresponding *N*-Boc-protected amino acid methyl ester (2.00 g) was dissolved in 30.0 cm^3 dry THF in nitrogen atmosphere, and $NaBH_4$ and LiCl were subsequently added in small portions. The mixture was stirred overnight at room temperature under moisture protection. After having added 20.0 cm^3 water slowly, 1.2 cm^3 acetic acid (20.0 mmol) was dropped in. After short stirring, the

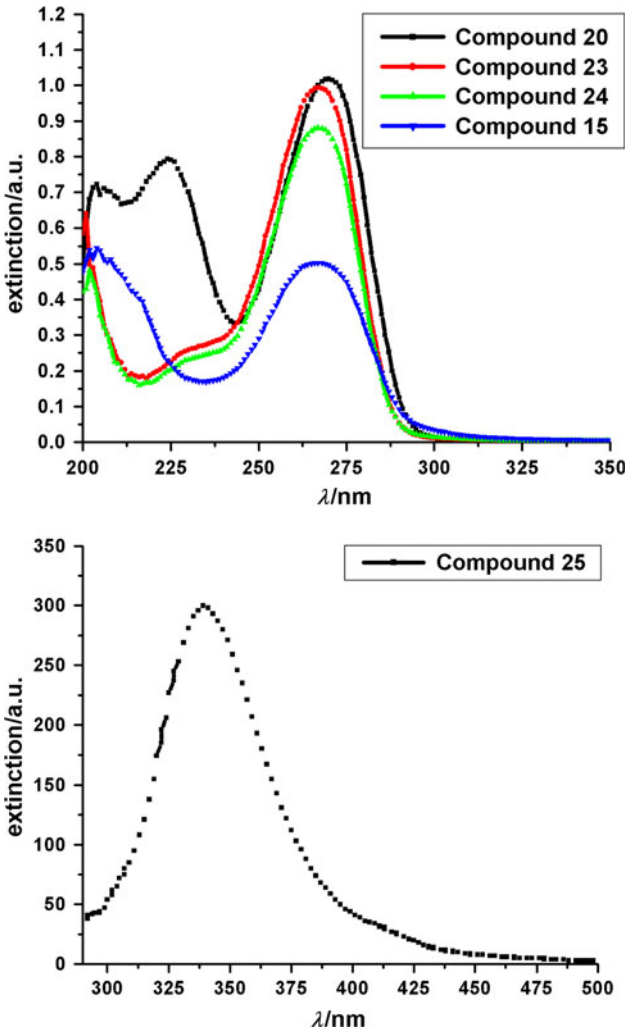


Fig. 3 Absorption spectra of compounds **15**, **20**, **23**, and **24** ($c = 8 \times 10^{-5}$ mol/dm^3) and the emission spectrum of compound **24** ($c = 4 \times 10^{-5}$ mol/dm^3) in methanol

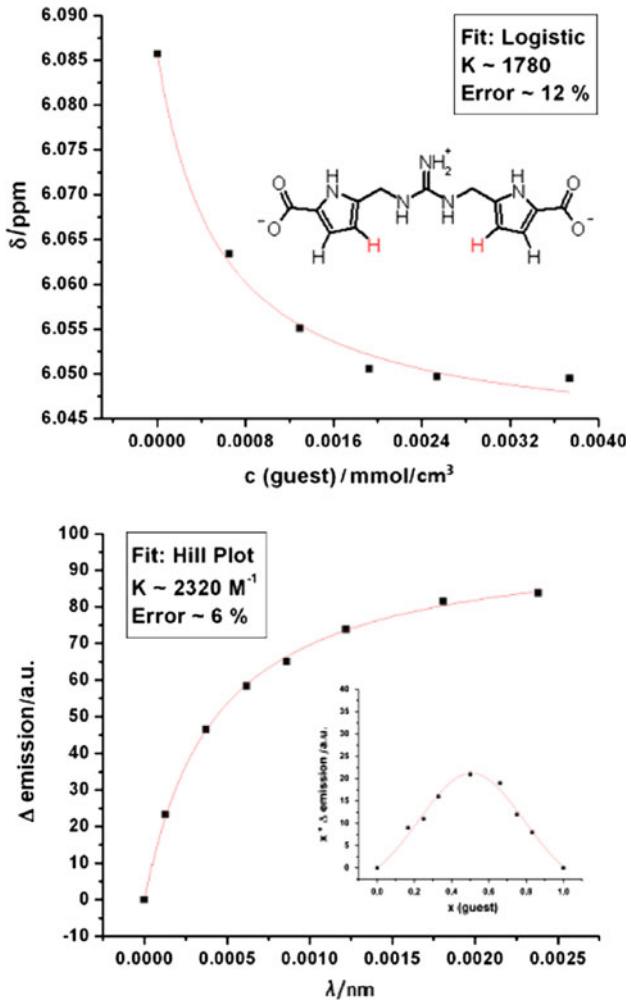


Fig. 4 Binding studies of **24** with tetrabutylammonium acetate by ^{1}H NMR ($c_{host} = 3.33 \times 10^{-3}$mol/dm^3) in DMSO (*left*) and fluorescence spectroscopy ($c_{host} = 3 \times 10^{-5}$mol/dm^3) in methanol (*right*); insert: Job's plot

THF was removed under reduced pressure. A 1:1 mixture of water and diethyl ether (50.0 cm^3 each) was added; the solid was completely dissolved. The organic phase was separated, and the aqueous layer was extracted with diethyl ether (3 × 50 cm^3). The combined ether phases were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/petroleum ether 1:2).

2-(tert-Butoxycarbonylamino)-4-methylpentan-1-ol ($C_{11}H_{23}NO_3$)

N-Boc-L-leucine methyl ester (2.00 g, 7.72 mmol) was reacted with 0.65 g $NaBH_4$ (17 mmol) and 0.72 g LiCl (17 mmol) to obtain 1.66 g colorless oil (7.2 mmol, 87%). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (d, 6 H, $J = 6.0$ Hz), 1.22 (m, 2 H), 1.40 (s, 9 H), 1.61 (m, 1 H), 3.46 (m, 1 H), 3.68 (bs, 2 H), 4.78 (bs, 2 H) ppm; MS (ESI–MS, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): m/z (%) = 218.2 (100, MH^+).

2-(tert-Butoxycarbonylamino)-3-phenylpropan-1-ol ($C_{14}H_{21}NO_3$)

N-Boc-L-phenylalanine methyl ester (2.00 g, 6.6 mmol) was reduced with 0.55 g $NaBH_4$ (14.5 mmol) and 0.62 g LiCl (14.5 mmol) to give 1.71 g of an off-white solid (6.2 mmol, 94%). M.p.: 88–89 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 1.40$ (s, 9 H), 2.76 (m, 1 H), 2.88 (d, 2 H, $J = 6.0$ Hz), 3.49–3.70 (m, 2 H), 3.87 (bs, 1 H), 4.86 (bs, 1 H), 7.19–7.28 (m, 3 H), 7.28–7.36 (m, 2 H) ppm; MS (ESI–MS, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): m/z (%) = 252.3 (100, MH^+).

2-(tert-Butoxycarbonylamino)-3-(1H-indol-3-yl)propan-1-ol ($C_{16}H_{22}N_2O_3$)

N-Boc-L-tryptophan methyl ester (2.00 g, 5.85 mmol) was reacted with 0.49 g $NaBH_4$ (12.9 mmol) and 0.55 g LiCl (12.9 mmol) to obtain 1.74 g of a white solid (5.5 mmol, 93%). M.p.: 119–120 °C; ^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 1.40 (s, 9 H), 2.79 (m, 1 H), 2.99 (d, 2 H, J = 6.0 Hz), 3.51–3.72 (m, 2 H), 4.00 (bs, 1 H), 4.89 (bs, 1 H), 7.01 (m, 1 H), 7.06–7.24 (m, 2 H), 7.34 (app. d, 1 H), 7.68 (app. d, 1 H), 8.29 (bs, 1 H)ppm; MS (ESI–MS, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): m/z (%) = 291.2 (100, MH^+).

3-[1-(Benzyloxycarbonyl)-1H-indol-3-yl]-2-(tert-butoxycarbonylamino)-propan-1-ol ($C_{24}H_{28}N_2O_5$)
Powdered sodium hydroxide (120 mg, 3.0 mmol) was added to a solution of 290 mg *N*-Boc-L-tryptophanol (1.0 mmol) and 290 mg tetrabutylammonium hydrogen sulfate (0.6 mmol) in 5.0 cm^3 dried CH_2Cl_2, and the mixture was stirred for 2.5 h at room temperature. Benzylchloroformate (412 mg, 2.4 mmol) was then added, and the mixture was allowed to stir for 20 h. After dilution with 10.0 cm^3 ethyl acetate and stirring for 0.5 h, it was washed three times with 5.0 cm^3 water. After being dried over $MgSO_4$, the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, ethyl acetate/petroleum ether 1:3) to afford the title compound as a white solid (380 mg, 0.921 mmol, 92%). M.p.: 76–78 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 9 H), 3.03 (m, 2 H), 4.16 (m, 2 H), 4.25 (m, 1 H), 4.70 (m, 1 H), 4.94 (bs, 1 H), 5.20 (s, 2 H), 6.95 (m, 1 H), 7.12 (m, 1 H), 7.21 (m, 1 H), 7.28–7.46 (m, 6 H), 7.65 (m, 1 H) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,346 (bm), 2,976 (m), 2,886 (m), 1,726 (m), 1,689 (s), 1,528 (m), 1,454 (m), 1,397 (m), 1,367 (m), 1,254 (s), 1,162 (s), 1,067 (m), 1,019 (m), 941 (m), 896 (m), 852 (m), 791 (m), 739 (s), 697 (s), 660 (m), 593 (m), 556 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): m/z (%) = 425.1 (48, M + H^+), 442.0 (25, M + NH_4^+), 849.3 (100, 2M + H^+), 866.4 (11, 2M + NH_4^+).

Syntheses and deprotections of the building blocks

6-(Hydroxymethyl)pyridine-2-carboxylic acid ethyl ester [114]
2,6-Pyridinedicarboxylic acid diethyl ester (27.9 g, 0.125 mol) and 3.8 g $NaBH_4$ (0.1 mol) were dissolved in 250 cm^3 dry THF and refluxed for 2 h under moisture protection. The solvent was removed, and 50.0 cm^3 water was added. After stirring for 10 min, the mixture was extracted with $CHCl_3$ (3 × 50.0 cm^3). The organic phases were combined and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel with ethyl acetate/ethanol 6:1 → 3:1 to give the product as colorless solid (15.39 g, 85.02 mmol, 85%).

6-(Aminomethyl)pyridine-2-carboxylic acid ethyl ester [115]
Thoroughly dried 6-(hydroxymethyl)pyridine-2-carboxylic acid ethyl ester (5.8 g, 35 mmol) was dissolved in small portions in 11.5 cm^3 well-stirred $SOCl_2$ under moisture protection, not allowing the temperature to rise over 0 °C. After 90 min the solution was allowed to reach room temperature and the excess of $SOCl_2$ was removed under reduced pressure without heating. Toluene (20.0 cm^3) was added to the oily residue, and the solution was washed with cold aqueous 1 M $NaHCO_3$ (2 × 10.0 cm^3) and dried over $MgSO_4$. Evaporation of the solvent afforded 6.5 g 2-(chloromethyl)pyridine-6-carboxylic acid ethyl ester (32.5 mmol, 83%) as an orange oil.

2-(Chloromethyl)pyridine-6-carboxylic acid ethyl ester (6.0 g, 30 mmol) in 10.0 cm^3 anhydrous DMF was slowly added to a solution of 6.12 g sodium phthalimide (36 mmol) in 10.0 cm^3 dry DMF. After stirring for 2 h at room temperature the reaction mixture was centrifuged, the solvent was removed under reduced pressure, and the residue was dissolved in 100.0 cm^3 $CHCl_3$. The resulting solution was washed with 0.2 M NaOH (2 × 100.0 cm^3), then with water, and dried. Removal of the solvent yielded a solid residue, which was dissolved in 500.0 cm^3 warm ethanol. Hydrazine (1.13 g, 35 mmol) was added, and the mixture was refluxed until disappearance of the starting material (monitored by TLC). The mixture was cooled to 5 °C and filtered, and the solvent was removed to finally obtain 4.05 g of yellow syrup (22.5 mmol, 75%).

2-[2-(Benzyloxycarbonylamino)ethoxy]acetic acid tert-butyl ester (**7c**, $C_{16}H_{23}NO_5$)
To a solution of 2.0 g 2-(benzyloxycarbonylamino)ethanol (12.5 mmol) in 60 cm^3 toluene, 5.73 g *tert*-butylbromoacetate (25.0 mmol) and 2.12 g tetrabutylammonium hydrogen sulfate (6.25 mmol) were added. The reaction mixture was vigorously stirred, and 30 cm^3 30% NaOH was slowly added. After 12 h of stirring at room temperature, another portion of *tert*-butylbromoacetate (1.15 g, 5.0 mmol) was added. Stirring was continued for 6 h, then the organic phase was separated. It was washed with 20 cm^3 5% aqueous acetic acid and with 3 × 20 cm^3 of water. After drying over $MgSO_4$ the solvent was removed at reduced pressure. The excess of *tert*-butylbromoacetate was evaporated in vacuo, and the oily raw material was purified by column chromatography with ethyl acetate/petroleum ether 1:4 to yield the benzyloxycarbonylamino acid ester as clear, colorless oil (3.36 g, 10.86 mmol, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9 H), 3.36 (t, 2 H, J = 5.2 Hz), 3.54 (t, 2 H, J = 5.2 Hz), 3.91 (s, 2 H), 5.07 (s, 2 H), 5.48 (bs, 1 H), 7.26–7.32 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.1 (+, 3 C), 40.0 (−, 1 C), 64.1 (−, 1 C), 65.6 (−, 1 C), 67.7 (−, 1 C), 69.6 (−, 1 C), 80.7 (Cquat, 1 C), 127.0 (+, 1 C), 127.7 (+, 2 C), 128.5 (+, 2 C), 135.6 (Cquat, 1 C), 155.5 (Cquat, 1 C), 168.7 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,351 (bm), 2,978 (m), 2,937 (m), 2,886 (m), 1,713 (s), 1,518 (m),

1,455 (m), 1,368 (m), 1,228 (s), 1,131 (s), 1,026 (m), 915 (m), 845 (m), 798 (m), 735 (m), 698 (m), 584 (m) cm^{-1}; MS (CI, NH_3): *m/z* (%) = 219.2 (90, M + NH_4^+–C_7H_8O), 254.2 (9, M + H^+–C_4H_8), 271.2 (63, M + NH_4^+–C_4H_8), 310.2 (9, M + H^+), 327.2 (100, M + NH_4^+).

General procedure 2 (GP 2): phase-transfer catalytic etherification of substituted amino alcohols

The *N*-Boc-amino alcohol was dissolved with 98.8 mg tetrabutylammonium hydrogen sulfate (0.4 mmol) in 6.0 cm^3 CH_2Cl_2. Aqueous NaOH (5.0 M, 6.0 cm^3) was added, 233 mg bromoacetic acid *tert*-butyl ester (1.2 mmol) in 1.0 cm^3 CH_2Cl_2 was dropped in, and the reaction mixture was vigorously stirred for 3 h at room temperature. The same amount bromoacetic acid *tert*-butyl ester was added again, and the heterogeneous solution was stirred overnight. The mixture was poured on 10 g ice in a separation funnel, the organic phase was separated, and the aqueous layer was extracted with dichloromethane (3 × 10.0 cm^3). The organic phases were combined and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography with ethylacetate/petroleum ether 1:4 to obtain the pure compound.

2-[2-(tert-Butoxycarbonylamino)ethoxy]acetic acid tert-butyl ester (**7a**, $C_{13}H_{25}NO_5$)
N-Boc-ethanolamine (192 mg, 1.2 mmol) was converted according to GP 2 to give **7a** as colorless oil (273 mg, 0.996 mmol, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 9 H), 1.42 (s, 9 H), 3.26 (m, 2 H), 3.53 (t, *J* = 5.2 Hz, 2 H), 3.90 (s, 2 H), 5.12 (br s, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1 (+, 3 C), 28.4 (+, 3 C), 40.4 (−, 1 C), 68.7 (−, 1 C), 70.7 (−, 1 C), 79.1 (Cquat, 1 C), 81.8 (Cquat, 1 C), 156.0 (Cquat, 1 C), 169.6 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,371 (bm), 2,978 (m), 2,932 (m), 1,761 (m), 1,714 (s), 1,509 (m), 1,486 (m), 1,416 (m), 1,367 (m), 1,250 (s), 1,202 (s), 1,137 (s), 762 (m) cm^{-1}; MS (CI, NH_3): *m/z* (%) = 181.1 (43, M + NH_4^+–$2C_4H_8$), 219.2 (24, M + H^+–C_4H_8), 237.2 (100, M + NH_4^+–C_4H_8), 276.2 (46, M + H^+), 293.3 (60, M + NH_4^+).

2-[2-(tert-Butoxycarbonylamino)-4-methylpentoxy]acetic acid tert-butyl ester (**7e**, $C_{17}H_{33}NO_5$)
N-Boc-L-leucinol (217 mg, 1.0 mmol) was reacted to obtain 256 mg of a white oily solid (0.77 mmol, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (d, 6 H, *J* = 7.2 Hz), 1.36 (m, 2 H), 1.38 (s, 9 H), 1.41 (s, 9 H), 1.61 (m, 1 H), 3.43 (m, 2 H), 3.70 (m, 1 H), 3.89 (s, 2 H), 4.83 (bs, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4 (+, 1 C), 22.9 (+, 1 C), 24.8 (+, 1 C), 28.1 (+, 3 C), 28.4 (+, 3 C), 41.0 (−, 1 C), 48.5 (+, 1 C), 68.4 (−, 1 C), 73.8 (−, 1 C), 78.9 (Cquat, 1 C), 82.8 (Cquat, 1 C), 155.6 (Cquat, 1 C), 166.2 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,354 (bm), 2,959 (m), 2,934 (m), 2,874 (m), 1,748 (m), 1,710 (s), 1,503 (m), 1,457 (m), 1,387 (m), 1,367 (s), 1,295 (m), 1,228 (s), 1,164 (s), 1,128 (s), 1,049 (m), 941 (m), 846 (m), 778 (m), 751 (m) cm^{-1}; MS (CI, NH_3): *m/z* (%) = 219.1 (13, M + H^+–$2C_4H_8$), 237.0 (20, M + NH_4^+–$2C_4H_8$), 275.2 (48, M + H^+–C_4H_8), 293.2 (69, M + NH_4^+–C_4H_8), 332.2 (100, M + H^+), 349.2 (83, M + NH_4^+).

2-[2-(tert-Butoxycarbonylamino)-3-phenylpropoxy]acetic acid tert-butyl ester (**7g**, $C_{20}H_{31}NO_5$)
N-Boc-L-phenylalaninol (250 mg, 1.0 mmol) was employed to yield 328 mg **7g** as a colorless wax (0.89 mmol, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 9 H), 1.39 (s, 9 H), 2.82 (m, 2 H), 3.37 (m, 2 H), 3.65 (m, 1 H), 3.87 (s, 2 H), 5.17 (bs, 1 H), 7.18–7.30 (m, 5 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1 (+, 3 C), 28.4 (+, 3 C), 37.1 (−, 1 C), 51.8 (+, 1 C), 68.5 (−, 1 C), 71.6 (−, 1 C), 79.2 (Cquat, 1 C), 82.9 (Cquat, 1 C), 126.3 (+, 1 C), 128.4 (+, 2 C), 129.5 (+, 2 C), 138.3 (Cquat, 1 C), 155.5 (Cquat, 1 C), 166.3 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,375 (bm), 2,978 (m), 2,932 (m), 2,880 (m), 1,746 (m), 1,710 (s), 1,497 (m), 1,456 (m), 1,389 (m), 1,367 (m), 1,294 (m), 1,230 (m), 1,163 (s), 1,130 (s), 1,058 (m), 943 (m), 917 (m), 846 (m), 742 (m), 701 (m) cm^{-1}; MS (CI, NH_3): *m/z* (%) = 253.1 (14, M + H^+–$2C_4H_8$), 271.0 (21, M + NH_4^+–$2C_4H_8$), 309.1 (82, M + H^+–C_4H_8), 327.1 (63, M + NH_4^+–C_4H_8), 366.2 (100, M + H^+), 383.2 (78, M + NH_4^+); HRMS (EI, 70 eV): calc. for $C_{20}H_{31}NO_5{*}^+$ 365.2202, found 365.2197.

2-[3-[1-(Benzyloxycarbonyl)-1H-indol-3-yl]-2-(tert-butoxycarbonyl-amino)-propoxy]acetic acid tert-butyl ester (**7i**, $C_{30}H_{38}N_2O_7$)
3-[1-(Benzyloxycarbonyl)-1*H*-indol-3-yl]-2-(*tert*-butoxycarbonylamino)-propan-1-ol (298 mg, 0.7 mmol) was used to give 236 mg **7i** as colorless oil (0.441 mmol, 63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9 H), 1.43 (s, 9 H), 3.06 (m, 2 H), 3.46 (m, 1 H), 3.98 (s, 2 H), 4.11 (m, 2 H), 4.61 (m, 2 H), 5.19 (bs, 1 H), 6.98 (m, 1 H), 7.10 (m, 1 H), 7.19 (m, 1 H), 7.29–7.41 (m, 7 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1 (+, 3 C), 28.4 (+, 3 C), 48.5 (−, 1 C), 51.0 (+, 1 C), 67.7 (−, 1 C), 68.5 (−, 1 C), 68.9 (−, 1 C), 79.1 (Cquat, 1 C), 81.8 (Cquat, 1 C), 108.9 (+, 1 C), 111.9 (Cquat, 1 C), 119.4 (+, 1 C), 121.9 (+, 1 C), 127.4 (+, 1 C), 127.9 (−, 1 C), 128.1 (+, 2 C), 128.4 (+, 2 C), 128.6 (+, 1 C), 136.8 (Cquat, 1 C), 137.4 (Cquat, 1 C), 155.6 (Cquat, 1 C), 167.6 (Cquat, 1 C), 169.0 (Cquat, 1 C), 169.6 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,061 (bm), 2,977 (m), 2,933 (m), 1,745 (s), 1,491 (m), 1,468 (m), 1,389 (m), 1,367 (m), 1,299 (m), 1,227 (s), 1,189 (s), 1,128 (s), 1,050 (m), 943 (m), 847 (m), 803 (m), 740 (m), 699 (m), 584 (m) cm^{-1}; MS (CI, NH_3): *m/z* (%) = 539.1 (33,

M + H^+), 556.1 (36, M + NH_4^+), 577.1 (100, M + K^+), 599.1 (64, M + H^+ + HOAc).

General procedure 3 (GP 3): NaH-catalyzed ether synthesis

In a nitrogen-flushed Schlenckflask, *N*-Boc-amino alcohol (5.0 mmol) was added to a suspension of 380 mg NaH (60% susp., 8.0 mmol) and 150 mg KI (0.8 mmol) in 30.0 cm^3 dry THF at 0 °C. After dropwise addition of 1.67 g ethyl bromoacetate (10.0 mmol) in 10.0 cm^3 dry THF, the reaction mixture was stirred for 4 h at room temperature. The NaH suspension and precipitated solids were settled by a centrifuge, and the THF solution was decanted off and evaporated to give the crude product. The residue was purified by column chromatography (petroleum ether/ethyl acetate, 9:1 → 4:1) to give the corresponding glycol-δ-amino acid ester.

2-[2-(tert-Butoxycarbonylamino)ethoxy]acetic acid ethyl ester (**7b**, $C_{11}H_{21}NO_5$)
N-Boc-ethanolamine (800 mg, 5.0 mmol) was reacted according to GP 3 to give **7b** as faintly yellow oil (727 mg, 2.955 mmol, 59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, 3 H, J = 7.1 Hz), 1.38 (s, 9 H), 3.28 (m, 2 H), 3.54 (t, 2 H, J = 5.2 Hz), 4.02 (s, 2 H), 4.15 (q, 2 H, J = 7.1 Hz), 5.11 (bs, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (+, 1 C), 28.4 (+, 3 C), 40.4 (−, 1 C), 61.0 (−, 1 C), 68.3 (−, 1 C), 70.8 (−, 1 C), 79.2 (Cquat, 1 C), 156.0 (Cquat, 1 C), 170.4 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,374 (bm), 2,978 (m), 2,935 (m), 1,761 (m), 1,706 (s), 1,511 (m), 1,455 (m), 1,367 (m), 1,248 (m), 1,206 (s), 1,136 (s), 1,025 (s), 864 (m), 782 (m), 717 (m), 581 (m) cm^{-1}; MS (CI, NH_3): *m/z* (%) = 192.1 (98, M + H^+–C_4H_8), 248.2 (16, M + H^+), 265.2 (40, M + NH_4^+); HRMS (PI-LSIMS FAB, glycerol): calc. for $C_{11}H_{22}NO_5^+$ 248.1498, found 248.1493.

2-[2-(tert-Butoxycarbonylamino)-4-methylpentoxy]acetic acid ethyl ester (**7f**, $C_{15}H_{29}NO_5$)
N-Boc-L-leucinol (1.09 g, 5.0 mmol) was reacted to obtain 790 mg **7f** as a white oily solid (2.62 mmol, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, 6 H, J = 7.1 Hz), 1.23 (t, 3 H, J = 7.1 Hz), 1.38 (s, 9 H), 1.39 (m, 2 H), 1.61 (m, 1 H), 3.48 (m, 2 H), 3.72 (m, 1 H), 4.01 (s, 2 H), 4.16 (q, 2 H, J = 7.1 Hz), 4.81 (bs, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (+, 1 C), 22.1 (+, 1 C), 22.9 (+, 1 C), 24.7 (+, 1 C), 25.7 (+, 1 C), 28.4 (+, 3 C), 40.6 (−, 1 C), 47.7 (−, 1 C), 61.1 (−, 1 C), 68.2 (−, 1 C), 71.4 (−, 1 C), 79.5 (Cquat, 1 C), 155.4 (Cquat, 1 C), 167.2 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,354 (bm), 2,958 (m), 2,921 (m), 2,874 (m), 1,739 (m), 1,690 (s), 1,517 (m), 1,454 (m), 1,388 (m), 1,366 (m), 1,277 (s), 1,251 (m), 1,163 (s), 1,115 (m), 1,049 (m), 1,003 (m), 870 (m), 780 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 304.2 (100, M + H^+).

2-[2-(tert-Butoxycarbonylamino)-3-phenylpropoxy]acetic acid ethyl ester (**7h**, $C_{18}H_{27}NO_5$)
N-Boc-L-phenylalaninol (1.25 g, 5.0 mmol) was employed to yield 820 mg of the product as a faintly yellow waxy solid (2.44 mmol, 49%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, 3 H, J = 7.1 Hz), 1.41 (s, 9 H),2.86 (m, 2 H), 3.42 (m, 2 H), 3.81 (s, 2 H), 4.07 (m, 1 H), 4.22 (q, 2 H, J = 7.1 Hz), 5.17 (bs, 1 H), 7.13–7.31 (m, 5 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (+, 1 C), 28.3 (+, 3 C), 37.7 (−, 1 C), 50.8 (+, 1 C), 61.0 (−, 1 C), 66.6 (−, 1 C), 68.5 (−, 1 C), 79.4 (Cquat, 1 C), 126.8 (+, 1 C), 128.4 (+, 2 C), 129.3 (+, 2 C), 138.2 (Cquat, 1 C), 155.5 (Cquat, 1 C), 167.1 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,366 (bm), 2,978 (m), 2,933 (m), 1,743 (m), 1,703 (s), 1,498 (s), 1,453 (m), 1,388 (m), 1,366 (m), 1,276 (m), 1,247 (m), 1,208 (m), 1,163 (s), 1,132 (s), 1,057 (m), 1,026 (m), 851 (m), 742 (m), 701 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 338.1 (100, M + H^+).

2-[3-[1-(Benzyloxycarbonyl)-1H-indol-3-yl]-2-(tert-butoxycarbonylamino)propoxy]acetic acid ethyl ester (**7j**, $C_{28}H_{34}N_2O_7$)
3-[1-(benzyloxycarbonyl)-1*H*-indol-3-yl]-2-(*tert*-butoxycarbonyl-amino)-propan-1-ol (298 mg, 0.7 mmol) was reacted to give 64 mg as colorless waxy solid (0.126 mmol, 18%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, 3 H, J = 7.1 Hz), 1.39 (s, 9 H), 3.08 (m, 2 H), 3.47 (m, 1 H), 3.96 (s, 2 H), 4.11 (m, 2 H), 4.15 (q, 2 H, J = 7.1 Hz), 4.63 (m, 2 H), 5.17 (bs, 1 H), 6.97 (m, 1 H), 7.12 (m, 1 H), 7.18 (m, 1 H), 7.26–7.43 (m, 7 H) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,060 (bm), 2,981 (m), 2,936 (m), 2,889 (m), 1,743 (s), 1,493 (m), 1,470 (m), 1,386 (m), 1,368 (m), 1,301 (m), 1,225 (s), 1,189 (s), 1,123 (s), 1,054 (m), 944 (m), 846 (m), 805 (m), 743 (m), 699 (m) cm^{-1}.

*Alternative preparation of **7b** catalyzed by potassium tert-butylate*

A 100-cm^3 Schlenckflask was evacuated and then filled with nitrogen several times. To a solution of 0.80 g *N*-Boc-ethanolamine (5.0 mmol) in 10.0 cm^3 dry THF were added 1.14 cm^3 ethyl bromoacetate (10.0 mmol) and 1.39 g potassium *tert*-butylate (12.0 mmol) in small portions. The mixture changed color to orange. The mixture was stirred for 3 h at 0 °C. The base suspension was settled by a centrifuge, the THF solution was decanted off, and the solvent was evaporated. The crude orange oil was purified by column chromatography (ethyl acetate/petroleum ether 1:1). The product (*Rf* = 0.5, EE/PE 1:1) was isolated as a slightly yellowish oil (0.58 g, 2.34 mmol, 47%).

*Synthesis of **7b** using azoacetic acid ethyl ester and copper(I)*

A solution of 1.60 g *N*-Boc-ethanolamine (10.0 mmol) in 30 cm^3 dichloromethane (DCM) was cooled to 5 °C in a nitrogen atmosphere. Copper(II) triflate (362 mg, 1.0 mmol, 10 mol%) and three drops of phenyl hydrazine were added, immediately followed by 120 mg tetramethylethylenediamine (TMEDA)(1.0 mmol, 10 mol%). After stirring for 30 min, 8.8 cm^3 15% azoacetic acid ethyl ester in DCM (1.71 g, 15.0 mmol) was slowly added over a period of 6 h at 5 °C. The mixture was allowed to warm up slowly to room temperature and was stirred overnight. The solution was filtered over alumina N, the filter cake was washed with dichloromethane, and the solvent was evaporated. The remaining oil was purified by column chromatography (ethyl acetate/petroleum ether 2:1 → 1:1) to yield the product (1.93 g, 7.81 mmol, 78%) as a clear yellow oil ($Rf = 0.3$, ethyl acetate/petroleum ether 1:2).

2-[2-[2-(tert-Butoxycarbonylamino)ethoxy]ethoxy]acetic acid ethyl ester ($C_{13}H_{25}NO_6$)

A solution of 500 mg 2-[2-(*tert*-butoxycarbonylamino)ethoxy]ethanol (2.5 mmol) in 10.0 cm^3 DCM was cooled to 5 °C in a nitrogen atmosphere. Copper(II) triflate (90 mg, 0.25 mmol, 10 mol%) and one drop of phenyl hydrazine were added, followed by 40 mg TMEDA (0.25 mmol, 10 mol%). After stirring for 30 min, 2.20 cm^3 15% azoacetic acid ethyl ester in DCM (0.43 g, 3.8 mmol) was dropped in over a period of 3 h at 5 °C. The mixture was allowed to warm up slowly to room temperature and was stirred overnight. The solution was filtered over alumina N, the filter cake was washed with DCM, and the solvent was evaporated. The raw material was purified by column chromatography (ethyl acetate/petroleum ether 2:1 → 1:1) to yield a yellow oil (468 mg, 1.69 mmol, 68%). $Rf = 0.2$ (EE/PE 1:2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$ (t, 3 H, $J = 7.1$ Hz), 1.43 (s, 9 H), 3.31 (m, 2 H), 3.54 (t, 2 H, $J = 5.2$ Hz), 3.65 (m, 2 H), 3.71 (m, 2 H), 4.13 (s, 2 H), 4.21 (q, 2 H, $J = 7.1$ Hz), 5.03 (bs, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.2$ (+, 1 C), 28.4 (+, 3 C), 40.4 (−, 1 C), 61.0 (−, 1 C), 61.2 (−, 1 C), 61.3 (−, 1 C), 68.7 (−, 1 C), 70.8 (−, 1 C), 79.1 (Cquat, 1 C), 156.0 (Cquat, 1 C), 170.4 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu} = 3{,}379$ (bm), 2,977 (m), 2,953 (m), 1,749 (m), 1,705 (s), 1,515 (m), 1,455 (m), 1,366 (m), 1,248 (m), 1,202 (s), 1,117 (s), 907 (m), 863 (m), 779 (m), 718 (m), 579 (m), 530 (m) cm^{-1}; MS (CI, NH_3): *m/z* (%) = 192.2 (8, $M + H^+ – CO_2 – C_4H_8$), 235.2 (100, $M + H^+ – C_4H_8$), 253.1 (16, $M + NH_4^+ – C_4H_8$), 292.2 (4, $M + H^+$), 309.2 (6, $M + NH_4^+$).

Example procedure for hydrogenolytic deprotection: 2-(2-aminoethoxy)acetic acid tert-butyl ester, hydroacetate (**10c**, $C_{10}H_{21}NO_5$)

Compound **7c** (1.55 g, 5.0 mmol) was dissolved in 20.0 cm^3 methanol, three spatula tips of palladium on charcoal (10% Pd) and 0.3 g acetic acid (5.0 mmol) were added, and the mixture was stirred for 2 days in hydrogen atmosphere (20 bar). The solution was filtered over Celite, the filter cake was washed with small amounts of methanol, and the solvent was removed under reduced pressure. The product was isolated as clear, colorless oil (1.14 g, 4.84 mmol, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.45$ (s, 9 H), 2.00 (s, 3 H), 3.15 (t, 2 H, $J = 5.2$ Hz), 3.77 (t, 2 H, $J = 5.2$ Hz), 3.99 (s, 2 H), 9.13 (bs, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.0$ (+, 1 C), 28.1 (+, 3 C), 39.5 (−, 1 C), 68.0 (−, 1 C), 68.4 (−, 1 C), 82.6 (Cquat, 1 C), 170.3 (Cquat, 1 C), 176.9 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu} = 3{,}373$ (bm), 2,977 (m), 2,929 (m), 1,737 (m), 1,666 (m), 1,556 (m), 1,398 (m), 1,369 (m), 1,241 (m), 1,128 (s), 1,014 (m), 839 (m), 721 (m), 652 (m) cm^{-1}; MS (CI, NH_3): *m/z* (%) = 120.1 (13, $M + H^+ – C_4H_8$), 176.1 (100, $M + H^+$).

2-(2-Aminoethoxy)acetic acid ethyl ester, hydrochloride (**10b**, $C_6H_{14}ClNO_3$)

To a solution of 0.52 g **7b** (2.0 mmol) in 10.0 cm^3 dried DCM, 4.0 cm^3 diethyl ether saturated with HCl was slowly added. After 3 h of stirring at room temperature, the solvent was evaporated. The residue was taken up in a little DCM, and the solvent was removed under reduced pressure again. This process was repeated once. The remaining sticky solid was dried under vacuum overnight. The yield was 0.38 g of a yellow, deliquescent solid (1.96 mmol, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (t, 3 H, $J = 7.1$ Hz), 3.32 (m, 2 H), 3.91 (m, 2 H), 4.09–4.21 (q, 2 H, $J = 7.1$ Hz), 4.18 (s, 2 H), 6.50 (bs, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$ (+, 1 C), 39.4 (−, 1 C), 61.3 (−, 1 C), 67.4 (−, 1 C), 68.2 (−, 1 C), 171.0 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu} = 3{,}470$ (bm), 2,937 (m), 2,916 (m), 1,726 (m), 1,669 (s), 1,516 (m), 1,430 (m), 1,183 (s), 1,127 (s), 1,020 (m), 965 (m), 836 (m), 799 (s), 721 (m), 673 (m), 517 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 147.8 (100, $M + H^+$), 294.9 (5, $2M + H^+$).

The same result is achieved if trifluoroacetic acid (TFA) is used instead of HCl in diethyl ether. The yields and the appearance of the product are comparable. Both products show no difference in reactivity. **10b**, trifluoroacetate ($C_8H_{14}F_3NO_5$): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$ (t, 3 H, $J = 7.1$ Hz), 3.32 (m, 2 H), 3.81 (t, 2 H, $J = 5.2$ Hz), 4.14 (s, 2 H), 4.21 (q, 2 H, $J = 7.1$ Hz), 7.78 (bs, 3 H) ppm; IR (FT-IR, film): $\bar{\nu} = 3{,}460$ (bm), 2,984 (m), 2,937

(m), 1,720 (m), 1,671 (s), 1,519 (m), 1,428 (m), 1,378 (m), 1,184 (s), 1,127 (s), 1,021 (m), 966 (m), 836 (m), 799 (s), 721 (m), 677 (m), 596 (m), 517 (m), 495 (m) cm^{-1}; MS (CI, NH_3, +Q1MS): *m/z* (%) = 148.1 (100, $M + H^+$); MS (CI, NH_3, −Q1MS): *m/z* (%) = 146.0 (100, $M - H^+$).

2-(2-Aminoethoxy)acetic acid (**10a**, $C_4H_9NO_3$)
Compound **7a** or **7b** (1.0 mmol) was dissolved in 0.5 cm^3 methanol, 1.0 cm^3 1 N aqueous HCl was added, and the mixture was stirred for 3 h. The solvent was evaporated, and the residue was lyophilized to yield **10a** as colorless sticky oil (118 mg, 1.0 mmol, quant). ^{1}H NMR (300 MHz, MeOH-*d4*): δ = 3.19 (t, 2 H, J = 5.2 Hz), 3.81 (t, 2 H, J = 5.2 Hz), 4.26 (s, 2 H), 4.86 (bs, 3 H), 8.08 (bs, 1 H) ppm; ^{13}C NMR (75 MHz, MeOH-*d4*): δ = 40.8 (−, 1 C), 68.4 (−, 1 C), 68.8 (−, 1 C), 173.2 (Cquat, 1 C) ppm; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 119.8 (100, $M + H^+$).

General procedure 4 (GP 4): thiourea synthesis with free acids in dioxane and water

Benzyloxycarbonyl isothiocyanate (250 mg, 1.3 mmol) in 4.0 cm^3 dioxane was added to a solution of the amino compound (1.0 mmol) in 2.2 cm^3 aqueous 1 M NaOH. The mixture was stirred at room temperature for 12 h. The organic solvent was removed under reduced pressure. The aqueous phase was acidified with 5% $KHSO_4$ solution to pH 2. After addition of 10.0 cm^3 ethyl acetate, the phases were separated and the water phase was extracted twice with 20.0 cm^3 ethyl acetate. The combined organic phases were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was suspended in 10.0 cm^3 diethyl ether, the ether was decanted off, and the remaining precipitate was dried. The crude product was purified by column chromatography on silica gel (ethyl acetate).

2-[2-[3-(Benzyloxycarbonyl)-2-thioureido]ethoxy]acetic acid (**12a**, $C_{13}H_{16}N_2O_5S$)
2-(2-Aminoethoxy)acetic acid (118 mg, 1.00 mmol) was used to give 262 mg of yellow oil (0.839 mmol, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.78 (t, 2 H, J = 5.2 Hz), 3.91 (t, 2 H, J = 5.2 Hz), 4.14 (s, 2 H), 5.19 (s, 2 H), 7.28–7.43 (m, 5 H), 8.10 (bs, 1 H), 9.95 (bs, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.5 (−, 1 C), 67.2 (−, 1 C), 67.2 (−, 1 C), 68.0 (−, 1 C), 127.3 (+, 2 C), 127.7 (+, 2 C), 127.8 (+, 1 C), 133.5 (Cquat, 1 C), 151.2 (Cquat, 1 C), 169.8 (Cquat, 1 C), 178.2 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,285 (bm), 2,950 (m), 1,719 (s), 1,512 (s), 1,452 (m), 1,396 (m), 1,315 (m), 1,218 (s), 1,128 (s), 1,082 (m), 1,023 (m), 974 (m), 838 (m), 738 (m), 694 (s), 580 (m), 490 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%) = 312.1 (73, M^{*+}), 221.0 (6, M^{*+}), 91.1 (100, $C_7H_7^{*+}$).

6-[3-(Benzyloxycarbonyl)-2-thioureido]hexanoic acid (**13a**, $C_{15}H_{20}N_2O_4S$)
ε-Aminohexanoic acid (131 mg, 1.0 mmol) was used to obtain 261 mg of an oily, colorless solid (0.806 mmol, 81%). ^{1}H NMR (300 MHz, MeOH-*d4*): δ = 1.37 (m, 2 H), 1.62 (m, 4 H), 2.39 (t, 2 H, J = 7.2 Hz), 3.61 (t, 2 H, J = 7.2 Hz), 5.17 (s, 2 H), 7.21–7.47 (m, 5 H) ppm; ^{13}C NMR (75 MHz, MeOH-*d4*): δ = 25.6 (−, 1 C), 27.5 (−, 1 C), 29.1 (−, 1 C), 34.9 (−, 1 C), 46.0 (−, 1 C), 68.8 (−, 1 C), 128.9 (+, 1 C), 129.5 (+, 2 C), 129.7 (+, 2 C), 136.9 (Cquat, 1 C), 154.9 (Cquat, 1 C), 177.6 (Cquat, 1 C), 181.2 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,390 (bm), 3,040 (m), 2,989 (m), 2,937 (m), 2,870 (m), 1,770 (m), 1,706 (s), 1,654 (s), 1,462 (m), 1,397 (m), 1,341 (m), 1,215 (m), 1,044 (m), 744 (m), 666 (m), 591 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 324.9 (100, $M + H^+$), 649.1 (46, $2M + H^+$), 666.1 (46, $2M + NH_4^+$).

2-[2-[3-(Benzyloxycarbonyl)-2-thioureido]-1-oxoethylamino]acetic acid (**14a**, $C_{13}H_{15}N_3O_5S$)
Glycylglycine (132 mg, 1.0 mmol) was employed to give 253 mg of an oily product (0.778 mmol, 78%). ^{1}H NMR (300 MHz, MeOH-*d4*): δ = 3.95 (s, 2 H), 4.38 (s, 2 H), 5.19 (s, 2 H), 7.22–7.48 (m, 5 H) ppm; ^{13}C NMR (75 MHz, MeOH-*d4*): δ = 41.8 (−, 1 C), 67.4 (−, 1 C), 68.8 (−, 1 C), 128.9 (+, 1 C), 129.5 (+, 2 C), 129.7 (+, 2 C), 137.0 (Cquat, 1 C), 154.8 (Cquat, 1 C), 170.9 (Cquat, 1 C), 173.0 (Cquat, 1 C), 182.1 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,299 (bm), 3,236 (m), 3,057 (m), 2,900 (m), 2,456 (m), 2,332 (m), 1,711 (s), 1,656 (m), 1,538 (s), 1,398 (m), 1,360 (m), 1,216 (s), 1,136 (m), 1,034 (m), 976 (m), 877 (m), 802 (m), 765 (m), 731 (m), 693 (m), 662 (m), 606 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 326.0 (86, $M + H^+$), 343.0 (26, $M + NH_4^+$), 651.0 (100, $2M + H^+$), 668.0 (39, $2M + NH_4^+$), 976.1 (17, $3M + H^+$), 993.2 (30, $3M + NH_4^+$), 1,301.3 (9, $4M + H^+$), 1,318.4 (16, $4M + NH_4^+$).

General procedure 5 (GP 5): preparation of benzyloxycarbonylthioureas from amino acid esters

Benzyloxycarbonylisothiocyanate (500 mg, 2.6 mmol) in 10.0 cm^3 dichloromethane was added slowly to a solution of the corresponding amino compound (2.0 mmol) and 300 mg (3.0 mmol) or 500 mg (5.0 mmol, if the amine salt is employed) triethylamine in 10.0 cm^3 dichloromethane at 2–5 °C. The solution was stirred at room temperature until TLC indicated no further reaction (2–6 h). All volatiles were removed under reduced pressure. Ethyl acetate (30.0 cm^3) was added, and the organic phase was washed with 5.0 cm^3 saturated ammonium chloride solution and twice with 10.0 cm^3 water. After drying over $MgSO_4$, the

solvent was evaporated and the residue was suspended in 5.0 cm^3 diethyl ether/petroleum ether 1:4. The product was allowed to settle completely, the ether mixture was decanted off, and after drying the precipitate, it was purified by column chromatography if necessary (ethyl acetate/petroleum ether 1:1 if not stated otherwise).

2-[2-[3-(Benzyloxycarbonyl)-2-thioureido]ethoxy]acetic acid ethyl ester (**12b**, $C_{15}H_{20}N_2O_5S$)

The TFA salt of 2-(2-aminoethoxy)acetic acid ethyl ester (520 mg, 2.0 mmol) was reacted according to GP 5 to give the thiourea **12b** as pale-yellow oil (574 mg, 1.77 mmol, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.20$ (t, 3 H, $J = 7.2$ Hz), 3.70 (t, 2 H, $J = 5.2$ Hz), 3.83 (t, 2 H, $J = 5.2$ Hz), 4.05 (s, 2 H), 4.15 (q, 2 H, $J = 7.2$ Hz), 5.11 (s, 2 H), 7.22–7.35 (m, 5 H), 8.50 (bs, 1 H), 9.90 (bs, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.2$ (+, 1 C), 45.4 (−, 1 C), 61.0 (−, 1 C), 68.1 (−, 1 C), 68.4 (−, 1 C), 69.0 (−, 1 C), 128.3 (+, 1 C), 128.7 (+, 2 C), 128.8 (+, 2 C), 134.6 (Cquat, 1 C), 152.4 (Cquat, 1 C), 170.3 (Cquat, 1 C), 179.4 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu} = 3{,}291$ (bm), 2,981 (m), 2,942 (m), 2,905 (m), 1,721 (s), 1,515 (s), 1,453 (m), 1,375 (m), 1,208 (s), 1,126 (s), 1,022 (s), 911 (m), 839 (m), 796 (m), 740 (m), 696 (m), 580 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z*(%) = 340.9 (100, $M + H^+$), 357.9 (8, $M + NH_4^+$), 681.1 (22, $2M + H^+$), 698.1 (14, $2M + NH_4^+$).

2-[2-[3-(Benzyloxycarbonyl)-2-thioureido]ethoxy]acetic acid tert-butyl ester (**12c**, $C_{17}H_{24}N_2O_5S$)

The acetate salt of 2-(2-aminoethoxy)acetic acid *tert*-butyl ester (470 mg, 2.0 mmol) was reacted according to GP 5 to yield **12c** as a colorless oil (640 mg, 1.82 mmol, 91%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.47$ (s, 9 H), 3.76 (t, 2 H, $J = 5.2$ Hz), 3.90 (t, 2 H, $J = 5.2$ Hz), 4.00 (s, 2 H), 5.17 (s, 2 H), 7.30–7.41 (m, 5 H), 8.30 (bs, 1 H), 9.93 (bs, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 28.1$ (+, 1 C), 45.6 (−, 1 C), 68.1 (−, 1 C), 68.8 (−, 1 C), 68.9 (−, 1 C), 81.9 (Cquat, 1 C), 128.4 (+, 2 C), 128.7 (+, 1 C), 128.8 (+, 2 C), 134.6 (Cquat, 1 C), 152.3 (Cquat, 1 C), 169.4 (Cquat, 1 C), 179.3 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu} = 3{,}290$ (bm), 2,977 (m), 2,937 (m), 2,883 (m), 1,720 (s), 1,515 (s), 1,453 (m), 1,368 (m), 1,319 (m), 1,220 (s), 1,187 (s), 1,123 (s), 1,023 (s), 961 (m), 913 (m), 840 (m), 758 (m), 735 (m), 696 (m), 583 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 369.0 (100, $M + H^+$), 386.0 (14, $M + NH_4^+$), 737.1 (19, $2M + H^+$), 754.1 (29, $2M + NH_4^+$).

6-[3-(Benzyloxycarbonyl)-2-thioureido]hexanoic acid methyl ester (**13b**, $C_{16}H_{22}N_2O_4S$)

ε-Aminohexanoic acid methyl ester hydrochloride (170 mg, 1.0 mmol) was used to obtain 281 mg of an oily, colorless solid (0.831 mmol, 83%). ^{1}H NMR (300 MHz, MeOH-*d4*): $\delta = 1.39$ (m, 2 H), 1.67 (m, 4 H), 2.40 (t, 2 H, $J = 7.2$ Hz), 3.62 (t, 2 H, $J = 7.2$ Hz), 3.65 (s, 3 H), 5.18 (s, 2 H), 7.23–7.45 (m, 5 H) ppm; ^{13}C NMR (75 MHz, MeOH-*d4*): $\delta = 25.4$ (−, 1 C), 26.9 (−, 1 C), 28.3 (−, 1 C), 34.4 (−, 1 C), 46.1 (−, 1 C), 52.1 (+, 1 C), 68.9 (−, 1 C), 128.8 (+, 1 C), 129.4 (+, 2 C), 129.5 (+, 2 C), 136.6 (Cquat, 1 C), 155.2 (Cquat, 1 C), 175.7 (Cquat, 1 C), 181.1 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu} = 3{,}040$ (m), 2,986 (m), 2,936 (m), 2,874 (m), 1,772 (m), 1,705 (s), 1,656 (s), 1,464 (m), 1,398 (m), 1,342 (m), 1,216 (m), 1,045 (m), 746 (m), 665 (m), 592 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 339.2 (100, $M + H^+$).

2-[2-[3-(Benzyloxycarbonyl)-2-thioureido]-1-oxoethylamino]acetic acid methyl ester (**14b**, $C_{14}H_{17}N_3O_5S$)

Glycylglycine methyl ester hydrochloride (364 mg, 2.0 mmol) was converted by GP 5 to the corresponding thiourea. The product was isolated as a colorless solid (540 mg, 0.839 mmol, 84%). M.p.: 137–138 °C; ^{1}H NMR (300 MHz, acetone-*d6*): $\delta = 3.68$ (s, 3 H), 4.04 (d, 2 H, *J* 1,1 = 6.0 Hz), 4.40 (d, 2 H, *J* 1,1 = 6.0 Hz), 5.23 (s, 2 H), 7.29–7.45 (m, 5 H), 7.83 (bs, 1 H), 9.98 (bs, 1 H), 10.32 (bs, 1 H) ppm; ^{13}C NMR (75 MHz, acetone-*d6*): $\delta = 41.6$ (−, 1 C), 48.9 (−, 1 C), 52.3 (+, 1 C), 68.2 (−, 1 C), 129.1 (+, 2 C), 129.2 (+, 2 C), 129.4 (+, 1 C), 136.6 (Cquat, 1 C), 154.1 (Cquat, 1 C), 154.2 (Cquat, 1 C), 168.6 (Cquat, 1 C), 170.6 (Cquat, 1 C), 180.6 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu} = 3{,}258$ (bm), 3,032 (m), 2,955 (m), 1,719 (s), 1,513 (s), 1,437 (m), 1,371 (s), 1,196 (s), 1,131 (m), 1,031 (m), 970 (m), 905 (m), 796 (m), 778 (m), 697 (m), 603 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 339.3 (31, $M + H^+$), 357.0 (46, $M + H^+ + MeCN$), 679.2 (69, $2M + H^+$), 696.2 (100, $2M + NH_4^+$); HRMS (EI, 70 eV): calc. for $C_{14}H_{17}N_3O_5S^{*+}$ 339.0889, found 339.0884.

5-[3-(Benzyloxycarbonyl)-2-thioureidomethyl]pyrrole-2-carboxylic acid methyl ester (**15**, $C_{16}H_{17}N_3O_4S$)

The TFA salt of 5-(aminomethyl)pyrrole-2-carboxylic acid methyl ester(534 mg, 2.0 mmol) was converted following GP 5 to give the corresponding thiourea as a beige solid (610 mg, 1.84 mmol, 92%). M.p.: 155–156 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.82$ (s, 3 H), 4.85 (d, 2 H, $J = 5.8$ Hz), 5.16 (s, 2 H), 6.15 (d, 1 H, $J = 6.0$ Hz), 6.81 (d, 1 H, $J = 6.0$ Hz), 7.28–7.41 (m, 5 H), 8.30 (s, 1 H), 10.01 (bs, 2 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 41.7$ (−, 1 C), 51.6 (+, 1 C), 68.5 (−, 1 C), 110.1 (+, 1 C), 115.4 (+, 1 C), 122.8 (Cquat, 1 C), 128.4 (+, 2 C), 128.8 (+, 2 C), 129.0 (+, 1 C), 132.7 (Cquat, 1 C), 134.3 (Cquat, 1 C), 152.4 (Cquat, 1 C), 161.3 (Cquat, 1 C), 180.1 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu} = 3{,}279$ (bm), 2,955 (m), 2,926 (m), 2,855 (m), 1,701 (s), 1,614 (m),

1,519 (m), 1,492 (s), 1,452 (m), 1,385 (m), 1,315 (m), 1,214 (s), 1,089 (m), 1,037 (m), 1,003 (m), 910 (m), 796 (m), 765 (m), 733 (m), 697 (m), 605 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 348.0 (44, M + H^+), 389.0 (12, M + H^+ + MeCN), 695.0 (100, 2M + H^+), 712.1 (19, 2M + NH_4^+); HRMS (EI, 70 eV): calc. for $C_{16}H_{17}N_3O_4S^{*+}$ 347.0940, found 347.0946; UV (MeOH): λ_{max} (ε) = 264 (6900), 209 (6100) nm (mol^{-1} dm^3 cm^{-1}).

6-(3-[Benzyloxycarbonyl)-2-thioureidomethyl]pyridine-2-carboxylic acid ethyl ester (**16**, $C_{18}H_{19}N_3O_4S$)

2-(Aminomethyl)pyridine-6-carboxylic acid ethyl ester (360 mg, 2.0 mmol) was submitted to GP 5 to give the corresponding thiourea as an orange oil (604 mg, 1.62 mmol, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (t, 3 H, *J* = 7.2 Hz), 4.09 (q, 2 H, *J* = 7.2 Hz), 5.06 (d, 2 H, *J* = 4.7 Hz), 5.23 (s, 2 H), 7.30–7.46 (m, 5H), 7.52 (d, 1 H, *J* = 7.7 Hz), 7.85 (dd, 1 H, *J* = 7.7 Hz), 8.06 (d, 1 H, *J* = 7.7 Hz), 8.12 (bs, 1 H), 10.81 (bs, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.2 (+, 1 C), 49.4 (−, 1 C), 61.0 (−, 1 C), 67.2 (−, 1 C), 122.2 (+, 1 C), 123.1 (+, 1 C), 124.1 (+, 1 C), 127.3 (+, 2 C), 127.7 (+, 2 C), 127.9 (+, 1 C), 133.5 (Cquat, 2 C), 136.8 (Cquat, 1 C), 146.7 (Cquat, 1 C), 151.2 (Cquat, 1 C), 154.2 (Cquat, 1 C), 178.0 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,425 (bm), 3,348 (bm), 2,960 (m), 2,929 (m), 1,709 (s), 1,591 (m), 1,495 (m), 1,453 (m), 1,394 (m), 1,305 (m), 1,220 (s), 1,163 (s), 1,086 (m), 1,053 (m), 1,024 (m), 910 (m), 861 (m), 761 (m), 735 (m), 697 (m), 581 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 373.9 (100, M + H^+), 747.1 (31, 2M + H^+); HRMS (PI-LSIMS FAB, glycerol): calc. for $C_{18}H_{20}N_3O_4S^+$ 374.1175, found 374.1165.

Syntheses and deprotections of the receptors

General procedure 6 (GP 6): preparation of symmetric 1,3-disubstituted benzyloxycarbonylguanidines

The benzyloxycarbonylthiourea (0.5 mmol) was dissolved together with the appropriate amino compound (0.6 mmol) and 130 mg triethylamine (1.3 mmol) in 5.0 cm^3 DCM. EDC hydrochloride (110 mg, 0.6 mmol) was added at 2–5 °C in one portion. The mixture was allowed to reach room temperature in 1 h and was then stirred overnight. In the case where TLC indicated thiourea still being present at this point, another portion of triethylamine (30 mg, 0.3 mmol) and EDC hydrochloride (54 mg, 0.3 mmol) was added and stirring was continued for 4 h. It was diluted with 25.0 cm^3 DCM, and the organic solution was washed with 5.0 cm^3 saturated ammonium chloride solution and twice with 10.0 cm^3 water. After drying over $MgSO_4$, the solvent was evaporated and the oily residue was purified by column chromatography with ethyl acetate/petroleum ether 4:1 to yield the guanidine.

Instead of EDC, mercury(II) chloride can be used in this reaction. DCM has to be replaced by DMF then. For example: the benzyloxycarbonylthiourea (0.5 mmol) was added to a solution of the appropriate amino compound (0.6 mmol) and 130 mg triethylamine (1.3 mmol) in 5.0 cm^3 DMF. Mercury(II) chloride (170 mg, 0.62 mmol) was added, and the reaction mixture was stirred for 15 h at room temperature. The mixture was filtered over Celite, and the solvent was removed under reduced pressure. The crude product was dissolved in H_2O and acidified with 5% $KHSO_4$ to pH = 3. The aqueous layer was extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by column chromatography as given.

2-[2-[N-(Benzyloxycarbonyl)-N-[2-(ethoxycarbonylmethoxy)ethyl]guanidinyl]ethoxy]acetic acid ethyl ester (**17b**, $C_{21}H_{31}N_3O_8$)

Thiourea **12b** (161 mg, 0.5 mmol) was reacted with 157 mg of the TFA salt of 2-(2-aminoethoxy)acetic acid ethyl ester (**10b**, 0.6 mmol) following GP 6 to give a clear yellow oil (166 mg, 0.366 mmol, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, 6 H, *J* = 7.1 Hz), 3.56 (m, 4 H), 3.70 (m, 4 H), 4.18 (q, 4 H, *J* = 7.4 Hz), 4.10 (s, 4 H), 5.12 (s, 2 H), 7.21–7.43 (m, 5 H), 9.00 (bs, 2 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (+, 2 C), 42.8 (−, 2 C), 47.5 (−, 2 C), 61.2 (−, 2 C), 67.2 (−, 2 C), 68.3 (−, 1 C), 70.8 (−, 2 C), 128.0 (+, 1 C), 128.1 (+, 2 C), 128.4 (+, 2 C), 136.8 (Cquat, 1 C), 160.0 (Cquat, 2 C), 161.5 (Cquat, 1 C), 170.1 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,284 (bm), 2,981 (m), 2,936 (m), 1,740 (s), 1,668 (m), 1,598 (s), 1,518 (m), 1,451 (m), 1,382 (m), 1,275 (m), 1,209 (s), 1,132 (s), 1,051 (m), 1,025 (m), 912 (m), 852 (m), 799 (m), 729 (m), 691 (m), 582 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 454.0 (100, M + H^+).

2-[2-[N-(Benzyloxycarbonyl)-N-[2-(ethoxycarbonylmethoxy)ethyl]guanidinyl]ethoxy]acetic acid tert-butyl ester (**17a**, $C_{25}H_{39}N_3O_8$)

Thiourea **12c** (176 mg, 0.5 mmol) was reacted with 158 mg of the TFA salt of 2-(2-aminoethoxy)acetic acid *tert*-butyl ester (**10c**, 0.6 mmol) following GP 6 to yield a clear, slightly yellow oil (198 mg, 0.389 mmol, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 18 H), 3.52 (m, 4 H), 3.67 (m, 4 H), 3.99 (s, 4 H), 5.11 (s, 2 H), 7.28–7.41 (m, 5 H), 9.23 (bs, 2 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$):

δ = 28.1 (+, 6 C), 41.6 (−, 2 C), 48.8 (−, 2 C), 66.4 (−, 2 C), 70.8 (−, 1 C), 82.0 (Cquat, 2 C), 127.5 (+, 1 C), 128.0 (+, 2 C), 128.3 (+, 2 C), 137.8 (Cquat, 1 C), 161.1 (Cquat, 2 C), 164.1 (Cquat, 1 C) ppm(further signals were not detectable); IR (FT-IR, film): $\bar{\nu}$ = 3,343 (bm), 2,977 (m), 2,929 (m), 1,743 (s), 1,633 (s), 1,599 (s), 1,455 (m), 1,386 (m), 1,368 (m), 1,303 (m), 1,228 (m), 1,129 (s), 1,052 (m), 942 (m), 845 (m), 801 (m), 743 (m), 699 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 510.2 (100, $M + H^+$); HRMS (LSIMSFAB, glycerol): calc. for $C_{25}H_{40}N_3O_8^+$ 510.2815, found 510.2808.

6-[N-(Benzyloxycarbonyl)-N-[5-(methoxycarbonyl)pentyl]-guanidinyl]hexanoic acid methyl ester (**18**, $C_{23}H_{35}N_3O_6$)

Thiourea **13b** (161 mg, 0.5 mmol) was reacted with 103 mg ε-aminohexanoic acid methyl ester hydrochloride (0.6 mmol) according to GP 6 to give a colorless oil (175 mg, 0.391 mmol, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (m, 4 H), 1.66 (m, 8 H), 2.42 (m, 4 H), 3.63 (m, 4 H), 3.68 (s, 6 H), 5.17 (s, 2 H), 7.25–7.43 (m, 5 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5 (−, 2 C), 27.1 (−, 2 C), 28.2 (−, 2 C), 34.5 (−, 2 C), 46.2 (−, 2 C), 52.0 (+, 2 C), 68.4 (−, 1 C), 128.0 (+, 1 C), 128.2 (+, 2 C), 128.4 (+, 2 C), 136.9 (Cquat, 1 C), 160.1 (Cquat, 2 C), 161.7 (Cquat, 1 C), 172.1 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,280 (bm), 2,986 (m), 2,938 (m), 1,743 (s), 1,666 (m), 1,597 (s), 1,519 (m), 1,452 (m), 1,384 (m), 1,276 (m), 1,213 (s), 1,134 (s), 1,056 (m), 1,027 (m), 913 (m), 854 (m), 801 (m), 732 (m), 693 (m) cm^{-1}.

5-[N-(Benzyloxycarbonyl)-N-[5-(methoxycarbonyl)-1H-pyrrol-2-ylmethyl]guanidinylmethyl]-1H-pyrrole-2-carboxylic acid methyl ester (**20**, $C_{23}H_{25}N_5O_6$)

Thiourea **15** (165 mg, 0.5 mmol) was reacted with 160 mg of the TFA salt of 5-(aminomethyl)pyrrole-2-carboxylic acid methyl ester (0.6 mmol) according to GP 6 to yield a yellow solid (203 mg, 0.434 mmol, 87%). M.p.: 122–124 °C; ^{1}H NMR (300 MHz, DMSO-*d6*): δ = 3.54 (s, 6 H), 4.41 (s, 4 H), 5.14 (s, 2 H), 6.12 (d, 2 H, *J* = 6.0 Hz), 6.77 (d, 2 H, *J* = 6.0 Hz), 7.38–7.42 (m, 5 H), 8.16 (s, 2 H), 10.81 (bs, 1 H), 11.05 (bs, 1 H) ppm; ^{13}C NMR (75 MHz, MeOH-*d4*): δ = 38.9 (−, 2 C), 51.8 (+, 2 C), 67.9 (−, 1 C), 109.9 (+, 2 C), 116.9 (+, 2 C), 122.1 (Cquat, 2 C), 128.8 (+, 1 C), 128.9 (+, 2 C), 129.5 (+, 2 C), 138.9 (Cquat, 1 C), 158.2 (Cquat, 1 C), 161.3 (Cquat, 2 C), 163.1 (Cquat, 2 C), 165.0 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,415 (bm), 3,281 (s), 2,949 (m), 1,679 (m), 1,642 (m), 1,584 (m), 1,549 (m), 1,490 (m), 1,443 (m), 1,390 (m), 1,333 (m), 1,277 (m), 1,220 (s), 1,127 (m), 1,065 (m), 1,002 (m), 927 (m), 799 (m), 764 (s), 701 (m), 627 (m), 597 (m), 508 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 468.0 (100, $M + H^+$); HRMS (PI-LSIMS FAB, glycerol): calc. for $C_{23}H_{26}N_5O_6^+$ 468.1883, found 468.1879; UV (MeOH): λ_{max} (ε) = 266 (12,800), 226 (9,800) nm (mol^{-1} dm^3 cm^{-1}).

3-(Benzyloxycarbonylamino)imidazo[1,5-a]pyridine-5-carboxylic acid ethyl ester (**21**, $C_{18}H_{17}N_3O_4$)

Thiourea **16** (187 mg, 0.5 mmol) was submitted to the conditions of GP 6 to give product **21** as a red glass (112 mg, 0.328 mmol, 66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (t, 3 H, *J* = 7.2 Hz), 4.31 (q, 2 H, *J* = 7.2 Hz), 5.18 (s, 2 H), 6.67 (t, 1 H, *J* = 7.2 Hz), 7.27–7.42 (m, 6 H), 7.58 (d, 2 H, *J* = 4.6 Hz), 8.61 (bs, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (+, 1 C), 62.5 (−, 1 C), 67.5 (−, 1 C), 116.4 (+, 1 C), 120.7 (+, 1 C), 121.6 (+, 1 C), 123.6 (+, 1 C), 124.9 (Cquat, 1 C), 128.2 (+, 2 C), 128.3 (+, 2 C), 128.7 (+, 1 C), 130.7 (Cquat, 1 C), 135.9 (Cquat, 1 C), 153.7 (Cquat, 1 C), 162.8 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,255 (bm), 2,981 (m), 2,908 (m), 1,722 (s), 1,531 (m), 1,454 (m), 1,408 (m), 1,372 (m), 1,266 (s), 1,235 (s), 1,212 (s), 1,171 (m), 1,141 (m), 1,106 (m), 1,036 (m), 913 (m), 872 (m), 810 (m), 743 (m), 698 (m), 595 (m), 495 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 340.0 (100, $M + H^+$), 679.1 (11, $2\,M + H^+$); UV (MeOH): λ_{max} (ε) = 380 (1,300), 280 (3,200), 230 (13,200) nm (mol^{-1} dm^3 cm^{-1}).

2-[2-[N-(Benzyloxycarbonyl)-N-[2-(methoxycarbonylmethylamino)-2-oxoethyl]guanidinyl]-1-oxoethylamino]acetic acid ethyl ester (**19**, $C_{19}H_{25}N_5O_8$)

Compound **14b** (161 mg, 0.5 mmol) was reacted with 110 mg glycylglycine hydrochloride (0.6 mmol) using GP 6 (10% *N*-methylpyrrolidone (NMP) was added to the reaction mixture) to give a pale-yellow solid (172 mg, 0.381 mmol, 76%). M.p.: 92–94 °C; ^{1}H NMR (300 MHz, DMSO-*d6*): δ = 3.66 (s, 6 H), 3.96 (m, 4 H), 4.08 (m, 4 H), 5.05 (s, 2 H), 7.28–7.42 (m, 5 H), 7.90 (bs, 1 H), 9.05 (bs, 2 H) ppm; ^{13}C NMR (75 MHz, DMSO-*d6*): δ = 41.5 (−, 2 C), 44.9 (−, 2 C), 52.2 (+, 2 C), 66.8 (−, 1 C), 128.3 (+, 1 C), 128.7 (+, 2 C), 129.0 (+, 2 C), 139.2 (Cquat, 1 C), 161.6 (Cquat, 2 C), 170.9 (Cquat, 1 C), 175.7 (Cquat, 2 C) ppm (further signals were not detectable); IR (FT-IR, film): $\bar{\nu}$ = 3,352 (m), 3,290 (bm), 3,069 (m), 2,951 (m), 1,744 (m), 1,639 (s), 1,572 (m), 1,530 (m), 1,434 (m), 1,378 (m), 1,330 (m), 1,283 (m), 1,259 (m), 1,203 (s), 1,171 (s), 1,094 (s), 1,030 (m), 1,009 (m), 983 (m), 941 (m), 794 (m), 719 (m), 672 (m), 603 (m), 539 (m), 456 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 452.1 (100, $M + H^+$), 903.5 (5, $2M + H^+$); HRMS (LSI-MSFAB, glycerol): calc. for $C_{19}H_{26}N_5O_8^+$ 452.1781, found 452.1782.

General procedure 7: deprotection of the benzyloxycarbonylguanidine esters

Deprotection of the Cbz–guanidine (GP 7a)
The symmetric 1,3-disubstituted benzyloxycarbonylguanidine ester (0.4 mmol) was dissolved, depending on the ester in the molecule, in 3.0 cm^3 ethanol or methanol. Three spatula tips of palladium on charcoal (10% Pd) were added. It was stirred in hydrogen atmosphere (30 bar) for 2 days at room temperature. The reaction mixture was diluted with 10.0 cm^3 of the respective alcohol and filtered over Celite. The filter cake was washed with small portions of this alcohol. The clear filtrate was evaporated to dryness to give the guanidine free base.

Synthesis of the guanidinium hexafluorophosphate salts (GP 7b)
The guanidine free base (0.2 mmol) was dissolved in 6.0 cm^3 methanol or ethanol, according to its ester. Ammonium hexafluorophosphate (38 mg, 0.24 mmol) was added, and the mixture was warmed to 40 °C for 3 h. The solvent was evaporated, and the residue was extracted with 1.0 cm^3 DCM thrice. The solvent was distilled off, and the remaining guanidinium salt was properly dried in vacuo. The products appear as colorless solids in nearly quantitative yield.

2-[2-[N-[2-(Ethoxycarbonylmethoxy)ethyl]guanidinyl]ethoxy]acetic acid ethyl ester (**22b**, $C_{13}H_{25}N_3O_6$)
Compound **17b** (181 mg, 0.4 mmol) was deprotected according to GP 7a to give the free base ($C_{13}H_{25}N_3O_6$) as colorless, sticky oil (97 mg, 0.369 mmol, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.22$ (t, 6 H, $J = 7.1$ Hz), 3.33 (m, 4 H), 3.62 (m, 4 H), 4.06 (s, 4 H), 4.12 (q, 2 H, $J = 7.1$ Hz), 7.76 (bs, 1 H), 9.71 (bs, 1 H), 10.43 (bs, 1 H) ppm; IR (FT-IR, film): $\bar{\nu} = 3{,}308$ (bm), 3,183 (bm), 2,971 (m), 2,927 (m), 2,882 (m), 1,749 (m), 1,630 (s), 1,586 (m), 1,404 (m), 1,317 (m), 1,208 (s), 1,134 (s), 1,049 (m), 881 (m), 704 (m), 587 (m) cm^{-1}.

The free base was reacted following GP 7b in ethanol to give the hexafluorophosphate salt ($C_{13}H_{26}F_6N_3O_6P$) as colorless, sticky oil (97 mg, 0.369 mmol, 92%). ^{1}H NMR (300 MHz, acetone-*d6*): $\delta = 1.24$ (t, 6 H, $J = 7.1$ Hz), 3.59 (m, 4 H), 3.79 (m, 4 H), 4.19 (q, 4 H, $J = 7.1$ Hz), 4.23 (s, 4 H), 5.16 (s, 2 H), 7.30 (m, 5 H) ppm; ^{19}F NMR (300 MHz, acetone-*d6*): $\delta = -70.2$ (+), −72.7 (+) ppm; ^{13}C NMR (75 MHz, MeOH-*d4*): $\delta = 14.6$ (+, 2 C), 43.2 (−, 2 C), 62.2 (−, 2 C), 69.1 (−, 2 C), 71.3 (−, 2 C), 158.8 (Cquat, 1 C), 172.3 (Cquat, 2 C), 171.0 (Cquat, 1 C) ppm; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 320.0 (100, $M + H^+$); HRMS (PI-LSIMS FAB, glycerol): calc. for $C_{13}H_{26}N_3O_6^+$ 320.1822, found 320.1827.

2-[2-[N-[2-(Carboxymethoxy)ethyl]guanidinyl]ethoxy]acetic acid hydrochloride (**6**, $C_9H_{18}ClN_3O_6$)
The guanidine free base **22b** (181 mg, 0.4 mmol) was dissolved in 5 cm^3 methanol, and 2.0 cm^3 aqueous hydrochloric acid (2 M, 4.0 mmol) was added. The mixture was stirred at room temperature until TLC showed complete consumption of the starting material (4–6 h). The solvent was evaporated, and the product was lyophilized to give the product as colorless, sticky oil (97 mg, 0.369 mmol, 92%). ^{1}H NMR (300 MHz, acetone-*d6*): $\delta = 3.51$ (m, 4 H), 3.71 (s, 4 H), 3.78 (m, 4 H), 7.60 (bs, 2 H), 8.71 (bs, 1 H) ppm; ^{13}C NMR (75 MHz, MeOH-*d4*): $\delta = 43.2$ (−, 2 C), 68.8 (−, 2 C), 71.3 (−, 2 C), 158.8 (Cquat, 1 C), 155.9 (Cquat, 1 C), 177.2 (Cquat, 2 C) ppm; IR (FT-IR, film): $\bar{\nu} = 3{,}178$ (bm), 2,935 (m), 2,250 (m), 1,736 (m), 1,638 (m), 1,435 (m), 1,349 (m), 1,218 (m), 1,134 (s), 1,070 (m), 1,010 (s), 875 (m), 824 (m), 762 (m), 682 (m), 669 (m), 623 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 264.1 (100, $M + H^+$).

5-[N-[5-(Methoxycarbonyl)-1H-pyrrol-2-ylmethyl]guanidinylmethyl]-1H-pyrrole-2-carboxylic acid methyl ester (**23**, $C_{15}H_{19}N_5O_4$)
Compound **20** (187 mg, 0.4 mmol) was reacted according to GP 7a to yield the free base ($C_{15}H_{19}N_5O_4$) as yellow solid (117 mg, 0.384 mmol, 96%). ^{1}H NMR (300 MHz, MeOH-*d4*): $\delta = 3.81$ (s, 6 H), 4.41 (s, 4 H), 6.12 (m, 2 H), 6.79 (m, 2 H) ppm; ^{13}C NMR (75 MHz, MeOH-*d4*): $\delta = 39.5$ (−, 2 C), 51.8 (+, 2 C), 110.2 (+, 2 C), 117.0 (+, 2 C), 124.1 (Cquat, 2 C), 133.5 (Cquat, 2 C), 157.3 (Cquat, 1 C), 163.0 (Cquat, 2 C) ppm; IR (FT-IR, film): $\bar{\nu} = 3{,}179$ (bm), 2,953 (m), 1,660 (s), 1,627 (s), 1,489 (m), 1,439 (m), 1,320 (s), 1,279 (m), 1,218 (s), 1,132 (m), 1,003 (s), 930 (m), 800 (m), 762 (s), 656 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 334.0 (100, $M + H^+$), 375.0 (38, $M + H^+ + MeCN$), 713.3 (13, $2M + H^+ + HCOOH$); HRMS (EI, 70 eV): calc. for $C_{15}H_{19}N_5O_4{}^{*+}$ 333.1437, found 333.1439.

The free base was reacted following GP 7b in methanol to yield the hexafluorophosphate salt as yellow solid (117 mg, 0.384 mmol, 96%). M.p.: 141–144 °C; ^{1}H NMR (300 MHz, acetone-*d6*): $\delta = 3.78$ (s, 6 H), 4.67 (s, 4 H), 6.23 (d, 2 H, $J = 3.6$ Hz), 6.75 (d, 2 H, $J = 3.6$ Hz), 7.76 (bs, 1 H), 11.09 (bs, 1 H) ppm; ^{13}C NMR (75 MHz, MeOH-*d4*): $\delta = 51.9$ (+, 2 C), 110.3 (+, 2 C), 117.0 (+, 2 C), 124.1 (Cquat, 2 C), 133.4 (Cquat, 2 C), 157.2 (Cquat, 1 C), 163.0 (Cquat, 2 C) ppm; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 334.0 (100,

M + H^+); UV (MeOH): λ_{max} (ε) = 263 (11,600) nm (mol^{-1} dm^3 cm^{-1}).

5-[N-(5-Carboxy-1H-pyrrol-2-ylmethyl)guanidinylmethyl]-1H-pyrrole-2-carboxylic acid (**24**, $C_{13}H_{15}N_5O_4$)
Compound **23** (187 mg, 0.4 mmol) was dissolved in 5 cm^3 methanol, and 0.8 cm^3 aqueous LiOH (1 M, 0.8 mmol) was added. The mixture was stirred at room temperature until TLC showed complete conversion (6–8 h). The solvent was evaporated, and the product was lyophilized to yield the guanidine bisacid lithium salt as a pale-beige powder (117 mg, 0.384 mmol, 96%). M.p.: 161–165 °C (decomp.); ^{1}H NMR (300 MHz, MeOH-*d4*): δ = 4.31 (s, 4 H), 6.02 (m, 2 H), 6.41 (m, 2 H) ppm; ^{13}C NMR (75 MHz, MeOH-*d4*): δ = 39.9 (−, 2 C), 108.6 (+, 2 C), 113.5 (+, 2 C), 130.6 (Cquat, 2 C), 132.0 (Cquat, 2 C), 137.3 (Cquat, 1 C), 170.1 (Cquat, 2 C) ppm; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 306.0 (100, M + H^+); UV (MeOH): λ_{max} (ε) = 264 (11,200) nm (mol^{-1} dm^3 cm^{-1}).

An alternative route to the receptors via the thiourea using trifluoroacetamide as reagent for guanidination

3-(2-Aminoethoxy)propionic acid ethyl ester hydrochloride ($C_7H_{16}ClNO_3$)
To a solution of 0.52 g 3-[2-(*tert*-butoxycarbonylamino)ethoxy]propionic acid ethyl ester (2.0 mmol) in 10.0 cm^3 DCM was slowly added 4.0 cm^3 diethyl ether saturated with HCl. After 3 h of stirring at room temperature, the solvent was evaporated. The residue was taken up in a little DCM, and the solvent was removed under reduced pressure again. The remaining sticky solid was dried under vacuum overnight. The yield was 0.38 g of a yellow, hygroscopic solid (1.96 mmol, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.94 (t, 3 H, *J* = 7.1 Hz), 2.56 (t, 2 H, *J* = 6.8 Hz), 3.21 (m, 2 H), 3.68–3.81 (m, 4 H), 4.08 (q, 2 H, *J* = 7.1 Hz), 8.11 (bs, 3 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (+, 1 C), 34.7 (−, 1 C), 39.5 (−, 1 C), 60.9 (−, 1 C), 65.6 (−, 1 C), 66.2 (−, 1 C), 172.1 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 3,468 (bm), 2,976 (m), 2,934 (m), 1,716 (m), 1,672 (s), 1,521 (m), 1,425 (m), 1,379 (m), 1,183 (s), 1,123 (s), 1,024 (m), 968 (m), 834 (m), 799 (s), 722 (m), 678 (m), 598 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): *m/z* (%) = 162.1 (100, M + H^+).

General procedure 8 (GP 8): preparation of symmetric thioureas from glycol-amino acid esters

To an ice-cold solution of the amino compound (3.5 mmol) in 20.0 cm^3 chloroform containing 727 mg triethylamine (7.2 mmol), 0.13 cm^3 thiophosgene (1.7 mmol) in 5.0 cm^3 chloroform was added dropwise, and the mixture was stirred for 2 days at room temperature. The solvent was evaporated and all volatiles were removed under reduced pressure. The residue was dissolved in 10.0 cm^3 ethanol and cooled to 0 °C for 3 h. It was filtered with suction, and the crystals were washed with a little ice-cold ethanol. The filtrate was reduced to about 2.0 cm^3, and the thiourea was precipitated by slow addition of diethyl ether. The solvent was decanted off, the residue was suspended in diethyl ether, and after the solid had settled completely, the ether was decanted off again. The product was dried in vacuum. If necessary, the material can be purified by column chromatography with ethyl acetate/petroleum ether 1:2.

2-[2-[3-[2-(Ethoxycarbonylmethoxy)ethyl]thioureido]ethoxy]acetic acid ethyl ester [116] (**E-4**, $C_{13}H_{24}N_2O_6S$)
2-(2-Aminoethoxy)acetic acid ethyl ester hydrochloride (640 mg, 3.5 mmol) was submitted to GP 8. The clean product was obtained as a clear, yellow sticky oil (417 mg, 1.24 mmol, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, 6 H, *J* = 7.1 Hz), 3.81 (m, 4 H), 3.98–4.13 (m, 8 H), 4.14–4.29 (q, 4 H, *J* = 7.1 Hz), 6.61 (bs, 2 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (+, 2 C), 40.8 (−, 2 C), 46.9 (−, 2 C), 54.2 (−, 2 C), 60.9 (−, 2 C), 169.0 (Cquat, 2 C), 181.7 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 2,979 (m), 2,944 (m), 2,870 (m), 1,740 (s), 1,496 (m), 1,418 (m), 1,350 (m), 1,261 (m), 1,206 (s), 1,123 (s), 1,026 (m), 861 (m), 805 (m), 661 (m), 579 (m) cm^{-1}; MS (CI, NH_3): *m/z* (%) = 337.2 (100, M + H^+), 354.2 (19, M + NH_4^+).

3-[2-[3-[2-(2-Ethoxycarbonylethoxy)ethyl]thioureido]ethoxy]propionic acid ethyl ester (**E-5a**, $C_{15}H_{28}N_2O_6S$)
3-(2-Aminoethoxy)propionic acid ethyl ester hydrochloride (690 mg, 3.5 mmol) was reacted after GP 8 to yield the thiourea as a clear, yellow oil (439 mg, 1.21 mmol, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, 6 H, *J* = 7.1 Hz), 2.51 (t, 4 H, *J* = 6.0 Hz), 3.51–3.70 (m, 8 H), 3.67 (t, 4 H, *J* = 6.3 Hz), 4.08 (q, 4 H, *J* = 7.1 Hz), 6.61 (bs, 2 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (+, 2 C), 34.9 (−, 2 C), 44.3 (−, 2 C), 60.7 (−, 2 C), 66.2 (−, 2 C), 69.5 (−, 2 C), 171.8 (Cquat, 2 C), 182.8 (Cquat, 1 C) ppm; IR (FT-IR, film): $\bar{\nu}$ = 2,978 (m), 2,942 (m), 2,874 (m), 1,728 (s), 1,546 (m), 146 (m), 1,373 (m), 1,261 (m), 1,189 (s), 1,124 (s), 1,064 (m), 860 (m), 802 (m), 659 (m), 603 (m) cm^{-1}; MS (CI, NH_3): *m/z* (%) = 364.9 (100, M + H^+), 381.9 (4, M + NH_4^+).

2-[2-[N-[2-(Ethoxycarbonylmethoxy)ethyl]-N-(2,2,2-trifluoroacetyl)guanidinyl]ethoxy]acetic acid ethyl ester (**E-6**)
To a solution of 364 mg compound **E-5a** (1.0 mmol) in 20.0 cm^3 acetone, 0.2 cm^3 methyl iodide (2.0 mmol) was added, and the reaction mixture was stirred at room temperature overnight under light protection. All volatiles

were removed under reduced pressure without heating. The residue was dissolved in 30.0 cm^3 of methanol and dichloromethane (1:1). Ammonium hexafluorophosphate (424 mg, 2.6 mmol) was added, and the solution was stirred overnight at room temperature. The solvents were distilled off, and the remaining yellow oil was taken up in 100 cm^3 of dichloromethane and washed with two 20 cm^3 portions of water. After drying over $MgSO_4$, the solvent was evaporated to give the according hexafluorophosphate in nearly quantitative yield.

It was redissolved in a mixture of 20.0 cm^3 toluene and 5.0 cm^3 chloroform, and 0.45 cm^3 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) (3.0 mmol) and 540 mg trifluoroacetamide (4.8 mmol) were added. The mixture was refluxed overnight under vigorous stirring. After cooling to room temperature the solvents were distilled off at reduced pressure. The oily raw material was purified by column chromatography with ethyl acetate/petroleum ether 1:2 to yield the guanidine as clear, yellow oil (279 mg, 0.773 mmol, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.25$ (t, 6 H, $J = 7.1$ Hz), 2.61 (m, 4 H), 3.61 (m, 4 H), 3.72 (m, 4 H), 4.16 (q, 4 H, $J = 7.1$ Hz), 6.59 (bs, 2 H), 9.67 (bs, 1 H) ppm; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): m/z (%) = 444.0 (100, $M + H^+$), 909.3 (6, $2M + Na^+$).

Deprotection to the free guanidine

The above material (270 mg, 0.75 mmol) was dissolved in 2.0 cm^3 methanol, and a solution of 138 mg potassium carbonate (1.0 mmol) in 0.5 cm^3 water was added. After warming the well-stirred mixture to 50 °C for 4 h, the solvents were evaporated. The residue was dissolved in a 1:1 mixture of DCM and water (10.0 cm^3). The phases were separated, and the aqueous layer was extracted with 5.0 cm^3 DCM twice. The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated to dryness. The product **E-7** was obtained as a yellow oil (232 mg, 0.68 mmol, 90%). ^{1}H NMR (300 MHz, MeOH-*d4*): $\delta = 1.25$ (t, 6 H, $J = 7.1$ Hz), 2.62 (t, 4 H, $J = 6.0$ Hz), 3.11 (t, 4 H, $J = 4.9$ Hz), 3.67 (t, 4 H, $J = 4.9$ Hz), 3.76 (t, 4 H, $J = 6.0$ Hz), 4.16 (q, 4 H, $J = 7.1$ Hz) ppm; ^{13}C NMR (75 MHz, MeOH-*d4*): $\delta = 14.5$ (+, 2 C), 35.5 (−, 2 C), 40.5 (−, 2 C), 61.8 (−, 2 C), 67.5 (−, 2 C), 67.6 (−, 2 C), 160.4 (Cquat, 1 C), 173.7 (Cquat, 2 C) ppm; IR (FT-IR, film): $\bar{\nu} = 3{,}419$ (bm), 2,986 (m), 2,934 (m), 2,891 (m), 1,670 (s), 1,438 (m), 1,379 (m), 1,276 (m), 1,189 (s), 1,123 (s), 1,029 (m), 840 (m), 800 (m), 721 (m), 606 (m) cm^{-1}; MS (ESI, CH_2Cl_2/MeOH + 10 mmol NH_4OAc): m/z (%) = 348.0 (100, $M + H^+$).

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