DOI: 10.1002/ejoc.200600324

2-(Guanidiniocarbonyl)furans as a New Class of Potential Anion Hosts: Synthesis and First Binding Studies

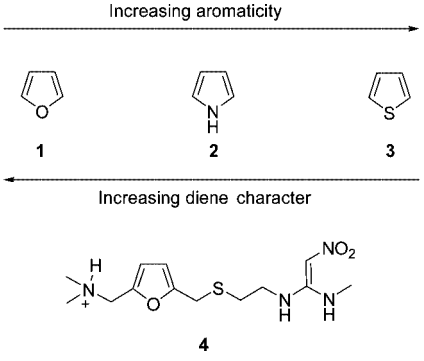
Carsten Schmuck*[a] and Uwe Machon[a]

Keywords: Furans / Guanidinium cations / Molecular recognition / Supramolecular chemistry

The synthesis of a new class of potential anion hosts, the 2-(guanidiniocarbonyl)furans **5a**–**d**, is presented in this study. The facile decomposition of furans under acidic conditions makes the synthesis of these compounds challenging. First binding studies showed that the (guanidiniocarbonyl)furans are much more acidic ($pK_a \approx 5.5$) than the analogous pyrroles ($pK_a \approx 7$) previously introduced by us for oxoanion binding in aqueous solvents. Hence, anion binding with the furan derivatives occurs only in acidic solutions below pH = 5. Therefore, carboxylates are not bound efficiently, whereas, for example, the less basic hydrogen sulfate is bound by **5b** with an association constant of $K = 600\ M^{-1}$ in aqueous DMSO even in the presence of a large excess of buffer.

Introduction

The furan heterocycle **1** has a lower extent of aromaticity and higher diene character than other heterocycles like pyrrole (**2**) and thiophene (**3**). The chemical behaviour of furans is therefore quite different and often resembles more that of an unsaturated than an aromatic compound. Nevertheless, furan compounds, which are ubiquitous and readily available from the vegetable biomass,[1,2] are versatile building blocks for organic synthesis[3–7] and for medicinal chemistry. For example, ranitidine **4** is a very efficient histamine receptor antagonist (type 2),[8] in which a furan is connected to a cationic ammonium ion and a bidentate hydrogen-bond donor (a urea analogue).



We were therefore interested in synthesizing cationic furans with similar hydrogen-bond donor functionalities. With regard to our long-standing expertise with acylated guanidinium compounds for anion binding, we decided to synthesize 2-(guanidiniocarbonyl)furans **5** as potentially new receptors for anion binding. So far there are only very few furan-based synthetic receptors known in the literature.[9] We present here the synthesis of the 2-(guanidiniocarbonyl)furans **5a**–**c** and some first binding studies.

Results and Discussion

The design of **5** was based on our analogous pyrrole compounds, a 2,5-disubstituted furan containing on one side a positively charged guanidiniocarbonyl cation and on the other side an ester or an amide that might be further functionalized with an amino acid (Figure 1).

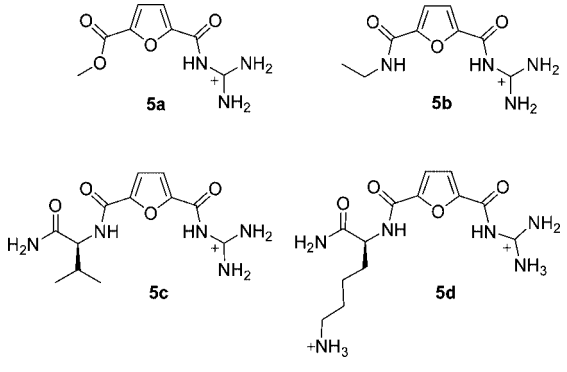
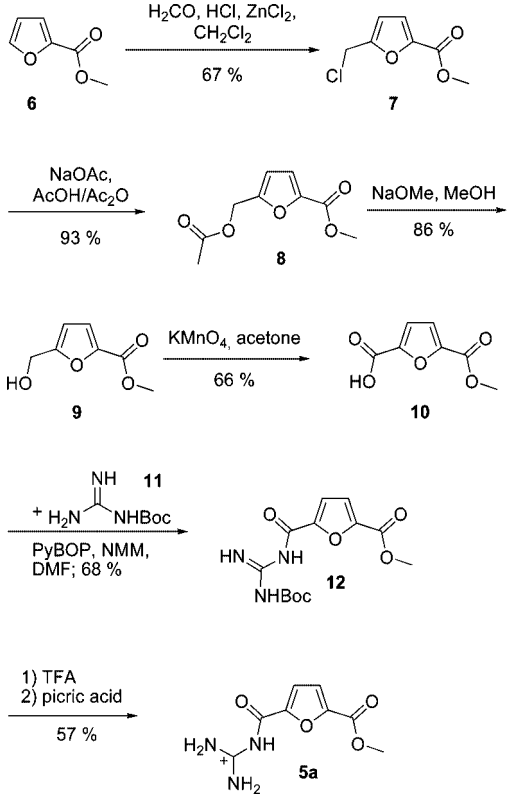


Figure 1. Target compounds **5a**–**5d**.

Scheme 1 describes the synthesis of the 2-(guanidiniocarbonyl)furan **5a**. The furan ester **7** was synthesized according to literature methods.[10,11] Chloromethylation of commercially available methyl furan-2-carboxylate (**6**) with paraformaldehyde, zinc chloride and anhydrous hydrogen chlo-

[a] Institut für Organische Chemie, Universität Würzburg, Am Hubland, 97074 Würzburg, Germany
Fax: +49-931-8884626
E-mail: schmuck@chemie.uni-wuerzburg.de

ride yielded **7**. The chloro substituent was replaced according to a literature procedure[12,13] to obtain **8** by heating **7** with anhydrous sodium acetate in acetic acid containing acetic anhydride. The selective hydrolysis of the acetic acid ester group of **8** by reaction with NaOMe in methanol solution gave the furfuryl alcohol **9**.[13] For the subsequent oxidation step, we first tested a literature procedure[14] reported for a related 2,5-substituted furfuryl alcohol: a two-step oxidation with MnO_2 in acetone with the corresponding aldehyde as an intermediate. During the first step of this reaction, we detected decomposition of the furan compound by TLC. So we decided to prepare **10** directly in a one-step oxidation of the hydroxymethyl group of **9** with potassium permanganate in acetone. The best yields obtained were about 66%. The moderate yield is most likely partly due to the decomposition of the product during the work up, which required precipitation of the free carboxylic acid from an aqueous solution with HCl. Also, losses may have occurred during the filtration of the large amounts of MnO_2. Reaction of the carboxylic acid **10** with the mono-Boc-protected guanidine **11** by using (1*H*-benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) as the coupling reagent gave the protected compound **12**. Deprotection of **12** was achieved by using TFA to provide the target compound **5a**, which was easily precipitated and isolated as the corresponding picrate salt.

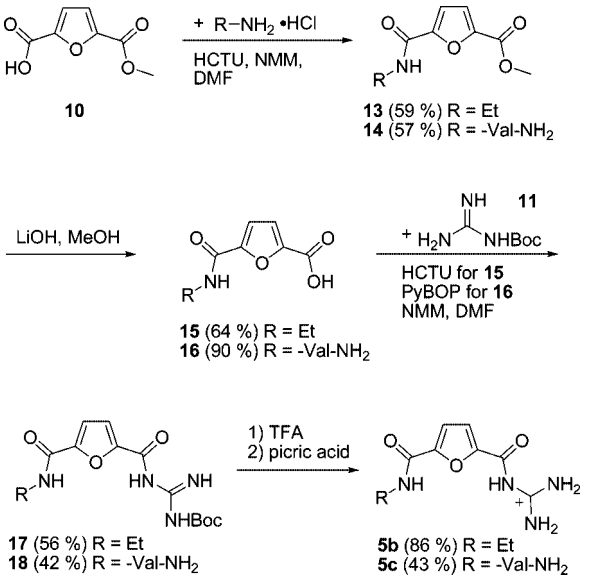


Scheme 1. Synthesis of compound **5a**.

The syntheses of compounds **5b** and **5c** were performed analogously to the pyridine compounds reported previously by us[15] starting from the carboxylic acid **10**. Coupling of the monoacid **10** with ethylamine by using *O*-(6-chloro-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HCTU) as the coupling reagent gave the corresponding amide **13** in a yield of 59%. However, for the actually isolated yield the specific work-up is very important. Flash chromatography on silica gel provided very low yields mainly because of decomposition of the product on the column. Even the use of triethylamine to deactivate the SiO_2 before chromatography could not prevent decomposition. Hence, for these furan systems the reversed phase flash column chromatography with octadecyl-functionalized silica gel (RP18) or the purification by extraction (with diethyl ether or ethyl acetate from the aqueous solution of the reaction mixture) lead to the best results. In this case PyBOP could not be used even though it gave better yields according to reaction monitoring by TLC. However, the coupling product **13** could not be separated from the phosphane oxide byproduct without significant losses. In general, product isolation and purification by using HCTU as the coupling reagent was much easier even though the initial coupling yields were significantly lower than those with PyBOP. To obtain the Boc-protected receptor **17** the methyl ester function of **13** was hydrolyzed with LiOH in methanol solution, and the carboxylic acid **15** was coupled with mono-Boc-protected guanidine **11** after activation with HCTU. Deprotection of **17** by using trifluoroacetic acid and precipitation of the picrate from a methanol solution provided the *N*-ethylcarbamoyl compound **5b**. For the yields of this step, the reaction conditions for the deprotection of the Boc-group with TFA proved to be crucial. If the temperature was too low (0 °C), the reaction time was too long for quantitative removal of the protecting group. Significant decomposition led to low yields (34%). If the deprotection was carried out at room temperature, the required reaction times were much shorter, but also the decomposition of the furan under these acidic conditions was much faster. Hence, the isolated yield was only 12%. The best yields were obtained by adding TFA at 0 °C and warming the mixture to room temperature within 20 minutes before work-up. We thus obtained an excellent yield of 86%.

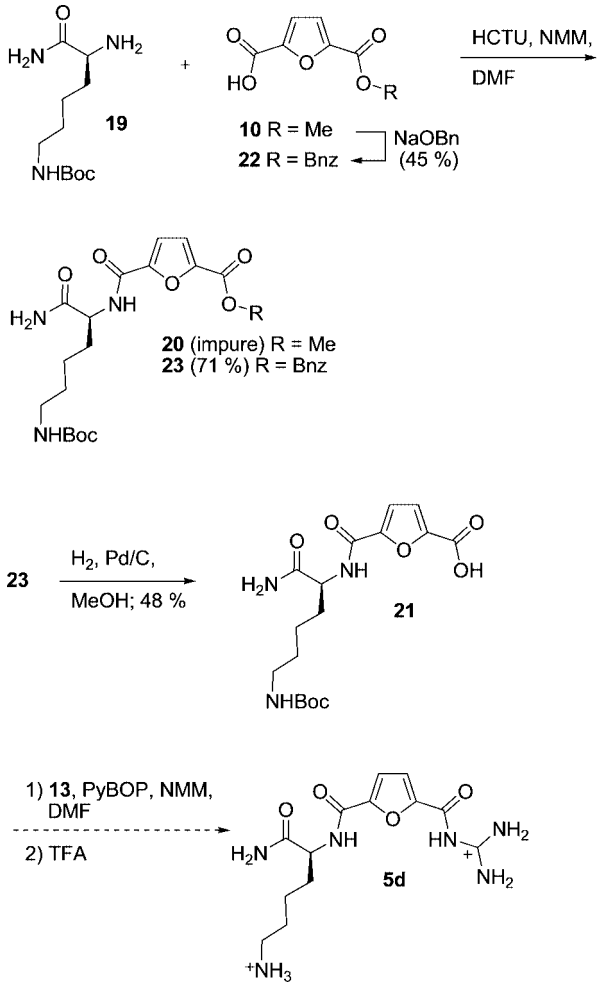
The valine-substituted compound **5c** was synthesized accordingly. Coupling of **10** with H-Val-NH_2 using HCTU in the presence of 4-methylmorpholine (NMM) yielded the ester **14**, which was hydrolyzed by using LiOH in MeOH to obtain the acid **16**. Coupling of **16** with mono-Boc-protected guanidine **11** to give **18** was achieved by using PyBOP as the activating agent, the reaction with HCTU failed in this case. However, extensive flash column chromatography with octadecyl-functionalized RP18 silica gel was needed to obtain **18** in pure form, which led to an isolated yield of only 42%. After deprotection of **18** with TFA, the picrate salt of compound **5c** was isolated from MeOH. The moderate isolated yield of 43% is most likely to be a result of the high solubility of **5c** in the methanol/water mixture (Scheme 2).

For the lysine derivative **5d** the same reaction route was tested (Scheme 3). The coupling of the amino acid derivative **19** and acid **10** by using HCTU was successful as moni-



Scheme 2. Synthesis of compounds **5b** and **5c**.

tored by TLC. However, compound **20** could not be isolated from the reaction mixture by reversed phase chromatography. Even after extensive chromatography, significant amounts of impurities were still present. As the yield of the crude product already dropped significantly as a result of the purification attempts, we decided to first hydrolyse the crude product, hoping that purification of the free acid **21** would be easier. The cleavage of the methyl ester with LiOH provided the acid **21** in quantitative yields according to TLC monitoring, but the acid **21** could not be separated from the impurities either. Because of the difficulties in isolating **21** in pure form, we tried a new route to compound **5d**. The idea was to replace the methyl ester by a more hydrophobic benzyl ester so that the intermediate could be purified more easily by reversed phase chromatography. The benzyl ester **22** can be easily obtained by treating the methyl ester of **10** with sodium benzylate in toluene. Then the coupling with the amino acid **19** could be achieved in a good yield of 71% under standard conditions for coupling reactions with HCTU. This time, indeed, the purification of the product by using RP18 chromatography was without any problems. The benzyl ester group of **23** could easily be deprotected by palladium-catalyzed hydrogenation to obtain the free acid **21** in a yield of 48%. This reaction was carried out only once, and no further attempts to optimize the yield were made. The use of the benzyl ester instead of the methyl ester provided a better synthesis for compound **21**. The following coupling reaction was carried out by using PyBOP under standard conditions, but again the Boc-protected (guanidiniocarbonyl)furan **Boc**–**5d** could not be isolated, either by extraction from an aqueous solution or by flash column chromatography on RP18. As in the analogous reaction in the synthesis of the valine derivative **5c**, HCTU did not work. However, the formation of **Boc**–**5d** could be proven by ^{1}H NMR spectroscopy from the crude reaction mixture. Therefore, we deprotected the crude product, hoping to obtain the pure compound **5d** after flash column chromatography. Unfortunately, the bis-cationic compound **5d** decomposed completely during purification. We could only prove its formation in a ^{1}H NMR spectrum of the crude product before the purification attempts. So far, we did not pursue the synthesis of **5d** any further, as any further investigations would also most likely be hampered by the limited stability of this compound especially in acidic aqueous solution. This instability would limit its use as an anion sensor significantly, especially under acidic conditions (vide infra).



Scheme 3. Attempted synthesis of compound **5d**.

After the successful synthesis of the three prototypes **5a**–**c** of this new class of cationic (guanidiniocarbonyl)furans, we performed some first binding studies with the ethyl amide derivative **5b** as host and *N*-acetylated amino acid carboxylates as substrates.[17] Initially, the same conditions were tried as those used for the (guanidiniocarbonyl)pyrroles: bis-Tris buffer, pH = 6.2 in 40% water in DMSO. However, no binding could be detected. Even though weaker binding was expected relative to that of the pyrrole receptors because of a repulsive interaction between the furan oxygen and the carboxylate substrate, the complete failure to see any binding was surprising. Even for (guanidiniocarbonyl)pyridines, which also exhibit a repulsive dipole

interaction between the pyridine nitrogen and the carboxylate anion, we could still detect binding affinities up to K = 500 M^{-1} under these conditions.[15]

We therefore investigated the protonation state of the (guanidiniocarbonyl)furans by potentiometric titrations of **5a** and **5b** (Figure 2). The titrations were carried out by starting with a 1 mM aqueous solution of the compounds adjusted to neutral pH with NaOH. Then 0.1 M hydrochloric acid was added stepwise, and the pH was recorded after each addition. A complete titration curve starting at basic pH could not be obtained, as the deprotonated compounds started to precipitate from solution at a pH > 7. From the titration curves one can already see that the basicity of the (guanidiniocarbonyl)furan is obviously lower than that of the pyrroles, which requires a lower pH for complete protonation. We determined the pK_a value of the (guanidiniocarbonyl)furans by using the Henderson–Hasselbach equation: 1 mM solutions of **5a** or **5b** were prepared and 0.5 equiv. NaOH (0.1 M) was added. The resulting pH value of the solution provided the pK_a values, which are 5.4 for **5a** and 5.6 for **5b**.

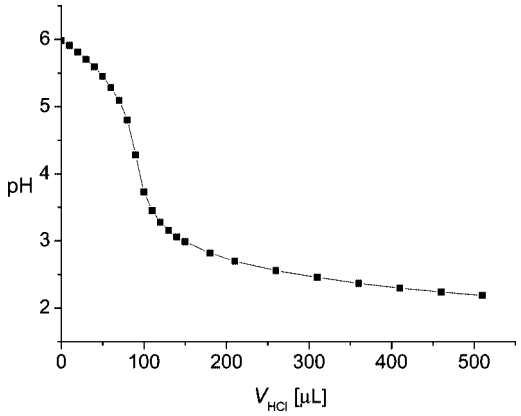


Figure 2. Potentiometric titration of a 1 mM aqueous solution of compound **5b** with 0.1 M hydrochloric acid.

The acidity of the guanidinium moiety is significantly increased relative to the analogous pyrrole compounds, which have pK_a values between 7 and 8.[16] The furan heterocycle is much less electron rich than a pyrrole. Hence, the furan is a more electron withdrawing substituent, which further reduces the electron density in the attached acylguanidinium, thereby increasing its acidity. At pH = 6.2, the (guanidiniocarbonyl)furans are not yet protonated. The deprotonated neutral form, however, is not expected to bind anions. Binding studies have to be performed under more acidic conditions at pH < 5 to ensure complete protonation. However, this precludes carboxylates as substrates, as then the carboxylate will also be protonated so that again no ion pairing can occur. Only less basic anions, which are still negatively charged at pH < 5, could serve as substrates.

Hence, we investigated the two singly charged anions hydrogen sulfate (tetrabutylammonium salt) and dihydrogen phosphate (potassium salt) as potential substrates for **5b**. Binding studies were performed at pH = 4.6 in water/DMSO (1:1) with 2 mM acetate buffer. To a solution of the furan cation ($c = 4 \times 10^{-5}$ M) in this solvent were added aliquots of a stock solution (c = 1 mM) of the anion. The complexation was monitored by the decrease in the UV absorbance of the furan moiety of **5b** at λ = 290 nm. The resulting binding isotherm (Figure 3) was then analyzed by using a nonlinear curve-fitting procedure for a 1:1-binding.[17] To improve the accuracy of the fit, the molar absorbance coefficient of the furan was determined from a Lambert–Beer dilution plot (ε = 4100 M/cm). For dihydrogen phosphate, no binding was observed, which means that the association constant is most likely smaller than 100 M^{-1}, the detection limit of the UV titration under these conditions. However, hydrogen sulfate is bound efficiently by **5b** with an association constant of K = 600 M^{-1} even in the presence of the large excess of acetate and acetic acid in the buffer.

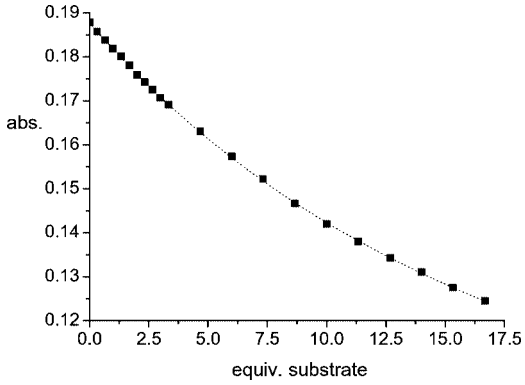


Figure 3. Binding isotherm at λ = 290 nm of **5b** (4×10^{-5} M) for the complexation of hydrogen sulfate in DMSO/water (1:1) at pH = 4.6. The dotted line represents the curve fitting for a 1:1 complexation.

Whereas molecular recognition of carboxylates by these new (guanidiniocarbonyl)furans is not possible because of the mismatched pK_a values of substrate and host, the less basic anion, hydrogen sulfate, is bound by host **5b** even under polar conditions. The calculated structure (Macromodel V. 8.0, MMFF force field, GB/SA solvation model)[18] for the complex between the hydrogen sulfate and furan **5b** is shown in Figure 4. In comparison to the (guanidiniocarbonyl)pyrroles the binding mode is slightly different. The oxoanion is shifted within the binding site so that only one oxygen interacts with the guanidinium cation. In this way,

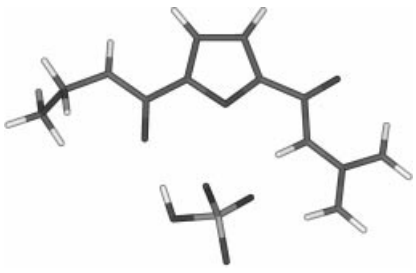


Figure 4. Energy-minimized structure for the complex between **5b** and hydrogen sulfate.

the repulsive interactions with the furan oxygen are minimized. In the usual bidentate binding mode normally observed for guanidinium cations, the lone pair of the second oxygen directly points towards the furan oxygen. Therefore, the guanidinium cation interacts with only one oxygen atom of the anion in a bifurcated fashion. Furthermore, the OH group of the hydrogen sulfate forms an H bond with the CO of the amide group in position 5 of the receptor.

Conclusions

We have shown here that cationic 2-(guanidiniocarbonyl)-furans **5** can be synthesized even though special attention has to be paid to the acid sensitivity of these compounds, which requires carefully controlled reaction and work-up conditions. The increased acidity of the (guanidiniocarbonyl)furans **5** relative to analogous pyrrole compounds makes them anion hosts that are selective for only weakly basic oxoanions such as hydrogen sulfate, because low pH values are required for the complete protonation of the guanidinium moiety. This prevents the binding of more basic anions such as carboxylates, which are normally bound more effectively by anion hosts. However, one factor limiting the use of these (guanidiniocarbonyl)furans for anion sensing will most likely be their limited stability under these acidic conditions.

Experimental Section

General Remarks: Solvents were dried and distilled before use. The starting materials and reagents were used as obtained from Aldrich or Fluka. The amino acid derivative **19** was synthesized by starting from Fmoc-Lys(Boc)-OH: the acid function was converted into the acyl chloride and hydrolyzed with aqueous ammonia to obtain the amide, finally the Fmoc group was cleaved with a piperidine solution. All experiments were run in oven-dried glassware. The compounds were dried in high vacuum over phosphorus pentoxide at room temperature overnight unless otherwise stated. The pH values were measured with a Knick pH meter 766 Calimatic at 25 °C. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 400 spectrometer. The chemical shifts are reported relative to the deuteriated solvents. The EI mass spectra were recorded with a Finnigan MAT 90 instrument, the ESI- and HR-mass spectra were recorded with a Finnigan MAT 900 S spectrometer. All UV spectra were measured in 10-mm rectangular cells with a Jasco V530 spectrometer.

Methyl 5-(Chloromethyl)furan-2-carboxylate (7): To a solution of methyl furan-2-carboxylate (**6**, 10.7 mL, 100 mmol) in dichloromethane (50 mL) were added anhydrous zinc chloride (3.75 g, 27.5 mmol) and paraformaldehyde (4.29 g, 143 mmol). The mixture was warmed to 35 °C, and anhydrous hydrogen chloride gas was bubbled through it for 2.5 h. The mixture was poured into cold water (250 mL), and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 50 mL), and the collected organic layers were washed with water (2 × 50 mL) and dried with potassium carbonate. The solvent was removed under reduced pressure, and the residual oil was distilled (72 °C/0.25 mbar) to obtain **7** (11.7 g, 67%) as a colourless oil that crystallized after a few days: m.p. 30 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C, TMS): δ = 3.90 (s, 3 H, OMe), 4.59 (s, 2 H, CH_2), 6.48 (d, $^3J_{HH}$ = 3.4 Hz, 1 H, furan CH), 7.12 (d, $^3J_{HH}$ = 3.5 Hz, 1 H, furan CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C, TMS): δ = 35.7, 51.0, 110.4, 117.8, 143.8, 153.1, 157.7 ppm. IR (KBr): $\tilde{\nu}$ = 3130, 2960, 1730, 1300, 760 cm^{-1}.

Methyl 5-(Acetoxymethyl)furan-2-carboxylate (8): To a solution of methyl 5-(chloromethyl)furan-2-carboxylate (**7**, 5.50 g, 31.5 mmol) in acetic acid (22 mL) and acetic anhydride (2.2 mL) was added anhydrous sodium acetate (11.0 g, 134 mmol). The reaction mixture was heated at 120 °C for 5.5 h, and after cooling, diethyl ether (40 mL) was added. The suspension was neutralized with a saturated sodium carbonate solution, and then the organic layer was separated. The aqueous layer was extracted with diethyl ether (5 × 30 mL). The combined organic phases were dried with magnesium sulfate, and the solvent was removed in vacuo. The residual oil was distilled (70 °C/0.04 mbar) to obtain **8** (5.85 g, 93%) as a colourless oil that crystallized after a few minutes: m.p. 39 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 27 °C, TMS): δ = 2.08 (s, 3 H, CH_3), 3.89 (s, 3 H, OMe), 5.07 (s, 2 H, CH_2), 6.49 (d, $^3J_{HH}$ = 3.5 Hz, 1 H, furan CH), 7.12 (d, $^3J_{HH}$ = 3.4 Hz, 1 H, furan CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 27 °C, TMS): δ = 20.0, 52.0, 57.6, 112.7, 118.7, 144.7, 153.5, 159.5, 170.8 ppm. IR (KBr): $\tilde{\nu}$ = 2951, 1737, 1309, 1214 cm^{-1}. EI-MS: *m*/*z* = 198.1 [M]$^+$.

Methyl 5-(Hydroxymethyl)furan-2-carboxylate (9): To methyl 5-(acetoxymethyl)furan-2-carboxylate (**8**, 5.50 g, 27.8 mmol) was added a methanol solution of sodium methoxide (322 mg sodium in 35 mL methanol). The mixture was stirred at room temperature for 24 h. The yellow solution was passed over a cation exchange resin, washed with methanol, and the solvent was removed in vacuo. The residue was distilled (109 °C/0.33 mbar) to give **9** (3.86 g, 89%) as a colourless oil that crystallized after a few days: m.p. 20 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 3.79 (s, 3 H, OMe), 4.45 (d, $^3J_{HH}$ = 5.8 Hz, 2 H, CH_2), 5.48 (t, $^3J_{HH}$ = 5.9 Hz, 1 H, OH), 6.49 (d, $^3J_{HH}$ = 3.5 Hz, 1 H, furan CH), 7.24 (d, $^3J_{HH}$ = 3.4 Hz, 1 H, furan CH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 51.7, 55.8, 109.2, 119.3, 142.8, 158.5, 160.3 ppm. IR (KBr): $\tilde{\nu}$ = 3402, 2953, 1719, 1524 cm^{-1}. EI-MS: *m*/*z* = 156.1 [M]$^+$.

5-(Methoxycarbonyl)furan-2-carboxylic Acid (10): Methyl 5-(hydroxymethyl)furan-2-carboxylate (**9**, 2.00 g, 12.8 mmol) was dissolved in acetone (200 mL) and cooled to 5 °C. Potassium permanganate (4.10 g, 26.1 mmol) was then added, the ice bath was removed, and the mixture was stirred for 40 min. Warming up and weak boiling of the acetone were observed. The MnO_2 was filtered off and washed with methanol (20 mL). The solvent was removed under reduced pressure, and the obtained yellow solid was dissolved in sodium hydroxide (0.1 M, 20 mL). The solution was acidified with concentrated hydrochloric acid to pH = 4, and the desired product was crystallized. The solid was collected, washed with water and dried in vacuo to obtain the desired acid **10** (1.46 g, 66%) as a slightly yellow solid: m.p. 173 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 3.85 (s, 3 H, OMe), 7.32 (d, $^3J_{HH}$ = 3.7 Hz, 1 H, furan CH), 7.39 (d, $^3J_{HH}$ = 3.6 Hz, 1 H, furan CH), 13.69 (br. s, 1 H, COOH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 52.3, 118.5, 119.1, 147.1, 147.5, 158.0, 158.9 ppm. IR (KBr): $\tilde{\nu}$ = 3130, 1737, 1688, 1294 cm^{-1}. EI-MS: *m*/*z* = 170.1 [M]$^+$.

***N*^{1}-(*tert*-Butoxycarbonyl)-*N*^{2}-[5-(methoxycarbonyl)furan-2-ylcarbonyl]guanidine (12):** To a stirred solution of 5-(methoxycarbonyl)furan-2-carboxylic acid (**10**, 100 mg, 0.59 mmol), PyBOP (307 mg, 0.59 mmol) and NMM (276 mg, 2.73 mmol) in DMF (4 mL) was added Boc-protected guanidine (**11**, 94.5 mg, 0.59 mmol). The solu-

tion was stirred at room temperature for 1 d. Then it was cooled in an ice bath, and water was added (6 mL). The precipitating white solid was collected and dried to obtain product **12** (125 mg, 68%): m.p. 152 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 1.45 (s, 9 H, CMe$_3$), 3.83 (s, 3 H, OMe), 7.15 (d, $^3J_{HH}$ = 3.6 Hz, 1 H, furan CH), 7.34 (d, $^3J_{HH}$ = 3.6 Hz, 1 H, furan CH), 8.68 (br. s, 1 H, NH), 9.58 (br. s, 1 H, NH), 11.0 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 27.6, 52.1, 82.3, 116.3, 119.2, 144.6, 154.1, 158.2, 159.1, 163.4, 167.9 ppm. IR (KBr): $\tilde{\nu}$ = 3358, 1723, 1644, 1244 cm^{-1}. EI-MS: *m*/*z* = 311.1 [M]$^+$.

Methyl 5-(Ethylcarbamoyl)furan-2-carboxylate (13): To a solution of 5-(methoxycarbonyl)furan-2-carboxylic acid (**10**, 300 mg, 1.76 mmol), HCTU (730 mg, 1.76 mmol) and NMM (535 mg, 5.29 mmol) in DMF (10 mL) was added ethylamine hydrochloride (144 mg, 1.76 mmol). The reaction mixture was stirred overnight at room temperature, and water (30 mL) was added. The mixture was extracted with ethyl acetate (16 × 15 mL). The combined organic layers were washed with brine (30 mL) and dried with magnesium sulfate. The solvent was evaporated to give **13** (206 mg, 59%) as a slightly yellow solid: m.p. 72 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 1.10 (t, $^3J_{HH}$ = 7.2 Hz, 3 H, ethyl CH$_3$), 3.26 (m, 2 H, ethyl CH$_2$), 3.85 (s, 3 H, OMe), 7.20 (d, $^3J_{HH}$ = 3.7 Hz, 1 H, furan CH), 7.37 (d, $^3J_{HH}$ = 3.5 Hz, 1 H, furan CH), 8.61 (br. t, $^3J_{HH}$ = 5.5 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 14.6, 33.6, 52.1, 114.2, 119.2, 144.2, 150.6, 156.7, 158.1 ppm. IR (KBr): $\tilde{\nu}$ = 3296, 2965, 1724, 1653 cm^{-1}. EI-MS: *m*/*z* = 197.1 [M]$^+$.

5-(Ethylcarbamoyl)furan-2-carboxylic Acid (15): To a solution of methyl 5-(ethylcarbamoyl)furan-2-carboxylate (**13**, 110 mg, 0.558 mmol) in methanol (5 mL) was added LiOH (133 mg, 5.58 mmol). The reaction mixture was stirred at room temperature for 30 min. The methanol was removed under reduced pressure, and the residue was dissolved in water (7 mL). The solution was acidified with hydrochloric acid to pH = 3 at 0 °C and extracted with ethyl acetate (6 × 10 mL). The collected organic layers were dried with magnesium sulfate, and the solvents were evaporated to dryness to give the desired product **15** (65 mg, 64%) as a slightly yellow solid: m.p. 125 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 1.10 (t, $^3J_{HH}$ = 7.2 Hz, 3 H, ethyl CH$_3$), 3.26 (m, 2 H, ethyl CH$_2$), 7.17 (d, $^3J_{HH}$ = 3.7 Hz, 1 H, furan CH), 7.27 (d, $^3J_{HH}$ = 3.6 Hz, 1 H, furan CH), 8.55 (t, $^3J_{HH}$ = 5.2 Hz, 1 H, NH), 13.47 (br. s, 1 H, COOH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 14.7, 33.5, 114.1, 118.5, 145.5, 150.2, 156.9, 159.0 ppm. IR (KBr): $\tilde{\nu}$ = 3421, 2966, 1717, 1641 cm^{-1}. EI-MS: *m*/*z* = 183.0 [M]$^+$.

***N*^{1}-(*tert*-Butoxycarbonyl)-*N*^{2}-[5-(ethylcarbamoyl)furan-2-ylcarbonyl]guanidine (17):** To a solution of 5-(ethylcarbamoyl)furan-2-carboxylic acid (**15**, 120 mg, 0.655 mmol), HCTU (271 mg, 0.655 mmol) and NMM (199 mg, 1.97 mmol) in DMF (4 mL) was added a solution of Boc-protected guanidine (**11**, 104 mg, 0.655 mmol) in DMF (4 mL). The reaction mixture was stirred for 1 d at room temperature. After adding water (20 mL) and stirring for 15 min, we extracted the mixture with ethyl acetate (5 × 20 mL). The collected organic layers were washed with brine (20 mL) and dried with sodium sulfate. The solvent was evaporated in vacuo to obtain the desired product **17** (120 mg, 56%) as a slightly brown solid: m.p. 113 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 1.11 (t, $^3J_{HH}$ = 7.2 Hz, 3 H, ethyl CH$_3$), 1.47 (s, 9 H, CMe$_3$), 3.26 (m, 2 H, ethyl CH$_2$), 7.13–7.14 (m, 2 H, furan CH), 8.50 (br. s, 1 H, NH), 8.66 (br. s, 1 H, NH), 9.46 (br. s, 1 H, NH), 10.87 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 14.8, 27.7, 33.5, 69.3, 114.11, 116.74, 149.3, 157.1, 158.8, 162.6 ppm. IR (KBr): $\tilde{\nu}$ = 3395, 2974, 1752, 1685, 1573, 1531, 1420, 1313 cm^{-1}. ESI-MS: *m*/*z* = 347.3 [M + Na]$^+$.

Methyl 5-{[(*S*)-1-Carbamoyl-2-methylpropyl]carbamoyl}furan-2-carboxylate (14): To a stirred solution of 5-(methoxycarbonyl)furan-2-carboxylic acid (**10**, 300 mg, 1.76 mmol), HCTU (730 mg, 1.76 mmol) and NMM (535 mg, 5.29 mmol) in DMF (10 mL) was added H-Val-NH$_2$ (hydrochloride salt, 269 mg, 1.76 mmol). The reaction mixture was stirred at room temperature for 1 d. After adding water (30 mL) and stirring for 15 min, we extracted the mixture with ethyl acetate (10 × 10 mL). The solvent of the combined organic layers was evaporated in vacuo to obtain a yellow solid. The crude product was purified by flash column chromatography on octadecyl-functionalized silica gel (methanol/water = 1:3) to give **14** (270 mg, 57%) as a white solid: m.p. 135 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 0.90 (dd, $^4J_{HH}$ = 6.7, $^3J_{HH}$ = 11.8 Hz, 6 H, valine CMe$_2$) 2.08 (m, 1 H, valine CH), 3.86 (s, 3 H, OMe), 4.27 (dd, $^3J_{HH}$ = 7.5, $^3J_{HH}$ = 8.8 Hz, 1 H, valine NCH), 7.15 (br. s, 1 H, NH), 7.40 (d, $^3J_{HH}$ = 3.7 Hz, 2 H, furan CH), 7.56 (br. s, 1 H, NH), 8.18 (d, $^3J_{HH}$ = 8.8 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 18.4, 19.3, 30.3, 52.2, 57.9, 114.9, 119.2, 144.5, 149.8, 156.8, 158.1, 172.4 ppm. IR (KBr): $\tilde{\nu}$ = 3365, 3227, 2966, 1724, 1638, 1297 cm^{-1}. ESI-MS: *m*/*z* = 291.3 [M + Na]$^+$.

5-{[(*S*)-1-Carbamoyl-2-methylpropyl]carbamoyl}furan-2-carboxylic Acid (16): To a solution of the substituted methyl furan-2-carboxylate (**14**, 50 mg, 0.186 mmol) in methanol (7 mL) was added LiOH (44.6 mg, 1.86 mmol). The reaction mixture was stirred at room temperature for 75 min. The methanol was removed under reduced pressure, and the residue was dissolved in water (5 mL). The solution was acidified with 5% hydrochloric acid to pH = 3–4 and extracted with ethyl acetate (6 × 10 mL). The combined organic layers were dried with sodium sulfate, and the solvents evaporated to dryness to give the desired product **16** (43 mg, 90%) as a white solid: m.p. 192 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 0.90 (dd, $^4J_{HH}$ = 6.8, $^3J_{HH}$ = 12.1 Hz, 6 H, valine CMe$_2$), 2.08 (m, 1 H, valine CH), 4.27 (dd, $^3J_{HH}$ = 7.4, $^3J_{HH}$ = 8.8 Hz, 1 H, Valine NCH), 7.15 (br. s, 1 H, NH), 7.28 (d, $^3J_{HH}$ = 3.6 Hz, 1 H, furan CH), 7.34 (d, $^3J_{HH}$ = 3.5 Hz, 1 H, furan CH), 7.56 (br. s, 1 H, NH), 8.07 (d, $^3J_{HH}$ = 8.8 Hz, 1 H, NH), 13.50 (br. s, 1 H, COOH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 18.3, 19.3, 30.3, 57.8, 114.9, 118.4, 149.4, 156.9, 159.0, 172.4 ppm. IR (KBr): $\tilde{\nu}$ = 3365, 3268, 2952, 1738, 1654, 1255 cm^{-1}. ESI-MS: *m*/*z* = 277.3 [M + Na]$^+$.

5-{[(*S*)-1-Carbamoyl-2-methylpropyl]carbamoyl}furan-2-carbonyl-(*tert*-butoxycarbonyl)guanidine (18): A solution of the furan-2-carboxylic acid (**16**, 100.0 mg, 0.393 mmol), Boc-protected guanidine (**11**, 93.9 mg, 0.590 mmol), PyBOP (205 mg, 0.393 mmol) and NMM (0.129 mL) in DMF (10 mL) was stirred at room temperature for 24 h. After the addition of water (25 mL), the solution was extracted with ethyl acetate (6 × 10 mL). The solvent of the combined organic phases was removed in vacuo to obtain an oil. The yellow crude product was taken up in water (10 mL) and lyophilized and purified by flash column chromatography on octadecyl-functionalized silica gel (methanol/water = 1:3) to give **18** (66.3 mg, 42%) as a white solid: m.p. 76 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 0.90 (dd, $^4J_{HH}$ = 6.7, $^3J_{HH}$ = 11.2 Hz, 6 H, valine CH$_3$), 1.46 (s, 9 H, CMe$_3$), 2.08 (m, 1 H, valine CH), 4.28 (dd, $^3J_{HH}$ = 7.5, $^3J_{HH}$ = 8.8 Hz, 1 H, valine NCH), 7.15 (br. s, 1 H, NH), 7.18 (d, $^3J_{HH}$ = 3.3 Hz, 1 H, furan CH), 7.30 (d, $^3J_{HH}$ = 3.7 Hz, 1 H, furan CH), 7.58 (br. s, 1 H, NH), 8.02 (d, $^3J_{HH}$ = 7.0 Hz, 1 H, NH), 8.66 (br. s, 1 H, NH), 9.44 (br. s, 1 H,

NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 18.4, 19.3, 27.7, 30.5, 57.7, 81.7, 115.1, 116.8, 148.6, 157.2, 158.9, 172.5, 173.2 ppm. IR (KBr): $\tilde{\nu}$ = 3384, 2979, 1737, 1638 cm^{-1}. ESI-MS: m/z = 396.3 [MH]$^+$.

5-[(Benzyloxy)carbonyl]furan-2-carboxylic Acid (22): To a solution of the methyl ester (**10**, 500 mg, 2.94 mmol) in toluene (70 mL) was added dropwise a sodium benzylate solution (54.2 mg Na in 5 mL benzylic alcohol). The mixture was heated at 110 °C for 12 h. After cooling to room temperature, the mixture was extracted with water (3 × 50 mL), and the combined aqueous layers were acidified with concentrated hydrochloric acid to pH = 3. The precipitated solid was collected, taken up in water (20 mL) and lyophilized to obtain **22** (318 mg, 45%) as a white solid: m.p. 153 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 5.36 (s, 2 H, benzylic CH$_2$), 7.32 (d, $^3J_{HH}$ = 3.64 Hz, 1 H, furan CH), 7.36–7.47 (m, 6 H, furan CH, 5 × benzene CH), 13.70 (br. s, 1 H, COOH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 66.5, 118.4, 119.4, 128.3, 128.4, 128.5, 135.5, 145.6, 147.5, 157.4, 158.7 ppm. IR (KBr): $\tilde{\nu}$ = 3119, 3006, 1726, 1698, 1281 cm^{-1}. EI-MS: m/z = 246.0 [MH]$^+$.

Benzyl Furan-2-carboxylate Derivative 23: To a solution of the benzylic ester (**22**, 92.8 mg, 0.377 mmol), HCTU (157 mg, 0.377 mmol) and NMM (1.14 mmol) in DMF (5 mL) was added H-Lys(Boc)-NH$_2$ chloride salt (**19**, 93.1 mg, 0.377 mmol), and the yellow solution was stirred at room temperature for 5 d. After the addition of water (30 mL), the solution was extracted with ethyl acetate (7 × 20 mL). The solvent of the combined organic phases was removed in vacuo to obtain a yellow solid. The crude product was purified by flash column chromatography on octadecyl-functionalized silica gel (methanol/water = 1:3) to give **23** (128 mg, 71%) as a white solid: m.p. 56 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 1.18–1.39 (m, 13 H, CMe$_3$, 2 × lysine CH$_2$), 1.70 (m, 2 H, lysine CH$_2$), 2.87 (m, 2 H, lysine CH$_2$), 4.34 (m, 1 H, lysine NCH), 5.36 (s, 2 H, benzylic CH$_2$), 6.73 (t, $^3J_{HH}$ = 4.9 Hz, 1 H, NH), 7.06 (br. s, 1 H, NH), 7.34–7.47 (m, 8 H, 5× benzene CH, 2 × furan CH, NH), 8.42 (d, $^3J_{HH}$ = 8.1 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 22.9, 28.2, 29.2, 31.4, 52.6, 66.3, 77.3, 114.8, 119.5, 128.2, 128.3, 128.5, 135.6, 144.3, 150.2, 155.5, 156.8, 157.5, 173.2 ppm. IR (KBr): $\tilde{\nu}$ = 3343, 2931, 1715, 1685, 1287 cm^{-1}. HRMS (ESI): calcd. for C$_{24}$H$_{31}$N$_3$NaO$_7$ [M + Na]$^+$ 496.20542; found 496.20664.

Furan-2-carboxylic Acid Derivative 21: A mixture of **23** (99.1 mg, 0.209 mmol) and Pd/C (10.2 mg) in methanol (5 mL) was hydrogenated at room temperature for 40 min. The mixture was filtered through Celite to remove Pd/C, and the solvent was evaporated to give **21** (38.5 mg, 48%) as a white solid: m.p. 105 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 1.19–1.36 (m, 13 H, CMe$_3$, 2 × lysine CH$_2$), 1.70 (m, 2 H, lysine CH$_2$), 2.87 (m, 2 H, lysine CH$_2$), 4.34 (m, 1 H, lysine NCH), 6.73 (br. s, 1 H, NH), 7.07 (br. s, 1 H, NH), 7.16 (d, $^3J_{HH}$ = 3.6 Hz, 1 H, furan CH), 7.24 (d, $^3J_{HH}$ = 3.6 Hz, 1 H, furan CH), 7.47 (s, 1 H, NH), 8.23 (d, $^3J_{HH}$ = 8.2 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 22.9, 28.2, 29.2, 31.5, 52.4, 54.5, 77.3, 114.7, 148.9, 155.5, 157.5, 173.3 ppm. IR (KBr): $\tilde{\nu}$ = 3352, 2938, 1685, 1276 cm^{-1}. HRMS (ESI): calcd. for C$_{17}$H$_{25}$N$_3$NaO$_7$ [M + Na]$^+$ 406.15847; found 406.15966.

General Procedure for the Boc-Deprotection of 12, 17 and 18 to Obtain the Picrates 5a, 5b and 5c: To the Boc-protected compound (50 mg) was added at 0 °C trifluoroacetic acid (5 mL). The ice bath was removed, and the solution was stirred for 1 h at room temperature. The excess trifluoroacetic acid was removed in vacuo, and the remaining residue was dissolved in methanol (2 mL). Then, a saturated solution of picric acid in water (8 mL) was added, and the mixture was stirred for 1 h at room temperature (for compound **5c** the solution was stirred for 1 d). The picrate salt precipitated, it was filtered, washed several times with cold water and dried to obtain a yellow solid.

5a: Yield 40.3 mg (57%); m.p. 187 °C. ^{1}H NMR (400 MHz, [D$_6$]-DMSO, 27 °C, TMS): δ = 3.89 (s, 3 H, OMe), 7.53 (d, $^3J_{HH}$ = 3.8 Hz, 1 H, furan CH), 7.58 (d, $^3J_{HH}$ = 3.3 Hz, 1 H, furan CH), 8.30 (br. s, 4 H, 2 × guanidine NH$_2$), 8.58 (s, 2 H, 2 × picrate CH), 11.30 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 52.6, 119.5, 119.6, 124.2, 125.2, 141.8, 146.3, 147.0, 154.6, 156.9, 157.7, 160.8 ppm. IR (KBr): $\tilde{\nu}$ = 3348, 3172, 1747, 1717 cm^{-1}. HRMS (ESI): calcd. for C$_8$H$_{10}$N$_3$O$_4$ [M]$^+$ 212.06658; found 212.06702.

5b: Yield 60.0 mg (86%); m.p. 244 °C. ^{1}H NMR (400 MHz, [D$_6$]-DMSO, 27 °C, TMS): δ = 1.13 (t, $^3J_{HH}$ = 7.2 Hz, 3 H, ethyl CH$_3$), 3.29 (m, 2 H, ethyl CH$_2$), 7.33 (d, $^3J_{HH}$ = 3.8 Hz, 1 H, furan CH), 7.55 (d, $^3J_{HH}$ = 3.8 Hz, 1 H, furan CH), 8.30 (br. s, 4 H, 2 × guanidine NH$_2$), 8.58 (s, 2 H, 2 × picrate CH), 8.64 (t, $^3J_{HH}$ = 5.8 Hz, 1 H, NH), 11.18 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO, 27 °C, TMS): δ = 14.6, 33.6, 114.6, 119.7, 124.1, 125.1, 141.8, 145.1, 150.6, 154.6, 156.6, 157.0, 160.8 ppm. IR (KBr): $\tilde{\nu}$ = 3356, 3158, 2952, 1726, 1568, 1266 cm^{-1}. HRMS (ESI): calcd. for C$_9$H$_{13}$N$_4$O$_4$ [M]$^+$ 225.0987; found 225.098.

5c: Yield 28.5 mg (43%); m.p. 106 °C. ^{1}H NMR (400 MHz, [D$_6$]-DMSO, 27 °C, TMS): δ = 0.91 (dd, 6 H, valine CMe$_2$), 2.08 (m, 1 H, valine CH), 4.32 (dd, 1 H, valine NCH), 7.16 (br. s, 1 H, NH), 7.52 (d, 1 H, furan CH), 7.57 (d, 1 H, furan CH), 7.59 (br. s, 1 H, NH), 8.28 (d, 1 H, NH), 8.33 (br. s, 4 H, 2 × guanidine NH$_2$), 8.58 (s, 2 H, 2 × picrate CH), 11.30 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 27 °C, TMS): δ = 18.4, 19.3, 30.3, 58.0, 115.6, 119.7, 124.2, 125.2, 141.9, 145.4, 150.0, 154.6, 156.7, 157.1, 160.8, 172.3 ppm. IR (KBr): $\tilde{\nu}$ = 3370, 1724, 1345, 1268 cm^{-1}. HRMS (ESI): calcd. for C$_{12}$H$_{18}$N$_5$O$_4$ [M]$^+$ 296.1353; found 296.135.

UV Titrations: All UV titrations were carried out by the addition of aliquots (1×10^{-3} M)of a solution of the substrate (tetrabutylammonium hydrogen sulfate or potassium dihydrogen phosphate) to a solution of **5b** (4×10^{-5} M) and recording the UV spectra after each addition at 25 °C. The receptor and the substrate were dissolved in a solution (4×10^{-3} M)of acetate buffer (pH = 4.6) in pure water and then diluted with the same volume of DMSO. Dilution was taken into account in analysis of the data in the 1:1 complexation model by nonlinear regression. Each titration was performed with 21 measurements.

Acknowledgments

Financial support by the Fonds der Chemischen Industrie and by the Deutsche Forschungsgemeinschaft (SCHM 1501) is gratefully acknowledged.

[1] a) H. Hibbert, H. B. Hill, *J. Am. Chem. Soc.* **1923**, *45*, 176–182; b) W. N. Haworth, W. G. M. Jones, *J. Chem. Soc.* **1944**, 667–670; c) W. N. Haworth, W. G. M. Jones, L. F. Wiggins, *J. Chem. Soc.* **1945**, 1–4.

[2] T. El Hajj, A. Masroua, J.-C. Martin, G. Descotes, *Bull. Soc. Chim. Fr.* **1987**, *5*, 855–861.

[3] a) C. O. Kappe, S. S. Murphree, A. Padwa, *Tetrahedron* **1997**, *53*, 14179–14233; b) O. Arjona, F. Iradier, R. Medel, J. Plumet, *Heterocycles* **1999**, *50*, 653–656; c) D. Fokas, J. E. Patterson, G. Slobodkin, C. M. Baldino, *Tetrahedron Lett.* **2003**, *44*, 5137–

5140; d) K. Wei, H.-T. Gao, W.-D. Z. Li, *J. Org. Chem.* **2004**, *69*, 5763–5765; e) R. Sedaghat-Herati, A. Chacon, M. E. Hansen, S. Yalaoui, *Macromol. Chem. Phys.* **2005**, *206*, 1981–1987.
[4] A. Gandini, M. N. Belgacem, *Prog. Polym. Sci.* **1997**, *22*, 1203–1379.
[5] a) O. Moldenhauer, G. Trautmann, W. Irion, R. Pfluger, H. Döser, D. Mastaglio, H. Marwitz, *Justus Liebigs Ann. Chem.* **1953**, *580*, 169–190; b) O. Moldenhauer, G. Trautmann, W. Irion, R. Pfluger, H. Döser, D. Mastaglio, H. Marwitz, *Justus Liebigs Ann. Chem.* **1953**, *583*, 37–62.
[6] Y.-H. Kuo, K.-S. Shih, *Chem. Pharm. Bull.* **1991**, *39*, 181–183.
[7] J. E. Semple, P. C. Wang, Z. Lysenko, M. M. Joullié, *J. Am. Chem. Soc.* **1980**, *102*, 7505–7510.
[8] N. R. Peden, J. H. Saunders, K. G. Wormsley, *Lancet* **1979**, *1*, 690–692.
[9] For receptors with furan building blocks in the structure see the following literature: a) M. J. Hynes, B. Maubert, V. McKee, R. M. Town, J. Nelson, *J. Chem. Soc., Dalton Trans.* **1994**, 1471–1478; b) M. J. Hynes, B. Maubert, V. McKee, R. M. Town, J. Nelson, *J. Chem. Soc., Dalton Trans.* **2000**, 2853–2859; c) V. Amendola, E. Bastianello, L. Fabbrizzi, C. Mangano, P. Pallavicini, A. Perotti, A. M. Lanfredi, F. Ugozzoli, *Angew. Chem. Int. Ed.* **2000**, *39*, 2917–2920; d) T. K. Chakraborty, S. Tapadar, S. K. Kumar, *Tetrahedron Lett.* **2002**, *43*, 1317–1320.
[10] J. F. Stubbins, P. M. Hudgins, D. C. Murphy, *J. Pharm. Sci.* **1980**, *69*, 534–537.
[11] S. Nielek, T. Lesiak, *J. Prakt. Chem.* **1988**, *330*, 825–829.
[12] G. Gonis, E. D. Amstutz, *J. Org. Chem.* **1962**, *27*, 2946–2947.
[13] P. A. Finan, *J. Chem. Soc.* **1963**, 3917–3918.
[14] T. Asami, S. Yoshida, *Heterocycles* **1994**, *38*, 2739–2746.
[15] C. Schmuck, U. Machon, *Chem. Eur. J.* **2005**, *11*, 1109–1118.
[16] C. Schmuck, *Chem. Eur. J.* **2000**, *6*, 709–718.
[17] K. A. Connors, *Binding Constants*, Wiley, New York, **1987**.
[18] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufiled, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440–467.

Received: April 11, 2006
Published Online: August 1, 2006

