Synthesis of α- and β-Substituted Aminoethane Sulfonamide Arginine–Glycine Mimics

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In this paper we present a synthesis of both α- and β-substituted aminoethane sulfonamide arginine mimics. The α-substituted sulfonamides were obtained starting from an alkene, whereas the β-substituted sulfonamides were derived from an amino acid derivative.

Introduction

Peptide bond replacements are important in the development of peptidomimetics, because they are often a first step from a biologically active peptide to analogs having improved properties,[1] e.g. with respect to degradation and biological activity. Recently, numerous peptide bond "surrogates" have been reported.[2] This has since been extended to the development of transition-state isosteres for hydrolysis of the peptide–amide bond.[3] Compounds containing these moieties are of interest as they may be useful in the development of enzyme inhibitors.[4] Although a wide variety of transition-state isosteres has hitherto been described, relatively little attention has been paid to the sulfonamide isostere.[5] In order to expand the possibilities for investigating these sulfonamides as transition-state analogs, it was decided to prepare one of the most challenging amino sulfonic acid derivatives, namely the analog corresponding to the amino acid arginine. Arginine sulfonamide derivatives are particularly interesting since arginine is often important as a binding determinant in protein–peptide interactions, as is the case, for example, in RGD-containing peptides.[6] Furthermore, arginine is present at the cleavage site of thrombin in fibrinogen. As a result, arginine derivatives have been used as starting substrates for the development of thrombin inhibitors.

We have introduced β-aminosulfonic acid derivatives as stable analogs of α-aminosulfonic acid derivatives.[7] As a consequence, two substituted β-aminosulfonic acid mimics of arginine are possible: one having the arginine side chain on the α-carbon (with respect to the sulfonamide moiety) and one with the side chain on the β-carbon atom (Figure 1). In this paper, we describe the synthesis of α- and β-substituted aminoethane sulfonamide mimics of the arginine–glycine peptide sequence.

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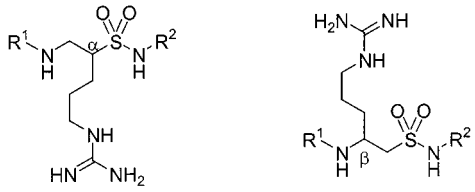
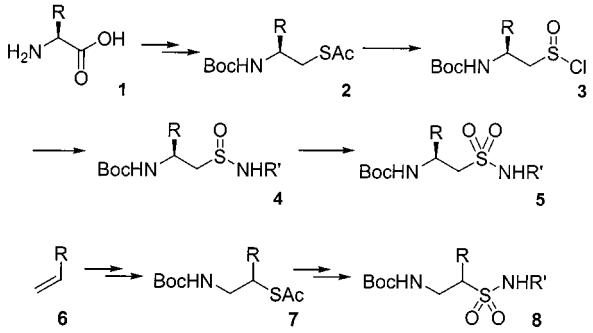


Figure 1. α- and β-substituted β-aminoethane sulfonamide mimics of arginine

Results and Discussion

The synthetic route used to obtain the β-substituted arginine–glycine sulfonamide isosteres was analogous to that for other β-substituted aminoethane sulfonamides developed previously by our group.[7] The key synthon along this route is a β-substituted aminoethane thioacetate **2**[7c] (Scheme 1). Reaction of this thioacetate with sulfuryl chloride and acetic anhydride gives the corresponding sulfinyl chloride **3**. Coupling of **3** with an appropriate amine gives a sulfinamide **4**, which can be oxidized to the desired sulfonamide **5**. For the α-substituted arginine sulfonamide mimic, a new route has been developed starting from alkene **6**. This route offers access to the corresponding thioacetate **7** required for the synthesis of the α-substituted sulfonamide derivatives **8**, and nicely complements the existing routes



Scheme 1. General representation of the synthesis of α- and β-substituted aminoethane sulfonamides

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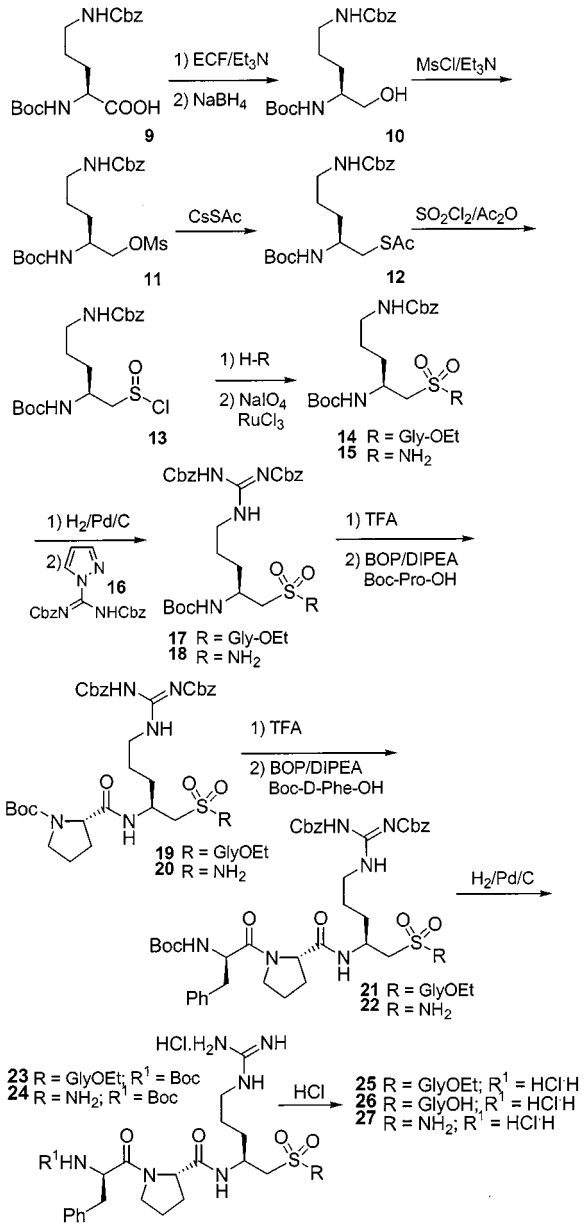
that we have developed starting from either an amino acid or an aldehyde.[8]

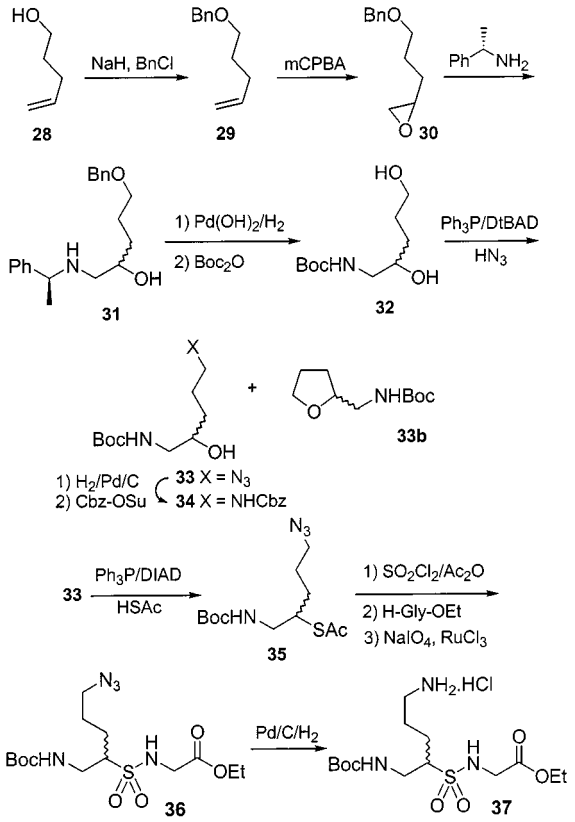
For two reasons, it was decided to start with the synthesis of an ornithine–glycine sulfonamide isostere. Firstly, it was synthetically more attractive to start with ornithine than with arginine, in view of anticipated problems in finding suitable protective groups for the guanidine moiety of arginine. Moreover, a number of convenient methods have been described in the literature[9] for the transformation of an ornithine side chain into an arginine side chain. Secondly, this strategy involving a side chain containing an amino function will also be applicable to the synthesis of lysine sulfonamide mimics.

In order to prepare the β-substituted arginine sulfonamide mimic (Scheme 2), the di-protected ornithine derivative **9** was converted into amino alcohol **10** in 83% yield by reduction of its in situ prepared mixed anhydride.[10] Alcohol **10** was then transformed into its mesylate **11** in 80% yield, from which the mesylate moiety was displaced in a substitution reaction using cesium thioacetate[11] to afford the key thioacetate **12** in 69% yield. After conversion into the corresponding sulfinyl chloride **13** by treatment of this synthon with sulfuryl chloride and acetic anhydride, a coupling reaction with an amine was carried out to obtain the desired sulfinamide, which was immediately oxidized to the corresponding sulfonamide. For the coupling reaction, two amines were selected: (i) H–Gly–OEt leading to ornithine–glycine sulfonamide derivative **14**, and (ii) ammonia to obtain primary sulfonamide **15**. In both cases, the amine also acted as a base, binding the liberated HCl. In this way, higher yields were obtained than by using, for example, triethylamine or *N*-methylmorpholine as the base.[12] The thus obtained sulfinamides were oxidized with $NaIO_4$ and a catalytic amount of $RuCl_3$ to produce the ornithine analogs **14** and **15** in overall yields of 57% and 63%, respectively. Subsequent hydrogenolysis of the Cbz side chain protective group and reaction with pyrazole **16**[9e][9f] gave the protected arginine–glycine sulfonamide mimics **17** (73%) and **18** (59%). In order to assess whether these sulfonamide mimics could be incorporated in a peptide sequence, we decided to couple them first with proline, and then to couple the product with D-phenylalanine. The resulting sequence can be considered as a sulfonamide mimic of a substrate sequence for thrombin. The D-Phe–Pro dipeptide moiety was introduced into sulfonamides **17** and **18** in two steps after cleavage of the Boc group to afford peptidosulfonamides **21** and **22** in overall yields of 77% and 62%, respectively. Deprotection of the guanidine function was carried out by hydrogenolysis to afford the corresponding HCl salts **23** and **24** in 66% and 92% yield, respectively. Subsequent removal of the Boc group with either HCl in diethyl ether or 1 M aqueous HCl gave analogs **25**, **26**, and **27** in quantitative yields.



Scheme 2. Synthesis of fully protected sulfonamide "β"-arginine mimics and elongation of the *N*-terminus

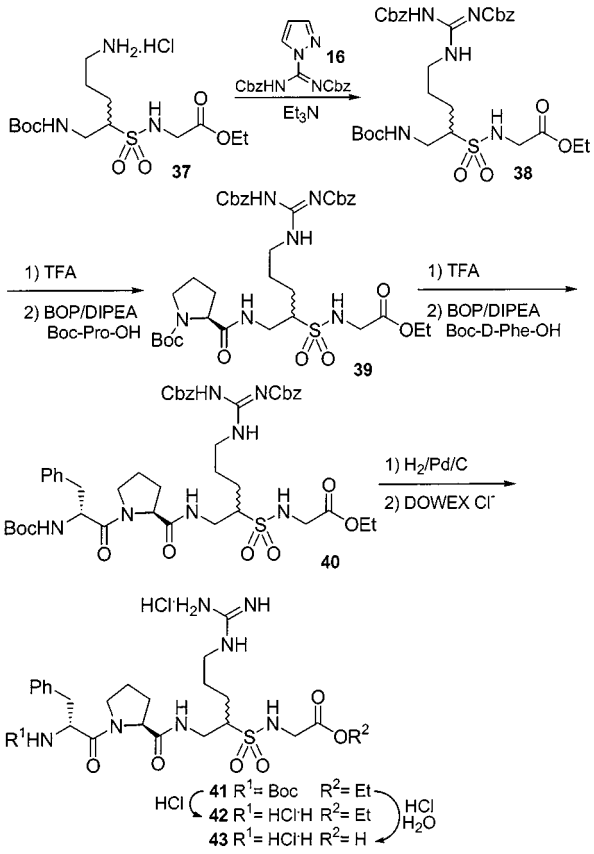
Our new route to α-substituted aminoethane sulfonamide arginine mimics started from 4-penten-1-ol **28** (Scheme 3). The alcohol function of **28** was protected with a benzyl group in 77% yield. The resulting alkene **29** was then epoxidized with *m*-CPBA affording epoxide **30** in 74% yield. In a first attempt to open the epoxide ring, chiral α-methylbenzylamine was used[13] since it was anticipated that this would lead to a separable mixture of diastereoisomers and perhaps even to a substantial diastereomeric excess of amino alcohol **31**. Unfortunately, this was not the case, although the regioselectivity was correct. In an attempt to optimize the diastereoselectivity of the reaction, it was carried out at several different temperatures. However, the diastereomeric ratio remained almost constant, i.e. around 1:1. Furthermore, the diastereomers were barely separable by TLC. The synthesis was thus continued by removing the benzyl protective groups from racemic **31** by hydrogenolysis and then protecting the free amine with a Boc group, thereby affording diol **32** in 93% yield. Remarkably, a considerable difference in the reactivities of the two diastereoisomers was observed during the hydrogenation. Unfortunately, however, it was not possible to take advantage of



Scheme 3. Synthesis of an "α"-ornithine–glycine mimic containing a sulfonamide isostere

this difference to separate the diastereomers. The next step was to convert the primary hydroxyl function in **32** to a group that could eventually be converted into the guanidine functionality of the arginine sulfonamide mimic. For this purpose, the azido group was chosen as a masked amine functionality[14] that may be converted into a guanidine group at a later stage. Reaction of diol **32** with HN_3, Ph_3P, and di-*tert*-butyl azodicarboxylate gave azido alcohol **33** in 55% yield. This azide was converted into the Cbz-protected **34** by catalytic reduction followed by reaction with Cbz–OSu. The use of di-*tert*-butyl azodicarboxylate, as opposed to, for example, the more commonly used diethyl azodicarboxylate, was crucial. Using the latter, it was not possible to separate the hydrazine derivative generated in the reaction from the product. Moreover, a by-product was formed, which seemingly originated from an intramolecular reaction. This product was obtained in 67% yield by carrying out a Mitsunobu reaction using diethyl azodicarboxylate and Ph_3P in the absence of HN_3, and was identified as the tetrahydrofuran derivative **33a**. Next, the remaining hydroxyl function had to be converted into a thioacetate moiety. Unfortunately, it was not possible to prepare the thioacetate of **34**, probably because of interference by the Cbz-protected amine. Consequently, it was decided to retain the azide as a masked amino function[14] in **33** and to convert the hydroxy function of this compound into a thioacetate. Again, a Mitsunobu reaction was employed to accomplish this. As in the preceding Mitsunobu reaction, the choice of dialkyl azodicarboxylate reagent proved to be crucial with regard to the ease of purification of the product. The use of thioacetic acid, Ph_3P, and diisopropyl azodicarboxylate[15] furnished thioacetate **35** in 69% yield. Subsequent treatment with acetic anhydride and sulfuryl chloride gave the corresponding sulfinyl chloride, which was used directly for coupling with glycine ethyl ester. The sulfinamides thus obtained were immediately oxidized to the corresponding sulfonamide **36** in 52% yield using $NaIO_4$ in the presence of $RuCl_3$ as a catalyst.

Following the strategy for the β-substituted ornithine sulfonamide mimic, the peptidosulfonamide derivative **36** was converted into the arginine–glycine analog by hydrogenation[16] to give the hydrochloric acid salt **37**. Subsequent introduction of the protected guanidine group (Scheme 4), using pyrazole derivative **16**,[9e][9f] afforded **38** in 65% yield. For comparison purposes, both a proline and a D-phenylalanine residue were introduced into the resulting "α"-arginine sulfonamide mimic following a procedure analogous to that outlined above for the preparation of the "β"-arginine sulfonamide mimic **23**. Indeed, after repeated Boc deprotection steps with TFA and BOP couplings (Scheme 4), **39** and **40** were obtained in yields of 69% and 63%, respectively. The guanidine group in peptidosulfonamide **40** was deprotected by hydrogenolysis, yielding sulfonamide **41** in 72% yield. Finally, treatment with either HCl in diethyl ether or 1 M aqueous HCl afforded analogs **42** and **43** in quantitative yields (Scheme 4).



Scheme 4. Synthesis of an "α"-arginine–glycine mimic containing a sulfonamide isostere

Conclusion

In this paper, we have described the preparation of the most challenging α- and β-substituted aminoethane sulfonamide mimics, viz. those corresponding to the amino acid arginine. For the β-substituted compounds, the successful approach described previously was followed starting from an amino acid derivative. The resulting "β"-arginine sulfonamide mimic was incorporated into a peptide sequence. Additionally, a new method has now been developed for the synthesis of the "α"-arginine sulfonamide mimic. This approach utilized an alkene derivative as the starting material. Although the racemic sulfonamide arginine was prepared, it is envisaged that homochiral compounds should be accessible by employing alternative chiral amines for ring-opening of the intermediate epoxide. The strategy presented in this paper, involving the use of an alkene as the starting material, might also be applied to the synthesis of other α-substituted aminoethane sulfonamides. In principle, α-substituted aminoethane sulfonamides corresponding to all proteinogenic amino acid analogs are accessible by starting from the appropriate alkene.

Experimental Section

General Remarks: DCM and DMF were dried with molecular sieves (4 Å). Triethylamine and DIPEA were successively distilled from ninhydrin and KOH. THF was distilled from $LiAlH_4$. All other chemicals were used as received from commercial suppliers. Reactions were carried out at ambient temperature unless stated otherwise. – TLC analysis was performed on Merck pre-coated silica gel 60 F-254 (0.25 mm) plates. Spots were visualized with UV light, ninhydrin, or Cl_2-TDM.[17] Solvents were evaporated under reduced pressure at 40 °C. – Column chromatography was performed on Merck kieselgel 60 (40–63 mm) and flash chromatography on Merck kieselgel 60H (5–40 mm). Sephadex LH-20 from Pharmacia was used for gel permeation chromatography. – ^{1}H NMR spectra were recorded with a Varian G-300 spectrometer (300.1 MHz); chemical shift values are given in ppm relative to TMS. – ^{13}C NMR spectra were recorded with a Varian G-300 spectrometer (75.5 MHz); chemical shift values are given in ppm relative to $CDCl_3$ (δ = 77.0) or [D_6]DMSO (δ = 39.7). ^{13}C spectra were recorded using the attached proton test (APT) sequence. – Fast-atom bombardment (FAB) mass spectrometry was carried out using a Jeol JMS SX/SX 102A four-sector mass spectrometer coupled with an HP-9000 data system. LC-electron spray (ES) mass spectrometry was carried out with a Shimadzu LCMS-QP8000 spectrometer. All compounds were purified by column chromatography, examined by TLC, and, as far as possible, rigorously characterized by proton and carbon NMR spectroscopy and electron-spray and FAB mass spectrometry. Compounds **23–27** and **41–43** were analyzed by HPLC and were found to be greater than 95% pure. HPLC analysis was carried out on a Gilson automated HPLC system 205 with a 233XL autosampler and a 119 UV/Vis detector.

***α-tert*-Butyloxycarbonyl-ε-(benzyloxycarbonyl)ornithinol (10):** To a solution of protected ornithine **9** (4.0 g, 10.9 mmol) and triethylamine (1.52 mL, 10.9 mmol) in THF (60 mL), ethyl chloroformate (1.04 mL, 10.9 mmol) was added dropwise at –10 °C. The resulting mixture was stirred for 15 min at 0 °C and then $NaBH_4$ (1.24 g, 32.8 mmol) was added. MeOH (100 mL) was then added dropwise with the temperature held at 0 °C. Following the addition, the mixture was stirred for 30 min at room temperature and then the solvent was evaporated. The residue was taken up in water and the resulting aqueous solution was extracted three times with EtOAc. The combined organic layers were washed with 1 M $KHSO_4$, 5% $NaHCO_3$ solution, and brine, and dried with Na_2SO_4. After column chromatography (eluent: MeOH/DCM, 2:98), evaporation of the solvent from the appropriate fraction afforded 3.17 g (83%) of alcohol **10**. R_f = 0.25 (EtOAc/hexanes, 1:1). – ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 1.50–1.65 (m, 4 H, $CH_2CH_2CH_2N$), 2.57 (br. s, 1 H, OH), 3.20 (q, 2 H, CH_2N), 3.50–3.70 (m, 3 H, $CHCH_2O$), 4.75, 4.95 (two br. s, 2 H, NH), 5.10 (s, 2 H, OCH_2Ph), 7.35 (m, 5 H, ArH). – ^{13}C NMR ($CDCl_3$): δ = 26.5 ($CH_2CH_2CH_2N$), 28.3 [$C(CH_3)_3$], 28.5 (CH_2CH_2N), 40.7 (CH_2N), 52.2 (CHN), 65.2 (CH_2O), 66.6 (OCH_2Ph), 79.5 [$C(CH_3)_3$], 128.0, 128.4, 136.5 (C^{Ar}), 156.3, 156.5 (C=O).

Mesylate 11: Alcohol **10** (6.78 g, 19.2 mmol) was dissolved in DCM (100 mL). To this solution, a solution of triethylamine (2.95 mL, 21.12 mmol) and mesyl chloride (1.56 mL, 20.16 mmol) in DCM (25 mL) was added dropwise at 0 °C. The resulting mixture was stirred for 90 min at room temperature, and then the solvent was evaporated and the residue was redissolved in EtOAc. This solution was washed with 5% $NaHCO_3$ solution and brine, and dried with Na_2SO_4. Concentration to dryness and crystallization of the residue from EtOAc/hexanes gave 6.6 g (80%) of mesylate **11**. R_f = 0.31 (EtOAc/hexanes, 1:1). – ^{1}H NMR ($CDCl_3$): δ = 1.44 [s, 9 H, $C(CH_3)_3$], 1.50–1.65 (m, 4 H, $CH_2CH_2CH_2N$), 3.02 (s, 3 H, CH_3SO_2), 3.23 (q, 2 H, CH_2N), 3.83 (br. s, 1 H, $CHCH_2O$), 4.20 (m, 2 H, $CHCH_2O$), 4.70, 4.90 (two br. s, 2 H, NH), 5.10 (s, 2 H, OCH_2Ph), 7.37 (m, 5 H, ArH). – ^{13}C NMR ($CDCl_3$): δ = 26.4 ($CH_2CH_2CH_2N$), 28.3 [$C(CH_3)_3$], 28.4 (CH_2CH_2N), 37.4 (CH_3SO_2), 40.6 (CH_2N), 49.5 (CHN), 66.7 (OCH_2Ph), 70.9 (CH_2O), 80.0 [$C(CH_3)_3$], 128.07, 128.10, 128.5, 136.6 (C^{Ar}), 155.3, 156.5 (C=O).

Thioacetate 12: To a suspension of Cs_2CO_3 (2.72 g, 8.35 mmol) in DMF (100 mL), thioacetic acid (1.29 mL, 18.1 mmol) was added at 0 °C under argon. After stirring for 15 min, mesylate **11** (6.53 g, 15.2 mmol) in DMF (20 mL) was added and the resulting solution was stirred overnight. It was then poured into iced water and extracted three times with EtOAc. The combined organic layers were washed with water, 5% $NaHCO_3$ solution, and brine, and dried with Na_2SO_4. Evaporation of the solvent, column chromatography of the residue (eluent: diethyl ether/hexanes, 1:1), and subsequent recrystallization from diethyl ether/hexanes gave 4.32 g (69%) of thioacetate **12**. R_f = 0.24 (diethyl ether/hexanes, 2:1). – ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 1.40–1.65 (m, 4 H, $CH_2CH_2CH_2N$), 2.34 (s, 3 H, CH_3CO), 3.00 (m, 2 H, $CHCH_2S$), 3.20 (q, 2 H, CH_2N), 3.70 (br. s, 1 H, $CHCH_2S$), 4.57, 4.95 (two br. s, 2 H, NH), 5.09 (s, 2 H, OCH_2Ph), 7.37 (m, 5 H, ArH). – ^{13}C NMR ($CDCl_3$): δ = 26.4 ($CH_2CH_2CH_2N$), 28.3 [$C(CH_3)_3$], 30.4 (CH_3CO), 31.4 (CH_2CH_2N), 33.8 ($CHCH_2S$), 40.6 (CH_2N), 50.2 (CHN), 66.5 (OCH_2Ph), 79.3 [$C(CH_3)_3$], 128.0, 128.4, 136.6 (C^{Ar}), 155.4, 156.4 (CONH), 195.5 (OCS).

Sulfinyl Chloride 13: Thioacetate **12** (1.23 g, 3.0 mmol) was dissolved in DCM (10 mL) under an argon atmosphere. After cooling to –20 °C, Ac_2O (283 μL, 3.0 mmol) and sulfuryl chloride (486 μL, 6.0 mmol) were added. The resulting mixture was stirred for 1 h at –5 °C and then the solvent was evaporated and the residue was dried in vacuo. The crude sulfinyl chloride, which was kept under argon, was used immediately for the preparation of the sulfinamide.

Boc–Orn(Cbz)–ψ[CH_2SO_2]–Gly–OEt (14): Under argon, sulfinyl chloride **13** (3.0 mmol) was dissolved in DCM (10 mL) and the solution was cooled to 0 °C. Then, a suspension of HCl·H–Gly–OEt (837 mg, 6.0 mmol) in DCM (20 mL) containing triethylamine (836 μL, 6.0 mmol) was added. The resulting mixture was stirred overnight and then the solvent was evaporated. Flash chromatography of the residue (eluent: EtOAc) yielded 1.13 g (78%) of the sulfinamide. R_f = 0.26 (EtOAc). For the oxidation step, the sulfinamide (2.33 mmol) was dissolved in DCM (5 mL), acetonitrile (5 mL), and water (8 mL). At 0 °C, $NaIO_4$ (646 mg, 3.0 mmol) and a catalytic amount of $RuCl_3·H_2O$ were added to the vigorously stirred solution. After stirring for 45 min at room temperature, DCM (25 mL) was added, the layers were separated, and the aqueous layer was extracted with three further portions of DCM. The combined organic layers were dried with $MgSO_4$. After removal of the solvent in vacuo, the product was purified by flash chromatography (eluent: EtOAc/hexanes, 55:45) yielding 850 mg (73%) of sulfonamide **14**. The overall yield was 57%. R_f = 0.68 (EtOAc). – ^{1}H NMR ($CDCl_3$): δ = 1.20 (t, 3 H, CH_3CH_2O), 1.43 [s, 9 H, C(CH_3)$_3$], 1.50–1.70 (m, 4 H, CH_2CH_2CH$_2$N), 3.10–3.35 (m, 4 H, CHCH_2S, CH$_2$CH_2N), 3.95 (two dd, Gly-C^{2}H$_2$), 4.15 (q, 2 H, CH$_3$CH_2O), 4.43 (br. s, 1 H, CHN), 4.85 (d, 1 H, NHBoc), 5.08 (s, 2 H, OCH$_2$Ph), 5.38 (br. s, 1 H, NHCbz), 6.10 (br. s, 1 H, Gly-NH), 7.37 (m, 5 H, ArH). – ^{13}C NMR ($CDCl_3$): δ = 13.9 (*C*H$_3$CH$_2$O), 25.7 (*C*H$_2$CH$_2$CH$_2$N), 28.3 [C(*C*H$_3$)$_3$], 31.2 (*C*H$_2$CH$_2$N), 39.8 (CH$_2$*C*H$_2$N), 44.3 (Gly-C^2), 46.4 (CHN), 57.6 (CH$_2$SO$_2$), 61.7 (CH$_3$*C*H$_2$O), 66.5 (OCH$_2$Ph), 80.1 [*C*(CH$_3$)$_3$], 128.0, 128.4, 136.6 (C^{Ar}), 156.4, 156.5 (CONH), 170.4 (Gly-C^1).

Boc–Orn(Cbz)–ψ[CH_2SO_2]–NH_2 (15): **13** (2.0 mmol) was dissolved in DCM (10 mL) under argon and the solution was cooled to –10 °C. NH_3 was then bubbled through the solution for 15 min The mixture was stirred overnight and then the solvent was evaporated. Flash chromatography of the residue (eluent: 8% MeOH in DCM) afforded 586 mg (73%) of the sulfinamide. R_f = 0.43 (10% MeOH in DCM). The sulfinamide was oxidized as described for **14** and subsequent column chromatography (eluent: 10% MeOH in DCM) yielded 520 mg (85%) of sulfonamide **15**. The overall yield was 63%. R_f = 0.59 (10% MeOH in DCM). – ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 9 H, C(CH_3)$_3$], 1.45–1.70 (m, 4 H, CH_2CH_2CH$_2$N), 2.85 (s, 2 H, NH$_2$), 3.05–3.25 (m, 4 H, CHCH_2S, CH$_2$CH_2N), 4.02 (br. s, 1 H, CHN), 5.03 (s, 2 H, OCH$_2$Ph), 5.50, 5.90 (m and br. s, 2 H, NHCbz, NHBoc), 7.30 (m, 5 H, ArH). – ^{13}C NMR ($CDCl_3$): δ = 26.1 (*C*H$_2$CH$_2$CH$_2$N), 28.3 [C(*C*H$_3$)$_3$], 31.3 (*C*H$_2$CH$_2$N), 40.1 (CH$_2$*C*H$_2$N), 47.1 (CHN), 59.0 (CH$_2$SO$_2$), 66.6 (OCH$_2$Ph), 80.2 [*C*(CH$_3$)$_3$], 127.96, 128.02, 128.4, 136.5 (C^{Ar}), 156.3, 156.7 (CONH). – ES-MS; *m*/*z*: 437.05 [M + Na]$^+$.

***N,N′*-Bis-Cbz-1-guanylpyrazole (16):** This compound was prepared as described by Wu et al.[9e][9f] Reaction of 1*H*-pyrazole-1-carboxamidine hydrochloride (1.47 g, 10 mmol) afforded 2.0 g (81%) of the monoprotected intermediate, which was crystallized from EtOH. Subsequent reaction of this intermediate with Cbz–OSu gave 2.1 g (66%) of bis-protected pyrazole **16**, which was purified by column chromatography (eluent: EtOAc/hexanes, 1:2) prior to crystallization from diethyl ether/hexanes.

Boc–Arg(Cbz$_2$)–ψ[CH_2SO_2]–Gly–OEt (17): Sulfonamide **14** (471 mg, 0.94 mmol) was dissolved in EtOH (8 mL). A catalytic amount of 10% Pd/C was added and the mixture was stirred for 4 h under a hydrogen atmosphere. The catalyst was then removed by filtration and the solution was concentrated to dryness. The residue was redissolved in THF (5 mL) and pyrazole compound **16** (356 mg, 0.94 mmol) was added. The resulting mixture was stirred overnight and then 2-aminoethanol (57 μL, 0.94 mmol) was added. After stirring for 10 min, the solvent was evaporated and the residue was redissolved in EtOAc. This solution was washed with 1 M $KHSO_4$, 5% $NaHCO_3$ solution, water, and brine, and dried with Na_2SO_4. Evaporation of the solvent and flash chromatography of the residue (eluent: EtOAc/hexanes, 4:6) afforded 466 mg (73%) of sulfonamide **17**. R_f = 0.43 (EtOAc/hexanes, 1:1). – ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, 3 H, CH_3CH$_2$O), 1.43 [s, 9 H, C(CH$_3$)$_3$], 1.50–1.75 (m, 4 H, CH_2CH_2CH$_2$N), 3.20 (m, 2 H, CHCH_2S), 3.47 (q, 2 H, CH$_2$CH_2N), 3.95 (two dd, Gly-C^{2}H$_2$), 4.19 (q, 2 H, CH$_3$CH_2O), 4.42 (br. s, 1 H, CHN), 4.95 (d, 1 H, NHBoc), 5.12, 5.17 (two s, 4 H, OCH$_2$Ph), 6.00 (br. s, 1 H, Gly-NH), 7.37 (m, 10 H, ArH), 8.36 (t, 1 H, CH$_2$CH$_2$CH$_2$N*H*), 11.74 (s, 1 H, NHCbz). – ^{13}C NMR ($CDCl_3$): δ = 14.0 (*C*H$_3$CH$_2$O), 25.4 (*C*H$_2$CH$_2$CH$_2$N), 28.3 [C(*C*H$_3$)$_3$], 31.7 (*C*H$_2$CH$_2$N), 40.4 (CH$_2$*C*H$_2$N), 44.4 (Gly-C^2), 46.8 (CHN), 57.6 (CH$_2$SO$_2$), 61.6 (CH$_3$*C*H$_2$O), 67.0, 68.1 (OCH$_2$Ph), 80.1 [*C*(CH$_3$)$_3$], 127.8, 128.0, 128.3, 128.6, 128.7, 134.5, 136.7 (C^{Ar}), 153.8, 156.0 (NCO$_2$) 163.6 (C=N), 170.2 (Gly-C^1).

Boc–Arg(Cbz$_2$)–ψ[CH_2SO_2]–NH_2 (18): Sulfonamide **18** was prepared from sulfonamide **15** (274 mg, 0.66 mmol) according to the procedure described for **17**. The product was purified by flash chromatography (eluent: 2.5% MeOH in DCM) to give 230 mg (59%) of sulfonamide **18**. R_f = 0.30 (5% MeOH in DCM). – ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 9 H, C(CH$_3$)$_3$], 1.50–1.70 (q, 4 H, CH_2CH_2CH$_2$N), 3.18 (m, 2 H, CH$_2$CH_2N), 3.30–3.60 (m, 2 H, CHCH_2S), 4.22 (m, 1 H, CHN), 5.07 (m, 1 H, NHBoc), 5.11, 5.15, 5.17 (d and s, 4 H, OCH$_2$Ph), 5.43 (br. s, 2 H, NH$_2$), 7.30 (m, 10 H, ArH), 8.38 (t, 1 H, CH$_2$CH$_2$CH$_2$N*H*), 11.73 (s, 1 H, NHCbz). – ^{13}C NMR ($CDCl_3$): δ = 25.6 (*C*H$_2$CH$_2$CH$_2$N), 28.3 [C(*C*H$_3$)$_3$], 31.4 (*C*H$_2$CH$_2$N), 39.9 (CH$_2$*C*H$_2$N), 47.0 (CHN), 59.9 (CH$_2$SO$_2$), 67.1, 68.2 (OCH$_2$Ph), 79.7 [*C*(CH$_3$)$_3$], 128.0, 128.2, 128.38, 128.43, 128.6, 128.7, 134.5, 136.5 (C^{Ar}), 153.8, 156.3, 156.5 [C(O)N], 163.5 (C=N).

Boc–Pro–Arg(Cbz$_2$)–ψ[CH_2SO_2]–Gly–OEt (19): To a solution of sulfonamide **17** (466 mg, 0.688 mmol) in DCM (7 mL), TFA (2.35 mL) was added at 0 °C. The mixture was stirred for 30 min and subsequently concentrated to dryness. The remaining TFA was removed from the residue by threefold coevaporation with THF and the solid was dissolved in DCM (5 mL). To this solution, Boc–Pro–OH (148 mg, 0.688 mmol), BOP (304 mg, 0.688 mmol), and DIPEA (360 μL, 2.06 mmol) were added. The reaction mixture was stirred overnight and then the solvent was evaporated. The residue was redissolved in EtOAc and the resulting solution was washed with 1 M $KHSO_4$, 5% $NaHCO_3$ solution, and brine, and dried with Na_2SO_4. Evaporation of the solvent and flash chromatography of the residue (eluent: EtOAc/hexanes, 3:2) gave 460 mg (86%) of peptidosulfonamide **19**. R_f = 0.14 (EtOAc/hexanes, 3:2). – ^{1}H NMR ($CDCl_3$/CD_3OD): δ = 1.21 (t, 3 H, CH_3CH$_2$O), 1.36 [s, 9 H, C(CH$_3$)$_3$], 1.50–2.10 (m, 8 H, CH_2CH_2CH$_2$N, Pro-C^{3}H$_2$, Pro-C^{4}H$_2$), 3.18–3.43 (m, 6 H, CHCH_2S, CH$_2$CH$_2$CH_2N, Pro-C^{5}H$_2$), 3.87 (d, Gly-C^{2}H$_2$), 4.14 (q, 2 H, CH$_3$CH_2O, Pro-C^{2}H$_2$), 4.45 (br. s, 1 H, CHN), 4.95 (d, 1 H, NHBoc), 5.06, 5.13 (two s, 4 H, OCH$_2$Ph), 6.44 (br. s, 1 H, SO$_2$CH$_2$CHNH), 7.31 (m, 10 H, ArH), 7.44 (br. s, 1 H, Gly-NH), 8.36 (t, 1 H, CH$_2$CH$_2$CH$_2$N*H*), 11.64 (s, 1 H, NHCbz). – ^{13}C NMR ($CDCl_3$/CD_3OD): δ = 13.8 (*C*H$_3$CH$_2$O), 24.0 (Pro-C^4), 25.2 (*C*H$_2$CH$_2$CH$_2$N), 28.1 [C(*C*H$_3$)$_3$], 29.5 (Pro-C^3), 31.0 (*C*H$_2$CH$_2$N), 40.1 (CH$_2$CH$_2$*C*H$_2$N), 44.0 (Gly-C^2), 45.3 (Pro-C^5), 47.1 (SO$_2$CH$_2$*C*HN), 56.4 (Pro-C^2), 60.6 (CH$_2$SO$_2$), 61.7 (CH$_3$*C*H$_2$O), 67.1, 68.1 (OCH$_2$Ph), 80.6 [*C*(CH$_3$)$_3$], 127.8, 128.0, 128.3, 128.5, 128.6, 134.5, 136.4 (C^{Ar}), 153.5, 155.8 [NC(O)O], 163.3 (C=N), 170.5 (Gly-C^1), 173.5 (Pro-C^1).

Boc–Pro–Arg(Cbz$_2$)–ψ[CH_2SO_2]–NH_2 (20): Peptidosulfonamide **20** was prepared from sulfonamide **18** (77 mg, 0.13 mmol) and Boc–

Pro–OH (28 mg, 0.13 mmol) according to the procedure described for **19**. The product was purified by flash chromatography (eluent: EtOAc/hexanes, 4:1), to yield 81 mg (90%) of **20**. R_f = 0.28 (EtOAc/hexanes, 3:1). – ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 9 H, C(CH_3)$_3$], 1.50–2.10 (m, 8 H, CH_2CH_2CH_2N), 3.20–3.50 (m, 2 H, CH_2CH_2N, CHCH_2S, Pro-C^{5}H$_2$), 4.19 (dd, 1 H, Pro-C^{2}H), 4.40 (br. s, 1 H, CHN), 5.11, 5.13, 5.17 (d and s, 4 H, OCH_2Ph), 5.63 (br. s, 2 H, NH_2), 7.17 (m, 1 H, NHCHCH_2S), 7.30 (m, 10 H, ArH), 8.38 (t, 1 H, $CH_2CH_2CH_2$N*H*), 11.70 (s, 1 H, NHCbz).

Boc–D-Phe–Pro–Arg(Cbz$_2$)–ψ[CH$_2$SO$_2$]–Gly–OEt (21): Peptidosulfonamide **21** was prepared from sulfonamide **19** (456 mg, 0.588 mmol) and Boc-D-Phe–OH (156 mg, 0.588 mmol) according to the procedure described for **19**. The product was purified by flash chromatography (eluent: EtOAc/hexanes, 3:1) to yield 488 mg (90%) of **21**. R_f = 0.34 (EtOAc/hexanes, 3:1). – ^{1}H NMR ($CDCl_3$): δ = 1.23 (t, 3 H, CH_3CH$_2$O), 1.36 [s, 9 H, C(CH_3)$_3$], 1.50–2.05 (m, 8 H, CH_2CH_2CH_2N, Pro-C^{3}H$_2$, Pro-C^{4}H$_2$), 2.63 (m, 1 H, Pro-C^{5}H^a), 2.91 (d, 2 H, Phe-C^{3}H$_2$), 3.15 (d, 2 H, CHCH_2SO$_2$), 3.41 (br. s, 2 H, CH_2CH_2CH_2N), 3.52 (m, 1 H, Pro-C^{5}H^b), 3.89 (q, Gly-C^{2}H$_2$), 4.16 (q, 2 H, CH_3CH_2O), 4.24 (m, 1 H, C*H*CH_2SO_2), 4.45 (m, 2 H, Phe-C^{2}H, Pro-C^{2}H), 5.09, 5.15 (two s, 4 H, OCH_2Ph), 7.14–7.45 (m, 15 H, ArH), 7.44 (br. s, 1 H, Gly-NH), 8.39 (t, 1 H, $CH_2CH_2CH_2$N*H*), 11.70 (s, 1 H, NHCbz). – ^{13}C NMR ($CDCl_3$): δ = 13.9 (*C*H_3CH$_2$O), 24.1 (Pro-C^4), 25.3 (*C*H_2CH$_2$CH$_2$N), 28.2 [C(*C*H_3)$_3$], 28.9 (Pro-C^3), 30.9 (*C*H_2CH$_2$N), 38.7 (Phe-C^3), 40.1, 40.2 (CH_2CH_2*C*H$_2$N), 44.1, 44.2 (Gly-C^2), 45.4 (Pro-C^5), 47.1 (SO_2CH_2*C*HN), 54.0 (Phe-C^2), 56.6 (Pro-C^2), 60.9 (CH_2SO_2), 61.8 (CH_3CH_2O), 67.1, 68.1 (OCH_2Ph), 80.2 [C(CH_3)$_3$], 127.1, 127.9, 128.0, 128.29, 128.32, 128.5, 128.6, 128.7, 129.3, 134.5, 135.9, 136.6 (C^{Ar}), 153.6, 155.6, 155.9, 156.0 [NC(O)O], 163.4 (C=N), 170.3 (Gly-C^1), 171.3, 171.7 (Phe-C^1), 172.4, 172.5 (Pro-C^1).

Boc–D-Phe–Pro–Arg(Cbz$_2$)–ψ[CH$_2$SO$_2$]–NH$_2$ (22): Peptidosulfonamide **22** was prepared from sulfonamide **20** (81 mg, 0.12 mmol) and Boc-D-Phe–OH (31 mg, 0.12 mmol) according to the procedure described for **19**. The product was purified by flash chromatography (eluent: EtOAc/hexanes, 4:1) to yield 68 mg (69%) of **22**. R_f = 0.16 (EtOAc/hexanes, 4:1). – ^{1}H NMR ($CDCl_3$): δ = 1.40 [s, 9 H, C(CH_3)$_3$], 1.45–1.90 (m, 7 H, CH_2CH_2CH_2N, Pro-C^{3}H^a, Pro-C^{4}H$_2$), 2.05 (m, 1 H, Pro-C^{3}H^b), 2.60 (m, 1 H, Pro-C^{5}H^a), 2.95 (m, 2 H, Phe-C^{3}H$_2$), 3.20 (m, 2 H, CH_2SO_2), 3.45 (m, 2 H, CH_2CH_2N), 3.57 (m, 1 H, Pro-C^{5}H^b), 4.28 (dd, 1 H, Pro-C^{2}H), 4.42 (m, 2 H, CHN, Phe-C^{2}H), 5.11, 5.13, 5.17 (d and s, 4 H, OCH_2Ph), 5.37 (d, 1 H, NHBoc), 5.47 (br. s, 2 H, NH_2), 7.07 (m, 1 H, NHCHCH_2S), 7.30 (m, 15 H, ArH), 8.38 (t, 1 H, $CH_2CH_2CH_2$N*H*), 11.75 (s, 1 H, NHCbz). – ^{13}C NMR ($CDCl_3$): δ = 24.3 (Pro-C^4), 25.8 (*C*H_2CH$_2$CH$_2$N), 28.4 [C(*C*H_3)$_3$], 28.7 (Pro-C^3), 31.2 (*C*H_2CH$_2$N), 38.7 (Phe-C^3), 40.1 (CH_2*C*H$_2$N), 46.0 (NH*C*HCH$_2$S), 47.2 (Pro-C^5), 54.2 (Phe-C^2), 58.7 (CH_2SO_2), 60.9 (Pro-C^2), 67.1, 68.2 (OCH_2Ph), 80.3 [C(CH_3)$_3$], 127.2, 128.0, 128.2, 128.6, 128.7, 128.8, 129.3, 134.5, 135.8, 136.6 (C^{Ar}), 153.8, 155.6, 156.3 (OCN), 163.6 (C=N), 171.5, 172.1 (Pro-C^1, Phe-C^1).

Boc–D-Phe–Pro–Argψ[CH$_2$SO$_2$]–Gly–OEt·HCl (23): To a solution of sulfonamide **21** (194 mg, 0.21 mmol) in EtOH (1 mL), acetic acid (20 μL) and 10% Pd/C (20 mg) were added and the mixture was stirred overnight under a hydrogen atmosphere. The catalyst was then removed by filtration and the solution was concentrated to dryness. The acetic acid salt was first purified on Sephadex LH-20 (eluent: DCM/MeOH, 1:1) and then converted into the hydrochloric acid salt **23** on a DOWEX Cl$^-$ column. Lyophilization gave 96 mg (66%) of the peptidosulfonamide. R_f = 0.55 (MeOH/37% NH_3 in H_2O/$CHCl_3$, 45:20:60). – ^{1}H NMR (D_2O): δ = 1.30 (t, 3 H, CH_3CH$_2$O), 1.38 [s, 9 H, C(CH_3)$_3$], 1.50–2.10 (m, 8 H, CH_2CH_2CH$_2$N, Pro-C^{3}H$_2$, Pro-C^{4}H$_2$), 3.00 (m, 2 H, Phe-C^{3}H$_2$), 3.10 (m, 1 H, Pro-C^{5}H^a), 3.25 (t, 2 H, CH_2CH_2CH_2N), 3.45 (d, 2 H, CH_2SO_2), 3.68 (br. s, 1 H, Pro-C^{5}H^b), 4.00 (s, Gly-C^{2}H$_2$), 4.25 (q, 2 H, CH_3CH_2O), 4.40 (m, 2 H, C*H*CH_2SO_2, Pro-C^{2}H), 4.63 (m, 1 H, Phe-C^{2}H), 7.25–7.45 (m, 5 H, ArH). – ^{13}C NMR (D_2O): δ = 12.6 (*C*H_3CH$_2$O), 23.3 (Pro-C^4), 23.5 (*C*$H_2CH_2CH_2$N), 26.8, 26.9 [C(*C*H_3)$_3$], 28.2 (Pro-C^3), 30.0 (*C*H_2CH_2N), 36.9 (Phe-C^3), 39.8 (CH_2CH_2*C*H$_2$N), 43.2 (Gly-C^2), 44.3 (SO_2CH_2*C*HN), 46.8 (Pro-C^5), 53.2 (Phe-C^2), 55.1 (CH_2SO_2), 60.1 (Pro-C^2), 61.7 (CH_3*C*H$_2$O), 80.3 [*C*(CH_3)$_3$], 126.3, 127.9, 128.6, 135.3 (C^{Ar}), 155.8 [NC(O)O], 170.9, 171.3, 171.5, 172.1 (Phe-C^1, Gly-C^1, Pro-C^1). – ES-MS; *m*/*z*: 654.15 [M – HCl + H]$^+$.

Boc–D-Phe–Pro–Argψ[CH$_2$SO$_2$]–NH$_2$·HCl (24): To a solution of sulfonamide **22** (60 mg, 0.072 mmol) in EtOH (1 mL), acetic acid (8 μL) and 10% Pd/C (20 mg) were added and the resulting mixture was stirred for 5 h under a hydrogen atmosphere. The catalyst was then removed by filtration, the solution was concentrated to dryness, and the residue was freed of excess acetic acid by twofold coevaporation with DCM. The acetic acid salt was converted into the hydrochloric acid salt **24** on a DOWEX Cl$^-$ column. Lyophilization gave 40 mg (92%) of the peptidosulfonamide. – ^{1}H NMR (D_2O): δ = 1.38 [s, 9 H, C(CH_3)$_3$], 1.50–2.05 (m, 8 H, CH_2CH_2CH_2N, Pro-C^{3}H$_2$, Pro-C^{4}H$_2$), 2.95 (d, 2 H, Phe-C^{3}H$_2$), 3.05 (m, 1 H, Pro-C^{5}H^a), 3.20 (t, 2 H, CH_2CH_2CH_2N), 3.40 (d, 2 H, CH_2SO_2), 3.63 (br. s, 1 H, Pro-C^{5}H^b), 4.20, 4.35, 4.60 (three m, 3 H, C*H*CH_2SO_2, Pro-C^{2}H, Phe-C^{2}H), 7.20–7.40 (m, 5 H, ArH). – ^{13}C NMR (D_2O): δ = 21.0, 23.2, 23.4, 23.5 (*C*$H_2CH_2CH_2$N, Pro-C^4), 26.6, 28.7 [C(*C*H_3)$_3$], 28.1, 30.0 (Pro-C^3), 29.9, 30.7 (*C*H_2CH_2N), 35.6, 36.5 (Phe-C^3), 39.6 (CH_2CH_2*C*H$_2$N), 44.3, 44.4 (SO_2CH_2*C*HN), 46.9, 49.1 (Pro-C^5), 52.1, 53.2 (Phe-C^2), 56.9 (CH_2SO_2), 59.7, 60.0 (Pro-C^2), 80.7 [*C*(CH_3)$_3$], 126.1, 126.5, 127.3, 127.8, 127.9, 128.1, 128.3, 128.5, 128.6, 135.2, 135.8 (C^{Ar}), 155.8, 156.3 [NC(O)O], 167.0 (C=N), 171.7, 172.0, 172.4, 172.8 (Phe-C^1, Gly-C^1, Pro-C^1). – FAB-MS; *m*/*z*: 568.2 [M – HCl + H]$^+$. – ES-MS; *m*/*z*: 568.10 [M – HCl + H]$^+$.

H–D-Phe–Pro–Argψ[CH$_2$SO$_2$]–Gly–OEt·2HCl (25): 23 (10 mg, 14 μmol) was dissolved in DCM (1 mL) and then HCl-saturated diethyl ether (1 mL) was added. After stirring for 45 min, the solvent was removed in vacuo and the residue was redissolved in water. Lyophilization yielded 10 mg of peptidosulfonamide **25**. – ^{1}H NMR (D_2O): δ = 1.30 (t, 3 H, CH_3CH$_2$O), 1.50–2.15 (m, 8 H, CH_2CH_2CH_2N, Pro-C^{3}H$_2$, Pro-C^{4}H$_2$), 2.78 (q, 1 H, Pro-C^{5}H^a), 3.15–3.60 (m, 7 H, Phe-C^{3}H$_2$, Pro-C^{5}H^b, CH_2CH_2CH_2N, CH_2SO_2), 4.01 (s, Gly-C^{2}H$_2$), 4.25 (q, 2 H, CH_3CH_2O), 4.30, 4.44, 4.59 (three m, 3 H, C*H*CH_2SO_2, Pro-C^{2}H, Phe-C^{2}H), 7.30–7.50 (m, 5 H, ArH). – FAB-MS; *m*/*z*: 554.2 [M – 2HCl + H$^+$].

H–D-Phe–Pro–Argψ[CH$_2$SO$_2$]–Gly–OH·2HCl (26): Sulfonamide **23** (11 mg, 15 μmol) was dissolved in 1 M aq. HCl (1 mL) and the resulting solution was stirred for 24 h at room temperature. Lyophilization gave 10 mg of peptidosulfonamide **26**. – ^{1}H NMR (D_2O): δ = 1.50–2.15 (m, 8 H, CH_2CH_2CH_2N, Pro-C^{3}H$_2$, Pro-C^{4}H$_2$), 2.78 (q, 1 H, Pro-C^{5}H^a), 3.15–3.60 (m, 7 H, Phe-C^{3}H$_2$, Pro-C^{5}H^b, CH_2CH_2CH_2N, CH_2SO_2), 4.01 (s, Gly-C^{2}H$_2$), 4.32, 4.43, 4.59 (three m, 3 H, C*H*CH_2SO_2, Pro-C^{2}H, Phe-C^{2}H), 7.30-7.50 (m, 5 H, ArH). – FAB-MS: *m*/*z* = 526.2 [M – 2HCl + H$^+$].

H–D-Phe–Pro–Argψ[CH$_2$SO$_2$]–NH$_2$·2HCl (27): Sulfonamide **24** (9.9 mg, 16 μmol) was dissolved in DCM (1 mL) and then HCl-saturated diethyl ether was added. After stirring for 45 min, the solvent was removed in vacuo and the residue was redissolved in water. Lyophilization gave 9.4 mg of peptidosulfonamide **27**. – ^{1}H NMR (D_2O): δ = 1.50–2.15 (m, 8 H, CH_2CH_2CH_2N, Pro-C^{3}H$_2$,

Pro-C^4H_2), 2.90 (d, 1 H, Pro-C^5H^a), 3.10–3.65 (m, 7 H, Pro-C^5H^b, $CH_2CH_2CH_2N$, CH_2SO_2, Phe-C^3H_2), 4.32, 4.41, 4.59 (three m, 3 H, $CHCH_2SO_2$, Pro-C^2H, Phe-C^2H), 7.30–7.50 (m, 5 H, ArH). – FAB-MS: m/z = 468.2 [M – 2 HCl + H^+].

1-Benzyloxy-4-pentene (29): At 0 °C, NaH (1.32 g, 55 mmol) was added to a solution of 4-penten-1-ol (5.16 mL, 50 mmol) in THF (75 mL). After stirring for 10 min at room temperature, benzyl chloride (5.75 mL, 50 mmol) was added and the mixture was refluxed overnight. After neutralization with 1 M aq. HCl, the solvent was evaporated and the residue was redissolved in diethyl ether. The resulting solution was washed with water (three times) and with brine, and dried with $MgSO_4$. Evaporation of the solvent and column chromatography of the residue (eluent: hexanes → diethyl ether/hexanes, 1:9) yielded 6.75 g (77%) of alkene **29**. R_f = 0.51 (diethyl ether/hexanes, 1:9). – ^{1}H NMR ($CDCl_3$): δ = 1.78 (q, 2 H, C^2H_2), 2.21 (q, 2 H, C^3H_2), 3.54 (t, 2 H, C^1H_2), 4.55 (s, 2 H, CH_2Ph), 5.00–5.12 (m, 2 H, C^5H_2), 5.81–5.94 (m, 1 H, C^4H), 7.25–7.45 (m, 5 H, ArH). – ^{13}C NMR ($CDCl_3$): δ = 29.0 (C^2), 30.3 (C^3), 69.7 (C^1), 72.8 (CH_2Ph), 114.6 (C^5), 127.4, 127.5, 128.3, 138.7 (C^{Ar}), 138.2 (C^4).

Epoxide 30: 1-Benzyloxy-4-pentene (1.15 g, 6.52 mmol) was dissolved in DCM (15 mL). A solution of dried 70% *m*-CPBA (1.95 g) in DCM (5 mL) was added and the mixture was stirred overnight. It was then filtered and further DCM (80 mL) was added. The diluted solution was washed with 10% $Na_2S_2O_3$ solution, 5% $NaHCO_3$ solution (twice), and brine, and dried with $MgSO_4$. Evaporation of the solvent and purification of the residue by column chromatography (eluent: diethyl ether/hexanes, 1:3) gave 930 mg (74%) of epoxide **30** as an oil. R_f = 0.43 (EtOAc/hexanes, 1:1). – ^{1}H NMR ($CDCl_3$): δ = 1.55–1.90 (m, 4 H, $C^2H_2C^3H_2C^4H$), 2.47 (q, 1 H, $C^5H^aH^bC^4H$), 2.74 (t, 1 H, CH^aH^bCH), 2.93 (m, 1 H, $C^5H_2C^4H$), 3.54 (m, 2 H, $C^2H_2C^1H_2O$), 4.52 (s, 2 H, CH_2Ph), 7.25–7.40 (m, 5 H, ArH). – ^{13}C NMR ($CDCl_3$): δ = 26.1 (C^2), 29.2 (C^3), 46.8 (C^5), 51.9 (C^4), 69.7 (C^1), 72.8 (CH_2Ph), 127.4, 127.5, 128.2, 138.4 (C^{Ar}).

Amino Alcohol 31: Epoxide **30** (4.16 g, 21.6 mmol) and (*S*)-α-methylbenzylamine (2.78 mL, 21.6 mmol) were dissolved in MeOH (30 mL) and the mixture was stirred overnight at 50 °C. The solvent was then removed in vacuo and the product was purified by column chromatography (eluent: 10% MeOH in DCM) to afford 4.98 g (73%) of a colorless oil. R_f = 0.46 (10% MeOH in DCM); 0.71, 0.83 (30% MeOH in DCM). – ^{1}H NMR ($CDCl_3$): δ = 1.39 (dd, 3 H, CH_3), 1.42–1.58 (m, 2 H, C^3H_2), 1.58–1.81 (m, 2 H, C^2H_2), 2.28–2.65 (four dd, 2 H, C^5H_2), 3.48 (two t, C^1H_2), 3.48–3.71 (two m, 1 H, C^4HO), 3.78 (two q, 1 H, CHN). – ^{13}C NMR ($CDCl_3$): δ = 23.8, 24.1 (CH_3), 25.9 (C^2), 31.9, 32.0 (C^3), 52.9, 53.5 (C^5), 57.7, 58.5 (CHN), 69.4, 69.9 (C^4), 70.2 (C^1), 72.8 (CH_2Ph), 126.4, 127.5, 128.2, 128.4, 144.8, 145.1, 126.9, 127.4, 138.3 (C^{Ar}).

Diol 32: 31 (4.98 g, 15.9 mmol) was dissolved in dioxane (100 mL), water (37 mL), and acetic acid (37 mL). After the addition of 20% $Pd(OH)_2$ on carbon (750 mg), the mixture was shaken for 4 days under hydrogen at 3 bar in a Parr apparatus. The catalyst was then removed by filtration and the solution was concentrated to dryness. The residue was freed of acetic acid by coevaporation with EtOH and then dissolved in dioxane (50 mL) and water (50 mL). A solution of Boc_2O (3.47 g, 15.9 mmol) in dioxane (50 mL) was added and the pH was adjusted to 8 with 1 M aq. NaOH. During the course of the reaction, the pH was kept at 8 by the addition of further 1 M NaOH. When the amine had been completely consumed (TLC control), the volatiles were removed in vacuo and the residue was redissolved in a small volume of water. The resulting solution was extracted with five portions of EtOAc, the combined organic layers were dried with Na_2SO_4, and the solvent was removed in vacuo. Column chromatography (eluent: 6% MeOH in DCM) gave 3.24 g (93%) of diol **32**. R_f = 0.28 (10% MeOH in DCM). – ^{1}H NMR ($CDCl_3$): δ = 1.38 [s, 9 H, $C(CH_3)_3$], 1.32–1.67 (m, 4 H, C^3H_2, C^4H_2), 2.95, 3.18 (m, 2 H, C^1H_2), 3.60 (m, 4 H, CHO, CH_2O), 4.03 (br. s, 1 H, C^5OH), 4.46 (br. s, 1 H, C^2OH), 5.38 (br. s, 1 H, NH). – ^{13}C NMR ($CDCl_3$): δ = 28.3 [$C(CH_3)_3$], 28.7 (C^3), 31.6 (C^4), 46.5 (C^1), 62.3 (C^5), 70.9 (C^2), 79.4 [$C(CH_3)_3$], 156.7 (C=O).

Azido Alcohol 33: To a cooled (0 °C) solution of triphenylphosphane (1.51 g, 5.76 mmol) in THF (20 mL) were sequentially added di-*tert*-butyl azodicarboxylate (1.32 g, 5.74 mmol), 1.1 M HN_3 solution in benzene[18] (5.22 mL), and a solution of diol **32** (1.26 g, 5.74 mmol) in THF (15 mL). The cooling bath was then removed and the reaction mixture was stirred overnight at room temperature. The solvent was subsequently evaporated and the residue was purified by column chromatography (eluent: EtOAc/hexanes, 1:2). Yield: 775 mg (55%). R_f = 0.40 (EtOAc/hexanes, 1:1). – ^{1}H NMR ($CDCl_3$): δ = 1.45 [s, 9 H, $C(CH_3)_3$], 1.47–1.85 (m, 4 H, C^3H_2, C^4H_2), 2.67 (br. s, 1 H, OH), 3.05 (q, 1 H, C^1H), 3.27 (q, 1 H, C^1H), 3.33 (t, 2 H, C^5H_2), 3.72 (m, 1 H, C^2H), 4.92 (br. s, 1 H, NH). – ^{13}C NMR ($CDCl_3$): δ = 25.0 (C^3), 28.3 [$C(CH_3)_3$], 31.6 (C^4), 46.8 (C^1), 51.4 (C^5), 70.9 (C^2), 79.7 [$C(CH_3)_3$], 156.8 (C=O).

THF Derivative 33a: To a solution of diol **32** (219 mg, 1.0 mmol) and triphenylphosphane (262 mg, 1.0 mmol) in THF (4 mL), diethyl azodicarboxylate (DEAD) (164 μL, 1.0 mmol) was added. The resulting mixture was stirred overnight and then the solvent was evaporated. Column chromatography of the residue (eluent: EtOAc/hexanes, 1:2) furnished 135 mg (67%) of tetrahydrofuran derivative **33a** as an oil. R_f = 0.50 (EtOAc/hexanes, 1:1). – ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 1.50–1.60, 1.83–2.00 (m, 4 H, C^3H_2, C^4H_2), 3.06, 3.38 (two m, 2 H, CH_2N), 3.69–3.88 (m, 2 H, C^5H_2), 3.93 (m, 1 H, C^2 H), 4.88 (br. s, 1 H, NH). – ^{13}C NMR ($CDCl_3$): δ = 25.8 (C^3), 28.4 [$C(CH_3)_3$], 28.5 (C^4), 44.5 (CH_2N), 68.0 (C^5), 78.1 (C^2), 79.2 [$C(CH_3)_3$], 156.1 (C=O). – FAB-MS: m/z = 202.16 [M + H^+].

Cbz-Protected Azide 34: A solution of azide **33** (240 mg, 0.98 mmol) in EtOH (25 mL) and chloroform (0.5 mL) containing 10% Pd/C (50 mg)[16] was shaken for 1 h under hydrogen at 3 bar in a Parr apparatus. The catalyst was then removed by filtration, the solution was concentrated to dryness, and the residue was coevaporated twice with DCM. It was then redissolved in DCM (7 mL) and triethylamine (139 μL, 1.0 mmol) and Cbz–OSu (244 mg, 0.98 mmol) were added. After stirring overnight, the solvent was removed in vacuo. The residue was redissolved in EtOAc, washed with 1 M $KHSO_4$, 5% $NaHCO_3$ solution, water, and brine, and dried with Na_2SO_4. After evaporation of the EtOAc, the product was purified by flash chromatography (eluent: 4% MeOH in DCM), yielding 220 mg (64%) of alcohol **34**. R_f = 0.25 (4% MeOH in DCM). – ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 1.50–1.70 (m, 4 H, C^3H_2, C^4H_2), 3.00 (m, 2 H, C^1H), 3.20 (m, 4 H, C^1H_2, C^2H, C^5H_2), 3.65 (br. s, 1 H, OH), 5.05 (s, 2 H, CH_2Ph), 5.15 (m, 2 H, NH), 7.30 (m, 5 H, ArH). – ^{13}C NMR ($CDCl_3$): δ = 26.0 (C^3), 28.2 [$C(CH_3)_3$], 31.5 (C^4), 40.8 (C^5), 46.7 (C^1), 66.6 (CH_2Ph), 71.0 (C^2), 79.6 [$C(CH_3)_3$], 128.0, 128.4, 136.6 (C^{Ar}), 156.6 (C=O).

Thioacetate 35: To a solution of triphenylphosphane (2.69 g, 10.3 mmol) in THF (40 mL), DIAD (2.02 mL, 10.3 mmol) was added at 0 °C. After stirring for 30 min at 0 °C, a precipitate had formed and the temperature was lowered to –10 °C. A solution of

alcohol **33** (1.25 g, 5.12 mmol) and thioacetic acid (730 μL, 10.3 mmol) in THF (15 mL) was then added. The resulting mixture was allowed to warm to room temperature and stirred overnight. After evaporation of the solvent, the product was purified by column chromatography (eluent: EtOAc/hexanes, 1:4), to yield 1.07 g (69%) of thioacetate **35**. R_f = 0.16 (EtOAc/hexanes, 1:5). – ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 1.50–1.80 (m, 4 H, C^3H_2, C^4H_2), 1.32 (s, 3 H, CH_3CO), 3.15–3.40 (m, 4 H, C^1H_2, C^5H_2), 3.55 (m, 1 H, C^2H), 4.78 (br. s, 1 H, NH). – ^{13}C NMR ($CDCl_3$): δ = 26.3 (C^3), 28.3 [$C(CH_3)_3$], 29.0 (C^4), 30.7 (CH_3CO), 44.3 (C^1), 44.7 (C^2), 51.0 (C^5), 79.5 [$C(CH_3)_3$], 155.8 [C(O)NH], 195.1 [$C(O)CH_3$].

Sulfonamide 36: Thioacetate **35** (1.023 g, 3.38 mmol) was dissolved in DCM (10 mL) under argon. After cooling to –20 °C, Ac_2O (319 μL, 3.38 mmol) and sulfuryl chloride (549 μL, 6.78 mmol) were added. The resulting mixture was stirred for 1 h at –5 °C and then the volatiles were evaporated and the residue was dried in vacuo. The crude sulfinyl chloride (3.38 mmol) was used immediately for the next reaction. It was dissolved in DCM (10 mL) and then a suspension of H–Gly–OEtHCl (944 mg, 6.76 mmol) in DCM (20 mL) containing triethylamine (943 μL, 6.78 mmol) was added under argon. The reaction mixture was stirred overnight and then the solvent was removed in vacuo. Flash chromatography of the residue (eluent: 5% MeOH in DCM) furnished 770 mg (60%) of the sulfinamide. R_f = 0.26 (5% MeOH in DCM). This sulfinamide (2.04 mmol) was dissolved in a mixture of DCM (5 mL), acetonitrile (5 mL), and water (7.5 mL). The resulting solution was cooled to 0 °C, whereupon $NaIO_4$ (567 mg, 2.67 mmol) and a catalytic amount of $RuCl_3 \cdot H_2O$ were added under vigorous stirring. The mixture was allowed to warm to room temperature and, after stirring for 20 min, the aqueous layer was extracted three times with DCM. The combined organic layers were dried with $MgSO_4$ and the solvent was removed in vacuo. Flash chromatography of the residue (eluent: 3% MeOH in DCM) gave 695 mg (87%) of sulfonamide **36**. The overall yield was 52%. R_f = 0.43 (5% MeOH in DCM). – ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, 3 H, CH_3CH_2), 1.43 [s, 9 H, $C(CH_3)_3$], 1.60–2.10 (m, 4 H, $CH_2CH_2CH_2$), 3.11 (m, 1 H, CH), 3.34 (t, 2 H, CH_2N_3), 3.53, 3.75 (m, 2 H, $CHCH_2N$), 3.94 (dd, 2 H, Gly-C^2H_2), 4.22 (q, 2 H, CH_2O), 5.27 (t, 1 H, NHCO), 5.45 ($NHSO_2$). – ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3CH_2), 24.0 ($CH_2CH_2CH_2N_3$), 26.0 ($CH_2CH_2N_3$), 28.3 [$C(CH_3)_3$], 39.0 (NCH_2CH), 44.4 (Gly-C^2), 51.1 (CH_2N_3), 61.9 (CH_2O), 62.6 (CH), 80.0 [$C(CH_3)_3$], 156.1 [C(O)NH], 169.8 (Gly-C^1). – ES-MS; *m/z*: 416.00 $[M + Na]^+$.

α-Substituted Aminoethane Sulfonamide Ornithine–Glycine Analog 37: A solution of azide **36** (151 mg, 0.38 mmol) in EtOH (25 mL) and chloroform (0.5 mL)[16] containing Pd/C was shaken under hydrogen at 3 bar in a Parr apparatus for 2.5 h. The catalyst was then removed by filtration and the solution was concentrated to dryness, to afford the hydrochloric acid salt **37** in quantitative yield. The crude product was used directly for the preparation of sulfonamide **38**.

α-Substituted Aminoethane Sulfonamide Arginine–Glycine Analog 38: Sulfonamide **37** (0.38 mmol) was dissolved in THF (4 mL) and then pyrazole compound **16** (145 mg, 0.38 mmol) and triethylamine (53 μL, 0.38 mmol) were added. After stirring overnight, the solvent was removed in vacuo and the residue was redissolved in EtOAc. This solution was washed with 1 M $KHSO_4$ and 5% $NaHCO_3$ solution, and dried with Na_2SO_4. After evaporation of the solvent and purification of the residue by flash chromatography (eluent: 2.5% MeOH in DCM), 168 mg (65%) of sulfonamide **38** was obtained. R_f = 0.75 (10% MeOH in DCM). – ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, 3 H, CH_3CH_2), 1.43 [s, 9 H, $C(CH_3)_3$], 1.60–2.05 (m, 4 H, $CH_2CH_2CH_2NH$), 3.20 (m, 1 H, CH), 3.45 (CH_2CH_2NH), 3.47, 3.72 (m, 2 H, $CHCH_2N$), 3.85 (s, 2 H, Gly-C^2H_2), 4.18 (q, 2 H, CH_2O), 5.10, 5.15 (two s, 4 H, OCH_2Ph), 5.35 (t, 1 H, NHBoc), 5.88 (br. s, 1 H, $NHSO_2$), 7.20–7.45 (m, 10 H, ArH), 8.38 (t, 1 H, CH_2NHC), 11.75 (s, 1 H, NHCbz). – ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3CH_2), 24.0 ($CH_2CH_2CH_2N_3$), 26.0 ($CH_2CH_2N_3$), 28.3 [$C(CH_3)_3$], 39.2 (NCH_2CH), 40.3 (CH_2CH_2N), 44.3 (Gly-C^2), 61.7 (CH_3CH_2O), 62.5 (CH), 67.1, 68.2 (OCH_2Ph), 79.8 [$C(CH_3)_3$], 128.0, 128.3, 128.4, 128.5, 128.6, 128.7, 134.6, 136.7 (C^{Ar}), 153.8 (CO_2CH_2Ph), 156.1 [$CO_2C(CH_3)$], 163.5 (C=N), 169.8 (Gly-C^1). – ES-MS: *m/z* = 678.10 $[M + H]^+$.

Peptidosulfonamide 39: To a solution of sulfonamide **38** (168 mg, 0.25 mmol) in DCM (1.5 mL), TFA (0.5 mL) was added. After stirring for 30 min, the solvent was evaporated and the residue was freed of TFA by threefold coevaporation with DCM. The residue was taken up in DCM (2 mL) and Boc–Pro–OH (62 mg, 0.29 mmol), BOP (128 mg, 0.29 mmol), and DIPEA (151 μL, 0.87 mmol) were added. The mixture was stirred overnight, and then the solvent was evaporated and the residue was redissolved in EtOAc. This solution was washed with 1 M $KHSO_4$, 5% $NaHCO_3$ solution, and brine, and dried with Na_2SO_4. Evaporation of the solvent and purification of the product by column chromatography (eluent: EtOAc/hexanes, 2:1) afforded 133 mg (69%) of peptidosulfonamide **39**. R_f = 0.23 (EtOAc/hexanes, 2:1). – ^{1}H NMR ($CDCl_3$): δ = 1.27 (t, 3 H, CH_3CH_2), 1.43 [s, 9 H, $C(CH_3)_3$], 1.50–2.25 (m, 8 H, $CH_2CH_2CH_2NH$, Pro-C^3H_2, Pro^4H_2), 3.20–3.75 (m, 4 H, Pro-C^5H_2, $CHCH_2N$, $CHCH^aN$), 3.46 (q, 2 H, $CH_2CH_2CH_2NH$), 3.92 (m, 3 H, Gly-C^2H_2, $CHCH^bN$), 4.19 (m, 2 H, CH_2CH_3, Pro-C^2H), 5.12, 5.17 (two s, 4 H, OCH_2Ph), 5.88, 6.17 (two br. s, 1 H, $NHSO_2$), 7.27–7.41 (m, 11 H, ArH, CH_2NHCO), 8.37 (t, 1 H, $CH_2CH_2CH_2NH$), 11.72 (NHCbz). – ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3CH_2), 24.1 ($CH_2CH_2CH_2NH$), 24.5 (br., Pro-C^4), 26.1 (Pro-C^3, CH_2CH_2NH), 28.4 [$C(CH_3)_3$], 38.0 (NCH_2CHS), 40.4, 40.5 ($CH_2CH_2CH_2NH$), 44.3, 44.4 (Gly-C^2), 47.1 (Pro-C^5), 60.7 (Pro-C^2), 61.8 (CH_3CH_2O), 62.0 (CHS), 67.1, 68.2 (OCH_2Ph), 80.5, 80.6 [$C(CH_3)_3$], 127.9, 128.1, 128.39, 128.44, 128.67, 128.75, 134.6, 136.7 (C^{Ar}), 153.8, 156.16 (CO_2CH_2Ph), 156.19 [$CO_2C(CH_3)_3$], 163.6 (C=N), 170.2 (Gly-C^1), 173.2 (Pro-C^1).

Peptidosulfonamide 40: Peptidosulfonamide **40** was prepared according to the procedure described for **39**. Starting from peptidosulfonamide **39** (133 mg, 0.172 mmol), 100 mg (63%) of peptidosulfonamide **40** was isolated following column chromatography (eluent: EtOAc/hexanes, 7:3). R_f = 0.32 (EtOAc/hexanes, 3:1). – ^{1}H NMR ($CDCl_3$): δ = 1.28 (dt, 3 H, CH_3CH_2), 1.39 [s, 9 H, $C(CH_3)_3$], 1.45–2.15 (m, 8 H, $CH_2CH_2CH_2NH$, Pro-C^3H_2, Pro^4H_2), 2.67 (m, 1 H, Pro-C^5H^a), 2.93 (m, Phe-C^3H_2), 3.23 (br. s, 1 H, CHS), 3.45 (t, 2 H, $CH_2CH_2CH_2NH$), 3.50–3.80 (m, 3 H, NCH^aCHS, Pro-C^5H^b), 3.94 (m, 3 H, NCH^bCHS, Gly-C^2H_2), 4.19 (dq, 2 H, CH_3CH_2O), 4.37 (two dd, 1 H, Pro-C^2H), 4.48 (q, 1 H, Phe-C^2H), 5.11, 5.16 (two s, 4 H, OCH_2Ph), 5.44 (d, 1 H, Phe-NH), 6.20, 6.32 (two t, 1 H, $NHSO_2$), 7.15–7.48 (m, 16 H, ArH, $CHCH_2NH$), 8.37 (t, 1 H, $CH_2CH_2CH_2NH$), 11.72 (NHCbz). – ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3CH_2), 24.0, 24.2, 24.5 ($CH_2CH_2CH_2NH$, Pro-C^4), 26.1, 26.2 ($CH_2CH_2N_3$), 28.3 [$C(CH_3)_3$], 28.5 (Pro-C^3), 38.5, 38.8 (NCH_2CHS, Phe-C^3), 40.5 ($CH_2CH_2CH_2NH$), 44.2, 44.3 (Gly-C^2), 46.8, 47.0 (Pro-C^5), 54.0 (Phe-C^2), 60.3, 60.5 (CHS), 61.6, 61.8 (Pro-C^2), 61.6, 61.7 (CH_3CH_2O), 67.0, 68.0 (OCH_2Ph), 80.1 [$C(CH_3)_3$], 127.0, 127.1, 127.8, 128.0, 128.3, 128.36, 128.45, 128.6, 128.7, 129.3, 134.6, 136.0, 136.1, 136.7 (C^{Ar}), 153.7 (CO_2CH_2Ph), 155.5 [$CO_2C(CH_3)_3$], 156.0 (CO_2CH_2Ph), 163.6 (C=N), 170.4, 170.5 (Gly-C^1), 171.4, 171.7 (Pro-C^1), 172.2 (Phe-C^1).

Peptidosulfonamide 41: Peptidosulfonamide **40** (102 mg, 0.111 mmol) was dissolved in EtOH (1 mL) containing acetic acid (10 μL). 10% Pd/C (20 mg) was added and the mixture was stirred overnight under a hydrogen atmosphere. The catalyst was then removed by filtration and the solution was concentrated to dryness. The acetic acid salt thus obtained was purified on a DOWEX Cl^- column. Lyophilization gave 55 mg (72%) of peptidosulfonamide **41**. R_f = 0.62 (MeOH/37% NH_3 in H_2O/$CHCl_3$, 45:20:60). – ^{1}H NMR (D_2O): δ = 1.25 (t, 3 H, C*H*$_3$CH$_2$O), 1.43 [s, 9 H, C(CH$_3$)$_3$], 1.60–2.10 (m, 8 H, C*H*$_2$C*H*$_2$CH$_2$NH, Pro-C^{3}H$_2$, Pro-C^{4}H$_2$), 3.00 (d, 3 H, Phe-C^{3}H$_2$, Pro-C^{5}H^a), 3.15 (t, 2 H, CH$_2$CH$_2$C*H*$_2$NH), 3.40 (m, 1 H, CHS), 3.60–3.85 (m, 3 H, NHC*H*$_2$CHS, Pro-C^{5}H^b), 4.03 (s, 2 H, Gly-C^{2}H$_2$), 4.28 (q, 2 H, CH$_3$C*H*$_2$O), 4.32 (m, 1 H, Pro-C^{2}H), 4.66 (m, 1 H, Phe-C^{2}H), 7.20–7.50 (m, 5 H, ArH). – ^{13}C NMR (D_2O): δ = 13.6 (*C*H$_3$CH$_2$O), 23.7 (*C*H$_2$CH$_2$CH$_2$NH), 24.2 (CH$_2$*C*H$_2$CH$_2$NH), 25.3 (Pro-C^4), 27.9 [C(*C*H$_3$)$_3$], 29.4 (Pro-C^3), 37.5 (Phe-C^3), 38.0 (NH*C*H$_2$CHS), 41.0 (CH$_2$CH$_2$*C*H$_2$NH), 44.3 (Gly-C^2), 47.9 (Pro-C^5), 54.4 (Phe-C^2), 61.1 (CHS), 61.5 (Pro-C^2), 63.0 (CH$_3$*C*H$_2$O), 82.0 [*C*(CH$_3$)$_3$], 127.6, 129.0, 129.6, 136.2 (C^{Ar}), 157.1 [C=N, *C*O$_2$C(CH$_3$)$_3$], 172.2, 174.4 (C=O). – FAB-MS: *m*/*z* = 654.3 [M – HCl + H]$^+$. – ES-MS; *m*/*z*: 654.45 [M – HCl + H]$^+$.

Peptidosulfonamide 42: Peptidosulfonamide **41** (14 mg, 20.3 μmol) was dissolved in DCM (1 mL) and then HCl-saturated diethyl ether (2 mL) was added. After stirring for 45 min, the volatiles were removed in vacuo and the residue was redissolved in water. Lyophilization gave 12 mg (94%) of peptidosulfonamide **42**. – ^{1}H NMR (D_2O): δ = 1.31 (t, 3 H, C*H*$_3$CH$_2$O), 1.60–2.10 (m, 8 H, C*H*$_2$C*H*$_2$CH$_2$NH, Pro-C^{3}H$_2$, Pro-C^{4}H$_2$), 2.80 (q, 1 H, Pro-C^{5}H^a), 3.15–3.33 (m, 2 H, Phe-C^{3}H$_2$), 3.27 (t, 2 H, CH$_2$CH$_2$C*H*$_2$NH), 3.42 (m, 1 H, CHS), 3.55 (m, 1 H, Pro-C^{5}H^b), 3.73 (m, 2 H, NC*H*$_2$CHS), 4.04 (d, 2 H, Gly-C^{2}H$_2$), 4.30 (q, 2 H, C*H*$_3$CH$_2$O), 4.36 (dd, 2 H, Pro-C^{2}H), 4.60 (t, 1 H, Phe-C^{2}H), 7.25–7.50 (m, 5 H, ArH). – ^{13}C NMR (D_2O): δ = 13.6 (*C*H$_3$CH$_2$O), 23.9 (*C*H$_2$CH$_2$CH$_2$NH), 24.3 (CH$_2$*C*H$_2$CH$_2$NH), 25.5, 25.6 (Pro-C^4), 29.7, 29.8 (Pro-C^3), 36.8 (Phe-C^3), 37.8, 37.9 (NH*C*H$_2$CHS), 41.1 (CH$_2$CH$_2$*C*H$_2$NH), 44.4 (Gly-C^2), 47.2 (Pro-C^5), 52.6, 53.4 (Phe-C^2), 61.0 (CHS), 61.5, 61.7 (Pro-C^2), 63.1 (CH$_3$*C*H$_2$O), 128.7, 129.7, 130.0, 133.9 (C^{Ar}), 157.1 (C=N), 168.5 (Phe-C^1), 172.2, 174.4 (Pro-C^1, Gly-C^1). – FAB-MS; *m*/*z*: 554.2 [M – 2HCl + H$^+$].

Peptidosulfonamide 43: Peptidosulfonamide **41** (15 mg, 21.7 μmol) was dissolved in 1 M HCl (3 mL) and the resulting solution was stirred for 48 h at room temperature. Lyophilization gave 13 mg (100%) of peptidosulfonamide **43**. – ^{1}H NMR (D_2O): δ = 1.60–2.10 (m, 8 H, C*H*$_2$C*H*$_2$CH$_2$NH, Pro-C^{3}H$_2$, Pro-C^{4}H$_2$), 2.80 (q, 1 H, Pro-C^{5}H^a), 3.15–3.33 (m, 2 H, Phe-C^{3}H$_2$), 3.27 (t, 2 H, CH$_2$CH$_2$C*H*$_2$NH), 3.43 (m, 1 H, CHS), 3.56 (m, 1 H, Pro-C^{5}H^b), 3.72 (m, 2 H, NC*H*$_2$CHS), 4.02 (d, 2 H, Gly-C^{2}H$_2$), 4.36 (dd, 2 H, Pro-C^{2}H), 4.60 (dd, 1 H, Phe-C^{2}H), 7.25–7.50 (m, 5 H, ArH). – ^{13}C NMR (D_2O): δ = 23.8, 23.9 (*C*H$_2$CH$_2$CH$_2$NH), 24.2 (CH$_2$*C*H$_2$CH$_2$NH), 25.4, 25.5 (Pro-C^4), 29.58, 29.65 (Pro-C^3), 36.7 (Phe-C^3), 37.7, 37.9 (NH*C*H$_2$CHS), 41.0 (CH$_2$CH$_2$*C*H$_2$NH), 44.1 (Gly-C^2), 48.0 (Pro-C^5), 53.2 (Phe-C^2), 61.0 (Pro-C^2), 61.3, 61.5 (CHS), 128.5, 129.4, 129.7, 133.7 (C^{Ar}), 157.1 (C=N), 168.2, 174.40 (C=O). – FAB-MS; *m*/*z*: 526.2 [M – 2HCl + H$^+$].

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