Solid-Phase Synthesis of Sulfamate Peptidomimetics

Josep Farrera-Sinfreu,[†,§] Fernando Albericio,[†,‡] and Miriam Royo*[,§]

Combinatorial Chemistry Unit and Institute for Research in Biomedicine, Barcelona Science Park, University of Barcelona, Josep Samitier 1, 08028-Barcelona, Spain, and Department of Organic Chemistry, University of Barcelona, Martí i Franqués 1, 08028-Barcelona, Spain

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A synthetic method for the preparation of sulfamate peptidomimetics is described. The methodology allows sulfamoylation in the solid phase using sulfamoyl chloride in DMA, followed by the acylation of the corresponding sulfamoylated product. Following this approach, several derivatives have been prepared starting from distinct alcohol sources, including α-, β-, and γ-hydroxyacids and phenols. The presence of protected amino functions on the building blocks opens the possibility of the addition of more diversity. This approach, which is compatible with Fmoc/Boc/Alloc protection, provides a useful and efficient tool for the preparation of new sulfamate peptidomimetics.

Introduction

Synthetic sulfamide- and sulfamate-based compounds play crucial roles in a broad range of biological processes. For example, a number of sulfamide analogues show therapeutic application as inhibitors of HIV protease,[1,2] such as carbonic anhydrase inhibitors,[3] or as potent and selective β_3-adrenergic receptor agonists.[4] Furthermore, sulfamate derivatives show therapeutic properties as inhibitors of steroid sulfatases[5] and aminoacyl-tRNA synthetases.[6]

Sulfamoyl chloride is a common reagent for the preparation of sulfamides and sulfamates in solution, and has been used for the preparation of sulfamides and sulfahydantoins on resin.[7] Although sulfamoylation is a powerful strategy for the construction of many sulfamate and sulfamide analogues, to the best of our knowledge no solid-phase sulfamate synthesis has been described.[8]

Because of the difficulty of the reproduction of a large number of solution-phase organic reactions on solid supports, we emphasized the development of a powerful solid-phase sulfamoylation, since its products are key intermediates in some of our laboratory programs. Thus, several sulfamoylation protocols first described in solution were evaluated, first using *trans*-hydroxyproline as the alcohol model. Once sulfamoylation conditions were established, other alcohols including α- and β-hydroxy acids and phenols were assayed.

Results and Discussion

trans-Hydroxyproline was chosen as the alcohol model because it was stable under the sulfamoylation conditions and allowed us to check sulfamate stability with respect to other reactions such as Fmoc- and Alloc-removal or acylation. A convenient protection system of the hydroxyl group was required to avoid on-resin polymerization. Tetrahydropyrane (THP) was a useful protecting group, orthogonal to Alloc and Fmoc chemistry and even compatible with that of Boc.[9] Fmoc-Hyp(THP)-OH was coupled to the Rink amide resin (see Scheme 1) using common coupling reagents in a solid-phase peptide synthesis (SPPS), such as *N,N*-diisopropylcarbodiimide (DIPCDI)/1-hydroxybenzotriazole (HOBt). THP was then removed by treatment of the resin with *p*-TsOH (5 mg/mL) in DCM/MeOH (19:1), which yielded the free alcohol in a quantitative yield. Sulfamoylation was then optimized on the Fmoc-Hyp-Rink amide resin.

Several sulfamoylation protocols were tested using sulfamoyl chloride (10 equiv) as a reagent. Given that the sulfamoylation methods of aliphatic alcohols in solution require a strong base such as NaH (5 equiv), this base was assayed in the solid phase using ethyleneglycol dimethyl ether (DME) as a solvent.[10,11] However, this method did not work properly when adapted to the solid phase. Although the desired product was detected by HPLC-MS when the reaction was carried out with a few milligrams (50 mg) of resin, no attempt to optimize the strategy was made because this base was difficult to remove from the resin, even with MeOH and H_2O washings. This problem was even aggravated when the reaction was scaled up to 1 g of resin. Similar problems were obtained when K_2CO_3 (3 equiv) was used, alone or in the presence of 18-crown-6 (3 equiv) in DCM. The use of weak bases such as NEt_3 (3 equiv) or DIEA (10 equiv) in DMF or DCM was abandoned because sulfamoylation was not achieved, and the starting material was obtained. This phenomenon may arise from the decomposition of sulfamoyl chloride in the presence of a base which can compete with sulfamoylation.[12] Furthermore, the presence of a base can also lead to over-sulfamoylation.

The use of other solvents which achieve good swelling of the resin, such as DCM, DMF, or THF without base, did not yield the sulfamoylated compound, even after heating the resin at 50 °C (DMF and THF) or using ultrasound

* To whom correspondence should be addressed. E-mail: mroyo@pcb.ub.es.
[†] Combinatorial Chemistry Unit.
[‡] Institute for Research in Biomedicine.
[§] Department of Organic Chemistry.

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Scheme 1. Synthesis of Dipeptide Analogues Using Fmoc-*trans*-Hyp(THP)-OH

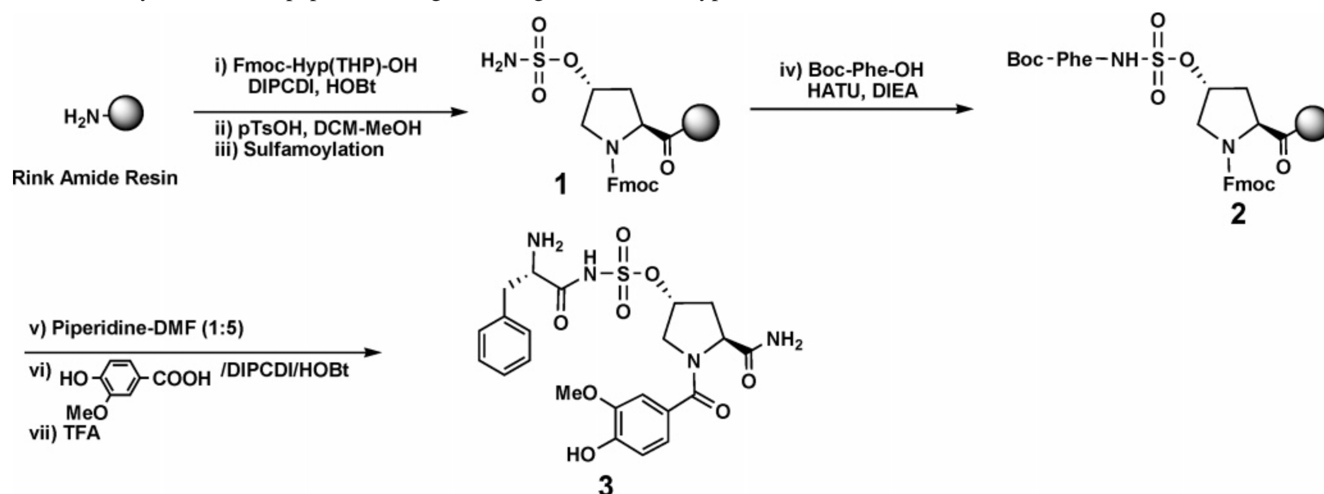


Table 1. Coupling of Boc-L-Phe-OH to the γ-Sulfamoyl-Fmoc-proline Rink Amide Resin[a]

	conditions	solvent	time (h)	HPLC (%)
1	DIPCDI (5 equiv), HOBt (5 equiv)	DMF	2	
2	DIPCDI (5 equiv), DMAP (0.5 equiv)	DCM	16	50
3	DIPCDI (5 equiv), DMAP (1 equiv)	DCM	2	60
4	DIPCDI (5 equiv), DMAP (5 equiv)	DCM	2	>95
5	HATU (5 equiv), DIEA (10 equiv)	DMF	2	>95

[a] Detection was made by HPLC-MS of cleaved product **2** at 220 nm.

methods (data not shown). When DCM was used, premature cleavage of compounds from the resin was detected.[13] Sulfamoyl chloride can also react with solvents such as DMF through its formyl proton, with its consequent destruction.[12]

Okada et al.[14] described a method in solution that circumvents all these problems, using sulfamoyl chloride in DMA in the absence of base. Unlike DMF, DMA does not react with sulfamoyl chloride and works as a moderate base, thereby avoiding the use of additional bases and, consequently, preventing both the decomposition of sulfamoyl chloride and the over-sulfamoylation of the sulfamoyl group. Given that the main problem encountered in solid-phase sulfamoylation is caused by the use of bases, a method that does not involve bases was considered a good alternative and was therefore tested.

Fmoc-Hyp-Rink amide resin was treated with sulfamoyl chloride (10 equiv) in DMA for 3 h. The expected final sulfamoylated product was obtained with high conversion (>95% by HPLC).[15] To test whether the Alloc-protecting group is compatible with sulfamate synthesis, the same experiment was performed using Alloc-Hyp-Rink amide resin. This experiment also gave the same result (>95% by HPLC). Furthermore, the advantage of this method is that it may also prevent epimerization at the α-carbon of the Pro, which easily racemizes in strong basic conditions, such as NaH.

Sulfamate elongation (Scheme 1, step iv) was then performed by acylation of the sulfamoyl group with Boc-Phe-OH (5 equiv) as a model, using several coupling methods (see Table 1). HATU (5 equiv) and DIEA (10 equiv) for 2 h (entry 5) gave the best results as a coupling method since the other alternative, which involves DIPCDI/DMAP (entry 4), favored racemization of the incoming protected amino acid. Deprotection of the N^{α} of hydroxyproline with piperidine, followed by the coupling of 4-hydroxy-3-methoxybenzoic acid (5 equiv) with DIPCDI (5 equiv) and HOBt (5 equiv), and the final acidolytic cleavage with TFA/H_2O (95:5) gave the expected product **3** with an excellent conversion (>95% by HPLC, see Supporting Information).

The same experiment was performed using Alloc-Hyp-Rink amide resin. Sulfamoylation in DMA, followed by Boc-Phe-OH coupling, removal of the Alloc group with $Pd(PPh_3)_4$ (0.1 equiv) in $PhSiH_3$ (24 equiv), followed by the coupling of 4-hydroxy-3-methoxybenzoic acid (5 equiv) with DIPCDI (5 equiv) and HOBt (5 equiv), and the final acidolytic cleavage with TFA/H_2O (95:5) rendered the expected product **3**, thereby demonstrating the versatility of Alloc chemistry in sulfamate synthesis.

Once sulfamoylation conditions were established, other kinds of alcohols were assayed such as α-hydroxy acids **6** and **7**, β-hydroxy acids **8** and **9**, and phenols **10** and **11** (see Figure 1).

α-Hydroxyisoleucine and α-hydroxyphenylacetic acid were coupled to the Rink amide resin in THF for 3 h using the hexafluoroacetone (HFA) protecting/activating approach.[16] These compounds are easily accessible from their natural amino acid counterparts. Sulfamoylation was performed using the optimized protocol in DMA, followed by reaction with Boc-Phe-OH and cleavage with TFA-H_2O (95:5), which gave the expected products (**12** and **13** in Figure 1) with over 95% purity in both cases, as shown by HPLC (see Supporting Information).

β-Sulfamate peptidomimetics were obtained starting from the β-hydroxy acids 2,2-dimethyl-3-hydroxy-propionic acid (**8**) and 3-hydroxybutyric acid (**9**), following the same protocol stated above but using DIPCDI (5 equiv) and HOBt (5 equiv) as a coupling method to incorporate them into the resin. The corresponding sulfamate derivatives (**14** and **15** in Figure 1) were obtained with high conversion (95% by HPLC, see Supporting Information) in both cases. For the reaction performed with compound **9**, no β-elimination was detected.[17]

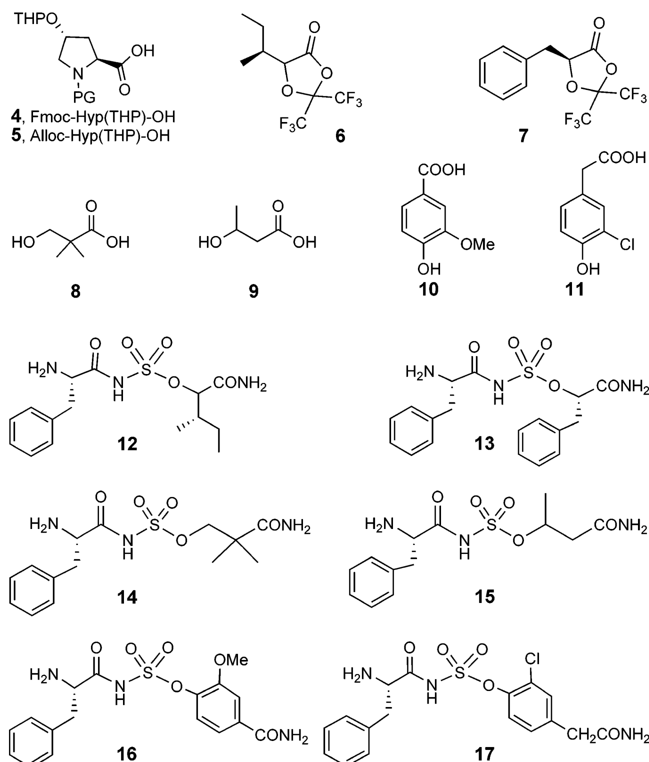
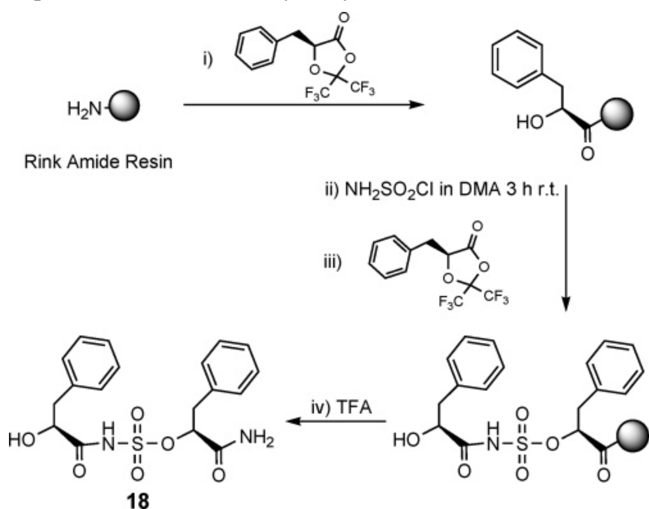


Figure 1. Building blocks (**4**−**11**) used in this study and sulfamated peptidomimetics (**12**−**17**) obtained.

Scheme 2. Solid-Phase Synthesis of Sulfamate Peptidomimetics with α-Hydroxy Acids as Monomer Units



The viability of the sulfamoylation protocol was also tested using two commercially available phenols **10** and **11**, which, after being coupled to the resin using DIPCDI/HOBt, were sulfamoylated and acylated with Boc-Phe-OH to give the expected final products (**16** and **17** in Figure 1) with high conversion, as shown by HPLC (see Supporting Information).

Sulfamate peptidomimetic oligomers were also obtained from HFA-hydroxy acids **6** and **7**, as described in Scheme 2, by repeating the sequence of reactions. Couplings of the HFA-hydroxy acids to the sulfamate moiety in THF proceeded with low yields after long reaction times because of the low reactivity of the sulfamoyl group. Thus, this coupling requires activation with a base, although the use of base appears to destroy HFA-hydroxy acids.[16] A battery of solvents and bases were assayed. The best conditions for this elongation were obtained when DIEA in THF was used (see Table 2). Compound **18** was obtained with 60% conversion, as shown by HPLC. The moderate conversion corroborates the destruction of HFA-hydroxy acid in the presence of base, which jeopardizes the coupling.

Table 2. Conditions Tested in the Coupling of HFA-Protected Hydroxy Acids (5 equiv) to the α-Sulfamoyl Rink Amide Resin[a]

solvent	base	time (h)	HPLC (%)
DMSO		7	
DMSO	DMAP (1 equiv)	3	5
DMSO	DIEA (5 equiv)	7	10
DMA		7	
DMA	DMAP (1 equiv)	3	2
DMA	DIEA (5 equiv)	7	10
THF		7	
THF	DMAP (1 equiv)	3	15
THF	DIEA (5 equiv)	7	40
THF	DIEA (5 equiv)	24	60

[a] Detection was made by HPLC-MS of product **18** at 220 nm.

In summary, a straightforward solid-phase synthesis of sulfamate derivatives has been developed with alcohol-containing building blocks incorporated on a Rink amide resin. Sulfamoylation was performed effectively with sulfamoyl chloride in DMA. The presence of protected amino function on the building blocks opens the possibility of adding more diversity. This approach, which is compatible with Fmoc/Boc/Alloc protection, provides a useful and efficient tool for the preparation of new sulfamate peptidomimetics.

Experimental Section

General Procedures. Solid-Phase Synthesis. Manual SPS was carried out in polypropylene syringes (disposable reaction vessels), each with a porous polypropylene disk at the bottom. Syringes of variable volume were used depending on the initial amount of dried resin. Typically, resin was added to the syringe and then the solvent used in the following reaction was added to produce a slurry. The resin was washed with the solvent (3 mL of solvent per 1 mL of swollen resin). The mixture was stirred using a Teflon rod for a given time, and after the treatment was finished, the solvent was removed by suction. Immediately before the performance of a reaction, the bottom part of the syringe was capped using a septum, and the solvents and reagents were then added. After it was manually stirred using a Teflon rod for 3 min, the mixture was allowed to react for a given time with shaker agitation. Washings between protecting-group removal, coupling, and subsequent protecting-group elimination steps were performed with DMF (5 × 1 min) and DCM (5 × 1 min) using 10 mL of solvent/g of resin each time.

Fmoc Group Removal. The resin was washed with DCM (5 × 1 min), followed by washes with DMF (5 × 1 min), and the Fmoc group was removed using piperidine/DMF (1:4, 1 × 1 min + 2 × 15 min), followed by washes with DMF (5 × 1 min) and DCM (5 × 1 min).

Alloc Group Removal. The resin was washed with DCM (5 × 1 min) and then was treated with $Pd(PPh_3)_4$ (0.1 equiv)

in the presence of $PhSiH_3$ (24 equiv) in DCM under Ar (2 treatments of 20 min). The resin was finally washed with DCM.

THP Group Removal. The resin was washed with DCM (5 × 1 min) and then was treated with a solution of *p*-TsOH (5 mg/mL) in DCM/MeOH (97:3) (2 × 1 h), preceded by a 3 min washing with the same solution. The resin was finally washed with DCM (5 × 1 min).

Carboxylic Acid Coupling. Couplings of distinct hydroxy acids or protected hydroxy amino acids (5 equiv) to the Rink amide MBHA resin were performed with DIPCDI (5 equiv) and HOBt (5 equiv) in DMF for 2 h at 25 °C. After the coupling, the resin was washed with DMF (5 × 1 min) and DCM (5 × 1 min). Couplings were monitored by the Kaiser test. Couplings of distinct carboxylic acids to a proline-derivative secondary amine were carried out following the conditions described above. In this case, couplings were monitored by the chloranil test.

HFA-Protected Hydroxy Acid Coupling to Rink Amide Resin. Rink amide MBHA resin was preswollen in THF. HFA/hydroxy acid (5 equiv) was then added, and the resin was shaken for 3 h. The resin was then washed with THF (5 × 1 min), DMF (5 × 1 min), and DCM (5 × 1 min). Couplings were monitored by the Kaiser test.

On-Resin Sulfamoylations. **(a) NaH in DME.** The resin (50 mg, 0.035 mmol) was preswollen in DME (1.5 mL). A suspension of NaH in oil (14 mg, 10 equiv) in DME was then added, and the resin was stirred for 2 h at 50 °C. A solution of sulfamoyl chloride (10 equiv) in DME was then added, and the resin was stirred at room temperature for 15 h. The resin was then treated with MeOH to remove the excess hydride and was washed with CH_2Cl_2, MeOH, and DMF.

(b) In DMA. The resin (50 mg, 0.035 mmol) was preswollen in DMA (1.5 mL) for 30 min. A solution of sulfamoyl chloride (10 equiv) in DMA was then added at 0 °C, and the resin was stirred at room temperature for 3 h. It was then filtered, washed with DMA, DMF, and CH_2Cl_2. The resin was then washed once with 5% DIEA in DMF to remove possible traces of acid and finally with DMF and DCM.

Acidolytic Cleavage with TFA. Resins were cleaved with TFA/H_2O (95:5) for 2 h at 25 °C. TFA was then evaporated, and the compounds were dissolved in H_2O/CH_3CN and then lyophilized.

HPLC Analysis. HPLC and HPLC-MS analysis were carried out with Waters equipment with a reverse-phase column Symmetry C_{18} 5 μm (4.6 × 150 mm) with a flow rate of 1 mL/min. A wavelength of 220 nm was selected for the purity analysis. The analysis was performed using a linear gradient of 0−100% of B in 10 min, where A is H_2O containing 0.045% TFA and B is CH_3CN containing 0.036% TFA.

1-(Fluoren-9-ylmethoxycarbonyl) 2-Carbamoyl-4-sulfamoyloxy-pyrrolidine (1). The spectra correspond to a mixture of two conformers, and so each proton and each carbon appear doubly assigned.^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.15−2.22 (m, 2H, CH_2), 2.43−2.70 (m, 2H, CH_2), 3.65−3.80 (m, 4H, 2 × CH_2), 4.18−4.30 (m, 7H, 3 × CH, 2 × CH_2), 4.42 (t, 1H, CH, J = 7.6 Hz), 5.08 (m, 2H, 2 × CH), 7.06 (s, 1H, carboxamide), 7.23 (s, 1H, carboxamide), 7.34 (t, 4H, 4 × CH, J = 7.2 Hz), 7.42 (t, 4H, 4 × CH, J = 7.2 Hz), 7.54 (s, 1H, carboxamide), 7.64−7.69 (m, 7H, 4 × CH, 1H carboxamide, 2H of NH_2), 7.90 (t, 4H, 4 × CH, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 35.9 (CH_2), 37.2 (CH_2), 46.4 (CH_2), 46.5 (CH_2), 52.1 (CH), 52.8 (CH), 57.7 (CH), 58.0 (CH), 66.7 (CH), 67.3 (CH), 77.2 (CH_2), 77.9 (CH_2), 120.0 (2 × CH), 120.1 (2 × CH), 125.1 (2 × CH), 125.4 (2 × CH), 127.1 (2 × CH), 127.2 (2 × CH), 127.6 (4 × CH), 140.5 (2 × C), 140.6 (2 × C), 143.5 (2 × C), 143.7 (2 × C), 153.7 (C), 153.9 (C), 172.7 (C), 173.1 (C). Yield: 90%. Purity by HPLC at 220 nm: 95%. MS Calcd for $C_{20}H_{22}N_3O_6S$: $[M + H]^+$ 432.1229. HR-ESI Found: $[M + H]^+$ 432.1238.

***N*-(2-Amino-3-phenyl-propionyl) (5-Carbamoyl-1-(4-hydroxy-3-methoxy-benzoyl)-pyrrolidin-3-yl) Sulfamate (3)**. ^{1}H NMR ($CDCl_3$ with two drops of CD_3OD, 400 MHz): δ 2.09−2.17 (m, 1H, CH_2), 2.52 (dd, 1H, CH_2, J = 14.0 Hz, J = 7.8 Hz), 2.76 (dd, 1H, CH_2, J = 14.4 Hz, J = 8.8 Hz), 3.12 (dd, 1H, CH_2, J = 14.4 Hz, J = 4.4 Hz), 3.61 (dd, 1H, CH_2, J = 9.0 Hz, J = 4.4 Hz), 3.72 (s, 3H, CH_3), 3.79 (bb, 1H, CH_2), 3.90−4.02 (m, 1H, CH), 4.61 (t, 1H, CH, J = 8.4 Hz), 4.95 (bb, 1H, CH), 6.70 (d, 1H, CH, J = 8.0 Hz), 6.95 (dd, 1H, CH, J = 8.0 Hz, J = 1.6 Hz), 7.02 (d, 1H, CH, J = 1.6 Hz), 7.07−7.19 (m, 5H, 5 × CH). ^{13}C NMR ($CDCl_3$ with two drops of CD_3OD, 100 MHz): δ 30.4 (CH_2), 35.1 (CH_2), 37.1 (CH_2), 55.5 (CH_3), 56.4 (CH), 56.7 (CH), 58.4 (CH), 111.1 (CH), 114.2 (CH), 121.3 (CH), 127.2 (CH), 128.7 (2 × CH), 129.0 (2 × CH). Purity by HPLC at 220 nm: 96%. MS Calcd for $C_{22}H_{27}N_4O_8S$: $[M + H]^+$ 507.1550. HR-ESI Found: $[M + H]^+$ 507.1545.

***N*-(2-Amino-3-phenyl-propionyl) (1-Carbamoyl-2-methyl-butyl) Sulfamate (12)**. ^{1}H NMR (CD_3OD, 400 MHz): δ 0.87 (t, 3H, CH_3, J = 7.2 Hz), 1.08 (d, 3H, CH_3, J = 6.8 Hz), 1.22−1.31 (m, 1H, CH_2), 1.51−1.57 (m, 1H, CH_2), 2.04−2.09 (m, 1H, CH), 3.01 (dd, 1H, CH_2, J = 14.8 Hz, J = 8.4 Hz), 3.24−3.28 (m, 1H, CH_2), 3.81 (dd, 1H, CH, J = 8.4 Hz, J = 4.8 Hz), 4.61 (d, 1H, CH, J = 3.6 Hz), 7.26−7.27 (m, 5H, 5 x CH). ^{13}C NMR (CD_3OD, 100 MHz): δ 11.0 (CH_3), 14.8 (CH_3), 23.6 (CH_2), 37.3 (CH), 37.7 (CH_2), 57.0 (CH), 81.7 (CH), 127.4 (CH), 128.8 (2 × CH), 129.5 (2 × CH). Purity by HPLC at 220 nm: 97%. MS Calcd for $C_{15}H_{24}N_3O_5S$: $[M + H]^+$ 358.1437. HR-ESI Found: $[M + H]^+$ 358.1428.

***N*-(2-Amino-3-phenyl-propionyl) (1-Carbamoyl-2-phenyl-ethyl) Sulfamate (13)**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.10−3.12 (m, 2H, CH_2), 3.28−3.36 (m, 2H, CH_2), 3.73 (dd, 1H, CH, J = 6.8 Hz, J = 5.2 Hz), 4.82 (t, 1H, CH, J = 5.0 Hz), 7.16−7.28 (m, 10H, 10 × CH), 7.74−7.76 (bb, NH_2), 7.90 (bb, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 36.7 (CH_2), 37.4 (CH_2), 55.9 (CH), 76.2 (CH), 126.1 (CH), 126.7 (CH), 127.8 (2 × CH), 128.3 (2 × CH), 129.5 (2 × CH), 129.7 (2 × CH), 135.5 (C), 136.6 (C), 171.6 (C), 172.9 (C). Purity by HPLC at 220 nm: >99%. MS Calcd for $C_{18}H_{22}N_3O_5S$: $[M + H]^+$ 392.1275. HR-ESI Found: $[M + H]^+$ 392.1269.

***N*-(2-Amino-3-phenyl-propionyl) (2-Carbamoyl-2-methyl-propyl) Sulfamate (14).** ^{1}H NMR (CD_3OD, 400 MHz): δ

1.20 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 3.02 (dd, 1H, CH_2, J = 14.4 Hz, J = 8.6 Hz), 3.30−3.34 (m, 1H, CH_2), 3.85 (dd, 1H, CH, J = 8.6 Hz, J = 5.2 Hz), 4.00 (d, 2H, CH_2, J = 2.4 Hz), 7.27−7.34 (m, 5H, 5 × CH). ^{13}C NMR (CD_3OD, 100 MHz): δ 23.1 (CH_3), 23.2 (CH_3), 38.6 (CH_2), 43.6 (C), 58.4 (CH), 75.8 (CH_2), 128.6 (CH), 130.1 (2 × CH), 130.7 (2 × CH), 136.7 (C). Yield: 72%. Purity by HPLC at 220 nm: 98%. MS Calcd for $C_{14}H_{22}N_3O_5S$: [M + H]$^+$ 343.1275. HR-ESI Found: [M + H]$^+$ 344.1275.

***N*-(2-Amino-3-phenyl-propionyl) (2-Carbamoyl-1-methyl-ethyl) Sulfamate (15).** The spectra correspond to a mixture of two diastereoisomers. Because each diastereisomer has not been identified, each proton and each carbon have been assigned doubly. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.05 (d, 3H, CH_3), 1.14 (d, 3H, CH_3), 2.04−2.09 (m, 2H, CH_2), 2.14−2.22 (m, 1H, CH_2), 2.46−2.50 (m, 1H, CH_2), 2.83−2.89 (m, 1H, CH_2), 2.95−3.00 (m, 1H, CH_2), 3.05−3.014 (m, 2H, CH_2), 3.60−3.63 (m, 1H, CH), 3.70−4.00 (bb), 4.43−4.48 (m, 1H, CH), 7.25−7.35 (m, 10H, 10 × CH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 21.4 (CH_3), 23.9 (CH_3), 37.4 (CH_2), 37.5 (CH_2), 43.5 (CH_2), 45.5 (CH_2), 54.2 (CH), 54.3 (CH), 64.3 (2 × CH), 127.8 (CH), 127.8 (CH), 129.1 (2 × CH), 129.2 (2 × CH), 130.1 (2 × CH), 130.3 (2 × CH). Yield: quantitative. Purity by HPLC at 220 nm: 96%. MS Calcd for $C_{13}H_{29}N_3O_5S$: [M + H]$^+$ 330.1124. ESI Found: [M + H]$^+$ 330.1115.

***N*-(2-Amino-3-phenyl-propionyl) (4-Carbamoyl-2-methoxy-phenyl) Sulfamate (16)**. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.91 (dd, 1H, CH_2, J = 14.2 Hz, J = 7.6 Hz), 3.14 (dd, 1H, CH_2, J = 14.2 Hz, J = 5.2 Hz), 3.71−3.77 (m, 1H, CH), 3.81 (s, 3H, CH_3), 7.25 (m, 5H, 5 × CH), 7.42 (d, 1H, J = 2.0 Hz), 7.43 (s, 1H, CH), 7.52 (d, 1H, CH, J = 2.0 Hz), 7.82 (bb, 4H, $2NH_2$), 7.93 (bb, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 36.8 (CH_2), 55.0 (CH_3), 55.8 (CH), 111.9 (CH), 119.6 (CH), 121.1 (CH), 126.7 (CH), 128.3 (2 × CH), 129.4 (2 × CH), 130.8 (C), 135.6 (C), 143.2 (C), 150.4 (C), 167.1 (C), 171.8 (C). Purity by HPLC at 220 nm: >99%. MS Calcd for $C_{17}H_{20}N_3O_6S$: [M + H]$^+$ 394.1067. HR-ESI Found: [M + H]$^+$ 394.1052.

***N*-(2-Amino-3-phenyl-propionyl) (4-Carbamoylmethyl-2-chloro-phenyl) Sulfamate (17)**. ^{1}H NMR (CD_3OD, 400 MHz): δ 2.98 (dd, 1H, CH_2, J = 14.8 Hz, J = 8.8 Hz), 3.32 (m, 1H, CH_2), 3.48 (s, 2H, CH_2), 3.88 (dd, 1H, CH, J_{CH-CH_2} = 8.8 Hz, J_{CH-CH} = 4.8 Hz), 7.21 (dd, 1H, CH, J_{CH-CH} = 8.4 Hz, J_{CH-CH} = 2.0 Hz), 7.31 (m, 5H, 5CH), 7.41 (d, 1H, J_{CH-CH} = 2.0 Hz), 7.47 (d, 1H, CH, J_{CH-CH} = 8.4 Hz). ^{13}C NMR (CD_3OD, 100 MHz): δ 38.4 (CH_2), 42.3 (CH_2), 58.3 (CH), 124.6 (CH), 128.1 (CH), 128.6 (CH), 129.5 (CH), 130.1 (2 × CH), 130.6 (2 × CH), 132.0 (C), 135.8 (C), 136.5 (C), 147.9 (C), 174.6 (C), 176.0 (C). Purity by HPLC at 220 nm: 95%. MS Calcd for $C_{17}H_{19}ClN_3O_5S$: [M + H]$^+$ 412.0728. HR-ESI Found: [M + H]$^+$ 412.0737.

(1-Carbamoyl-2-phenyl-ethyl) *N*-(2-Hydroxy-3-phenyl-propionyl) Sulfamate (18). ^{1}H NMR (CD_3OD, 400 MHz): δ 2.78 (dd, 1H, CH_2, J = 14.2 Hz, J = 7.6 Hz), 3.15 (dd, 1H, CH_2, J = 14.2, J = 4.0 Hz), 3.19 (dd, 2H, CH_2, J = 5.8 Hz, J = 3.0 Hz), 4.14 (m, 1H, CH), 5.18 (m, 1H, CH), 7.20−7.28 (m, 10H, 10 × CH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 35.8 (CH_2), 36.8 (CH_2), 53.2 (CH), 76.4 (CH), 127.1 (CH), 127.2 (CH), 127.8 (CH), 127.9 (2 × CH), 128.4 (2 × CH), 128.5 (2 × CH), 129.4 (CH), 139.1 (2 × C), 169.7 (C), 170.3 (C). Purity by HPLC at 220 nm: >99%. MS Calcd for $C_{18}H_{21}N_2O_6S$: [M + H]$^+$ 393.1115. HR-ESI Found: [M + H]$^+$ 393.1123.

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Supporting Information Available. HPLC chromatograms and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Abbreviations: Alloc, allyloxycarbonyl; Boc, *tert*-butoxycarbonyl; DCM, dichloromethane; DHP, 3,4-dihydro-2*H*-pyrane; DIEA, *N,N*-diisopropylethylamine; DIPCDI, *N,N′*-diisopropylcarbodiimide; DMA, *N,N*-dimethylacetamide; DMAP, *N,N*-4-dimethylaminopyridine; DME, ethylene glycol dimethyl ether; DMF, *N,N*-dimethylformamide; Fmoc, 9-fluorenylmethoxycarbonyl; HATU, *N*-{(dimethylamino)-1*H*-1,2,3 -triazolo-[4,5-*b*]pyridin-1-yl-methylene}-*N*-methylmethanaminium-hexafluorophosphate *N*-oxide; HFA, hexafluoroacetone; HIV, human immunodeficiency virus; HOBt, 1-hydroxy-1,2,3-benzotriazole; MBHA, *p*-methylbenzhydrylamine; MeOH, methanol; *p*-TsOH, *p*-toluensulfonic acid; RP-HPLC, reversed-phase high-performance liquid chromatography; SPPS, solid-phase peptide synthesis; TFA, trifluoroacetic acid; THF, tetrahydrofuran; THP, tetrahydropyran; amino acid symbols denote the L configuration.

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