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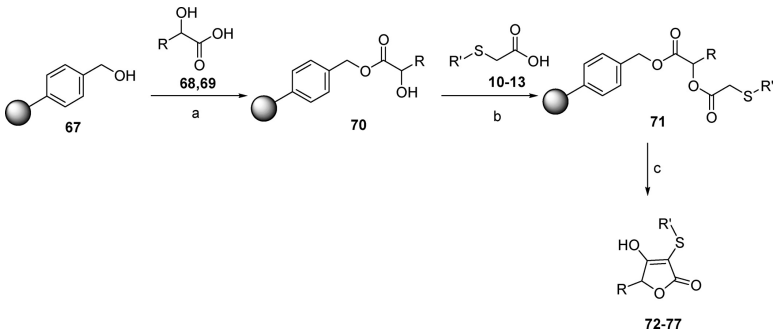

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Synthesis of Tetramic and Tetronic Acids as β-Secretase Inhibitors

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The aspartic protease β-secretase (BACE-1) is an attractive target for the therapy of Alzheimer's disease. The known inhibitors share a high analogy to the substrate peptide and, thus, display undesired pharmacological properties. Compact nonpeptidic lead structures are scarce. Here, we report the activities of tetronic and tetramic acids on BACE-1 inhibition. The compounds feature a low molecular weight and compact scaffold, which is accessible by solid-phase-supported diverse synthesis.

Introduction

Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder and currently affects nearly 2% of the population in industrialized countries.[1] One in 10 individuals over 65, and nearly half of those over 85, are likely to be struck by the disease. The increase of the older population in the developed countries will turn AD into a dramatic issue for our healthcare systems soon. Until now, there has been no cure for AD. Intensive investigation has provided insight into the biology of the disease and revealed several options for treatment. Brains of patients struck by AD are characterized by two hallmark proteinaceous aggregates: amyloid plaques and neurofibrillary tangles.[2]

β-Amyloid plaques are specific for AD, whereas tangles are also found in other disorders.[3] This divides the followers of the two hypotheses into "tauists and baptists". The "amyloid hypothesis", assigns the central role to the accumulation of β-amyloid peptide (Aβ) in the brain.[4] Aβ peptides derive from the abnormal cleavage of the β-amyloid precursor protein (β-APP), a protein found throughout the body whose normal function remains obscure (http://www.alz.org). β-Secretase (BACE-1), a member of the pepsin family of aspartyl proteases, plays a critical role in this amyloid cascade. Recent reports have demonstrated a direct correlation between increased BACE-1 activity and Aβ production in AD brain tissue.[5] Furthermore, BACE-1 gene knockout mice display reduced Aβ production.[6] Several aspartic proteases have been targeted successfully for drug development; therefore, BACE-1 inhibition has been recognized by several companies and academic groups as a suitable therapeutic approach to slow or halt the progression of AD.[7]

To date, numerous BACE-1 inhibitors have been published. Most of these inhibitors share a peptidic character and mimic the scissile amide bond of the natural substrate by a noncleavable transition state isostere.[8] Despite all progress made in the design of such peptidelike molecules, they have the same problems of all peptidic structures: low oral bioavailability and poor blood−brain barrier permeation. Therefore, nonpeptidic BACE-1 inhibitors are of great interest for AD drug development.

Tipranavir (**1**) is an active site inhibitor of the HIV-1 aspartyl protease that entered phase III clinical trials recently. Cocrystallization with the HIV-1 protease and structure determination revealed that the acidic proton and the corresponding hydroxyl interact with the catalytic aspartates.[9] Acylated tetronic and tetramic acids display some similarity to the Tipranavir motif and were investigated as HIV-1 protease inhibitors.[10,11] Moreover, tetronates are more compact than hydroxypyrones, which makes them more likely to meet the special requirements of the BACE-1 active site geometry, which is unusually long and narrow.[8] Furthermore, extended inhibitors that occupy all BACE subsites do not display much improved binding and must be regarded as poor leads. At the onset, there were no reports exploring the potential of tetronates and tetramates as BACE-1 inhibitors, and now there is just one very recent patent application by Hoffmann La Roche.[12]

Here, we report the identification of tetronic, tetramic, and N-substituted tetramic acids that inhibit BACE-1 in the micromolar range. The biological activity of the synthesized compounds was determined using a FRET assay described by F. Grüninger-Leitch.[13] We were interested in covering a diverse set of substituents in a short time; therefore, we decided to employ a solid-phase supported synthesis, which enabled the parallel synthesis of compounds, accompanied by simplified purification and a rapid isolation.

Results and Discussion

General Considerations. We have chosen tetronic and tetramic acid scaffolds for our approach because they are related to the homologous 4-hydroxypyran-2-one (**2**) class of HIV-1 active-site inhibitors.[14] Tetronic acids were identified by Roche scientists as weak inhibitors of BACE independent from our investigations.[12] However, this resulted in the support of our program by M. Brockhaus, Hofmann-La Roche by a fluorescence resonance energy transfer assay (FRET).[13] The investigation of the structure−activity relationship (SAR) of the different scaffolds commenced with

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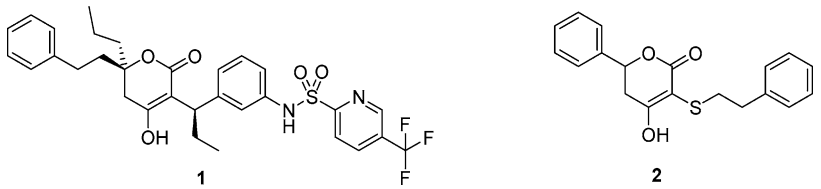


Figure 1. Structures of tipranavir (**1**) and a 4-hydroxypyran-2-one derivative (**2**).

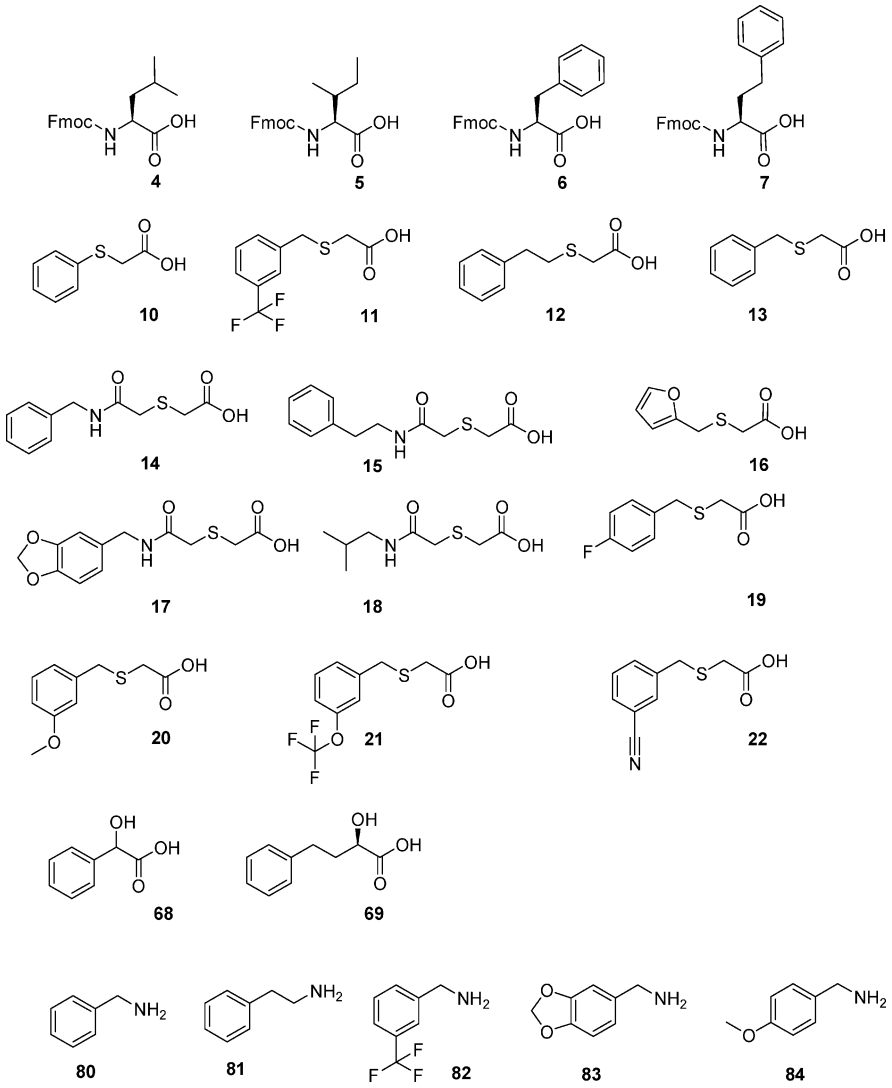


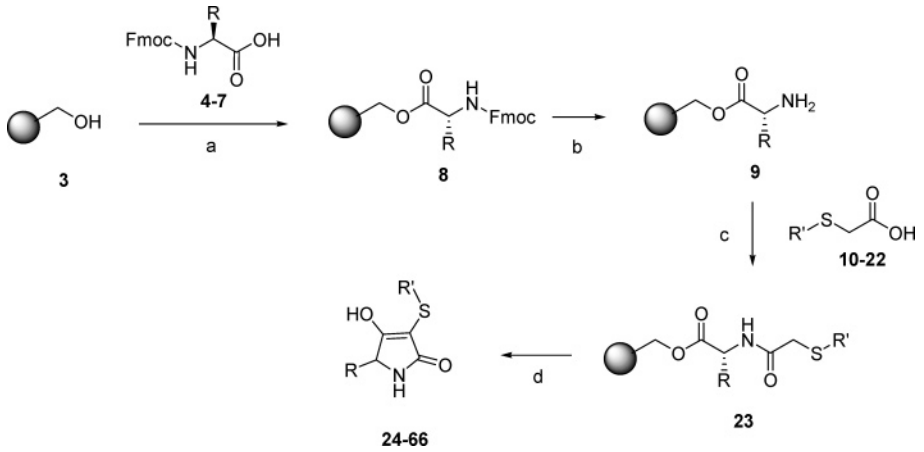
Figure 2. Building blocks.

the variation of thioacetic acids and selected lipophilic amino acids or α-hydroxycarboxylic acids. (Figure 2) We reasoned further that a sulfoxide or a sulfone replacement of the thioether motif may increase the activity by an additional interaction with amino acids of the active site. The N-substituted tetramic acids questioned the "substituent flip" in the binding site. This flip was suggested by some crude modeling of the active site, which may harbor the inhibitors in two orientations. These orientations derive from an almost 180° flip along the C−O axis of the hydroxyl group.

Synthesis. Syntheses of tetramic acid derivatives **24**−**66** were achieved by the reactions depicted in Scheme 1 (see also Figure 3). The synthesis of tetronic[15] and tetramic[16−19] acids is well established. Very recently, tetramic acids were prepared in solution and on solid support to provide inhibitors for the hepatitis C virus.[20] We decided on modifications of the Rivero/Ganesan[19,21] approaches and employed the Sieber[22] methodology for the preparation of preloaded Wang resins. This approach provides derivatized resins with high substitution levels and minimized dipeptide formation, particularly in comparison to conventional attachment methods involving DCC and DMAP. The resulting Fmoc-protected α-amino acid resins **8** were deprotected using a solution of 20% piperidine in DMF, and the formation of free amines was monitored using the qualitative Kaiser test.[23] Thioacetic acid derivatives **10**−**22** were then coupled onto the resin using PyBOP, HOBt, and DIEA in DMF. Upon treatment with KOBu^t in THF, the resin-bound compounds **23** underwent cyclizative Dieckmann-like condensation to release the racemic tetramic acid derivatives **24**−**66**.[19]

Syntheses of tetronic acid derivatives **72**−**77** were obtained by reactions depicted in Scheme 2 (see also Figure 4). The

Scheme 1.[a] Solid-Phase Synthesis of Tetramic Acids



[a] Reagents and conditions: (a) 2,6 dichlorobenzoyl chloride, pyridine, r.t., 20 h; (b) 20% piperidine, DMF, r.t., 2 h; (c) PyBOP, HOBt, DIEA, DMF, r.t., 20 h; (d) KOBu^t, THF, reflux, 1h.

reaction sequence began with the condensation of α-hydroxycarboxylic acids **68** and **69** onto the hydroxymethyl resin **67** with a catalytic amount of *p*-toluenesulfonic acid in toluene. The esterification was initially evaluated in solution with mandelic acid and (a) benzyl alcohol as a mimic for the hydroxymethyl resin in an acid-catalyzed condensation and (b) benzyl chloride as a mimic for the Merrifield resin in a base-mediated condensation. Both reactions were monitored by HPLC, and the acid-catalyzed esterification provided purer products. We moved on to investigate the condensation reaction with standard Wang resin and hydroxymethyl polystyrene resin from Novabiochem. We obtained the desired tetronic acids with both resins, but the hydroxymethyl polystyrene resin resulted in a much better yield and improved purity of the isolated products.

In the next step, thioacetic acid derivatives **10**−**13** were coupled onto the resin **70** by PyBOP/HOBt/DIEA at standard conditions. Cyclization/cleavage with KOBu^t in THF released the tetronic acids **72**−**77** as racemates. Most compounds were obtained as racemic mixtures unless they give rise to diastereomers (isoleucine). This is due to the racemization in the cyclization release. This was confirmed by determination of [α_D] of selected examples.

The preparation of N-substituted tetramic acids **87**−**101** is outlined in Scheme 3 (see also Figure 5). Bromoacetyl bromide **78** was bound to Wang resin **3** using triethylamine in dichloromethane. The bromide on resin **79** was substituted with primary amines **80**−**84** to give the resin-bound secondary amines **85**, which were coupled with thioacetic acid derivatives **10**−**12** under PyBroP/DIEA conditions. The amide coupling of secondary amines is notoriously difficult, and many coupling reagents are either ineffective or inconvenient. PyBroP has been reported for the rapid and effective coupling of secondary amines; therefore, we chose this coupling reagent for our approach.[24−26] Resin **86** was finally treated with KOBu^t in THF to undergo cyclative cleavage to release the desired N-substituted tetramic acids **87**−**101**.

The sulfotetramic acid derivatives **108** and **109** were obtained from D,L-leucine **102**, which was protected as benzyl ester **104** by heating with benzyl alcohol **103** and *p*-toluenesulfonic acid in toluene (Scheme 4). Subsequently, the ester was coupled with (benzylthio)acetic acid **11** by the EDAC/HOBt method to afford **105**. The sulfide motif in **105** was oxidized by treatment with unpurified 70% *m*CPBA (1.2 equiv) in dichloromethane at −50 °C, resulting in a 1:2 mixture of the corresponding sulfoxide **106** and sulfone **107**. We were interested in both structures; therefore, we did not investigate other methods leading to a selective oxidation. The mixture was separated by flash chromatography on silica gel (EtOAc), resulting in a 1:1 diastereomeric mixture of the sulfoxide **106** and the racemic sulfone **107**. The treatment of **106** and **107** with KOBu^t in THF induced cyclative condensation to release the sulfotetramic acid derivatives **108** (1:1 diastereomer mixture) and racemic **109**.

Inhibitor Properties. The SAR of the tetronic and tetramic acids (Table 1 and 2) does not display a clear trend. Tetramic acids bearing a *meta*-trifluoromethyl aryl group separated by a S−CH_2 motif from the five-membered ring display the highest activities, whereas tetronic acids with the same substituents are less active. The N-substituted tetramic acids provide more consistent data. Compounds sharing a CH_2−CH_2−aryl and a CH_2−aryl substitution on either side display the best activities. The absolute position of these two groups seems unimportant. This fact suggests that there might be two orientations in the binding site or an allosteric regulation. The sulfoxide and sulfone substitution does not increase activity, which makes a hydrogen bond interaction at this position less likely.

Conclusions

We have synthesized tetronic, tetramic, and N-substituted tetramic acids via solid-phase-supported methodology. Several compounds thereof inhibit BACE-1 in the micromolar range. The Clog *P* and the PSA (**100**: Clog *P* = 3.85, tPSA = 77) of the best compounds are in a suitable range to target the central nervous system and leave enough space in chemical diversity to enhance activity, even by polar substituents. The acidic enol feature could reduce the blood−brain barrier penetration. This aspect, as well as further optimization of the activity, is the object of further investigation.

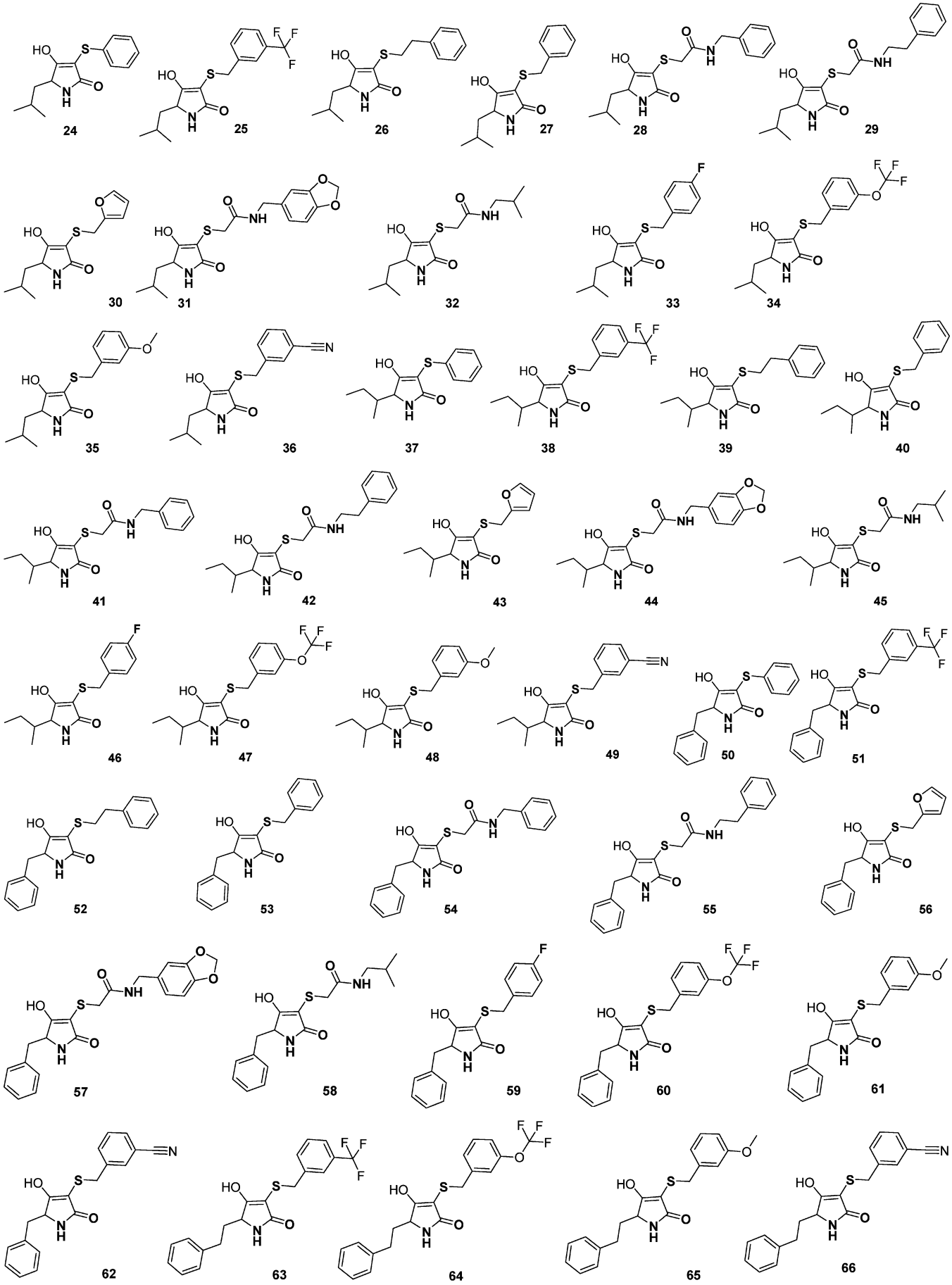
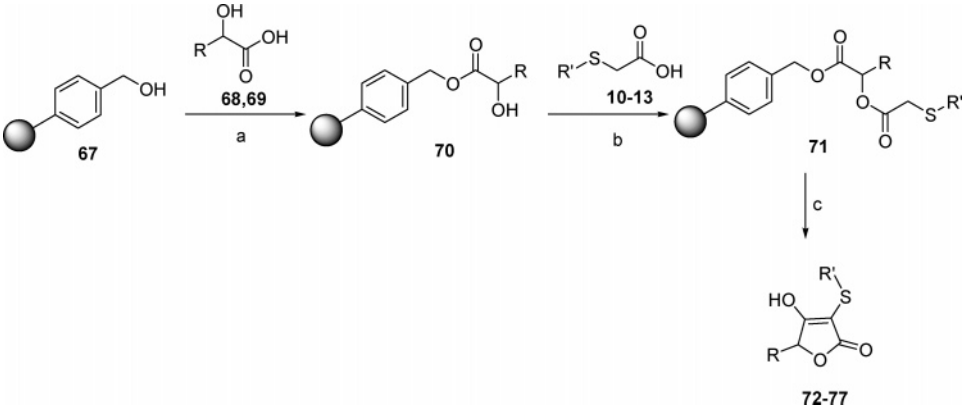


Figure 3. Tetramic acids **24**−**66**.

Scheme 2.[a] Solid-Phase Synthesis of Tetronic Acids



[a] Reagents and conditions: (a) *p*-toluenesulfonic acid, toluene, reflux, 20 h; (b) PyBoP, HOBt, DIEA, DMF, r.t., 20 h; (c) KOBu^t, THF, reflux, 1 h.

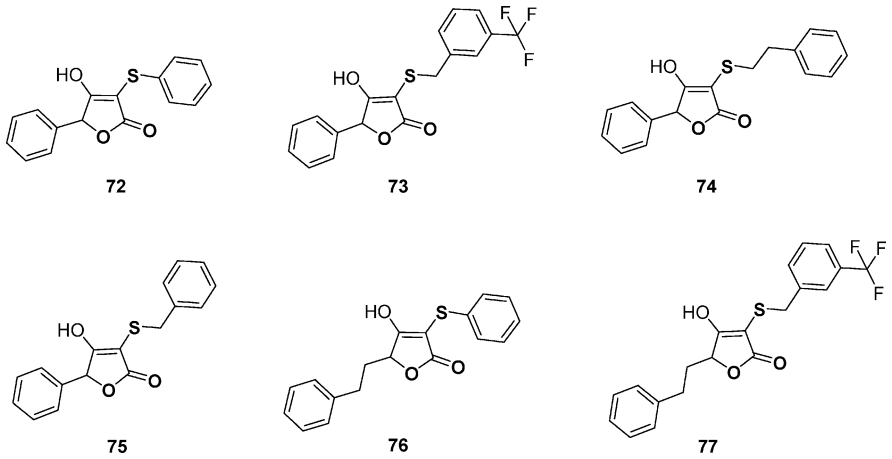
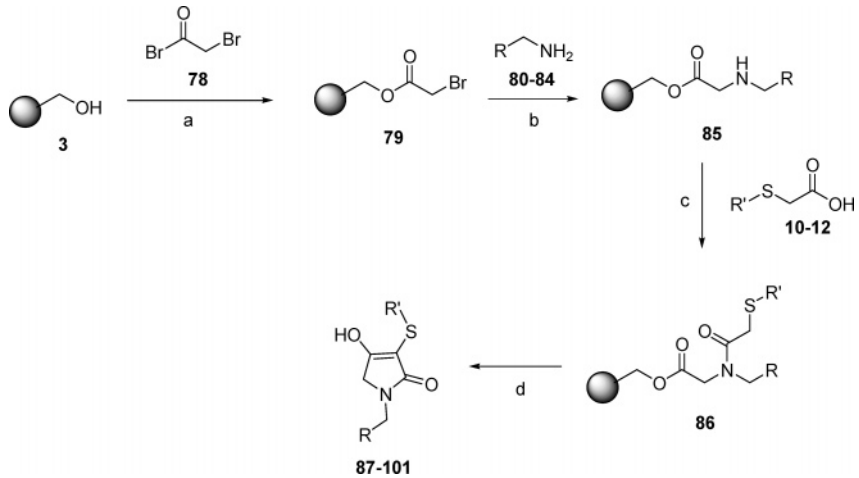


Figure 4. Tetronic acids **72**−**77**.

Scheme 3.[a] Solid-Phase Synthesis of N-Substituted Tetramic Acids



[a] Reagents and conditions: (a) Et_3N, r.t., 2 h; (b) Et_3N, r.t., 20 h; (c) PyBroP, DIEA, CH_2Cl_2, r.t., 20 h; (d) KOBu^t, THF, reflux, 1 h.

Experimental Section

General. ^{1}H- and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in DMSO-d_6 or $CDCl_3$ at room temperature (r.t.); chemical shift δ in parts per million.

Fluorescence Resonance Energy Transfer (FRET) Assay. Enzyme and Substrate. The substrate (Lucifer yellow-SEVNDLDAEFKR-dabsyl) was synthesized on TentaGel S-Rink amide resin (0.25 mmol/g, Rapp Polymer, Tübingen) following a standard procedure as described in ref 13. Full-length BACE-1 expressed from baculovirus was utilized as enzyme. The preparation was published previously.[13]

Assay. The FRET assay was performed at 20 °C on a FLUOstar (BMG Lab Technologies, D-77656 Offenburg) using 96-well microtiter plates (Dynex Microfluor 2, Chantilly, VA) as described elsewhere (see Supporting Information for details).

General Procedure for Solid-Phase Synthesis of Tetramic Acids (24−**66).** Wang resin (**3**, 300 mg, 0.33 mmol)

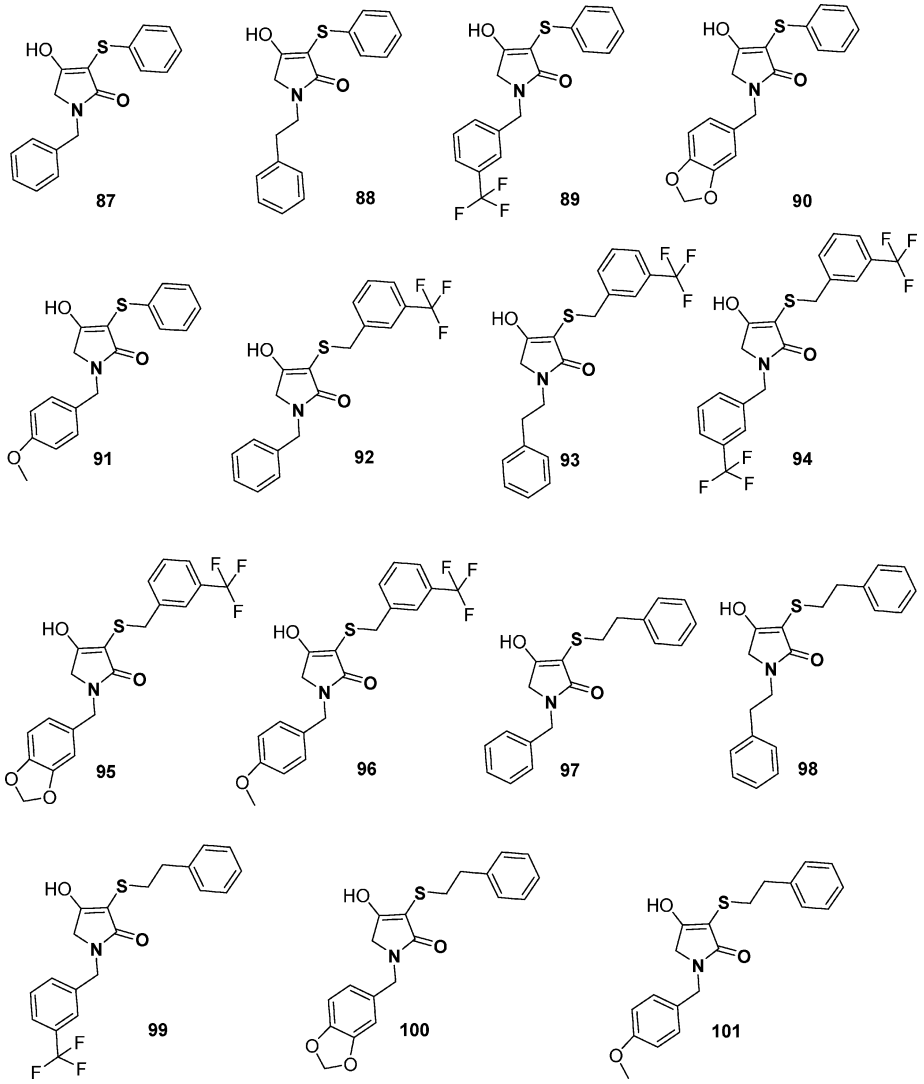


Figure 5. N-Substituted tetramic acids **87**−**101**.

was swollen in DMF (3 mL) at r.t. for 15 min, followed by the addition of a solution of Fmoc-protected amino acid (**4**−**7**, 0.66 mmol, in 1.5 mL DMF) and pyridine (86 mg, 1.08 mmol). After agitation for 20 min, dichlorobenzoyl chloride (138 mg, 0.66 mmol) was added, and the reaction mixture was shaken for 20 h, filtered, and washed (DMF, CH_2Cl_2, DMF, 5 × 5 mL each).

The loaded resin (**8**) was resuspended in DMF (5 mL, 5 min) at r.t., then treated with a solution of 20% piperidine in DMF (1 × 5 min, 1 × 25 min, 5 mL each), filtered, and washed (DMF, CH_2Cl_2, DMF, 5 × 5 mL each).

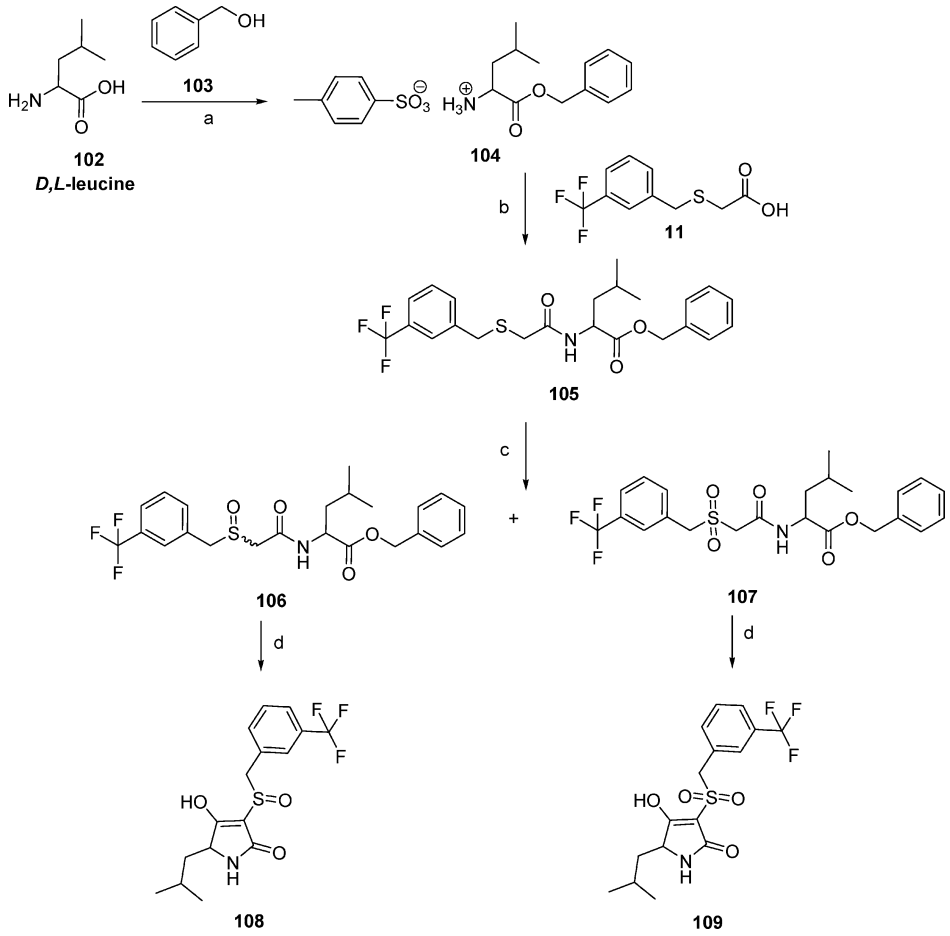
The resin (**9**) again was swollen in DMF (3 mL) at r.t. for 5 min, then treated with a solution of thioacetic acid derivative (**10**−**22**, 1 mmol), PyBOP (520 mg, 1 mmol), HOBt (153 mg, 1 mmol), and DIEA (259 mg, 2 mmol) in 2 mL of DMF. The reaction mixture was agitated for 20 h, filtered, and washed (DMF, CH_2Cl_2, THF, 5 × 5 mL each).

Cyclative cleavage was accomplished by resuspending the resin (**23**) in THF (4 mL), treating the suspension with $KOBu^t$ (45 mg, 0.4 mmol), and stirring under reflux for 1 h. The product was filtered off, the resin was washed (EtOAc, 3 × 10 mL), and the combined filtrates were treated with 1 N NaOH (3 × 10 mL). The combined basic layers were washed with *n*-hexane (2 × 10 mL), acidified with 2 N HCl, and extracted with EtOAc (3 × 10 mL). The solvent was removed after drying (Na_2SO_4) in vacuo to yield the crude product (**24**−**66**).

4-Hydroxy-5-isobutyl-3-(3-trifluoromethylbenzylsulfanyl)-1,5-dihydropyrrol-2-one (25). ^{1}H NMR (300 MHz, DMSO-d_6): 11.31 (s, acidic OH), 7.73 (s, NH), 7.54−7.46 (m, 4 arom H), 4.05−3.87 (m, CH_2), 3.78 (dd, CH, J = 3.0, 9.8 Hz), 1.70−1.59 (m, CH), 1.39 (ddd, 1H, CH_2, J = 3.1, 8.4, 9.7 Hz), 0.98−0.86 (m, 1H, CH_2), 0.8 (d, CH_3, J = 6.0 Hz), 0.78 (d, CH_3, J = 6.2 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 177.8 (C−OH), 172.0 (C═O), 140.4, 133.2, 129.3, 125.4, 123.6 (Ph), 94.3 (C), 54.7 (CH), 41.8, 35.4 (2 CH_2), 24.4, 23.7 (2 CH_3), 21.6 (CH). MS (EI): 345 (16, M^+), 289 (16), 186 (24), 159 (100), 99 (56), 86 (20).

3-Benzylsulfanyl-4-hydroxy-5-isobutyl-1,5-dihydropyrrol-2-one (27). ^{1}H NMR (300 MHz, DMSO-d_6): 11.3 (s, acidic OH), 7.73 (s, NH), 7.25−7.23 (m, 5 arom H), 3.88 (d, CH, J = 3.9 Hz), 3.83 (dd, CH_2, J = 2.5, 9.4 Hz), 1.74−1.65 (m, CH), 1.45 (ddd, 1H, CH_2, J = 3.3, 9.7, 13.1 Hz), 1.4 (ddd, 1H, CH_2, J = 4.3, 9.8, 13.7 Hz), 0.85 (d, CH_3, J = 3.8 Hz), 0.83 (d, CH_3, J = 3.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 176.1 (C−OH), 171.1 (C═O), 137.6, 128.0, 127.3, 125.8 (Ph), 94.3 (C), 53.6 (CH), 40.8, 35.2 (2 CH_2), 23.5, 22.9 (2 CH_3), 20.7 (CH).

Scheme 4.[a] Synthesis of Sulfotetramic Acids **108** and **109**



[a] Reagents and conditions: (a) *p*-toluenesulfonic acid, toluene, reflux, 14 h, (b) EDAC, HOBt, Et_3N, CH_2Cl_2, r.t., 20 h; (c) *m*CPBA, CH_2Cl_2, −50 °C, 1 h; (d) KOBu^t, THF, reflux, 1 h.

Table 1. Tetramic Acids **24**−**66**

code	yield (%)[a]	purity (%)[b]	FRET IC_{50} (μM)	code	yield (%)[a]	purity (%)[b]	FRET IC_{50} (μM)
24	26	99	inactive	**46**	30	68	inactive
25	48	45	194	**47**	35	100	inactive
26	56	83	inactive	**48**	32	100	inactive
27	45	96	inactive	**49**	38	95	inactive
28	45	80	inactive	**50**	45	100	inactive
29	42	100	inactive	**51**	57	98	inactive
30	37	55	200	**52**	50	95	inactive
31	45	85	inactive	**53**	45	94	inactive
32	38	39	inactive	**54**	63	74	inactive
33	25	69	inactive	**55**	54	83	inactive
34	42	100	inactive	**56**	60	70	145
35	40	100	inactive	**57**	62	70	inactive
36	45	98	inactive	**58**	54	83	inactive
37	30	100	inactive	**59**	35	76	inactive
38	27	95	60	**60**	40	64	inactive
39	21	78	inactive	**61**	42	93	inactive
40	49	93	inactive	**62**	45	98	inactive
41	25	62	inactive	**63**	36	100	inactive
42	23	98	inactive	**64**	35	72	inactive
43	31	76	200	**65**	38	100	inactive
44	45	60	>200	**66**	40	60	inactive
45	27	50	inactive				

[a] overall yields. [b] All of the final products were checked by HPLC.

***N*-Benzyl-2-(4-hydroxy-5-isobutyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl-sulfanyl)-acetamide (28).** ^{1}H NMR (300 MHz, DMSO-d_6): 12.5 (broad s, acidic OH), 8.91 (t, NH, J = 5.2 Hz), 8.52 (t, NH, J = 5.2 Hz), 7.81 (s, NH), 7.35−7.25 (m, 5 arom H), 4.31−4.27 (m, CH_2), 3.92 (dd, CH, J = 2.7, 9.3 Hz), 3.38 (s, CH_2), 1.82−1.73 (m, CH), 1.54 (ddd, 1H, CH_2, J = 3.3, 9.7, 13.0 Hz), 1.19 (ddd, 1H, CH_2, J = 4.3, 9.7, 13.6 Hz), 0.89 (d, CH_3, J = 2.5 Hz), 0.87 (d, CH_3, J = 2.6 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 170.9 (C−OH), 169.9 (C=O), 168.4 (C=O), 139.1, 138.6, 128.2, 127.1, 126.8 (Ph), 54.6 (CH), 42.2, 34.5, 33.7 (3 CH_2), 24.2, 23.5 (2 CH_3), 21.5 (CH).

Table 2. Tetronic Acids **72**−**77**, N-Substituted Tetramic Acids **87**−**101**, Sulfo-tetramic Acids **108**/**109**

code	yield (%)[a]	purity (%)[b]	FRET IC_{50} (μM)	code	yield (%)[a]	purity (%)[b]	FRET IC_{50} (mM)
72	17	100	105	**93**	13	88	184
73	13	98	inactive	**94**	13	100	258
74	12	63	>200	**95**	18	76	265
75	17	90	inactive	**96**	10	100	241
76	15	98	>200	**97**	14	84	459
77	13	98	>200	**98**	12	88	424
87	15	96	inactive	**99**	15	91	212
88	19	100	inactive	**100**	13	62	139
89	34	95	>200	**101**	12	73	>200
90	15	94	inactive	**108**	60	95	>200
91	14	95	>200	**109**	68	100	>200
92	16	100	212				

[a] overall yields. [b] All of the final products were checked by HPLC.

2-(4-Hydroxy-5-isobutyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl-sulfanyl)-*N*-phenylethylacetamide (29). ^{1}H NMR (300 MHz, DMSO-d_6): 12.5 (broad s, acidic OH), 8.6 (s, NH), 7.8 (s, NH), 7.30−7.20 (m, 5 arom H), 3.95−3.93 (m, CH), 3.35−3.29 (m, 4H, CH_2), 2.74 (t, CH_2, J = 7.3 Hz), 1.78−1.73 (m, CH), 1.55 (ddd, 1H, CH_2, J = 3.5, 9.1, 12.7 Hz), 1.22 (ddd, 1H, CH_2, J = 4.3, 9.5, 13.5 Hz), 0.89 (d, CH_3, J = 1.9 Hz), 0.87 (d, CH_3, J = 1.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 178.1 (C−OH), 171.9 (C═O), 170.0 (C═O), 139.1, 128.5, 128.2, 126.0 (Ph), 95.7 (C), 54.6 (CH), 41.5, 40.7, 37.7, 34.7 (4 CH_2), 24.2, 23.4 (2 CH_3), 21.5 (CH).

4-Hydroxy-5-isobutyl-3-(3-methoxybenzylsulfanyl)-1,5-dihydropyrrol-2-one (35). ^{1}H NMR (300 MHz, DMSO-d_6): 11.3 (broad s, acidic OH), 7.70 (s, NH), 7.17−7.12 (m, 1 arom H), 6.79−6.73 (m, 3 arom H), 3.86−3.79 (m, 3H, CH, CH_2), 3.70 (s, CH_3), 1.69−1.50 (m, CH), 1.45 (ddd, 1H, CH_2, J = 3.3, 9.7, 13.1 Hz), 1.11−0.99 (m, 1H, CH_2), 0.84 (d, CH_3, J = 3.8 Hz), 0.82 (d, CH_3, J = 3.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 177.1 (C−OH), 171.9 (C═O), 159.0, 129.0, 121.1, 114.2, 112.3 (Ph), 95.0 (C), 54.8 (CH_3), 41.6, 36.0 (2 CH_2), 24.3, 23.6 (2 CH_3), 21.5 (CH). MS (EI): 307 (27, M^+), 156 (30), 153 (16), 121 (100), 99 (15), 91 (11).

3-(4-Hydroxy-5-isobutyl-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl-sulfanylmethyl)-benzonitrile (36). ^{1}H NMR (300 MHz, DMSO-d_6): 11.36 (broad s, acidic OH), 7.74 (s, NH), 7.66 (d, 1 arom H, J = 7.5 Hz), 7.56−7.54 (m, 2 arom H), 7.48 (d, 1 arom H, J = 7.5 Hz), 3.98−3.83 (m, 3H, CH, CH_2), 1.72−1.63 (m, CH), 1.45 (ddd, 1H, CH_2, J = 3.1, 9.9, 12.9 Hz), 1.11−0.97 (m, 1H, CH_2), 0.85 (d, CH_3, J = 2.3 Hz), 0.83 (d, CH_3, J = 2.4 Hz) ^{13}C NMR (75 MHz, DMSO-d_6): 177.9 (C−OH), 171.8 (C═O), 140.4, 133.8, 132.2, 130.4, 129.3 (Ph), 118.7 (CN), 110.9 (Ph), 94.0 (C), 54.5 (CH), 41.6, 35.1 (2 CH_2), 24.2, 23.6 (2 CH_3), 21.5 (CH). MS (EI): 302 (12, M^+), 246 (10), 186 (28), 116 (100), 99 (73), 89 (22).

5-*sec*-Butyl-4-hydroxy-3-phenylsulfanyl-1,5-dihydropyrrol-2-one (37). (1.4:1 diasteromer mixture assigned by ^{1}H NMR) ^{1}H NMR (300 MHz, DMSO-d_6): 7.71 (s, NH), 7.67 (s, NH), 7.23−7.17 (m, 2 arom H), 7.06−7.03 (m, 3 arom H), 4.10 (s, CH), 4.03 (s, CH), 1.85−1.78 (m, CH), 1.45−1.19 (m, 1H, CH_2), 1.07−0.99 (m, 1H, CH_2), 0.92−0.77 (m, 5 H, CH_3), 0.63 (d, 1H, CH_3, J = 6.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 178.9 (C−OH), 171.2 (C═O), 136.7, 127.9, 124.6, 124.0 (Ph), 60.5, 58.7, 34.9 (CH), 25.6 (CH_2), 14.9, 11.1 (2 CH_3).

5-*sec*-Butyl-4-hydroxy-3-(3-trifluoromethylbenzylsulfanyl)-1,5-dihydropyrrol-2-one (38). (1.4:1 diasteromer mixture assigned by ^{1}H NMR) ^{1}H NMR (300 MHz, DMSO-d_6): 11.35 (broad s, acidic OH), 7.71−7.49 (m, NH, 4 arom H), 4.157 (d, CH, J = 7.0 Hz), 4.13 (d, CH, J = 7.0 Hz), 3.97−3.81 (m, CH_2), 1.75−1.65 (m, CH), 1.38−1.16 (m, CH_2), 0.89−0.67 (m, 5H, CH_3), 0.36 (d, 1H, CH_3, J = 6.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 175.7 (C−OH), 172.3 (C═O), 140.1, 132.8, 129.3, 128.9, 128.6, 125.0, 123.1 (Ph), 95.1 (C), 60.8, 59.0 (CH), 35.0 (CH_2), 34.7 (CH), 26.1, 21.2 (CH_2), 15.6, 11.3 (2 CH_3). MS (EI): 345 (18, M^+), 250 (18), 191 (63), 186 (18), 159 (100), 128 (18), 99 (15), 86 (15).

3-Benzylsulfanyl-5-*sec*-butyl-4-hydroxy-1,5-dihydropyrrol-2-one (40). (1:1 diasteromer mixture assigned by ^{1}H NMR) ^{1}H NMR (300 MHz, DMSO-d_6): 11.19 (broad s, acidic OH), 7.57 (s, NH), 7.52 (s, NH), 7.24−7.17 (m, 5 arom H), 4.01 (d, CH, J = 2.7 Hz), 3.96 (d, CH, J = 2.7 Hz), 3.87−3.79 (m, CH_2), 1.75−1.66 (m, CH), 1.37−1.14 (m, CH_2), 0.87−0.82 (m, 3H, CH_3), 0.74−0.69 (m, 2H, CH_3), 0.41 (d, 1H, CH_3, J = 6.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 175.0 (C−OH), 172.2 (C═O), 138.2, 128.4, 127.7, 126.3 (Ph), 95.7 (C), 60.6, 58.8 (CH), 35.6 (CH_2), 35.0, 34.6 (CH), 26.0, 21.2 (CH_2), 15.5, 11.4 (2 CH_3).

5-*sec*-Butyl-4-hydroxy-3-(3-methoxybenzylsulfanyl)-1,5-dihydropyrrol-2-one (48). (1:1 diasteromer mixture assigned by ^{1}H NMR) ^{1}H NMR (300 MHz, DMSO-d_6): 11.22 (broad s, acidic OH), 7.53 (s, NH), 7.49 (s, NH), 7.14 (t, 1 arom H, J = 7.8 Hz), 6.84−6.72 (m, 3 arom H), 3.97 (d, CH, J = 5.1 Hz), 3.93 (d, CH, J = 5.1 Hz), 3.87−3.73 (m, CH_2), 3.71 (s, CH_3), 1.74−1.65 (m, CH), 1.37−1.14 (m, CH_2), 0.87−0.82 (m, 3H, CH_3), 0.73−0.68 (m, 2H, CH_3), 0.41 (d, 1H, CH_3, J = 6.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 175.4 (C−OH), 172.7 (C═O), 158.4, 140.0, 129.1, 121.0, 114.2, 112.3 (Ph), 96.1 (C), 61.0, 59.1 (CH), 54.9 (CH_3), 36.0 (CH_2), 35.4, 35.0 (CH), 26.3, 21.5 (CH_2), 15.9, 11.9 (2 CH_3). MS (EI): 307 (17, M^+), 156 (33), 153 (15), 121 (100), 99 (12), 91 (11).

(5-*sec*-Butyl-4-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrol-3-ylsulfanylmethyl)-benzonitrile (49). (1:1 diasteromer mixture assigned by ^{1}H NMR) ^{1}H NMR (300 MHz, DMSO-d_6): 11.27 (broad s, acidic OH), 7.67−7.44 (m, NH, 4 arom H), 4.10 (d, CH, J = 6.1 Hz), 4.08 (d, CH, J = 6.1 Hz), 3.88−3.80 (m, CH_2), 1.71−1.66 (m, CH), 1.35−1.23 (m, 1H, CH_2), 1.21−1.07 (m, 1H, CH_2), 0.87−0.70 (m, 5 H, CH_3), 0.36 (*d*, 1H, CH_3, J = 6.7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 175.7 (C−OH), 172.1 (C═O), 140.3, 133.5, 131.9, 130.3, 129.0, 118.4 (Ph), 110.7 (CN), 94.7 (C), 60.7, 58.8, 35.2 (CH), 34.5, 25.9, 21.0 (CH_2), 15.4, 11.4 (2 CH_3). MS (EI): 302 (15, M^+), 186 (44), 116 (100), 99 (80), 89 (24).

5-Benzyl-4-hydroxy-3-phenylsulfanyl-1,5-dihydropyrrol-2-one (50). ^{1}H NMR (300 MHz, DMSO-d_6): 12.22 (broad s, acidic OH), 7.82 (s, NH), 7.29−7.20 (m, 5 arom H), 7.06−6.95 (m, 3 arom H), 6.45−6.42 (m, 2 arom H), 4.43 (t, CH, J = 3.8 Hz), 3.11−2.98 (m, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): 179.0 (C−OH), 170.8 (C═O), 136.9, 135.2, 129.9, 128.5, 127.8, 126.5, 124.7, 124.2 (Ph), 93.5 (C), 56.8 (CH), 35.9 (CH_2). MS (EI): 297 (100, M^+), 206 (92), 200 (12), 188 (24), 178 (16), 151 (19), 120 (29), 109 (22), 91 (65).

5-Benzyl-4-hydroxy-3-(3-trifluoromethylbenzylsulfanyl)-1,5-dihydropyrrol-2-one (51). ^{1}H NMR (300 MHz, DMSO-d_6): 11.6 (s, acidic OH), 7.57−7.38 (m, NH, 4 arom H), 7.21−7.11 (m, 5 arom H), 4.12 (t, CH, J = 4.8 Hz), 3.76 (s, CH_2), 2.95 (dd, 1H, CH_2, J = 3.9, 13.7 Hz), 2.66 (dd, 1H, CH_2, J = 6.2, 13.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 175.4 (C−OH), 171.1 (C═O), 139.7, 135.8, 132.5, 129.1, 128.8, 127.5, 126.0, 124.8, 123.3 (Ph), 95.6 (C), 56.3 (CH), 36.9, 35.5 (2 CH_2). MS (EI): 379 (48, M^+), 346 (10), 288 (10), 220 (16), 189 (39), 159 (100), 91 (50).

5-Benzyl-3-benzylsulfanyl-4-hydroxy-1,5-dihydropyrrol-2-one (53). ^{1}H NMR (300 MHz, DMSO-d_6): 11.57 (broad s, acidic OH), 7.58 (s, NH), 7.26−7.14 (m, 10 arom H), 4.17 (t, CH, J = 4.6 Hz), 3.66 (s, CH_2), 2.97 (dd, 1H, CH_2, J = 4.1, 13.8 Hz), 2.76 (dd, 1H, CH_2, J = 5.8, 13.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 174.3 (C−OH), 170.9 (C═O), 137.5, 135.3, 128.8, 127.4, 127.0, 126.0, 125.6 (Ph), 96.9 (C), 55.8 (CH), 36.3, 35.7 (2 CH_2).

***N*-Benzyl-2-(5-benzyl-4-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl-sulfanyl)-acetamide (54).** ^{1}H NMR (300 MHz, DMSO-d_6): 12.62 (broad s, acidic OH), 8.94 (s, NH), 8.52 (s, NH), 7.66 (s, NH), 7.31−7.18 (m, 10 arom H), 4.46−4.28 (m, 3H, CH, CH_2), 3.39−3.19 (m, CH_2), 3.05−2.82 (m, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): 171.6 (C−OH), 170.1 (C═O), 168.5 (C═O), 139.1, 138.4, 135.6, 129.5, 129.0, 128.2, 127.6, 127.1 126.8, 126.3 (Ph), 97.1 (C), 55.5, 53.5 (CH), 42.7, 37.9, 36.9, 34.5, 33.7 (3 CH_2);

5-Benzyl-4-hydroxy-3-(3-methoxybenzylsulfanyl)-1,5-dihydropyrrol-2-one (61). ^{1}H NMR (300 MHz, DMSO-d_6): 11.8 (broad s, acidic OH), 7.53 (s, NH), 7.24−7.14 (m, 6 arom H), 6.81−6.72 (m, 3 arom H), 4.15 (t, CH, J = 4.5 Hz), 3.71 (s, CH_3), 3.65 (d, CH_2, J = 3.3 Hz), 3.04−2.95 (m, 1H, CH_2), 2.76−2.70 (m, 1H, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): 175.2 (C−OH), 171.6 (C═O), 159.2, 139.8, 136.1, 129.5, 127.8, 126.3, 121.2, 114.4, 112.3 (Ph), 96.9 (C), 56.6 (CH), 54.9 (CH_3), 37.2, 35.3 (2 CH_2). MS (EI): 341 (37, M^+), 190 (60), 153 (15), 121 (100), 91 (64).

3-(5-Benzyl-4-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl-sulfanylmethyl)-benzonitrile (62). ^{1}H NMR (300 MHz, DMSO-d_6): 11.66 (broad s, acidic OH), 7.68−7.65 (m, NH), 7.56−7.40 (m, 4 arom H), 7.25−7.14 (m, 5 arom H), 4.16 (t, CH, J = 4.7 Hz), 3.72 (d, CH_2, J = 4.6 Hz), 2.97 (dd, 1H, CH_2, J = 4.0, 13.8 Hz), 2.71 (dd, 1H, CH_2, J = 6.1, 13.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 175.9 (C−OH), 171.4 (C═O), 140.3, 135.1, 133.5, 132.1, 130.3, 129.4, 127.7, 126.2 (Ph), 118.7 (CN), 110.9 (Ph), 95.9 (C), 55.5 (CH), 37.1, 35.7 (2 CH_2). MS (EI): 336 (16, M^+), 189 (25), 116 (66), 91 (100).

4-Hydroxy-3-(3-methoxybenzylsulfanyl)-5-phenethyl-1,5-dihydropyrrol-2-one (65). ^{1}H NMR (300 MHz, DMSO-d_6): 11.3 (s, acidic OH), 7.77 (s, NH), 7.30−7.25 (m, 2 arom H), 7.20−7.11 (m, 4 arom H), 6.81−6.80 (m, 2 arom H), 6.70 (dd, 1 arom H, J = 2.1, 8.0 Hz), 3.96−3.92 (m, CH), 3.85−3.81 (m, CH_2), 3.66 (s, CH_3), 2.43−2.40 (m, CH_2), 1.96−1.86 (m, 1H, CH_2), 1.60−1.55 (m, 1H, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): 175.5 (C−OH), 171.6 (C═O), 158.6, 141.0, 139.6, 128.7, 127.9, 125.4, 120.7, 113.9, 111.6 (Ph), 95.3 (C), 55.1 (CH_3), 54.4 (CH), 35.5, 33.2, 29.7 (3 CH_2). MS (EI): 355 (20, M^+), 204 (51), 149 (12), 121 (100), 99 (33), 91 (33).

General Procedure for Solid-Phase Synthesis of Tetronic Acids (72−77). Hydroxypolystyrene resin (**67**, 400 mg, 0.39 mmol) was swollen in toluene (4 mL) at r.t., followed by the addition of α-hydroxy acid (**68/69**, 1.57 mmol) and *p*-toluenesulfonic acid (15 mg, 0.08 mmol). After agitation for 20 h under reflux, the resin (**70**) was washed (toluene, CH_2Cl_2, DMF, 5 × 5 mL each); resuspended in DMF (3 mL); and treated with a solution of thioacetic acid derivative (**10**−**13**, 1.18 mmol), PyBOP (614 mg, 1.18 mmol), HOBt (181 mg, 1.18 mmol), and DIEA (304 mg, 2.35 mmol) in 2 mL of DMF. The reaction mixture was agitated for 20 h, filtered, and washed (DMF, CH_2Cl_2, THF, 5 mL each).

Cyclative cleavage was accomplished by resuspending the resin (**71**) in THF (4 mL), treating the suspension with KOBu^t (53 mg, 0.47 mmol), and stirring under reflux for 1 h. The product was filtered off, the resin was washed (EtOAc, 3 × 10 mL), and the combined filtrates were treated with 1 N NaOH (3 × 10 mL). The combined basic layers were washed with *n*-hexane (2 × 10 mL), acidified with 2 N HCl, and extracted with EtOAc (3 × 10 mL). The solvent was removed after drying (Na_2SO_4) in vacuo to yield the crude product (**72**−**77**).

4-Hydroxy-5-phenyl-3-(3-trifluoromethylbenzylsulfanyl)-5*H*-furan-2-one (73). MS (EI): 366 (13, M^+), 348 (76), 320 (9), 280 (13), 248 (13), 159 (100), 109 (9).

3-Benzylsulfanyl-4-hydroxy-5-phenyl-5*H*-furan-2-one (75). ^{1}H NMR (300 MHz, DMSO-d_6): 7.33−7.28 (m, 8 arom H), 7.01−6.98 (m, 2 arom H), 5.78 (s, CH), 4.06−3.92 (m, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): 180.4 (C−OH), 171.4 (C═O), 137.5, 134.3, 128.8, 128.6, 128.3, 128.0, 127.1, 126.6 (Ph), 89.9 (C), 78.8 (CH), 35.5 (CH_2). MS (EI): 298 (9, M^+), 280 (16), 91 (100), 77 (11), 65 (19).

4-Hydroxy-5-phenethyl-3-phenylsulfanyl-5*H*-furan-2-one (76). ^{1}H NMR (300 MHz, DMSO-d_6): 7.33−7.12 (m, 10 arom H), 5.01 (dd, CH, J = 3.3, 8.2 Hz), 2.71 (dd, CH_2, J = 6.4, 9.3 Hz)), 2.26 (ddt, 1H, CH_2, J = 3.3, 8.1, 12.4 Hz), 1.99−1.86 (m, 1H, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): 185.3 (C−OH), 171.3 (C═O), 140.2, 135.6, 128.7, 128.1, 125.8, 125.5, 125.1 (Ph), 87.7 (C), 77.1 (CH), 33.9, 29.9 (2 CH_2).

4-Hydroxy-5-phenethyl-3-(3-trifluoromethylbenzylsulfanyl)-5*H*-furan-2-one (77). ^{1}H NMR (300 MHz, DMSO-d_6): 7.52−7.45 (m, 5 arom H), 7.30−7.11 (m, 5 arom H), 4.74 (dd, CH, J = 3.3, 7.9 Hz), 3.99 (q, CH_2, J = 13.1 Hz), 2.46−2.39 (m, CH_2), 2.09−1.98 (m, 1H, CH_2), 1.59 (ddt, 1H, CH_2, J = 5.3, 8.0, 9.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 182.6 (C−OH), 171.8 (C═O), 140.8, 139.2, 129.4, 128.6, 128.5, 126.2, 125.6, 123.8 (Ph), 90.0 (C), 77.2 (CH), 35.6, 33.2, 30.0 (3 CH_2).

General Procedure for Solid-Phase Synthesis of N-Substituted Tetramic Acids (87−101). Wang resin (**3**, 300 mg, 0.33 mmol) was swollen in CH_2Cl_2 (3 mL) at r.t. for 15 min and subsequently treated with Et_3N (101 mg, 1 mmol), followed by dropwise addition of a solution of bromoacetylbromide in CH_2Cl_2 (**78**, 121 mg, 0.66 mmol, in 1.5 mL of CH_2Cl_2). After agitation for 2 h at r.t., the resin was filtered and washed (CH_2Cl_2, DMF, CH_2Cl_2, 5 × 5 mL each). To ensure completion of the reaction, the resin was subjected to a second treatment with Et_3N (101 mg, 1 mmol) and a solution of bromoacetylbromide in CH_2Cl_2 (121 mg, 0.66 mmol, in 1.5 mL CH_2Cl_2) and agitated for 2 h at r.t. The resin was filtered and washed (CH_2Cl_2, DMF, CH_2Cl_2, 5 × 5 mL each).

The loaded resin (**79**) was resuspended in DMF (4 mL, 5 min) at r.t., then treated with Et_3N (101 mg, 1 mmol) and amine (**80**−**84**, 1 mmol). The reaction mixture was agitated for 20 h, filtered, and washed (DMF, CH_2Cl_2, DMF, 5 × 5 mL each).

The resin again was swollen in DMF (3 mL) at r.t. for 5 min, then treated with a solution of thioacetic acid derivative (**10**−**12**, 1 mmol), PyBroP (466 mg, 1 mmol), and DIEA (259 mg, 2 mmol) in 2 mL of DMF. The reaction mixture was agitated for 20 h, filtered, and washed (DMF, CH_2Cl_2, THF, 5 × 5 mL each).

Cyclative cleavage was accomplished by resuspending the resin (**86**) in THF (4 mL), treating the suspension with $KOBu^t$ (45 mg, 0.4 mmol), and stirring under reflux for 1 h. The product was filtered off, the resin was washed (EtOAc, 3 × 10 mL), and the combined filtrates were treated with 1 N NaOH (3 × 10 mL). The combined basic layers were washed with *n*-hexane (2 × 10 mL), acidified with 2 N HCl, and extracted with EtOAc (3 × 10 mL). The solvent was removed after drying (Na_2SO_4) in vacuo to yield the crude product (**87**−**101**).

1-Benzyl-4-hydroxy-3-phenylsulfanyl-1,5-dihydropyrrol-2-one (87). ^{1}H NMR (300 MHz, DMSO-d_6): 12.4 (broad s, acidic OH), 7.38−7.33 (m, 2 arom H), 7.28−7.20 (m, 5 arom H), 7.14−7.08 (m, 3 arom H), 4.52 (s, CH_2), 3.95 (s, CH_2). ^{13}C NMR (75 MHz, DMSO-d_6): 176.4 (C−OH), 169.8 (C═O), 137.5, 136.8, 128.5, 128.3, 127.1, 126.8, 125.3, 124.6 (Ph), 92.4 (C), 49.5, 44.8 (2 CH_2).

4-Hydroxy-3-phenylsulfanyl-1-(3-trifluoromethylbenzyl)-1,5-dihydropyrrol-2-one (89). ^{1}H NMR (300 MHz, DMSO-d_6): 7.65−7.52 (m, 4 arom H), 7.27−7.22 (m, 2 arom H), 7.13−7.11 (m, 3 arom H), 4.62 (s, CH_2), 4.00 (s, CH_2). MS (EI): 365 (93, M^+), 159 (100), 135 (45), 109 (77).

1-Benzo[1,3]dioxol-5-yl-methyl-4-hydroxy-3-phenylsulfanyl-1,5-dihydropyrrol-2-one (90). ^{1}H NMR (300 MHz, DMSO-d_6): 12.4 (broad s, acidic OH), 7.29−7.24 (m, 2 arom H), 7.14−7.11 (m, 3 arom H), 6.88 (d, 1 arom H, J = 7.9 Hz), 6.78 (d, 1 arom H, J = 1.3 Hz), 6.72 (dd, 1 arom H, J = 1.3, 7.9 Hz), 6.00 (s, CH_2), 4.40 (s, CH_2), 3.90 (s, CH_2). MS (EI): 341 (13, M^+), 232 (85), 135 (100), 109 (14), 77 (24).

***H*-Leu-OBzl·*p*-tosylate (104).** D,L-Leucine (**102**, 262.4 mg, 2 mmol) was dissolved in toluene (10 mL) and treated with *p*-toluenesulfonic acid (457 mg, 2.4 mmol) and benzyl alcohol (**103**, 3.46 g, 32 mmol). The mixture was refluxed under a Dean−Stark trap (14 h), cooled to r.t., treated with diethyl ether (10 mL), and stored in the refrigerator to precipitate a salt that was filtered and dried in vacuo to give **104** as a colorless solid (732 mg, 93%).

Benzyl-2-(2-(3-(trifluoromethyl)benzylthio)acetamido)-4-methylpentanoate (105). EDAC (288 mg, 1.5 mmol) and HOBt hydrate (276 mg, 1.8 mmol) were added to a solution of 2-(3-(trifluoromethyl)benzylthio)acetic acid (**10**; 375 mg, 1.5 mmol) dissolved in CH_2Cl_2 (5 mL), and the resulting mixture was stirred at r.t. for 10 min. Then *H*-Leu-OBzl·*p*-tosylate (**104**, 610 mg, 1.55 mmol) and Et_3N (228 mg, 2.25 mmol) were added, and the mixture was stirred for 20 h. CH_2Cl_2 (20 mL) was added, and the solution was washed with 0.1 N HCl (3 × 30 mL), 0.1 N NaOH solution (3 × 30 mL), and brine (30 mL) and dried ($MgSO_4$). The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel ($CHCl_3$) to give compound **105** as a colorless oil (377 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.58 (m, 9 arom H), 7.04 (d, NH, J = 8.5 Hz), 5.19 (d, CH_2, J = 4.5 Hz), 4.72−4.64 (m, CH_2), 3.78 (s, CH_2), 3.12 (s, CH_2), 1.76−1.66 (m, CH_2), 1.63−1.54 (m, CH), 0.94 (d, CH_3, J = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 172.7, 168.3 (2 C═O), 138.0, 135.4, 132.6, 131.8, 129.5, 128.7, 125.9, 124.4 (Ph), 122.3 (F_3C), 67.3 (CH_2), 51.2 (CH), 41.3, 36.1, 35.0 (3 CH_2), 25.1 (CH), 22.9, 21.9 (2 CH_3).

Oxidation of 105 with *m*CPBA. A solution of *m*CPBA (217 mg, 1.26 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a stirred solution of **105** (377 mg, 0.83 mmol) in CH_2Cl_2 (2 mL) at −50 °C. The mixture was stirred at −50 °C for 1 h, then CH_2Cl_2 was added (5 mL), and the solution was washed with a saturated solution of $NaHCO_3$ (3 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated in vacuo to yield a mixture of crude **106** and crude **107**, which were separated by flash chromatography on silica gel (EtOAc) to give compound **106** as a colorless solid (115 mg, 29.5%) and compound **107** as a colorless solid (235 mg, 58.3%).

Benzyl-2-(2-(3-(trifluoromethyl)benzylsulfinyl)-acetamido)-4-methylpentanoate (106). ^{1}H NMR (300 MHz, $CDCl_3$): 7.63−7.61 (m, 2 arom H), 7.55−7.50 (m, 2 arom H), 7.35−7.34 (m, 5 arom H), 7.14 (d, NH, J = 7.7 Hz), 5.19 (dd, CH_2, J = 4.0, 8.2 Hz), 4.69−4.62 (m, CH), 4.26 (dd, CH_2, J = 12.4, 54.8 Hz), 3.46 (ddd, CH_2, J = 14.9, 41.4, 67.8 Hz), 1.75−1.63 (m, CH_2, CH), 0.94 (td, CH_3, J = 2.5, 4.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 172.4, 164.3 (2 C═O), 135.1, 133.7, 130.5, 130.2, 129.4, 128.4, 126.9, 125.3 (Ph), 121.8 (F_3C), 67.1 (CH_2), 55.4 (CH_2), 52.6 (CH), 51.4, 40.5 (2 CH_2), 24.8 (CH), 22.7, 21.4 (2 CH_3). ESI-MS m/z 492.1 ($(M + Na)^+$).

Benzyl-2-(2-(3-(trifluoromethyl)benzylsulfonyl)-acetamido)-4-methylpentanoate (107). ^{1}H NMR (300 MHz, $CDCl_3$): 7.76 (s, 1 arom H), 7.69−7.66 (m, 2 arom H), 7.52 (*t*, 1 arom H, J = 7.8 Hz), 7.36−7.34 (m, 5 arom H), 7.00 (d, NH, J = 8.0 Hz), 5.19 (d, CH_2, J = 3.0 Hz), 4.70−4.62 (m, CH), 4.52 (d, CH_2, J = 2.3 Hz), 3.80 (q, CH_2, J = 14.7 Hz), 1.73−1.60 (m, CH_2, CH), 0.93 (d, CH_3, J = 5.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 172.4, 161.6 (2 C═O), 135.3, 129.7, 128.9, 126.3 (Ph), 125.6 (F_3C), 67.6 (CH_2), 58.6, 57.1 (2 CH_2), 51.9 (CH), 40.8 (CH_2), 25.0 (CH), 22.9, 21.8 (2 CH_3). ESI-MS m/z 508.2 ($(M + Na)^+$).

3-(3-(Trifluoromethyl)benzylsulfinyl)-4-hydroxy-5-isobutyl-1*H*-pyrrol-2(5*H*)-one (108). Compound **106** (115 mg, 0.25 mmol) was dissolved in THF (3 mL) and treated with $KOBu^t$ (34 mg, 0.3 mmol). The mixture was stirred under reflux for 1 h, then EtOAc (10 mL) was added, and the solution was extracted with 1 N NaOH (3 × 10 mL). The combined basic layers were washed with *n*-hexane (2 × 10 mL), acidified with 2 N HCl and extracted with EtOAc (3 × 10 mL). The solvent was removed after drying (Na_2SO_4) in vacuo to yield the crude **108** (105 mg) as a yellow oil, which was crystallized from EtOAc/*n*-hexane (54 mg, 60%). Colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6): 8.04 (s, NH), 7.66−7.59 (m, 4 arom H), 4.78 (ddd, CH, J = 11.6, 37.5, 28.2 Hz), 1.78−1.60 (m, CH), 1.45 (td, 1H CH_2, J = 10.5, 21.5 Hz), 1.19−1.07 (m, 1H, CH_2), 0.85 (d, CH_3, J = 6.5 Hz), 0.77 (d, CH_3, J = 6.3 Hz).

3-(3-(Trifluoromethyl)benzylsulfonyl)-4-hydroxy-5-isobutyl-1*H*-pyrrol-2(5*H*)-one (109). (68%) ^{1}H NMR (300 MHz,

DMSO-d_6): 7.71 (d, NH, $J = 4.9$ Hz), 7.61−7.58 (m, 4 arom H), 4.65 (dd, CH_2, $J = 13.7$, 32.7 Hz), 3.95 (dd, CH, $J = 2.9$, 9.9 Hz), 1.73−1.64 (m, CH), 1.47 (ddd, 1H, CH_2, $J = 3.0$, 9.9, 12.9 Hz), 1.07−0.98 (m, 1H, CH_2), 0.82 (d, CH_3, $J = 6.5$ Hz). ^{13}C NMR (75 MHz, DMSO-d_6): 182.8 (C−OH), 167.9 (C═O), 134.7, 130.8, 129.3, 129.2, 128.6, 126.8, 125.7, 124.8 (Ph), 122.2 (F_3C), 99.8 (C), 58.4 (CH_2), 55.5 (CH), 40.9 (CH_2), 24.0, 23.2 (2 CH_3), 21.0 (CH).

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Supporting Information Available. Analytical data (^{1}H NMR, ^{13}C NMR, HPLC, MS, and IR) of representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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