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Synthesis of the Thiazole–Thiazoline Fragment of Largazole Analogues

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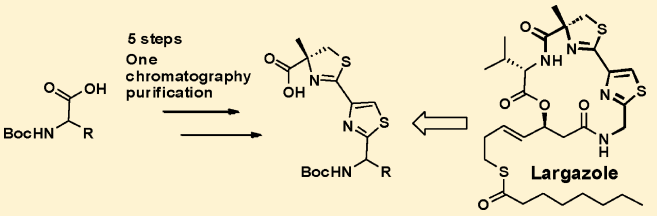
Supporting Information

ABSTRACT: The thiazole–thiazoline fragment of the marine natural product largazole, a potent histone deacetylase 1 inhibitor, has been synthesized in five steps. The methodology provides rapid access to thiazole-4-carbonitrile, thiazole-4-carbimidate, thiazole–oxazoline, and other thiazole–thiazoline derivatives that are important intermediates in the total synthesis of many natural products with important biological properties.



Microorganisms are important sources of bioactive secondary metabolites, which serve as novel leads for developing pharmaceuticals.[1−3] A large group of secondary metabolites are peptide derivatives with azole/azoline heterocycles, such as thiazole, oxazole, thiazoline, or oxazoline incorporated into the peptide backbone.[4−6] Many subclasses of these compounds have been named after the organism of origin; however, we use "azotides" here to cover azole/azoline-containing peptides in general. Two of the most studied azotides are GE2270A[7−9] and largazole,[10−12] which have a thiazole heterocycle directly connected to a thazoline or oxazoline (Figure 1). GE2270A belongs to a large group of potent natural antibiotics, many of which contain a thiazole–oxazoline motif.[9,13,14] Such compounds selectively inhibit bacterial protein synthesis and have shown antibacterial activity against vancomycin-resistant strains of bacteria, making them potentially interesting antibiotics of last resort.[15−18] The total syntheses of GE2270A and related natural products have been heavily investigated, but even the least complex compounds of this family are not trivial to synthesize.

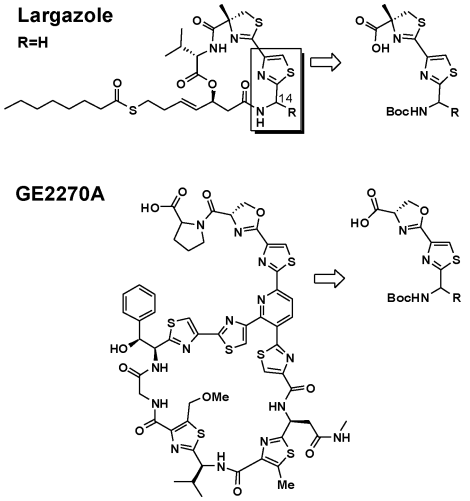


Figure 1. Azole–azoline building blocks for the synthesis of largazole and GE2270A.

Largazole contains a thiazole–thiazoline motif and is among the most potent known inhibitors of an important enzyme known as histone deacetylase 1.[10,19−21] Largazole selectively inhibits the growth of fibroblast cancer cells at 1/10 of the concentration required to inhibit nontransformed cells and also inhibits tumor growth in vivo.[10,22] The reason for this selectivity is not yet understood, despite more than 40 derivatives having been included in studies of structure–activity relationships.[11] A few of these reported derivatives are more potent histone deacetylase inhibitors than largazole itself, and all have been modified within the glycine-derived thiazole segment (Figure 1, boxed).[11] A recently published crystal structure of largazole bound to the histone deacetylase 8 enzyme (HDAC 8) suggests that substituents on the α-carbon (the C14 position), with L-configuration on the glycine–thiazole segment, would come into close proximity to the side chains of a tyrosine (Y100) and the conserved aspartate (D101) in the L2 loop of HDAC8.[23] On the other hand, substituents on the α-carbon (the C14 position) with D-configuration are predicted to be in close proximity to a phenylalanine residue (F208) in another loop formed by residues 202–212. Therefore, both L- and D-amino acid substitution at the glycine position of largazole may lead to potent, isoform-selective histone deacetylase inhibitors. Surprisingly, only one recently reported derivative has been modified at the C14 position (Figure 1).[24] We have been interested in oxazole, thiazole, and oxazoline as conformational constraints in

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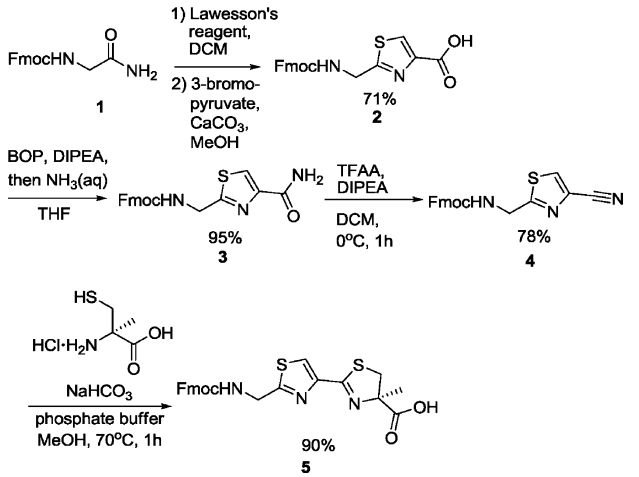
cyclic peptides[25,26] and in developing isoform-specific histone deacetylase inhibitors.[27] We therefore decided to explore new derivatives of largazole as prospective inhibitors of important histone deacetylase enzymes. Toward this objective, we present here a new robust and rapid method for synthesizing the thiazole–thiazoline fragment of largazole derivatives, also recognizing the potential value of these heterocyclic units for the synthesis of a multitude of other natural products.

With the future goal of conducting the total synthesis of largazole derivatives by both solid- and solution-phase synthesis, both Fmoc- and Boc-protected building blocks were desired. Synthesis of the Boc-protected glycine-derived thiazole–thiazoline building block has been described previously.[11,12,20,24,28–30] The most common strategy starts from the Boc-protected glycine thioamide, obtained from the corresponding commercially available Boc-protected glycine amide. However, as the Fmoc-protected glycine derivative was also desired (Scheme 1), a synthesis was started from Fmoc-

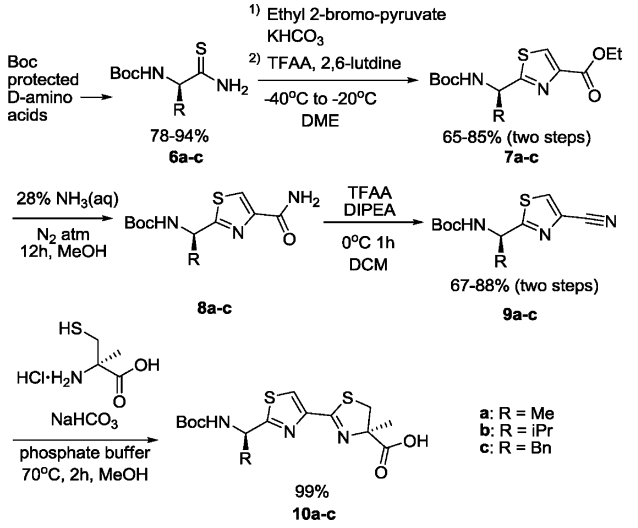
Scheme 1. Synthesis of the Fmoc-Protected Thiazole–Thiazoline Building Block



Gly-NH_2 (**1**), which was converted to the corresponding thioamide using Lawesson's reagent. The glycine-derived thiazole acid (**2**) was synthesized by direct condensation with bromopyruvate as described[31,32] and converted to the corresponding amide (**3**) using benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP), diisopropylethylamine (DIPEA), and aqueous ammonia, before dehydrating to the nitrile derivative (**4**) using trifluoroacetic anhydride (TFAA). The final condensation with α-methyl cysteine[33,34] required a short reaction time in order to minimize loss of the Fmoc-protecting group. The Fmoc-protected thiazole–thiazoline building block (**5**) was obtained in 47% overall yield in five steps from Fmoc-protected glycine amide (**1**). Yields were comparable to the best reported yields (15–49%) for synthesis of the corresponding Boc-protected building block from Boc-protected glycine thioamide.[24,28–30]

Because of the risk of losing the Fmoc-protecting group in the final condensation, the Boc-protecting group was chosen for synthesis of the remaining building blocks. A synthetic route combining previously reported methods for individual steps was explored for generating the D-alanine-, D-valine-, and D-phenylalanine-derived building blocks (Scheme 2). Boc-protected amino acids were converted to thioamides (**6a–c**) in two steps, followed by a modified Hantzsch reaction using

Scheme 2. Synthesis of Thiazole–Thiazoline Building Blocks via a Modified Hantzsch Reaction



condensation with 2-bromo-pyruvate ethyl ester and dehydration with trifluoroacetic anhydride.[35] This method is critical because applying D-phenylalanine thioamide (**6c**) to direct condensation with bromopyruvate as above (Scheme 1) leads to a partly racemized product. The generated thiazole ethyl ester building blocks (**7a–c**) were converted to the corresponding thiazole-4-carbonitrile derivatives (**9a–c**) through aminolysis of the ester by aqueous ammonia,[36] followed by dehydration to the nitrile.[37] Finally, the nitriles were condensed with α-methyl cysteine to give the desired compounds (**10a–c**) in overall yields of 43–72% from the thioamides.[34] These yields match the best published yields (15–49%) for generating the corresponding glycine-derived building block from Boc-protected glycine thioamide by similar routes.[24,28–30] The overall yield of 72% for the D-phenylalanine derived building block (**10c**) is higher than the 40% reported previously for this compound.[24] This improvement stems mainly from the one-step conversion of the ester (**7c**) to the amide (**8c**) here versus the two-step procedure reported.

However, a more efficient approach for producing a library of thiazole–thiazoline building blocks was desired. The final condensation with α-methyl cysteine worked well and directly gave the desired free carboxylic acid. Therefore, we examined whether the thiazole-4-carbonitrile intermediate could be obtained directly from the thioamide (Scheme 3). Gratifyingly, replacing the pyruvate derivative with 3-bromo-2-keto-propano-nitrile[38,39] (**11**) in the L-amino acid series did give the corresponding thiazole-4-carbonitriles (**13a–c**) in good yields (Scheme 3). The 3-bromo-2-keto-propano-nitrile (**11**) was formed from a neat mixture of 2-bromo-acetyl bromide and triethylsilyl cyanide and used directly in the condensation reaction.[38,39] The choice of trifluoroacetic anhydride as dehydration agent proved to be crucial because no desired product was detected when the trifluoroacetic anhydride was substituted with tosyl chloride, mesyl chloride, or acetic anhydride. The final condensation with α-methyl cysteine gave the desired thiazole–thiazoline building blocks (**14a–c**) from the corresponding Boc-protected amino acid thioamides without racemization. The ^1H and ^{13}C NMR spectra showed single diastereomers. The synthesis was completed in three steps, with the need for only one chromatographic purification,

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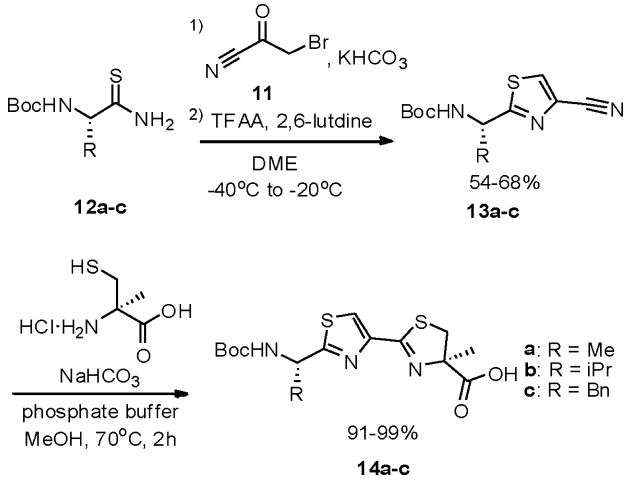
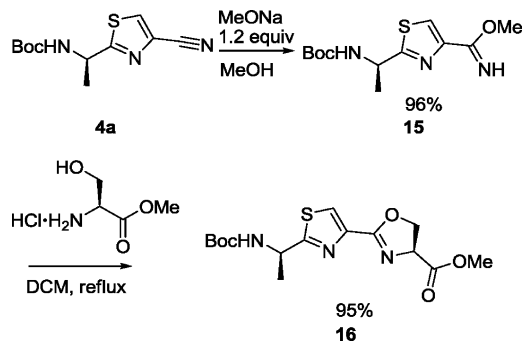
Scheme 3. Optimized Synthesis of Thiazole−Thiazoline Building Blocks



in overall yields of 52−64%, which was comparable to the method described in Scheme 2 using five steps and 2−3 chromatography purifications.

Having ready access to the thiazole-4-carbonitrile building blocks, this new method appeared suitable for the synthesis of the thiazole−oxazoline fragment of azotides in general. However, initial attempts to directly convert nitriles to oxazolines were not successful. Instead, the nitrile was almost quantitatively converted to the methyl imidate using methoxide in methanol by analogy to previously reported methods (Scheme 4).[40] The crude imidate (**15**) could then be

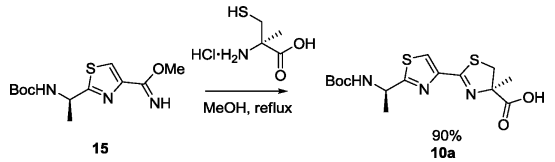
Scheme 4. Synthesis of the Thiazole−Oxazoline Building Block via the Imidate



condensed with serine under mild conditions to afford the desired thiazole−oxazoline (**16**) in 95% yield by analogy to previous reports for the glycine derivative.[30,32,41]

The imidate (**15**) was also reacted with α-methyl-cysteine to give **10a** as the sole product (Scheme 5), with no trace of the inverted product **14a** observed.[42] This confirmed that no

Scheme 5. Synthesis of the Thiazole−Thiazoline Building Block via the Imidate



racemization had occurred as a result of exposure to sodium methoxide during imidate formation.

Both thiazole−oxazoline and thiazole−thiazoline units are easily oxidized to thiazole−oxazole and thiazole−thiazole units, respectively.[32] These thiazole−thiazole/oxazole units are common motifs in natural azotides, e.g., GE2270A and microcin B17,[43,44] and the developed methodology may thus find important uses in the total synthesis of a broad range of natural products and biologically important derivatives.

In conclusion, methods have been described here that enable rapid synthetic access to a series of novel thiazole−thiazoline building blocks with important potential uses in the synthesis of largazole derivatives and of many other natural products. These methods produce thiazole-4-carbonitrile and thiazole-4-carbimidate derivatives of amino acids, which are known intermediates in the synthesis of a wide range of natural products. In addition, there are more than 3000 compounds known in the scientific literature to have a thiazole-4-carbonitrile component. Thiazole-4-carbonitrile and thiazole-4-carbimidate derivatives are readily converted under mild conditions and in good yield to thiazole−oxazoline and thiazole−thiazoline building blocks, which are also components of many important naturally occurring and synthetic compounds with diverse biological properties. Finally, we note that the key precursor in our preparation of thiazole-4-carbonitriles was 3-bromo-2-keto-propano-nitrile, a rarely used reagent.[39] Our reported syntheses may find substantial utility in the preparation of compounds featuring thiazole, thiazoline, oxazole, oxazoline, and their combination motifs.

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 298 K with TMS as internal standard. High resolution mass spectrometry (HRMS) was performed on a TOF instrument by direct infusion of compounds in acetonitrile, using sodium formate clusters as an internal calibrant. Solvents and reagents were reagent grade unless otherwise stated and used without further purification. All known compounds gave identical ^{1}H NMR spectral data in $CDCl_3$ to that reported in the references cited.

2-[[[(9*H*-Fluoren-9-yl)methoxy]carbonylamino]methyl]-thiazole-4-carboxylic Acid (Fmoc-Gly-Tz-OH) (2). Starting from Fmoc-Gly-NH_2 (**1**) (3.20 g, 10.8 mmol) and using the described procedure,[32] we obtained the resulting Fmoc-Gly-Tz-OH (**2**) as a white solid (2.92 g, 71%): ^{1}H NMR as described.[45] HRMS-TOF (m/z): $[M + H]^+$ calcd for $C_{20}H_{17}N_2O_4S^+$, 381.0909; found, 381.0904.

(9*H*-Fluoren-9-yl)methyl (4-Cyanothiazol-2-yl)-methylcarbamate (Fmoc-Gly-Tz≡N) (4). Fmoc-Gly-Tz-OH (**2**) (2.11 g, 5.53 mmol) and BOP (2.69 g, 6.08 mmol) were dissolved in THF (200 mL) before DIPEA was added (1.08 mL, 6.08 mmol), and the mixture was stirred for 20 min. Then, 28% NH_3 (aq) (1.5 mL, 5 equiv) was added in one portion, and the resulting slurry was stirred for a further 2 h. The reaction was poured into a separation funnel with Et_2O (200 mL), and the pH was adjusted to <2 with HCl (aq) (2M). The funnel was shaken, a white precipitate formed and was collected, and the aqueous phase was transferred back into the funnel. Et_2O (200 mL) was added, the funnel was shaken, an additional white precipitate was formed and collected, and the aqueous phase was again transferred back to the funnel before this process was repeated. All the collected precipitate was stirred in saturated $NaHCO_3$ (aq) (500 mL) for 1 h. The slurry was filtered and washed with Et_2O (100 mL) to yield the amide **3** as a white powder (95%, 2.01 g). The last part of general procedure C was followed, and the obtained Fmoc-Gly-Tz-NH_2 was dehydrated to the corresponding nitrile (**4**) (78%, 1.56 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.77 (d, J = 7.3 Hz, 2H), 7.59 (d, J = 7.0 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.32 (t, J = 7.3 Hz, 2H), 5.57−5.46 (m, 1H), 4.68 (d, J = 5.9 Hz, 2H), 4.51 (d, J = 6.3 Hz,

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2H), 4.24 (t, J = 6.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 141.3, 130.9, 127.8, 127.1, 124.9, 120.1, 113.7, 67.2, 47.1, 42.6. HRMS-TOF (m/z): $[M + Na]^+$ calcd for $C_{20}H_{15}N_3NaO_2S^+$, 384.0783; found, 384.0777.

(*R*)-2-[2-[[[(9*H*-Fluoren-9-yl)methoxy]carbonylamino]-methyl]thiazol-4-yl]-4-methyl-4,5-dihydrothiazole-4-carboxylic Acid (Fmoc-Gly-Tz-Tzin-OH) (5). Starting from Fmoc-Gly-Tz≡N (**4**) (300 mg, 0.8 mmol) and following general procedure E over 1 h, we obtained Fmoc-Gly-Tz-Tzin-OH (**5**) as a pale yellow solid (360 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.77 (d, J = 7.7 Hz, 2H), 7.59 (d, J = 7.1 Hz, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.31 (t, J = 7.3 Hz, 2H), 5.59−5.54 (m, 1H), 4.70 (d, J = 5.9 Hz, 1H), 4.49 (d, J = 6.7 Hz, 2H), 4.23 (t, J = 6.7 Hz, 1H), 3.95−3.84 (m, 1H), 3.39 (d, J = 11.6 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 162.2, 144.5, 143.6, 141.3, 127.8, 127.1, 124.9, 123.2, 120.0, 84.0, 67.2, 47.1, 42.6, 40.9, 24.3. HRMS-TOF (m/z): $[M + H]^+$ calcd for $C_{24}H_{22}N_3O_4S_2^+$, 480.1046; found, 480.1046.

General Procedure A: Synthesis of Boc-Protected Amino Acid Thioamides. Each Boc-amino acid (2.5 g) was dissolved in DCM (50 mL) before BOP (1.01 equiv) and DIPEA (1.02 equiv) were added. The solution was stirred for 20 min at rt, and then 28% NH_3 (aq) (5.0 equiv) was added in one portion, and the resulting slurry was stirred at rt for an additional 2 h. The solution was filtered, the solvent was removed in vacuo, and the residue was suspended in EtOAc (150 mL) and filtered. The filtrate was washed with saturated $NaHCO_3$ (aq) (3 × 50 mL) and brine (50 mL) and dried over $MgSO_4$, and the solvent was removed in vacuo. The crude amide was dissolved in DCM (50 mL) and stirred for 12 h at rt in the presence of Lawesson's reagent (0.7 equiv). The solution was filtered through a plug of Celite using DCM (2 × 50 mL), and the solvent was removed from the filtrate in vacuo. The residue was dissolved in EtOAc (150 mL), washed with $NaHCO_3$ (6 × 50 mL) and brine (50 mL), and dried over $MgSO_4$, and solvent was removed in vacuo to yield the Boc-protected amino acid thioamide.

(*R*)-*tert*-Butyl 1-Amino-1-thioxopropan-2-ylcarbamate (Boc-D-Ala(S)-NH$_2$) (6a). Starting from Boc-D-Ala-OH (2.5 g, 13.2 mmol) and following procedure A, we obtained Boc-D-Ala(S)-NH$_2$ (**6a**) as a colorless solid (2.1 g, 78%): ^{1}H NMR as described.[46]

(*R*)-*tert*-Butyl 1-Amino-3-methyl-1-thioxobutan-2-ylcarbamate (Boc-D-Val(S)-NH$_2$) (6b). Starting from Boc-D-Val-OH (2.5 g, 11.5 mmol) and following the general procedure A, we obtained Boc-D-Val(S)-NH$_2$ (**1b**) as a colorless solid (2.5 g, 94%): ^{1}H NMR as described.[47]

(*R*)-*tert*-Butyl 1-Amino-3-phenyl-1-thioxopropan-2-ylcarbamate (Boc-D-Phe(S)-NH$_2$) (6c). Starting from Boc-D-Phe-OH (5.0 g, 18.8 mmol) and following general procedure A (doubling all amounts), we obtained Boc-D-Phe(S)-NH$_2$ (**6c**) as a colorless solid (4.5 g, 86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.52 (s, 1H), 7.32−7.19 (m, 5H), 5.38 (d, J = 8.2 Hz, 1H), 4.73−4.61 (m, 1H), 3.12 (bs, 2H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4, 155.4, 136.5, 129.3, 128.6, 127.0, 80.6, 61.3, 41.7, 28.3. HRMS-TOF (m/z): $[M + H]^+$ calcd for $C_{14}H_{21}N_2O_2S^+$, 281.1318; found, 281.1317.

General Procedure B: Synthesis of Boc-Protected Amino Acid Thiazole Ethyl Esters. The Boc-protected amino acid thioamide (see below) was dissolved in dry DME (25 mL), and $KHCO_3$ (1.6 equiv) was added. The suspension was stirred at −40 °C under N_2 atmosphere, while 2-ethyl-bromo pyruvate (1.3 equiv) in dry DME (20 mL) was added dropwise. After complete addition, the temperature was raised to −20 °C, and the reaction was stirred for 6 h under a N_2 atmosphere. The reaction was filtered, and the solvent was evaporated in vacuo. The residue was redissolved in dry DME (25 mL), and the solution was stirred at −40 °C under a N_2 atmosphere. TFAA (3.2 equiv) and 2,6-lutidien (7.8 equiv) in dry DME (10 mL) was added dropwise. After complete addition, the temperature was raised to −20 °C, and the reaction was stirred for 1 h under a N_2 atmosphere. The solvent was evaporated in vacuo, and the residue was redissolved in EtOAc (250 mL) and washed with H_2O (50 mL), 20% citric acid (aq) (3 × 50 mL), and brine (50 mL). The organic phase was dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was purified on silica gel by vacuum liquid chromatography (VLC), eluting with a stepwise gradient of pure PE to 70:30 PE/EtOAc.

(*R*)-Ethyl 2-[1-(*tert*-Butoxycarbonylamino)ethyl]thiazole-4-carboxylate (Boc-D-Ala-Tz-OEt) (7a). Starting from Boc-D-Ala(S)-NH$_2$ (**6a**) (2.1 g, 10.3 mmol) and following general procedure B, we obtained Boc-D-Ala thiazole ethyl ester (**7a**) as a pale yellow solid (1.7 g, 65%): R_f = 0.3 (2:1 PE/EtOAc); ^{1}H NMR as described.[47]

(*R*)-Ethyl 2-[1-(*tert*-Butoxycarbonylamino)-2-methylpropyl]-thiazole-4-carboxylate (Boc-D-Val-Tz-OEt) (7b). Starting from Boc-D-Val(S)-NH$_2$ (**6b**) (2.5 g, 10.8 mmol) and following general procedure B, we obtained Boc-D-Val-Tz-OEt (**7b**) as a clear oil (3.0 g, 85%): R_f = 0.4 (2:1 PE/EtOAc); ^{1}H NMR as described.[47]

(*R*)-Ethyl 2-[1-(*tert*-Butoxycarbonylamino)-2-phenylethyl]-thiazole-4-carboxylate (Boc-D-Phe-Tz-OEt) (7c). Starting from Boc-D-Phe(S)-NH$_2$ (**6c**) (2.5 g, 8.92 mmol) and following general procedure B, we obtained Boc-D-Phe-Tz-OEt (**7c**) as a pale yellow solid (2.8 g, 83%): R_f = 0.4 (2:1 PE/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.51−7.18 (m, 3H), 7.10 (dd, J = 7.9, 1.5 Hz, 2H), 5.28 (bs, 2H), 4.44 (q, J = 7.1 Hz, 2H), 3.35 (dd, J = 13.7, 5.9 Hz, 2H),1.41 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 161.4, 154.9, 147.3, 136.2, 129.4, 128.6, 127.2, 127.0, 80.3, 61.5, 53.9, 41.6, 28.2, 14.4. HRMS-TOF (m/z): $[M + H]^+$ calcd for $C_{19}H_{25}N_2O_4S^+$, 377.1530; found, 377.1530.

General Procedure C: Synthesis of Thiazole-4-carbonitriles from Thiazole Ethyl Esters. The thiazole ethyl ester (see below) was dissolved in MeOH (10 mL), and 28% NH_3 (aq) (5 mL) was added. The reaction was stirred for 12 h under a N_2 atmosphere. The solvent was removed in vacuo, and the residue was coevaporated twice with toluene to yield the crude amide. The crude amide was suspended in DCM (2 mL), and DIPEA (2.8 equiv) was added. The mixture was cooled to 0 °C, and TFAA (1.3 equiv) was added dropwise. The reaction was stirred for 1 h at 0 °C. The solvent was removed in vacuo, and the residue was redissolved in EtOAc (10 mL). The solution was washed with H_2O (5 mL), 20% citric acid (aq) (3 × 5 mL), and brine (5 mL). The organic phase was dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was purified on silica gel by VLC and eluted using a stepwise gradient of pure PE to 1:1 PE/EtOAc.

(*R*)-*tert*-Butyl 1-(4-Cyanothiazol-2-yl)ethylcarbamate (Boc-D-Ala-Tz≡N) (9a). Starting from Boc-D-Ala-Tz-OEt (**7a**) (836 mg, 2.8 mmol) and following the general procedure C, we obtained Boc-D-Ala-Tz≡N (**9a**) as a colorless solid (471 mg, 67%): R_f = 0.5 (2:1 PE/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 5.23−4.99 (m, 2H), 1.62 (d, J = 6.7 Hz, 3H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.3, 126.6, 113.9, 48.9, 28.3, 21.2. HRMS-TOF (m/z): $[M + Na]^+$ calcd for $C_{11}H_{15}N_3NaO_2S^+$, 276.0783; found, 276.0777.

(*R*)-*tert*-Butyl 1-(4-Cyanothiazol-2-yl)-2-methylpropylcarbamate (Boc-D-Val-Tz≡N) (9b). Starting from Boc-D-Val-Tz-OEt (**7b**) (563 mg, 1.7 mmol) and following the general procedure C, we obtained Boc-D-Val-Tz≡N (**9b**) as a clear oil (450 mg, 80%): R_f = 0.6 (2:1 PE/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 5.28−5.12 (m, 1H), 4.94−4.84 (m, 1H), 2.38 (d, J = 6.1 Hz, 1H), 1.46 (s, 9H), 1.00 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 155.4, 130.0, 126.7, 113.9, 80.5, 58.0, 33.1, 28.3, 19.2, 17.3. HRMS-TOF (m/z): $[M + Na]^+$ calcd for $C_{13}H_{19}N_3NaO_2S^+$, 304.1096; found, 304.1088.

(*R*)-*tert*-Butyl 1-(4-Cyanothiazol-2-yl)-2-phenylethylcarbamate (Boc-D-Phe-Tz≡N) (9c). Starting from Boc-D-Phe-Tz-OEt (**7c**) (725 mg, 1.9 mmol) and following the general procedure C, we obtained Boc-D-Phe-Tz≡N (**9c**) as a colorless solid (561 mg, 88%): R_f = 0.6 (2:1 PE:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.35−7.20 (m, 3H), 7.14−7.05 (m, 2H), 5.35−5.05 (m, 2H), 3.29 (d, J = 6.2 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6, 130.3, 129.4, 128.8, 127.2, 113.9, 53.9, 41.2, 28.2. HRMS-TOF (m/z): $[M + Na]^+$ calcd for $C_{17}H_{19}N_3NaO_2S^+$, 352.1096; found, 352.1093.

General Procedure D: Synthesis of Boc-Amino Acid Thiazole−Thiazoline Acids. The Boc-amino acid thiazole-4-carbonitrile (see below) and (*R*)-α-methylcysteine hydrochloride (1.9 equiv) were dissolved in MeOH (12.5 mL). $NaHCO_3$ (5.0 equiv) was added, together with 0.1 M phosphate buffer (pH = 5.95, 6.25 mL), and the solution was degassed briefly by N_2 gas. The reaction mixture was stirred at 70 °C for 2 h under N_2 atmosphere. The reaction was cooled

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in an ice bath, and H_2O (12.5 mL), together with saturated $NaHCO_3$ (aq) (6.25 mL), was added to the cold reaction. The resulting mixture was washed with EtOAc (2 × 10 mL). The aqueous phase was acidified to pH 2−3 with 1 M $KHSO_4$ (aq) and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed in vacuo.

(*R*)-2-[2-[(*R*)-1-(*tert*-Butoxycarbonylamino)ethyl]thiazol-4-yl]-4-methyl-4,5-dihydrothiazole-4-carboxylic Acid (Boc-D-Ala-Tz-Tzin-OH) (10a) from Boc-D-Ala-Tz≡N. Starting from Boc-D-Ala-Tz≡N (**9a**) (253 mg, 1.0 mmol) following the general procedure D, we isolated Boc-D-Ala-Tz-Tzin-OH (**10a**) as a white solid (370 mg, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 5.20 (br, 1H), 5.10 (br, 1H), 3.87 (d, J = 11.6 Hz, 1H), 3.35 (d, J = 11.6 Hz, 1H), 1.68 (s, 3H), 1.61 (d, J = 6.9 Hz, 3H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 174.7, 165.3, 155.0, 147.7, 122.4, 84.0, 80.4, 48.8, 41.0, 28.3, 24.1, 21.6. HRMS-TOF (m/z): $[M + H]^+$ calcd for $C_{15}H_{22}N_3O_4S_2^+$, 372.1052; found, 372.1046.

(*R*)-2-[2-[(*R*)-1-(*tert*-Butoxycarbonylamino)ethyl]thiazol-4-yl]-4-methyl-4,5-dihydrothiazole-4-carboxylic Acid (Boc-D-Ala-Tz-Tzin) Acid (10a) from Boc-D-Ala-Tz(NH)-OMe. Boc-D-Ala-Tz(NH)-OMe (**15**) (51.4 mg, 0.18 mmol) and (*R*)-α-methylcysteine hydrochloride (50.0 mg, 0.30 mmol) were dissolved in MeOH (0.5 mL), and the mixture was stirred at 50 °C for 3 h. The reaction was cooled to 0 °C, and saturated $NaHCO_3$ (aq) (5 mL) was added. The aqueous solution was washed with EtOAc (2 × 2 mL). The aqueous phase was acidified with 20% citric acid (aq) (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (3 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo to yield the pure thiazoline (**5a**) as a pale yellow solid (60.2 mg, 90%): ^{1}H NMR identical to the above-described data.

(*R*)-2-[2-[(*R*)-1-(*tert*-Butoxycarbonylamino)-2-methylpropyl]-thiazol-4-yl]-4-methyl-4,5-dihydrothiazole-4-carboxylic Acid (Boc-D-Val-Tz-Tzin-OH) (10b). Starting from Boc-D-Val-Tz≡N (**9b**) (310 mg, 1.10 mmol) and following the general procedure D, we isolated Boc-D-Val-Tz-Tzin-OH (**10b**) as a white solid (436 mg, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 5.27−5.18 (m, 1H), 4.92−4.84 (m, 1H), 3.85 (d, J = 11.5 Hz, 1H), 3.35 (d, J = 11.6 Hz, 1H), 2.44−2.35 (m, 1H), 1.68 (s, 3H), 1.46 (s, 9H), 1.00 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 173.1, 165.6, 155.4, 148.1, 121.4, 84.3, 80.3, 57.9, 40.7, 33.2, 28.3, 24.3, 19.4, 17.4. HRMS-TOF (m/z): $[M + H]^+$ calcd for $C_{17}H_{26}N_3O_4S_2^+$, 400.1359; found, 400.1359.

(*R*)-2-[2-[(*R*)-1-(*tert*-Butoxycarbonylamino)-2-phenylethyl]-thiazol-4-yl]-4-methyl-4,5-dihydrothiazole-4-carboxylic Acid (Boc-D-Phe-Tz-Tzin-OH) (10c). Starting from Boc-D-Phe-Tz≡N (**9c**) (300 mg, 0.9 mmol) and following the general procedure D, we obtained Boc-D-Phe-Tz-Tzin-OH (**10c**) as a pale yellow solid (410 mg, 99%): ^{1}H NMR as described.[24] HRMS-TOF (m/z): $[M + H]^+$ calcd for $C_{21}H_{26}N_3O_4S_2^+$, 448.1365; found, 448.1360.

(*S*)-*tert*-Butyl 1-Amino-1-thioxopropan-2-ylcarbamate (Boc-L-Ala(S)-NH$_2$) (12a). Starting from Boc-L-Ala-OH (5.0 g, 26.4 mmol) and following the general procedure A (doubling all amounts), we obtained Boc-L-Ala(S)-NH_2 (**12a**) as a white solid (4.4 g, 82%): ^{1}H NMR as described.[48]

(*S*)-*tert*-Butyl 1-Amino-3-methyl-1-thioxobutan-2-ylcarbamate (Boc-L-Val(S)-NH$_2$) (12b). Starting from Boc-L-Val-OH (5.0 g, 23.0 mmol) and following the general procedure A (doubling all amounts), we obtained Boc-L-Val(S)-NH_2 (**12b**) as white solid (4.7 g, 88%): ^{1}H NMR as described.[49]

(*S*)-*tert*-Butyl 1-Amino-3-phenyl-1-thioxopropan-2-ylcarbamate (Boc-L-Phe(S)-NH$_2$) (12c). Starting from Boc-L-Phe-OH (5.0 g, 18.8 mmol) and following the general procedure A (doubling all amounts), we obtained Boc-L-Phe(S)-NH_2 (**12c**) as white solid (4.5 g, 85%): ^{1}H NMR as described.[35]

General Procedure E: Synthesis of Thiazole-4-carbonitriles from Thioamides. Bromoacetyl bromide (383 mg, 1.9 mmol) was added dropwise to TMS cyanide (198 mg, 2.0 mmol) under a N_2 atmosphere, and the resulting mixture was heated to 70 °C for 1.5 h to form the cyclization agent (**11**). The thioamide (see below) was dissolved in dry DME (3 mL), and $KHCO_3$ (5.0 mmol) was added. The mixture was stirred at −40 °C while the cyclization agent was added dropwise. After complete addition, the reaction was stirred for 6 h at −20 °C under a N_2 atmosphere. The suspension was filtered, and the solvent was evaporated in vacuo. The residue was redissolved in 3 mL dry DME and stirred at −40 °C. TFAA (3.0 mmol) and 2,6-lutidine in dry DME (2 mL) were added dropwise under a N_2 atmosphere. After complete addition, the temperature was raised to −20 °C, and the reaction was stirred for 1 h. The solvent was evaporated in vacuo. The residue was redissolved in EtOAc (10 mL) and washed with H_2O (5 mL), 20% citric acid (aq) (3 × 5 mL), and brine (5 mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified on silica gel by VLC eluting with a stepwise gradient of pure PE to 1:1 PE/EtOAc.

(*S*)-*tert*-Butyl 1-(4-Cyanothiazol-2-yl)ethylcarbamate (Boc-L-Ala-Tz≡N) (13a). Starting from Boc-L-Ala(S)-NH_2 (**12a**) (205 mg, 1.0 mmol) and following the general procedure E, we obtained Boc-L-Ala-Tz≡N (**13a**) as a white solid (172 mg, 68%): R_f = 0.5 (2:1 PE:/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 5.27−4.96 (m, 2H), 1.62 (d, J = 6.9 Hz, 3H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.3, 154.9, 130.4, 126.5, 113.9, 80.6, 48.8, 28.3, 21.1. HRMS-TOF (m/z): $[M + Na]^+$ calcd for $C_{11}H_{15}N_3NaO_2S^+$, 276.0783; found, 276.0775.

(*S*)-*tert*-Butyl 1-(4-Cyanothiazol-2-yl)-2-methylpropylcarbamate (Boc-L-Val-Tz≡N) (13b). Starting from Boc-L-Val(S)-NH_2 (**12b**) (210 mg, 0.9 mmol) and following the general procedure E, we obtained Boc-L-Val-Tz≡N (**13b**) as a white solid (137 mg, 54%): R_f = 0.6 (2:1 PE/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 5.22 (d, J = 7.1 Hz, 1H), 4.94−4.84 (m, 1H), 2.44−2.31 (m, 1H), 1.46 (s, 9H), 0.99 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 155.4, 130.0, 126.7, 113.9, 80.5, 58.0, 33.1, 28.3, 19.2, 17.3. HRMS-TOF (m/z): $[M + Na]^+$ calcd for $C_{13}H_{19}N_3NaO_2S^+$, 304.1096; found, 304.1088.

(*S*)-*tert*-Butyl 1-(4-Cyanothiazol-2-yl)-2-phenylethylcarbamate (Boc-L-Phe-Tz≡N) (13c). Starting from Boc-L-Phe(S)-NH_2 (**12c**) (281 mg, 1.0 mmol) and following the general procedure E, we obtained Boc-L-Phe-Tz≡N (**13c**) as a white solid (214 mg, 65%): R_f = 0.6 (2:1 PE/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.31−7.23 (m, 3H), 7.12−7.07 (m, 2H), 5.30−5.10 (m, 2H), 3.34−3.26 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 154.9, 135.7, 130.4, 129.4, 128.8, 127.2, 126.7, 113.9, 80.7, 53.9, 41.1, 28.2. HRMS-TOF (m/z): $[M + Na]^+$ calcd for $C_{17}H_{19}N_3NaO_2S^+$, 352.1096; found, 352.1093.

(*R*)-2-[2-[(*S*)-1-(*tert*-Butoxycarbonylamino)ethyl]thiazol-4-yl]-4-methyl-4,5-dihydrothiazole-4-carboxylic Acid (Boc-L-Ala-Tz-Tzin-OH) (14a). Starting from Boc-L-Ala-Tz≡N (**12a**) (370 mg, 1.5 mmol) and following the general procedure D, we isolated Boc-L-Ala-Tz-Tzin-OH (**14a**) as a white solid (494 mg, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 5.28 (bs, 1H), 5.08 (bs, 1H), 3.89 (d, J = 11.5 Hz, 1H), 3.32 (d, J = 11.5 Hz, 1H), 1.68 (s, 3H), 1.60 (d, J = 6.9 Hz, 3H), 1.45 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 174.6, 165.1, 155.0, 147.9, 122.0, 84.2, 80.3, 48.7, 41.0, 28.3, 24.2, 21.6. HRMS: HRMS-TOF (m/z): $[M + H]^+$ calcd for $C_{15}H_{22}N_3O_4S_2^+$, 372.1052; found, 372.1042.

(*R*)-2-[2-[(*S*)-1-(*tert*-Butoxycarbonylamino)-2-methylpropyl]-thiazol-4-yl]-4-methyl-4,5-dihydrothiazole-4-carboxylic Acid (Boc-L-Val-Tz-Tzin-OH) (14b). Starting from Boc-L-Val-Tz≡N (**12b**) (338 mg, 1.2 mmol) and following the general procedure D, we isolated Boc-L-Val-Tz-Tzin-OH (**14b**) as a white solid (465 mg, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 5.25 (d, J = 8.7 Hz, 1H), 4.93−4.84 (m, 1H), 3.89 (d, J = 11.6 Hz, 1H), 3.34 (d, J = 11.6 Hz, 1H), 2.45−2.34 (m, 1H), 1.69 (s, 3H), 1.46 (s, 9H), 0.99 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 173.0, 165.4, 155.4, 148.0, 121.7, 84.2, 80.2, 57.9, 40.8, 33.2, 28.3, 24.2, 19.3, 17.3. HRMS-TOF (m/z): $[M + H]^+$ calcd for $C_{17}H_{26}N_3O_4S_2^+$, 400.1365; found 400.1360.

(*R*)-2-[2-[(*S*)-1-(*tert*-Butoxycarbonylamino)-2-phenylethyl]-thiazol-4-yl]-4-methyl-4,5-dihydrothiazole-4-carboxylic Acid (Boc-L-Phe-Tz-Tzin-OH) (14c). Starting from Boc-L-Phe-Tz≡N (**12c**) (329 mg, 1.0 mmol) and following the general procedure D, we isolated Boc-L-Phe-Tz-Tzin-OH (**14c**) as a white solid (443 mg, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.33−7.18 (m, 3H), 7.16−7.10 (m, 2H), 5.26 (bs, 2H), 3.90 (d, J = 11.6 Hz, 1H),

3.45−3.21 (m, 3H), 1.70 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 172.9, 165.2, 155.0, 148.1, 136.1, 129.5, 128.6, 127.0, 121.9, 84.4, 80.4, 53.7, 41.3, 40.9, 28.3, 24.3. HRMS-TOF (m/z): $[M + H]^+$ calcd for $C_{21}H_{26}N_3O_4S_2^+$, 448.1365; found, 448.1356.

(*R*)-Methyl 2-[1-(*tert*-Butoxycarbonylamino)ethyl]thiazole-4-carbimidate (Boc-D-Ala-Tz(NH)-OMe) (15). Boc-D-Ala-Tz≡N (**4a**) (100 mg, 0.39 mmol) was dissolved in MeOH (1 mL). The solution was cooled to 0 °C, and sodium methoxide (26.5 mg, 0.49 mmol) was added in one portion. The resulting slurry was stirred at rt for 3 h. The solvent was removed in vacuo without heat. The resulting solid was suspended in Et_2O (20 mL) and filtered. The solvent was removed in vacuo to yield the crude imidate (**15**) as a white solid (110 mg, 98%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.61 (s, 1H), 5.25−4.94 (m, 2H), 3.93 (s, 3H), 1.61 (d, J = 6.8 Hz, 3H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 154.9, 147.5, 130.3, 119.7, 80.3, 53.4, 48.7, 28.3, 21.7. HRMS-TOF (m/z): $[M + H]^+$ calcd for $C_{12}H_{19}N_3NaO_3S^+$, 308.1039; found, 308.1040.

(*S*)-Methyl 2-[2-[(*R*)-1-(*tert*-Butoxycarbonylamino)ethyl]-thiazol-4-yl]-4,5-dihydrooxazole-4-carboxylate (Boc-D-Ala-Tz-Oxin-OMe) (16). Boc-D-Ala-Tz(NH)-OMe (**15**) (50.0 mg, 0.18 mmol) and L-Ser-OMe hydrochloride (30.0 mg, 0.19 mmol) were added to DCM (1 mL), and the mixture was refluxed overnight. The resulting slurry was absorbed directly onto a plug of silica gel and washed with PE (5 mL). The product was then eluted with 1:1 PE/EtOAc. The solvent was evaporated in vacuo to yield the oxazoline (**16**) as a white solid (59.2 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 5.27 (bs, 1H), 5.16−5.06 (m, 1H), 4.97 (dd, J = 10.5, 8.0 Hz, 1H), 4.71 (td, J = 8.4, 3.6 Hz, 1H), 4.62 (ddd, J = 10.6, 8.7, 2.0 Hz, 1H), 3.81 (s, 3H), 1.62 (d, J = 6.9 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9, 171.3, 161.4, 154.8, 143.3, 124.3, 80.2, 69.9, 68.6, 52.7, 48.8, 28.3, 21.9. HRMS-TOF (m/z): $[M + H]^+$ calcd for $C_{15}H_{22}N_3O_5S^+$, 356.1275; found, 356.1281.

■ ASSOCIATED CONTENT

Supporting Information

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

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