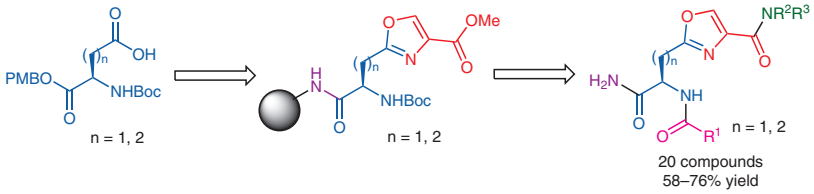
Synthesis S. Murru et al. Paper

Synthesis of Novel Oxazolyl Amino Acids and Their Use in the Parallel Synthesis of Disubstituted Oxazole Libraries

Siva Murru[a]
Ramesh Bista[a]
Adel Nefzi*[b]

[a] University of Louisiana Monroe, 700 University Avenue, Monroe, Louisiana, 71209, USA
murru@ulm.edu
[b] Torrey Pines Institute for Molecular Studies, 11350 SW Village Parkway, Port St Lucie, Florida 34987, USA
adeln@tpims.org



Received: 06.11.2017
Accepted after revision: 14.11.2017
Published online: 19.01.2018
DOI: 10.1055/s-0036-1589148; Art ID: ss-2017-m0597-op

Abstract Novel chiral oxazolyl alanine and homologues are synthesized and utilized as building blocks for the solid-phase parallel synthesis of novel trifunctional oxazole small molecules in good to excellent overall yields and with high purity. The orthogonal deprotection strategy of oxazolyl amino acids, prepared from serine methyl ester and amino acids such as aspartic and glutamic acids, allows multiple sites of diversification to make a variety of pharmacologically relevant small molecules. The general nature of this approach allows the preparation of a large number of small molecules and peptidomimetics.

Key words solid-phase synthesis, oxazolyl amino acids, amino acids, oxazoles, heterocycles, parallel synthesis, small molecules, drug discovery

Unnatural amino acids are utilized as building blocks and molecular scaffolds in construction of combinatorial libraries for drug-discovery research.[1] They represent a nearly infinite array of diverse structural elements for the development of new therapeutic drugs.[2] Alternatively, they also have been used as molecular probes for the better understanding of biological systems. In continuation of our interest toward the synthesis of unnatural amino acids and their use as building blocks for the solid-phase parallel synthesis[3] of novel small molecules and heterocyclic peptidomimetics,[4] we report herein the parallel synthesis of oxazolyl alanine and oxazolyl homoalanine from the condensation of serine methyl ester with aspartic and glutamic acids, respectively.

Various oxazole-containing natural products have been isolated from natural sources, particularly from the marine environment. Many of them are structurally complex and possess a wide range of pharmacological activities such as antitumor, antibacterial, antiviral, and antimalarial.[5] Other synthetic oxazole derivatives are also found to be associated with antifungal, antitubercular, and anti-inflammatory activities.[6] Many FDA-approved drugs such as 'Oxaprozin', an anti-inflammatory drug, and 'Dalfopristin', a streptogramin antibiotic drug, contain an oxazole ring.[7]

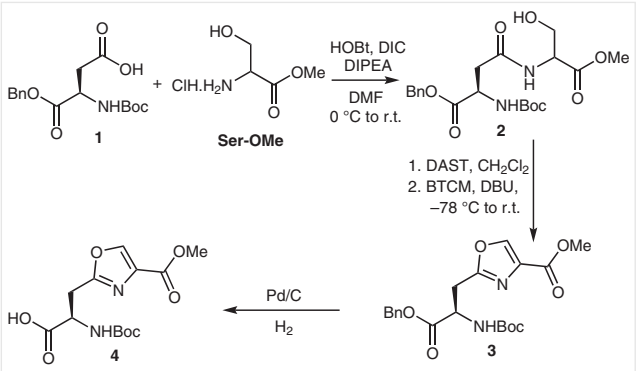
We have experience in synthesizing a variety of heterocyclic amino acids and utilizing them as chiral building blocks for the construction of pharmaceutically relevant small-molecule libraries.[4] In order to expand the scope and diversity of our small-molecule libraries, we used aspartic and glutamic acid side chains as precursors for the synthesis of oxazole alanine and oxazole homoalanine amino acids. Analogous synthetic heterocyclic amino acids, such as thiazolyl alanine and quinolyl alanine, are commercially available and have been utilized for peptidomimetics research.[8] Compared to its thiazole analogues, oxazolyl alanine is not well explored as a building block for making small molecules, peptidomimetics and other materials.

As part of our in-house medicinal chemistry program, we planned to synthesize a diverse range of molecules based upon the substituted oxazole core unit. In particular, our preferred strategy involves the solution-phase preparation of an appropriately functionalized and protected core, followed by solid-phase attachment, assembly, and derivatization. Here, we describe a combined solution-solid-phase scheme in which a solution-generated heterocyclic scaffold is 'side-chain diversified' on the solid phase into four distinct compound series. Accordingly, we envisaged that the new orthogonally protected chiral oxazolyl alanine **4**, a useful building block for peptidomimetics and small molecules, would be obtained from protected L-aspartic acid **1** (Scheme 1). There are several advantages of our approach, including: (i) the use of economically viable and commercially available starting materials such as Boc- and benzyl-protected L-aspartic acids, (ii) biomimetic syntheses of oxazole amino acids using serine methyl ester that provides a carboxyl group on the oxazole ring, (iii) selective cleavage of the benzyl (Bn) group provides a free carboxylic acid which

can easily be used as the anchoring point of the solid support, (iv) orthogonal deprotection of the amine and the carboxyl group allows for two sites of diversification, which permits the parallel synthesis of a large number of small molecules in a relatively short period of time, and most importantly, (v) the oxazole ring is not directly attached to the α-carbon and hence no enol racemization possibility during synthesis, which avoids additional purification requirements.

Oxazolyl alanine compounds acts as factor XIA inhibitors,[9a] potential neuroprotective agents,[9b] BACE 1 inhibitors,[9c] potent and selective neutral endopeptidase inhibitors,[9d] vla-1 integrin antagonists,[9e] and as nep inhibitors for fsad.[9f] Despite the fact that the oxazolyl alanine compounds are useful precursors for making biologically relevant molecules, only a few methods have been reported for their preparation;[9] these include: (i) making racemic oxazolyl alanine starting from chloromethylene oxazole, (ii) treating carboxylic acids with aminoketones, (iii) treating glutamides with aminophenols in the presence of Meerwein's reagent, (iv) making chiral oxazolyl alanine via cyclodehydration of the hydroxy peptide. Additionally, there is no report on utilizing oxazolyl aminoacids as building blocks for solid-phase parallel synthesis. In continuation of our interest in the parallel synthesis of small molecules for drug discovery, we have synthesized oxazolyl alanine in solution phase, and utilized for the solid-phase parallel synthesis of diverse trifunctional oxazole small molecules.

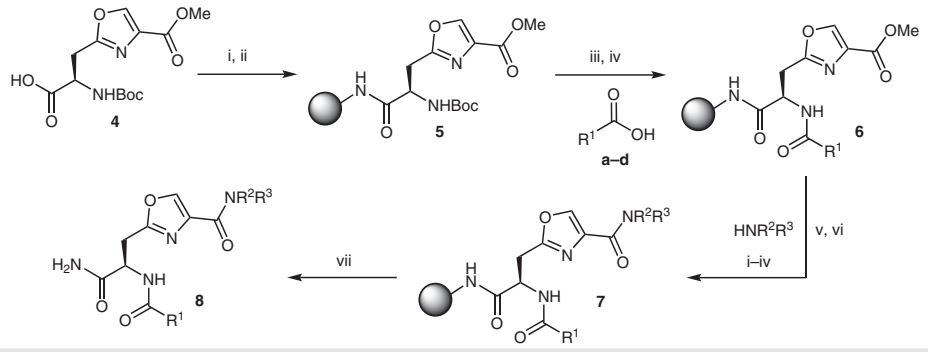
For our studies, initially we chose Boc- and Bn-protected L-aspartic acid and serine methyl ester (Ser-OMe). Following our previous approach,[4c,e] similar to the biosynthetic pathway, the serine methyl ester was coupled with protected aspartic acid **1** to yield the corresponding β-hydroxy peptide **2**. The cyclization of Boc-β-hydroxypeptide **2** with the fluorinating reagent diethylaminosulfur trifluoride (DAST) at –78 °C was performed to yield the oxazoline derivative, which was followed by ring oxidation using bromotrichloromethane (BTCM) along with DBU as the base to give the desired orthogonally protected oxazolyl alanine



Scheme 1 Biomimetic synthesis of *N*-Boc oxazolyl alanine ester **4** starting from L-aspartic acid and serine methyl ester. *Reagents and conditions*: (i) HOBt, DIC, DIPEA, CH_2Cl_2, 0 °C to r.t.; (ii) DAST, CH_2Cl_2, –78 °C; (iii) $BrCCl_3$, DBU, CH_2Cl_2, 0 °C; (iv) 10% Pd/C, EtOH/EtOAc (1:1), H_2 (balloon).

methyl ester **3**. Selective Pd-catalyzed reductive cleavage of the benzyl protecting group led to the corresponding oxazolyl alanine derivative **4** with a free carboxylic acid group (Scheme 1), which can be used as the anchoring point of the solid support for the parallel synthesis.

Having the oxazolyl alanine building block in hand, we then proceeded to synthesize a library of trifunctional oxazole small molecules. As the solid-phase organic synthesis (SPOS)[3,10] is an effective tool to generate structurally diverse compounds, we employed the tea-bag approach[3,11] for the rapid solid-phase parallel synthesis of functionalized oxazole small molecules. First, we loaded the oxazolyl alanine **4** on to *p*-methylbenzhydrylamine (MBHA) resin using *N*,*N*′-diisopropylcarbodiimide (DIC) (coupling reagent) and 1-hydroxybenzotriazole (HOBt) (racemization suppressant) in DMF. Next, the resulting resin-bound *N*-Boc-oxazolyl alanine **5** was treated with 55% TFA in CH_2Cl_2 to remove the Boc protection and the resulting free amine was then acylated with a set of carboxylic acids **a**–**d** [i.e., propionic acid (**a**), cyclohexane carboxylic acid (**b**), (3,5-bis-trifluoromethylphenyl)acetic acid (**c**), adamantyl acetic acid (**d**)] to afford



Scheme 2 Solid-phase parallel synthesis of oxazole-derived small molecules via C-terminus and N-terminus extension. *Reagents and conditions*: (i) MBHA resin, DIPEA, CH_2Cl_2, 5 min; (ii) HOBt, DIC, DMF, overnight; (iii) 55% TFA in CH_2Cl_2, 30 min; (iv) 10 equiv of DIC in DMF, 15 h; (v) 1 M aq NaOH, dioxane/H_2O, 6 h; (vi) HOBt, DIC, DMF, overnight; (vii) HF cleavage.

N-acylated products **6**. These *N*-acylated products were subsequently treated with 1 M aqueous NaOH solution to hydrolyze the methyl ester group in order to obtain the free carboxylic acid group, which was then amidated utilizing primary and secondary amines **i**–**iv** [piperidine (**i**), *n*-butylamine (**ii**), *N*-Boc-piperazine (**iii**), benzylamine (**iv**)] to afford a variety of amidation products **7** (Scheme 2, Table 1).

The amidation products with *N*-Boc-piperazine (**iii**) provide an additional site for diversification via Boc deprotection followed by acylation using another set of carboxylic acids **e**–**h** [fluorenylacetic acid (**e**), naphthylacetic acid (**f**), butyric acid (**g**), phenylacetic acid (**h**)]. After completion of the cyclization, the compounds were cleaved from the resin by using HF to afford 16 diverse trifunctional oxazole products **8** (Scheme 2, Table 1) in good yields and high purities, and these were characterized by LCMS, ^{1}H and ^{13}C NMR. The use of heterocyclic amines such as piperidine (**i**) and *N*-Boc-piperazine (**iii**) led to the bis-heterocyclic compounds **8a**(**i**), **8b**(**i**), **8c**(**i**), **8d**(**i**), **8a**(**iii**)**e**, **8b**(**iii**)**f**, **8c**(**iii**)**g**, and **8d**(**iii**)**h** having both five- and six-membered heterocyclic rings, where one is an aromatic and the other is a saturated heterocycle. It is noteworthy to mention here that the presence of two or more heterocyclic cores in one single molecule generally increases the number of potential targets by the square power, thereby improving the chances of hits and lead molecule identification. Many approved drugs contain more than one type of heterocycle, often bis-nitrogen heterocycles.[12]

Table 1 Solid-Phase Parallel Synthesis of Oxazole-Derived Small Molecules Starting from L-Aspartic Acid

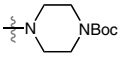
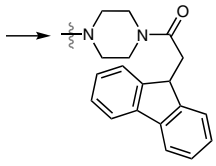
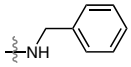
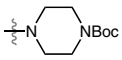
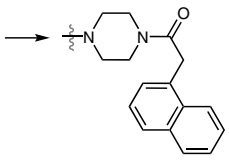
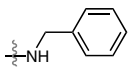
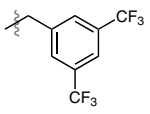
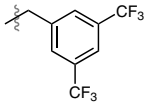
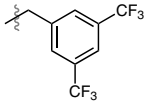
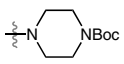
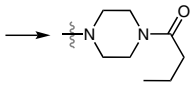
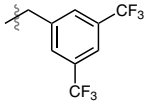
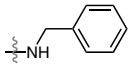
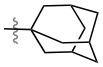
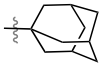
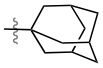
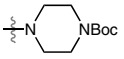
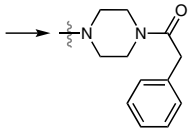
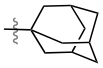
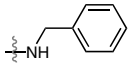
Product[a]	R^1	$-NR^2R^3$	Deprotection/Acylation	Yield (%)[b]	Purity (%)[c]
8a(**i**)			–	59	92
8a(**ii**)			–	72	95
8a(**iii**)**e**				68	93
8a(**iv**)			–	76	98
8b(**i**)			–	66	94
8b(**ii**)			–	73	91
8b(**iii**)**f**				65	94
8b(**iv**)			–	69	94
8c(**i**)			–	58	88

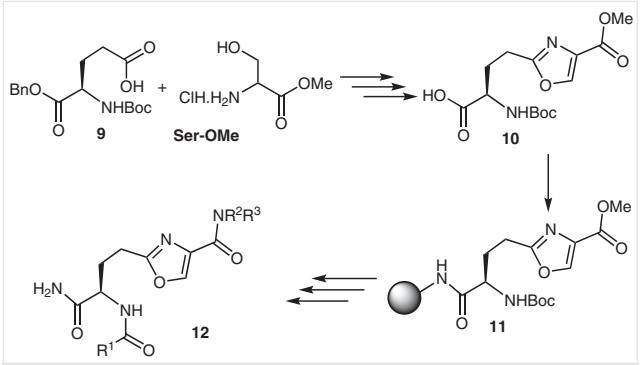
Table 1 (continued)

Product[a]	R^1	$-NR^2R^3$	Deprotection/Acylation	Yield (%)[b]	Purity (%)[c]
8c(ii)			–	64	92
8c(iii)g				59	94
8c(iv)			–	74	91
8d(i)			–	67	88
8d(ii)			–	73	92
8d(iii)h				62	95
8d(iv)			–	75	97

[a] See Scheme 2 for the general structure of products **8**.
[b] Based on crude mass recovery.
[c] Based on integration of the areas of the total ion current (TIC) peaks in LCMS.

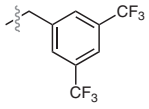
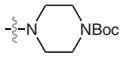
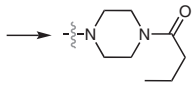
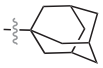
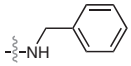
With the success of synthesizing oxazolyl alanine **4** and its use as a building block for parallel synthesis, we extended our methodology to prepare its homologue **10** starting from protected glutamic acid **9**, which has an additional methylene group (Scheme 3). Similar to oxazolyl alanine **4**, the oxazolyl alanine homologue **10** was also utilized as a building block for the solid-phase parallel synthesis and the obtained trifunctional small molecules **12** are shown in Scheme 3 and Table 2.

In conclusion, we have developed a solution-phase synthetic approach for chiral oxazolyl alanine and its homologue starting from aspartic and glutamic acids, respectively. These heterocyclic amino acid building blocks have been utilized for the solid-phase parallel synthesis of a pharmacologically relevant small-molecule library of 20 compounds with high diversity. We have used a variety of carboxylic acids and amines for the *N*- and *C*-functionalizations, respectively. This approach is useful for incorporation of an oxazole moiety into peptidomimetics to generate combinatorial libraries for the purpose of drug discovery. We are in the process of preparing a larger small-molecule library of oxazole compounds.



Scheme 3 Solid-phase parallel synthesis of diverse oxazole small molecules via C-terminus and N-terminus extension using the procedures outlined in Schemes 1 and 2

Table 2 Trifunctional Oxazole Small Molecules Starting from L-Glutamic Acid

Product[a]	R^1	$-NR^2R^3$	Deprotection/Acylation	Yield (%)[a]	Purity (%)[b]
12a(i)				63	89
12b(ii)				69	92
12c(iii)g				66	97
12d(iv)				72	94

[a] See Scheme 3 for the general structure of products **12**.
[b] Based on crude mass recovery.
[c] Based on integration of the areas of the total ion current (TIC) peaks in LCMS.

All the reagents were commercial grade and were purified according to established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed on a rotary evaporator under reduced pressure. VWR silica gel (60–120 mesh size) was used for column chromatography. Reactions were monitored by TLC on aluminum-backed silica G TLC plates w/UV254. Hydrofluoric acid cleaves were performed in specially equipped and ventilated hoods with full personal protective equipment. Melting points were obtained using a MEL-TEMP apparatus. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Bruker 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6. ^{1}H and ^{13}C shifts are expressed in ppm relative to the internal solvent peak of either DMSO-d_6 or $CDCl_3$. Coupling constants are reported in Hz. LCMS (ESI) traces were recorded using a Agilent Triple Quad LC–MS instrument on samples with concentrations of 1 mg/mL in 50:50 MeCN/H_2O at both 214 nm and 254 nm, using a reverse phase Vydac column with a gradient of 5% to 95% formic acid in MeCN. The purities of the crude samples were estimated based on the UV traces recorded. Low-resolution mass spectra were recorded using a Agilent GC–MS 7890 instrument. High-resolution mass spectra were obtained using a Thermo LTQ Orbitrep spectrometer. Details of the syntheses of the intermediates 4-methoxy benzyl *N*2-(*tert*-butoxycarbonyl)-*N*4-(3-hydroxy-1-methoxy-1-oxopropan-2-yl)-L-asparaginate (Boc-L-Asp-OBn-Ser-OMe) (**2**) and methyl (*R*)-2-{3-(benzyloxy)-2-[(*tert*-butoxycarbonyl)amino]-3-oxopropyl}oxazole-4-carboxylate (Boc-L-Asp-Oxz-OBn) (**3**) are provided in the Supporting information.

(*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-[4-(methoxycarbonyl)oxazol-2-yl]propanoic Acid (Boc-L-Asp-Oxz-OH) (4)

The oxazole ester (Boc-L-Asp-Oxz-OBn) **3** (2.43 g, 6 mmol) was dissolved in EtOH/EtOAc (1:1, 20 mL) and treated with 10% Pd/C (0.1 equiv). The resulting mixture was stirred in the presence of H_2 gas (1 atm) for 2 h. The progress of the reaction was monitored by TLC. After complete conversion, the mixture was filtered through a pad of Celite and the residue washed with EtOAc. The volatile organic solvents were removed in vacuo and the crude residue washed with hexane to give the title product **4**.

Yield: 1.75 g (93%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 9 H), 3.12 (d, *J* = 9.2 Hz, 1 H), 3.24 (d, *J* = 5.6 Hz, 1 H), 3.80 (s, 3 H), 4.03 (q, *J* = 7.2 Hz, 1 H), 4.39 (br s, 1 H), 8.76 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5, 30.4, 52.1, 60.1, 78.8, 132.7, 146.0, 155.6, 161.6, 162.6, 172.5.

ESI-MS: *m*/*z* = 315 $[M + H]^+$.

Solid-Phase Parallel Synthesis of 8a(i)–d(iv), 12a(i)–d(iv)]; General Procedure

Step 1

A set of sixteen 50 mg sealed polypropylene mesh bags containing *p*-methylbenzhydrylamine hydrochloride salt resin (MBHA) (1.15 mol/g, 100–200 mesh) was prepared.[11] The reactions were carried out by placing all the bags in plastic reaction bottles. Following neutralization of the resin with 5% diisopropylethylamine (DIPEA) in CH_2Cl_2, Boc-L-Asp-Oxz-OH **4** (2 equiv) was coupled using HOBt (2 equiv) and DIC (2 equiv) in anhydrous DMF while shaking the reaction vessels overnight. Completion of the coupling was monitored by the Kaiser (ninhydrin) test.[13]

Step 2

Following removal of the Boc group with 10 mL of 55% TFA/CH_2Cl_2 for 30 min and neutralization with 10 mL of 5% DIPEA at room temperature for 2 hrs, the free amine group was coupled with four different carboxylic acids (5 equiv) which resulted in new amide functionalities. The completion of the amide coupling process was monitored by the Kaiser (ninhydrin) test.

Step 3

After removal of the solvents and multiple washes with DMF and CH_2Cl_2, dioxane (10 mL) and 1 M aq NaOH solution (10 mL) were added and the mixture was left shaking overnight at room temperature to deprotect the methyl ester group. The free carboxylic acid group was coupled with four different types of amines (5 equiv) to obtain new amide functionalities.

Step 4

The resin was washed with DMF (× 3), and CH_2Cl_2 (× 3) and then the products were cleaved from the resin support in the presence of HF at 0 °C for 1.5 hours. The HF was removed by a steady stream of nitrogen gas at room temperature. The products were then extracted with 95 %

acetic acid for 1 hour, transferred to a vial and lyophilized upon freezing. After three cycles of freezing and lyophilizing, the samples were transferred in 50:50 acetonitrile and water to pre-weighed vials. Upon drying to completion, the samples were re-weighed and their crude masses recorded. The structures of the products were confirmed by LCMS and NMR analysis. (Full details are provided in the Supporting Information).

(*R*)-3-[4-(Piperidine-1-carbonyl)oxazol-2-yl]-2-propionamidopropanamide [8a(i)]

Yield: 11.1 mg (59%); semi-solid.

^{1}H NMR (400 MHz, $CDCl_3$): d 1.17 (t, 3 H, J = 8.0 Hz), 1.63-1.69 (m, 6 H), 2.28 (q, 2 H, J = 8.0 Hz), 3.13 (dd, 1 H, J_1 = 16.0 Hz, J_2 = 8.0 Hz), 3.38 (dd, 1 H, J_1 = 16.0 Hz, J_2 = 4.0 Hz), 3.70 (brs, 4 H), 4.96 (d, 1 H, J = 4.0 Hz), 5.45 (brs, 1 H), 6.82 (brs, 1 H), 6.94 (d, 1 H, J = 4.0 Hz), 7.99 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): *d* 9.6, 20.6, 23.5, 24.6, 29.6, 29.8, 49.8, 136.5, 142.1, 160.6, 160.8, 172.0, 174.1.

ESI-MS: 345 $[M + Na]^+$.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{23}N_4O_4$: 323.1714; found: 323.1712.

(*R*)-2-(3-Amino-3-oxo-2-propionamidopropyl)-*N*-butyloxazole-4-carboxamide [8a(ii)]

Yield: 12.8 mg (72%); white solid.

^{1}H NMR (400 MHz, CD_3OD): δ = 0.95 (t, J = 7.2 Hz, 3 H), 1.06 (t, J = 7.2 Hz, 3 H), 1.39 (m, 2 H), 1.55 (m, 2 H), 2.22 (q, J = 7.6 Hz, 2 H), 3.14 (dd, J_1 = 15.6 Hz, J_2 = 8.8 Hz, 1 H), 3.30–3.35 (m, 5 H), 4.89 (t, J = 7.2 Hz, 1 H), 8.23 (s, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 10.0, 14.0, 21.0, 29.8, 31.2, 32.6, 39.7, 51.8, 137.3, 142.6, 162.8, 162.9, 174.8, 176.9.

ESI-MS: m/z = 333 $[M + Na]^+$.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{23}N_4O_4$: 311.1714; found: 311.1708.

(*R*)-3-(4-{4-[2-(9*H*-Fluoren-9-yl)acetyl]piperazine-1-carbonyl}oxazol-2-yl)-2-propionamidopropanamide [8a(iii)e]

Yield: 20 mg (68%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (br s, 3 H), 2.23 (br s, 2 H), 2.76 (d, J = 5.2 Hz, 2 H), 3.23–3.37 (m, 4 H), 3.59–4.02 (m, 6 H), 4.61 (s, 1 H), 5.00 (br s, 1 H), 5.91–6.14 (m, 1 H), 6.90–6.94 (m, 2 H), 7.28 (t, J = 7.6 Hz, 2 H), 7.36 (t, J = 7.2 Hz, 2 H), 7.52 (d, J = 7.6 Hz, 2 H), 7.74 (d, J = 7.6 Hz, 2 H), 8.07 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.6, 29.5, 30.1, 37.6, 42.4, 43.7, 45.3, 46.3, 50.0, 120.0, 124.6, 127.2, 127.5, 136.0, 140.7, 143.6, 146.8, 160.8, 170.4, 172.4, 174.2.

ESI-MS: m/z = 530 $[M + H]^+$, 552 $[M + Na]^+$.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{29}H_{32}N_5O_5$: 530.2398; found: 530.2409.

(*R*)-2-(3-Amino-3-oxo-2-propionamidopropyl)-*N*-benzyloxazole-4-carboxamide [8a(iv)]

Yield: 150 mg (76%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, J = 7.2 Hz, 3 H), 2.23 (q, J = 7.6 Hz, 2 H), 3.20 (dd, J_1 = 16.0 Hz, J_2 = 6.8 Hz, 1 H), 3.27 (dd, J_1 = 16.0 Hz, J_2 = 6.0 Hz, 1 H), 4.60 (d, J = 6.0 Hz, 2 H), 4.94 (q, J = 7.2 Hz, 1 H), 5.39 (br s, 1 H), 6.49–6.54 (m, 2 H), 7.08 (br s, 1 H), 7.29–7.37 (m, 5 H), 8.15 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.5, 29.5, 30.0, 43.1, 50.0, 127.7, 127.9, 128.8, 136.1, 137.8, 141.5, 160.1, 161.2, 171.7, 174.1.

ESI-MS: m/z = 367 $[M + Na]^+$.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{17}H_{21}N_4O_4$: 345.1557; found: 345.1555.

(*R*)-*N*-{1-Amino-1-oxo-3-[4-(piperidine-1-carbonyl)oxazol-2-yl]propan-2-yl}cyclohexanecarboxamide [8b(i)]

Yield: 14.3 mg (66%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19–1.26 (m, 3 H), 1.30 (d, J = 12.0 Hz, 2 H), 1.41–1.69 (m, 8 H), 1.70–1.87 (m, 4 H), 2.16 (t, J = 11.6 Hz, 1 H), 3.12 (dd, J_1 = 16.4 Hz, J_2 = 6.4 Hz, 1 H), 3.38 (dd, J_1 = 16.4 Hz, J_2 = 4.8 Hz, 1 H), 3.71 (br s, 3 H), 4.95 (q, J = 6.4 Hz, 1 H), 5.44 (br s, 1 H), 6.79 (br s, 1 H), 6.95 (d, J = 7.2 Hz, 1 H), 8.00 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 25.57, 25.61, 25.65, 29.4, 29.5, 29.8, 45.2, 49.6, 136.6, 142.2, 160.6, 160.8, 172.1, 176.4.

ESI-MS: m/z = 399 $[M + Na]^+$.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{19}H_{29}N_4O_4$: 377.2183; found: 377.2184.

(*R*)-2-[3-Amino-2-(cyclohexanecarboxamido)-3-oxopropyl]-*N*-butyloxazole-4-carboxamide [8b(ii)]

Yield: 15.3 mg (73%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, J = 8.0 Hz, 3 H), 1.22–1.38 (m, 2 H), 1.39–1.43 (m, 3 H), 1.57 (s, 8 H), 1.85–1.97 (m, 3 H), 3.21 (dd, J_1 = 16.0 Hz, J_2 = 8.0 Hz, 1 H), 3.29 (dd, J_1 = 16.0 Hz, J_2 = 8.0 Hz, 1 H), 3.41 (q, J = 8.0 Hz, 2 H), 4.95 (q, J = 6.8 Hz, 1 H), 5.38 (br s, 1 H), 6.51–6.58 (m, 1 H), 6.75 (br s, 1 H), 8.11 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 20.1, 25.6, 29.4, 29.6, 29.9, 31.7, 38.8, 45.1, 49.9, 136.3, 141.2, 160.1, 161.1, 171.9, 176.4.

ESI-MS: m/z = 387 $[M + Na]^+$.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{18}H_{29}N_4O_4$: 365.2183; found: 365.2183.

(*R*)-*N*-[1-Amino-3-(4-{4-[2-(naphthalen-1-yl)acetyl]piperazine-1-carbonyl}oxazol-2-yl)-1-oxopropan-2-yl]cyclohexanecarboxamide [8b(iii)f]

Yield: 20.3 mg (65%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19–1.35 (m, 5 H), 1.65–1.75 (m, 5 H), 2.08 (br s, 1 H), 3.18 (br s, 2 H), 3.52 (br s, 3 H), 3.75 (br s, 3 H), 3.97 (br s, 1 H), 4.19 (s, 2 H), 4.94 (br s, 1 H), 5.58–5.91 (m, 1 H), 6.78 (br s, 2 H), 7.34 (d, J = 8.0 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 1 H), 7.52 (t, J = 8.4 Hz, 2 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.88 (d, J = 8.0 Hz, 1 H), 7.98 (d, J = 8.0 Hz, 1 H), 8.06 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 29.3, 29.5, 30.2, 30.3, 38.4, 42.4, 45.0, 46.2, 49.8, 123.3, 125.4, 126.0, 126.3, 126.5, 128.0, 128.9, 130.9, 131.8, 133.9, 136.1, 143.6, 143.7, 160.8, 170.0, 172.3, 176.3, 176.4.

ESI-MS: m/z = 568 $[M + Na]^+$.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{30}H_{36}N_5O_5$: 546.2711; found: 546.2715.

(*R*)-2-[3-Amino-2-(cyclohexanecarboxamido)-3-oxopropyl]-*N*-benzyloxazole-4-carboxamide [8b(iv)]

Yield: 15.8 mg (69%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.26 (m, 2 H), 1.32–1.38 (m, 1H), 1.58 (s, 5 H), 1.65–1.79 (m, 2 H), 3.20 (dd, J_1 = 16.0 Hz, J_2 = 6.4 Hz, 1 H), 3.27 (dd, J_1 = 16.0 Hz, J_2 = 5.6 Hz, 1 H), 4.60 (d, J = 5.6 Hz, 2 H), 4.92 (t, J = 6.4 Hz, 1 H), 5.37 (br s, 1 H), 6.50–6.57 (m, 2 H), 7.07 (br s, 1 H), 7.29–7.33 (m, 5 H), 8.16 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 25.6, 29.3, 29.6, 29.8, 43.1, 45.1, 49.8, 127.7, 127.8, 128.8, 136.1, 137.8, 141.5, 160.1, 161.2, 171.8, 176.5.

ESI-MS: m/z = 421 $[M + Na]^+$.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{21}H_{27}N_4O_4$: 399.2027; found: 399.2025.

(*R*)-2-{2-[3,5-Bis(trifluoromethyl)phenyl]acetamido}-3-[4-(piperidine-1-carbonyl)oxazol-2-yl]propanamide [8c(i)]

Yield: 17.3 mg (58%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (br s, 3 H), 1.52 (s, 2 H), 3.68 (br s, 2 H), 4.15–4.25 (m, 6 H), 4.70 (q, J = 8.0 Hz, 2 H), 7.23 (s, 1 H), 7.61 (s, 1 H), 7.92–7.96 (m, 3 H), 8.24 (s, 1 H), 8.55 (d, J = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 30.7, 41.2, 43.2, 51.1, 79.3, 120.6, 122.4, 125.1, 130.4 (1C, q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 139.6, 142.7, 160.6, 160.8, 169.6, 172.3.

ESI-MS: m/z = 543 $[M + Na]^+$.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{22}H_{23}F_6N_4O_4$: 521.1618; found: 521.1615.

(*R*)-2-(3-Amino-2-{2-[3,5-bis(trifluoromethyl)phenyl]acetamido}-3-oxopropyl)-*N*-butyloxazole-4-carboxamide [8c(ii)]

Yield: 18.7 mg (64%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.2 Hz, 3 H), 1.28 (q, J = 7.6 Hz, 2 H), 1.45 (t, J = 7.6 Hz, 2 H), 3.04 (dd, J_1 = 15.2 Hz, J_2 = 8.0 Hz, 1 H), 3.17–3.24 (m, 3 H), 3.74 (s, 1 H), 4.68 (q, J = 6.8 Hz, 1 H), 7.24 (s, 1 H), 7.59 (s, 1 H), 7.92–7.94 (m, 3 H), 8.05 (br s, 1 H), 8.33 (s, 1 H), 8.59 (d, J = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 20.0, 30.9, 31.7, 38.4, 41.3, 51.1, 79.6, 120.6, 122.5, 125.2, 130.3 (1C, q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 136.6, 139.8, 139.9, 141.7, 160.3, 161.5, 169.5, 172.0.

ESI-MS: m/z = 531 $[M + Na]^+$.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{21}H_{23}F_6N_4O_4$: 509.1618; found: 509.1615.

(*R*)-2-{2-[3,5-Bis(trifluoromethyl)phenyl]acetamido}-3-[4-(4-butyrylpiperazine-1-carbonyl)oxazol-2-yl]propanamide [8c(iii)g]

Yield: 20 mg (59%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.2 Hz, 3 H), 1.51 (q, J = 7.2 Hz, 2 H), 2.28 (br s, 2 H), 3.04 (dd, J_1 = 15.2 Hz, J_2 = 8.4 Hz, 1 H), 3.23 (dd, J_1 = 15.6 Hz, J_2 = 5.2 Hz, 1 H), 3.47 (br s, 6 H), 3.67–3.85 (m, 4 H), 4.71 (q, J = 6.8 Hz, 1 H), 7.26 (s, 1 H), 7.61 (s, 1 H), 7.93 (s, 3 H), 8.36 (s, 1 H), 8.56 (d, J = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 18.5, 30.9, 34.6, 41.3, 51.0, 79.6, 120.63, 120.66, 120.7, 122.5, 125.2, 129.8, 130.5 (1C, q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 136.2, 140.0, 143.8, 160.6, 161.0, 169.4, 171.2, 172.0.

ESI-MS: m/z = 614 $[M + Na]^+$.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{25}H_{28}F_6N_5O_5$: 592.1989; found: 592.2000.

(*R*)-2-(3-Amino-2-{2-[3,5-bis(trifluoromethyl)phenyl]acetamido}-3-oxopropyl)-*N*-benzyloxazole-4-carboxamide [8c(iv)]

Yield: 23.1 mg (74%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.05 (dd, J_1 = 15.6 Hz, J_2 = 8.0 Hz, 1 H), 3.26 (dd, J_1 = 16.0 Hz, J_2 = 5.6 Hz, 1 H), 3.62–3.78 (m, 2 H), 4.41 (s, 2 H), 4.68 (q, J = 6.8 Hz, 1 H), 7.16–7.28 (m, 5 H), 7.64 (s, 1 H), 7.93 (s, 2 H), 8.42 (s, 1 H), 8.66 (d, J = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.2, 40.8, 42.4, 51.1, 120.9, 122.6, 127.3, 128.1, 128.3, 128.7, 130.3 (1C, q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 137.3, 139.5, 140.2, 160.2, 163.0, 169.2, 172.5.

ESI-MS: m/z = 565 $[M + Na]^+$.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{24}H_{21}F_6N_4O_4$: 543.1462; found: 543.1464.

(3*R*,5*R*,7*R*)-*N*-{(*R*)-1-Amino-1-oxo-3-[4-(piperidine-1-carbonyl)oxazol-2-yl]propan-2-yl}adamantane-1-carboxamide [8d(i)]

Yield: 16.5 mg (67%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61–1.77 (m, 12 H), 1.84 (br s, 6 H), 2.00–2.04 (m, 3 H), 3.15 (dd, J_1 = 16.0 Hz, J_2 = 6.0 Hz, 1 H), 3.36 (dd, J_1 = 16.0 Hz, J_2 = 6.0 Hz, 1 H), 3.62–3.85 (m, 4 H), 4.95 (q, J = 6.0 Hz, 1 H), 5.80 (s, 1 H), 6.89 (br s, 1 H), 7.11 (d, J = 7.2 Hz, 1 H), 8.02 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 25.6, 26.7, 28.0, 29.9, 36.4, 39.0, 40.7, 49.7, 136.6, 142.4, 160.7, 160.8, 172.5, 178.4.

ESI-MS: m/z = 451 $[M + Na]^+$.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{23}H_{33}N_4O_4$: 429.2496; found: 429.2492.

2-{(*R*)-2-[(3*R*,5*R*,7*R*)-Adamantane-1-carboxamido]-3-amino-3-oxopropyl}-*N*-butyloxazole-4-carboxamide [8d(ii)]

Yield: 23.0 mg (73%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.2 Hz, 3 H), 1.39 (q, J = 7.6 Hz, 2 H), 1.56 (t, J = 7.2 Hz, 2 H), 1.67–1.78 (m, 6 H), 1.83 (br s, 6 H), 2.05 (s, 3 H), 3.20 (dd, J_1 = 14.8 Hz, J_2 = 6.0 Hz, 1 H), 3.28 (dd, J_1 = 15.6 Hz, J_2 = 6.0 Hz, 1 H), 3.39 (q, J = 6.8 Hz, 2 H), 4.96 (q, J = 6.8 Hz, 1 H), 5.69 (br s, 1 H), 6.81 (d, J = 6.4 Hz, 2 H), 6.92 (d, J = 7.6 Hz, 1 H), 8.12 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 20.1, 28.0, 29.9, 31.7, 36.4, 38.8, 39.1, 40.7, 49.8, 136.3, 141.2, 160.2, 161.2, 172.3, 178.5.

ESI-MS: m/z = 439 $[M + Na]^+$.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{22}H_{33}N_4O_4$: 417.2496; found: 417.2495.

(3*R*,5*R*,7*R*)-*N*-[(*R*)-1-Amino-1-oxo-3-{4-[4-(2-phenylacetyl)piperazine-1-carbonyl]oxazol-2-yl}propan-2-yl]adamantane-1-carboxamide [8d(iii)h]

Yield: 19.5 mg (62%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (d, J = 12.0 Hz, 3 H), 1.75 (d, J = 12.8 Hz, 3 H), 1.81 (s, 6 H), 2.03 (s, 3 H), 3.18 (dd, J_1 = 15.6 Hz, J_2 = 5.6 Hz, 1 H), 3.28 (br s, 1 H), 3.50 (br s, 3 H), 3.69 (br s, 3 H), 3.77–3.96 (m, 4 H), 4.95 (q, J = 6.0 Hz, 1 H), 5.71–5.82 (m, 1 H), 6.74 (s, 1 H), 6.81–6.93 (m, 1 H), 7.23–7.27 (m, 3 H), 7.33 (t, J = 7.2 Hz, 2 H), 8.07 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0, 30.0, 36.4, 39.0, 40.7, 41.1, 42.3, 46.1, 49.8, 127.1, 128.5, 128.9, 134.6, 136.1, 143.6, 143.7, 160.7, 160.9, 169.8, 172.3, 178.4.

ESI-MS: m/z = 548 $[M + H]^+$.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{38}N_5O_5$: 548.2867; found: 548.2871.

2-{(*R*)-2-[(3*R*,5*R*,7*R*)-Adamantane-1-carboxamido]-3-amino-3-oxopropyl}-*N*-benzyloxazole-4-carboxamide [8d(iv)]

Yield: 19.4 mg (75%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (d, *J* = 12.0 Hz, 3 H), 1.70 (d, *J* = 12.4 Hz, 3 H), 1.76 (s, 6 H), 1.88 (s, 1 H), 1.95 (br s, 3 H), 3.15 (dd, J_1 = 16.0 Hz, J_2 = 5.6 Hz, 1 H), 3.23 (dd, J_1 = 16.0 Hz, J_2 = 6.4 Hz, 1 H), 4.57 (t, *J* = 5.2 Hz, 2 H), 4.92 (q, *J* = 6.4 Hz, 1 H), 5.64 (br s, 1 H), 6.80 (br s, 1 H), 6.89 (d, *J* = 7.2 Hz, 1 H), 7.29–7.34 (m, 5 H), 8.15 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9, 29.9, 36.3, 39.0, 40.6, 40.7, 43.1, 49.8, 127.6, 127.8, 128.8, 136.0, 137.8, 141.5, 160.2, 161.4, 172.2, 178.4.

ESI-MS: *m*/*z* = 473 [M + Na]$^+$.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{31}N_4O_4$: 451.2340; found: 451.2345.

(*R*)-4-[4-(Piperidine-1-carbonyl)oxazol-2-yl]-2-propionamidobutanamide [12a(i)]

Yield: 12.2 mg (63%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.2 Hz, 3 H), 1.62–1.68 (m, 6 H), 2.09–2.16 (m, 1 H), 2.25 (q, *J* = 7.6 Hz, 2 H), 2.29–2.35 (m, 1 H), 2.84–2.90 (m, 1 H), 2.95–3.01 (m, 1 H), 3.67–3.78 (m, 4 H), 4.63 (q, *J* = 6.8 Hz, 1 H), 5.80 (br s, 1 H), 6.71 (br s, 1 H), 7.00 (br s, 1 H), 7.95 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.6, 23.5, 24.5, 24.6, 25.6, 29.5, 29.6, 51.5, 136.3, 141.5, 161.0, 163.3, 173.5, 174.2.

ESI-MS: *m*/*z* = 359 [M + Na]$^+$.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{25}N_4O_4$: 337.1870; found: 337.1866.

(*R*)-2-[4-Amino-3-(cyclohexanecarboxamido)-4-oxobutyl]-*N*-butyloxazole-4-carboxamide [12b(ii)]

Yield: 15.0 mg (69%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.6 Hz, 3 H), 1.21–1.28 (m, 3 H), 1.41 (q, *J* = 8.0 Hz, 4 H), 1.60–1.68 (m, 2 H), 1.81 (t, *J* = 14.8 Hz, 4 H), 2.07–2.17 (m, 2 H), 2.36 (q, *J* = 7.2 Hz, 1 H), 2.78–2.86 (m, 1 H), 2.89–3.38 (m, 1 H), 3.42 (q, *J* = 6.8 Hz, 2 H), 4.57 (q, *J* = 7.6 Hz, 1 H), 5.39 (br s, 1 H), 6.16 (d, *J* = 6.8 Hz, 1 H), 6.27 (br s, 1 H), 6.83 (br s, 1 H), 8.08 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 20.0, 24.6, 25.6, 25.8, 25.9, 29.4, 29.5, 29.9, 31.8, 38.4, 44.2, 51.9, 136.6, 141.6, 160.4, 164.1, 173.7, 175.8.

ESI-MS: *m*/*z* = 401 [M + Na]$^+$.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{31}N_4O_4$: 379.2340; found: 379.2338.

(*R*)-2-{2-[3,5-Bis(trifluoromethyl)phenyl]acetamido}-4-[4-(4-butyrylpiperazine-1-carbonyl)oxazol-2-yl]butanamide [12c(iii)g]

Yield: 23.1 mg (66%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 6.8 Hz, 3 H), 1.67 (q, *J* = 7.6 Hz, 4 H), 2.07–2.14 (m, 1 H), 2.33 (t, *J* = 6.8 Hz, 3 H), 2.81–2.88 (m, 1 H), 2.93–3.00 (m, 1 H), 3.54 (s, 2 H), 3.69–4.10 (m, 6 H), 4.62 (d, *J* = 6.0 Hz, 1 H), 5.83 (br s, 1 H), 6.70 (br s, 1 H), 7.12 (br s, 1 H), 7.76–7.78 (m, 3 H), 8.02 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 18.6, 24.3, 29.5, 35.2, 42.3, 51.7, 121.3, 121.8, 124.6, 129.5, 131.8 (1C, q, 1JC-F = 272 Hz, CF_3), 137.0, 142.8, 163.2, 169.4, 171.9, 172.8.

ESI-MS: *m*/*z* = 628 [M + Na]$^+$.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{30}F_6N_5O_5$: 606.2146; found: 606.2150.

2-{(*R*)-3-[(3*R*,5*R*,7*R*)-Adamantane-1-carboxamido]-4-amino-4-oxobutyl}-*N*-benzyloxazole-4-carboxamide [12d(iv)]

Yield: 19.2 mg (72%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.64–1.74 (m, 5 H), 1.80 (s, 8 H), 2.01 (s, 3 H), 2.10–2.17 (m, 1 H), 2.30–2.37 (m, 1 H), 2.76–2.82 (m, 1 H), 2.85–2.91 (m, 1 H), 4.54–4.60 (m, 3 H), 5.45 (br s, 1 H), 6.30 (d, *J* = 7.2 Hz, 1 H), 6.43 (br s, 1 H), 7.29–7.33 (m, 5 H), 8.12 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 28.0, 28.7, 36.4, 39.1, 40.7, 43.1, 51.4, 127.6, 127.9, 128.7, 136.0, 137.9, 141.1, 160.4, 163.7, 173.1, 178.6.

ESI-MS: *m*/*z* = 487 [M + Na]$^+$.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{33}N_4O_4$: 465.2496; found: 465.2503.

Funding Information

The authors would like to thank the State of Florida Funding, NIH (1R21CA191351-01A1 Nefzi/Piedrafita), NIH (1R01AI105836-01A1, Nefzi/Piedrafita), and Louisiana Biomedical Research Network (Murru) for providing generous financial support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589148.

References

(1) Magrioti, V.; Moutevelis-Minakakis, P.; Kokotos, G. *Synthesis of non-natural amino acids and their applications for the development of medicinally interesting compounds. Essays on Contemporary Peptide Science*; Cordopatis, P., Ed.; Research Signpost: India, **2011**, 1–17.

(2) Saladino, R.; Botta, G.; Crucianelli, M. *Mini Rev. Med. Chem.* **2012**, *12*, 277.

(3) (a) Toy, P. H.; Lam, Y. *Solid-Phase Organic Synthesis: Concepts, Strategies, and Applications*; John Wiley & Sons: Hoboken, **2012**. (b) Eifler-Lima, V. L.; Graebin, C. S.; Uchoa, F. D. T.; Duarte, P. D.; Correa, A. G. *J. Braz. Chem. Soc.* **2010**, *21*, 1401. (c) Krchňák, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61. (d) Grabowska, U.; Rizzo, A.; Farnell, K.; Quibell, M. *J. Comb. Chem.* **2000**, *2*, 475. (e) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149. (f) Merrifield, B. *Science* **1986**, *232*, 341. (g) Geysen, H. M.; Meleon, R. H.; Barteling, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3998.

(4) (a) Rohde, K. H.; Michaels, H. A.; Nefzi, A. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2206. (b) Eans, S. O.; Ganno, M. L.; Mizrachi, E.; Houghten, R. A.; Dooley, C. T.; McLaughlin, J. P.; Nefzi, A. *J. Med. Chem.* **2015**, *58*, 4905. (c) Murru, S.; Nefzi, A. *ACS Comb. Sci.* **2014**, *16*, 39. (d) Michaels, H. A.; Velosa, D. C.; Nefzi, A. *ACS Comb. Sci.* **2014**, *16*, 1. (e) Murru, S.; Dooley, C.; Nefzi, A. *Tetrahe-*

dron Lett. **2013**, *54*, 7062. (f) Liu, A.; Nefzi, A. *J. Comb. Chem.* **2010**, *12*, 566. (g) Nefzi, A.; Appel, J.; Arutyunyan, S.; Houghten, R. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5169.

(5) (a) Chen, H.; Wang, J.; Zhou, S.; Liu, H. *J. Org. Chem.* **2014**, *79*, 7872. (b) Turner, C. D.; Liang, H. S. *Curr. Org. Chem.* **2011**, *15*, 2846. (c) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 196. (d) Moloney, M. G.; Trippier, P. C.; Yaqoob, M.; Wang, Z. *Curr. Drug Discovery Technol.* **2004**, *1*, 181.

(6) (a) Giddens, A. C.; Boshoff, H. I. M.; Franzblau, S. G.; Barry, C. E. III.; Copp, B. R. *Tetrahedron Lett.* **2005**, *46*, 7355. (b) Crank, G.; Neville, M.; Ryden, R. *J. Med. Chem.* **1973**, *16*, 1402. (c) Crank, G.; Foulis, M. J. *J. Med. Chem.* **1971**, *14*, 1075.

(7) (a) Allington, D. R.; Rivey, M. P. *Clin. Ther.* **2001**, *23*, 24. (b) Brown, K.; Cavalla, J. F.; Green, D.; Wilson, A. B. *Nature* **1968**, *219*, 164.

(8) (a) Ma, Z.; Cowart, D. M.; Ward, B. P.; Arnold, R. J.; DiMarchi, R. D.; Zhang, L.; George, G. N.; Scott, R. A.; Giedroc, D. P. *J. Am. Chem. Soc.* **2009**, *131*, 18044. (b) Mennen, S. M.; Blank, J. T.; Tran-Dube, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195.

(9) (a) Pinto, D. J.; Smallheer, J. M.; Corte, J. R.; Hu, Z.; Cavallaro, C. L.; Gilligan, P. J.; Quan, M. L.; Smith, L. M. WO2007070826 A1, **2007**. (b) Campiani, G.; De Angelis, M.; Armaroli, S.; Fattorusso, C.; Catalanotti, B.; Ramunno, A.; Nacci, V.; Novellino, E.; Grewer, C.; Ionescu, D.; Rauen, T.; Griffiths, R.; Sinclair, C.; Fumagalli, E.; Mennini, T. *J. Med. Chem.* **2001**, *44*, 2507. (c) Xu, Y.-Z.; Yuan, S.; Bowers, S.; Hom, R. K.; Chan, W.; Sham, H. L.; Zhu, Y. L.; Beroza, P.; Pan, H.; Brecht, E.; Yao, N.; Lougheed, J.; Yan, J.; Tam, D.; Ren, Z.; Ruslim, L.; Bova, M. P.; Artis, D. R. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3075. (d) Zhang, W.; Liu, W.; Jiang, X.; Jiang, F.; Fu, L. *Synth. Commun.* **2012**, *42*, 2772. (e) Boyd, S. A.; Demeese, J.; Farouz, F. S.; Gunawardana, I.; Jacobson, I. C.; Kasar, R. A.; Lehuerou, Y.; Lupher, M. L.; Mclaughlin, M.; Miller, S.; Thomas, A.; Thorsett, E. D.; Xu, R.; Yanik, M.; Zhang, G. Patent WO2005016883 A3, **2005**. (f) Challenger, S.; Cook, A. S.; Gillmore, A. T.; Middleton, D. S.; Pryde, D. C.; Stobie, A. WO2002079143 A1, **2002**. (g) Glossop, M. S.; Bazin, R. J.; Dack, K. N.; Fox, D. N. A.; MacDonald, G. A.; Mills, M.; Owen, D. R.; Phillips, C.; Reeves, K. A.; Ringer, T. J.; Strang, R. S.; Watson, C. A. L. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3406. (h) Kolb, H. C.; Sun, Q. US 6562944, **2003**.

(10) (a) Brown, R. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293. (b) Baxter, A. D. *Curr. Opin. Chem. Biol.* **1997**, *1*, 79. (c) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527.

(11) (a) Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5131. (b) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *J. Org. Chem.* **2004**, *69*, 3603.

(12) (a) Li, Z.; Gever, J. R.; Rao, S.; Widjaja, K.; Prusiner, S. B.; Silber, B. M. *ACS Med. Chem. Lett.* **2013**, *4*, 397. (b) Helal, C. J.; Sanner, M. A.; Cooper, C. B.; Gant, T.; Adam, M.; Lucas, J. C.; Kang, Z. J.; Kupchinsky, S.; Ahlijanian, M. K.; Tate, B.; Menniti, F. S.; Kelly, K.; Peterson, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5521. (c) http://www.3dchem.com/top50.asp (accessed Dec 15, 2017) (d) Soural, M.; Bouillon, I.; Krchnak, V. *J. Comb. Chem.* **2008**, *10*, 923.

(13) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595.