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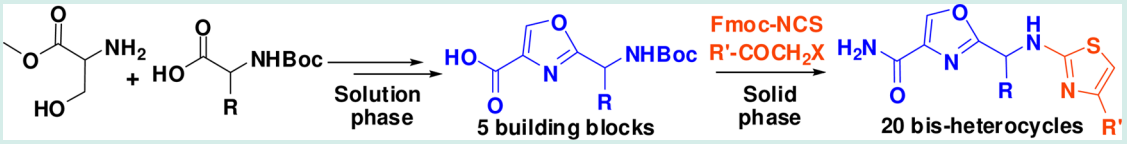
Combinatorial Synthesis of Oxazol-Thiazole Bis-Heterocyclic Compounds

Siva Murru and Adel Nefzi*

Torrey Pines Institute for Molecular Studies, 11350 SW Village Parkway, Port St Lucie, Florida 34987, United States

Supporting Information



ABSTRACT: A combinatorial library of novel oxazol-thiazole bis-heterocycles was synthesized in good to excellent overall yields with high purity using a solution and solid-phase parallel synthesis approach. Oxazole amino acids, prepared from serine methyl ester and amino acids via coupling and cyclodehydration, were treated with Fmoc-NCS and α-haloketones for the parallel synthesis of diverse bis-heterocycles. Fmoc-isothiocyanate is used as a traceless reagent for thiazole formation. Oxazole diversity can be achieved by using variety of amino acids, whereas thiazole diversity is produced with various haloketones.

KEYWORDS:

INTRODUCTION

Natural products play an important role in the development of new drugs[1] and provide the inspiration to develop new strategies toward the diversity-oriented synthesis of novel small-molecule libraries. An extraordinary group of biologically active natural products, often from a marine environment,[2] contains bis-thiazoles, bis-oxazoles and bis-oxazol-thiazole systems, which are derived from biosynthetic cyclizations of precursor amino acids Cys, Ser and Thr.[3] Thiazole/oxazole modified microcins (TOMMs)[3b,c] are a widespread natural product platform and exhibit a wide range of biological activities, including cytotoxicity,[4a] immunosuppression,[4b] multiple drug resistance pump inhibition,[4c] as well as antibacterial and antiviral activities.[4d] For example, in the ribosomal peptide group, microcin B17 is a DNA gyrase inhibitor,[5a] Goadsporin is a secondary metabolism inducer,[5b] and Ritonavir is a HIV-1 protease inhibitor.[5c] In addition, the heterocyclic motif, either thiazole or oxazole itself, is potentially bioactive and can interact with nucleic acids and proteins. The aminothiazole ring system is a useful structural element in medicinal chemistry and has found broad applications in drug development as antihypertensive,[6a] antibacterial,[6b] and anti-HIV agents.[6c] Many oxazole derivatives are found to be associated with various biological activities[7] such as antifungal, antitubercular, anti-inflammatory activities, etc.

Biosynthesis of oxazoles and thiazoles occurs in β-hydroxy-(thio) peptides (Ser, Thr or Cys) via cyclodehydration followed by an oxidation reaction.[3b,c] Inspired by this natural pathway, chemists developed methods for biomimetic synthesis of oxazole/thiazole based peptides/peptidomimetics. Reported methods include (i) condensation of thioamide and haloketones (modified Hantzsch's procedure),[8] (ii) cyclodehydration of β-hydroxy(thio)amides to give 1,3-azolines using either Mitsunobu conditions or the Burgess reagent, followed by ring oxidation to yield 1,3-azoles,[4c,9] (iii) oxidation of β-hydroxy-(thio)amides β-keto(thio)amide and cyclization (Robinson–Gabriel) affords oxazoles and thiazoles,[10] and (iv) a condensation reaction between N-protected imino ethers and Ser- or Cys-esters.[11] Most of these methods report the synthesis of either oxazole or thiazole amino acids and their application to macrocyclic peptide synthesis. The major disadvantages of cyclodehydration methods for generation of thiazoles are the required use of either *S*-protected Cysteine substrates or thioamides, requiring multiple steps.[10b] Recently, McAlpine et al. reported a multistep synthesis of Sanguinamide-B analogues containing directly linked (C2–C4′) oxazol-thiazole using thioamide as the thiazole precursor.[12] Though the oxazol-thiazole bis-heterocyclic moiety is encountered in many bioactive natural products, there is no report on the parallel synthesis for these pharmacologically important molecules.

Prompted by the above investigation and in continuation of our work in the generation of heterocyclic compounds[8d,e,13] from amino acids and short peptides, we envisaged the synthesis of oxazole amino acid building blocks and utilizing them for the parallel synthesis of oxazol-thiazole bis-heterocycles. Our strategy involves the solution-phase synthesis of oxazole amino acid building blocks and solid-phase synthesis of thiazoles. The main advantages of our approach are (i) biomimetic synthesis of oxazole amino acids and their use as building blocks for the solid-phase synthesis, (ii) use of Fmoc-NCS as a thioamide equivalent for the thiazole cyclization, and (iii) rapid generation of diverse bis-heterocycles using haloketones. Similar to the biosynthetic pathway, our approach

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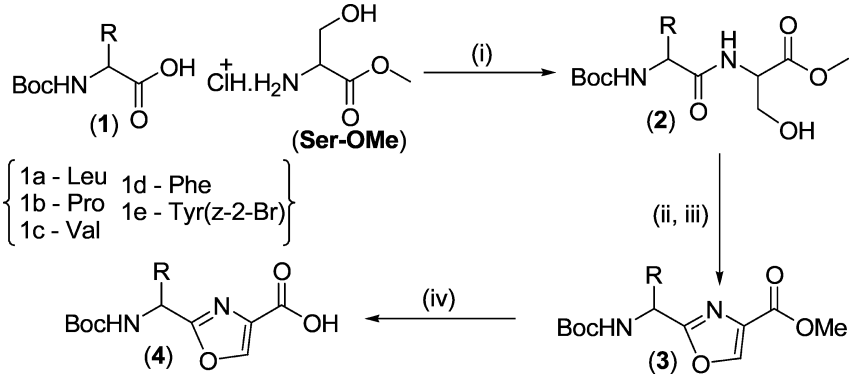
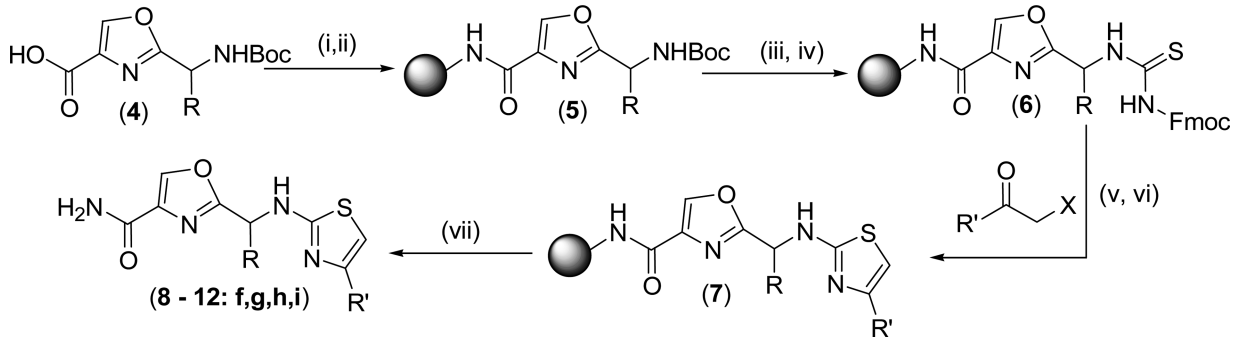
Scheme 1. Biomimetic Synthesis of Non-Natural Oxazole Amino Acid Building Blocks Starting from Amino Acids and Serine Methyl Ester[a]



[a] Reaction conditions: (i) HOBt, DIC, DIPEA, DCM, 0 °C to RT; (ii) DAST, DCM, −78 °C; (iii) $BrCCl_3$, DBU, DCM, 0 °C; (iv) 1N NaOH(aq), Dioxane/H_2O, 10% $KHSO_4$(aq).

Scheme 2. Solid-Phase Parallel Synthesis of Oxazol-Thiazole Bis-Heterocycles (5R × 4R' = 20 RR') via Hantzsch Cyclization Starting from Resin-Bound Oxazole Amino Acids[a]



[a]Reaction conditions: (i) MBHA resin, DIEA, DCM, 5 min; (ii) HOBt, DIC, DMF, overnight; (iii) 55% TFA in DCM, 30 min; (iv) Fmoc-NCS (3 equiv), 10 h; (v) Piperidine/DMF (20%), 10 min; (vi) Halo ketone, DMF, 80 °C; (vii) HF-cleavage.

is also based on cyclodehydration of β-hydroxy peptides to oxazolines followed by oxidation and hydrolysis affording oxazole amino acids (Scheme 1).

For our studies, we chose Boc-protected amino acids because of their compatibility with basic reaction conditions. To optimize the reaction conditions, we initially used Boc-Leu-OH as the coupling partner with Ser-OMe. As shown in Scheme 1, β-hydroxy peptide **2a** (Boc-Leu-Ser-OMe) was synthesized from Boc-Leu-OH (**1a**) and Ser-OMe·HCl utilizing standard coupling conditions (DIEA, DIC and HOBt) in DMF. Following the procedure by Wipf and Williams,[14] cyclization of Boc-β-hydroxypeptide **2a** with fluorinating reagent DAST at −78 °C was performed to yield oxazoline ester, followed by the addition of $BrCCl_3$ and DBU in the same flask at 0 °C resulted in the oxidation to oxazole ester (**3a**, 68%). Boc-oxazole amino acid **4a** is obtained quantitatively (93%) by the hydrolysis of **3a** using of 1N aq. NaOH (3 equiv) at 0 °C. The overall yield after four reaction steps for **4a** is 63%.

To determine if any racemization occurs during the synthesis, we have prepared possible diasteromers of **4a** with Boc-L-Phe-OH and Boc-L-Val-OH. The LC-MS analysis of these diastereomers shows very little racemization (2−5%) as observed by others in a similar methodology.[10a,12,14] Consequently, the same synthetic approach was used for other Boc-protected amino acids such as Boc-Pro-OH (**1b**), Boc-Val-OH (**1c**), Boc-Phe-OH (**1d**) and Boc-Tyr(Z-2-Br)-OH (**1e**) and are converted smoothly to the corresponding oxazole amino acids (**4b**−**e**) in moderate to good overall yields (59%, 64%, 56% and 48%, respectively). These heterocyclic amino acids served as building blocks for the parallel synthesis of oxazol-thiazole bis-heterocycles as outlined in Scheme 2.

Having oxazole amino acid building blocks in hand, the next step is to synthesize a library of oxazol-thiazole bis-heterocycles. Because solid-phase organic synthesis (SPOS)[15] is an effective tool to generate structurally diverse compounds, we employed the tea-bag approach[15b] for the rapid solid-phase parallel synthesis of diverse bis-heterocycles. First, we loaded the oxazole amino acid building blocks on to *p*-methylbenzhydrylamine (MBHA) resin using DIC and HOBt in DMF. Next, the resin-bound Boc-oxazole was treated with 55% TFA in DCM to remove Boc-protection and the resulting free amine was reacted with Fmoc-isothiocyanate to form the substituted thiourea. Following Fmoc-deprotection using 20% piperidine in DMF, monosubstituted thioureas were treated with four different haloketones while heated overnight at 80 °C in DMF to generate the corresponding thiazole ring. After completion of the cyclization, compounds were cleaved from the resin and the desired 20 diverse oxazol-thiazole bis-heterocycles were obtained in good yields and high purity (Table 1).

We used four different haloketones for thiazole cyclizations, namely 1-chloropinacolone (**f**), 2-bromoacetophenone (**g**), 2-chloro-3′,4′-dihydroxyacetophenone (**h**), 1-adamantyl chloromethyl ketone (**i**). Products were obtained in good yields and purities. Using proline oxazole (**4b**), we obtained a cascade of

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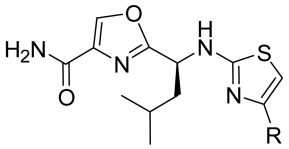
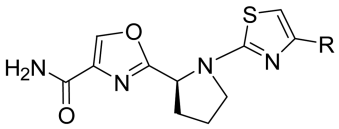
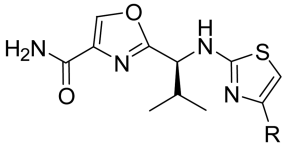
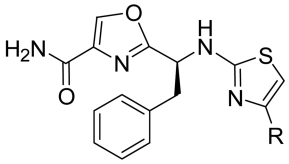
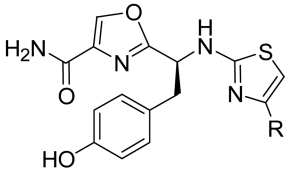
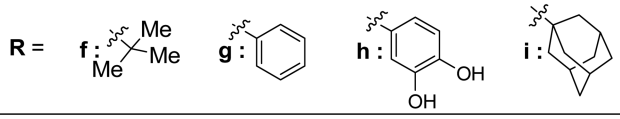
Table 1. Solid-Phase Parallel Synthesis of Oxazol-Thiazole Bis-Heterocycles

Bis-heterocycle	Compound	Purity (%)[a]	Yield (%)[b]	Purity (%)[c]
	8f	90	78	>99
	8g	71	62	>99
	8h	89	68	98
	8i	66	56	96
	9f	92	86	>99
	9g	76	69	98
	9h	86	72	>99
	9i	81	67	97
	10f	79	71	>99
	10g	68	64	>99
	10h	78	61	>99
	10i	73	59	97
	11f	91	82	>99
	11g	77	71	>99
	11h	91	85	>99
	11i	86	63	>99
	12f	93	81	>99
	12g	69	64	>99
	12h	88	76	>99
	12i	75	68	95
				

[a]Based on integration of LCMS chromatogram of the crude product. [b]Based on the product obtained after HPLC purification. [c]Purity of the compounds obtained after HPLC purification.

three distinct heterocycles oxazole, pyrrolidine and thiazole present in products **9f–9i**. It should be noted here that the combination of two or three heterocyclic cores in one molecule increases the number of potential targets by the square power and improves the chances of identifying hits. Many approved drugs contain five- and six-membered heterocycles, often bis- or tris-nitrogen heterocycles.[16]

In conclusion, we have developed an approach for the parallel synthesis of pharmacologically relevant bis-heterocycles containing oxazole and thiazole structures in the core. We have used a variety of amino acids for the oxazole diversity and different halo-ketones for thiazole diversity. This approach is useful to incorporate oxazole and thiazole moiety into peptides and peptidomimetics to generate combinatorial librairies for the purpose of drug discovery. We are in the process of preparing a large library of oxazol-thiazole bis-heterocyclic compounds. The screening results will be reported elsewhere.

EXPERIMENTAL SECTION

Synthesis of Methyl 2-(2-(*tert*-Butoxycarbonylamino)-4-methylpentanamido)-3-hydroxy Propanoate (2a). Diisopropylethylamine (10 mmol, 1.8 mL) was added to a solution of Boc-L-leucine (**1a**) (10 mmol, 2.49 g) in DCM (8 mL). The solution was cooled to 0 °C, and a solution of DIC (10 mmol, 1.7 mL) was added. After the solution was stirred at 0 °C for 1 h, a solution of L-Ser-OMe·HCl (10 mmol, 1.56 g) was added and the solution was stirred at room temperature for another 8 h. After filtration and removal of the solvent on rotavap, the residue was dissolved in ethylacetate and washed with 10% citric acid (50 mL) followed by saturated $NaHCO_3$(aq) solution and water wash. The organic extract was dried over $MgSO_4$ followed by evaporation of the organic solvent obtain the hydroxy peptide **2a** and is used for the next step without any further purification.

Synthesis of Methyl 2-(1-(*tert*-Butoxycarbonylamino)-3-methylbutyl)oxazole-4-carboxylate (3a). Diethylaminosulfur trifluoride (DAST) (10 mmol, 1.34 mL) was added dropwise to the solution of β-hydroxy peptide (**2a**, obtained from previous step) in CH_2Cl_2 at −78 °C (acetone−dryice bath). After completion of cyclization (monitered by TLC), the reaction mixture was allowed to warm to 0 °C and bromotrichloromethane ($BrCCl_3$) (10 mmol, 0.97 mL) was added dropwise, followed by DBU (10 mmol, 1.5 mL). The reaction was monitered by TLC till completion and then quenched with saturated $NaHCO_3$(aq) solution. The reaction mixture was extracted with EtOAc and dried over $MgSO_4$,

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filtered, and concentrated on rotavap. Purification of the residue by flash chromatography (5−10% ethyl acetate in hexane) gave the desired oxazole ester **3a** in 68% yield.

Synthesis of 2-(1-(*tert*-Butoxycarbonylamino)-3-methylbutyl)oxazole-4-carboxylic acid (4a). Oxazole ester **3a** (6.8 mmol, 2.31 g) was dissolved in dioxane (12 mL) and added to a 1N NaOH(aq) solution (18 mL) slowly with the help of a dropping funnel while the solution stirred at 0 °C. The reaction was monitered by TLC till the starting material disappeared and acidified with 10% $KHSO_4$ to pH 5 followed by removal of the organic solvent in vacuo. Then the residue is diluted with water and extracted with ethylacetate (3 × 40 mL). Organic fractions were combined and dried over $MgSO_4$ followed by evaporation of the organic solvent. The crude product obtained was washed with hexane to get a white solid in 93% yield.

General Procedure for the Solid-Phase Parallel Synthesis of Oxazol-Thiazole Bis-Heterocycles (8−12 f, g, h, i). A 20 set of 50 mg sealed polypropylene mesh bags containing *p*-methylbenzhydrylamine hydrochloride salt (MBHA) resin (1.15 m equiv/g, 100−200 mesh) was prepared.[15b] Reactions were carried out by placing all the bags in polyethylene bottles. The bags (containing resin) were washed with dichloromethane (DCM), isopropanol and DCM in a sequence followed by the neutralization with 5% diisopropylethylamine (DIEA) in DCM. Boc-Oxazole amino acid (**4**) (2 equiv) was coupled using the conventional reagents hydroxybenzotriazole (HOBt, 2 equiv) and diisopropylcarbodiimide (DIC, 2 equiv) in anhydrous DMF with shaking for overnight. Completion of the coupling was monitored by the ninhydrin test.[17]

Following the removal of the Boc group with 55% TFA/DCM for 30 min and neutralization with 5% DIEA/DCM, the solution was treated with Fmoc-NCS to obtain thiourea and the completion was monitored by the ninhydrin test. Then the Fmoc group was deprotected with 20% piperidine in DMF (2 × 10 min) and the bags were divided into four sets and treated with α-haloketones to at 80 °C for overnight. The resin was then washed with DMF (3×), and DCM (3×) followed by a HF cleave,[18] which provided the desired oxazol-thiazole bis-heterocycles. All the prodcuts were confirmed by LC-MS and NMR analysis.

(*S*)-2-(1-(*tert*-Butoxycarbonylamino)-3-methylbutyl)-oxazole-4-carboxylic Acid (4a). A white powder: 1.87 g, 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87−0.90 (m, 6H), 1.33 (s, 9H), 1.56−1.61 (m, 1H), 1.67−1.70 (m, 2H), 4.96 (d, 1H, *J* = 8.0 Hz), 6.04 (brs, 1H), 8.20 (s, 1H), 10.77 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 22.5, 24.7, 28.3, 43.2, 47.5, 80.0, 133.2, 144.5, 155.6, 163.8, 167.7. ESI-MS: 321 (M + Na). HRMS (ESI-TOF): calcd for $C_{14}H_{23}N_2O_5$ (M + H^+), 299.1607; found, 299.1602.

(*S*)-2-(1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl)oxazole-4-carboxylic Acid (4b). A white powder: 1.66 g, 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28, 1.42 (2xs, 9H), 1.91−1.95 (m, 1H), 1.99−2.06 (m, 2H), 2.10−2.13 (m, 1H), 3.44−3.63 (m, 2H), 4.98, 5.08 (2xbrs, 1H), 8.18, 8.23 (2xs, 1H), 8.96 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 28.4, 31.3, 32.5, 46.5, 46.8, 54.5, 54.8, 80.5, 138.7, 143.9, 154.0, 154.6, 164.0, 166.0, 166.4. ESI-MS: 305 (M + Na). HRMS (ESI-TOF) *m*/*z*: (M + H) calcd for $C_{13}H_{19}N_2O_5$, 283.1294; found, 283.1291.

(*S*)-2-(1-(*tert*-Butoxycarbonylamino)-2-methylpropyl)-oxazole-4-carboxylic Acid (4c). A white powder: 1.81 g, 64% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.86 (s, 3H), 0.88 (s, 3H), 1.37 (s, 9H), 3.74 (s, 1H), 4.51 (brs, 1H), 7.49 (brs, 1H), 8.31 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.0, 19.3, 28.6, 54.6, 60.1, 78.8, 115.4, 125.6, 138.6, 141.1, 155.7, 164.0. ESI-MS: 307 (M + Na). HRMS (ESI-TOF) *m*/*z*: (M + H) calcd for $C_{13}H_{21}N_2O_5$, 285.1450; found, 285.1448.

(*S*)-2-(1-(*tert*-Butoxycarbonylamino)-2-phenylethyl)-oxazole-4-carboxylic Acid (4d). A white powder: 1.85 g, 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 9H), 3.24 (d, 2H, *J* = 6.8 Hz), 5.26 (d, 1H, *J* = 7.6 Hz), 5.99 (brs, 1H), 7.09 (d, 2H, *J* = 6.0 Hz), 7.27−7.31 (m, 3H), 8.20 (s, 1H), 11.53 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 40.4, 50.4, 67.0, 80.3, 126.8, 127.1, 128.6, 133.2, 135.7, 144.7, 155.3, 164.0, 166.1. ESI-MS: 355 (M + Na). HRMS (ESI-TOF) *m*/*z*: (M + H) calcd for $C_{17}H_{21}N_2O_5$, 333.1450; found, 333.1447.

(*S*)-2-(1-(*tert*-Butoxycarbonylamino)-2-(4-hydroxyphenyl)ethyl)oxazole-4-carboxylic Acid (4e). A white powder: 1.67 g, 48% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.37 (s, 9H), 2.56 (s, 1H), 2.94−3.00 (m, 1H), 3.08−3.13 (m, 1H), 4.84 (d, 1H, *J* = 6.8 Hz), 6.69 (d, 2H, *J* = 8.0 Hz), 7.03 (d, 2H, *J* = 8.0 Hz), 8.66 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.6, 50.8, 63.0, 78.8, 115.4, 127.7, 130.5, 132.4, 141.5, 155.5, 156.3, 162.6, 165.0. ESI-MS: 371 (M + Na). HRMS (ESI-TOF) *m*/*z*: (M + H) calcd for $C_{17}H_{21}N_2O_6$, 349.1400; found, 349.1397.

(*S*)-2-(1-(4-*tert*-Butylthiazol-2-ylamino)-3-methylbutyl)oxazole-4-carboxamide (8f). A white powder: 15.1 mg, 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (d, 3H, *J* = 8.0 Hz), 0.98 (d, 3H, *J* = 8.0 Hz), 1.22 (s, 9H), 1.71 (m, 1H), 1.84 (m, 2H), 4.90 (t, 1H, *J* = 7.0 Hz), 5.58 (brs, 1H), 5.86 (brs, 1H), 6.07 (s, 1H), 6.80 (brs, 1H), 8.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 22.5, 24.7, 29.6, 34.6, 43.5, 52.1, 98.8, 135.6, 141.6, 162.5, 162.7, 164.7, 166.9. ESI-MS: 359 (M + Na). HRMS (ESI-TOF) *m*/*z*: (M + H) calcd for $C_{16}H_{25}N_4O_2S$, 337.1698; found, 337.1695.

(*S*)-2-(3-Methyl-1-(4-phenylthiazol-2-ylamino)butyl)-oxazole-4-carboxamide (8g). A white powder: 12.7 mg, 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, 6H, *J* = 6.4 Hz), 1.74 (m, 1H), 1.86 (m, 2H), 5.03 (t, 1H, *J* = 7.2 Hz), 5.78 (brs, 2H), 6.71 (s, 1H), 6.79 (brs, 1H), 7.28 (d, 1H, *J* = 7.2 Hz), 7.36 (t, 2H, *J* = 7.2 Hz), 7.77 (d, 2H, *J* = 7.2), 8.17 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 22.5, 24.8, 43.4, 52.1, 101.7, 126.0, 127.8, 128.6, 134.6, 135.7, 141.8, 151.4, 162.5, 164.5, 167.5. ESI-MS: 379 (M + Na). HRMS (ESI-TOF) *m*/*z*: (M + H) calcd for $C_{18}H_{21}N_4O_2S$, 357.1385; found, 357.1383.

(*S*)-2-(1-(4-(3,4-Dihydroxyphenyl)thiazol-2-ylamino)-3-methylbutyl)oxazole-4-carboxamide (8h). A white powder: 15.2 mg, 68% yield. ^{1}H NMR (400 MHz, MeOH-d_4): δ 0.93 (d, 3H, *J* = 6.4 Hz), 0.96 (d, 3H, *J* = 6.4 Hz), 1.68 (m, 1H), 1.76 (m, 1H), 1.87 (m, 1H), 5.15 (dd, 1H, J^1 = 14.0 Hz, J^2 = 8.0 Hz), 6.70 (d, 1H, *J* = 8.4 Hz), 6.72 (s, 1H), 7.05 (dd, 1H, J^1 = 8.0 Hz, J^2 = 2.0 Hz), 7.18 (d, 1H, *J* = 2.0 Hz), 7.44 (brs, 1H), 7.54 (brs, 1H), 8.13 (d, 1H, *J* = 8.0 Hz), 8.51 (s, 1H), 8.86 (brs, 1H), 8.93 (brs, 1H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 22.3, 23.0, 24.8, 31.1, 42.5, 50.8, 99.1, 113.8, 116.0, 117.5, 127.1, 136.6, 142.2, 145.4, 145.5, 150.6, 162.3, 165.0, 167.1. ESI-MS: 411 (M + Na). HRMS (ESI-TOF) *m*/*z*: (M+ H) calcd for $C_{18}H_{21}N_4O_4S$, 389.1284; found, 389.1279.

(*S*)-2-(1-(4-Adamantylthiazol-2-ylamino)-3-methylbutyl)oxazole-4-carboxamide (8i). A white powder: 13.32 mg, 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95−0.99 (m, 6H), 1.69−1.86 (m, 15H), 2.03 (brs, 3H), 4.82 (t, 1H,

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J = 7.2 Hz), 5.74 (brs, 1H), 6.04 (s, 1H), 6.81 (brs, 1H), 8.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 21.9, 24.1, 27.9, 35.8, 36.2, 41.1, 42.7, 51.9, 98.0, 135.1, 141.2, 161.8, 163.6, 166.8. ESI-MS: 437 (M + Na). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{22}H_{31}N_4O_2S$, 415.2168; found, 415.2156.

(*S*)-2-(1-(4-*tert*-butylthiazol-2-yl)pyrrolidin-2-yl)-oxazole-4-carboxamide (9f). A white powder: 15.8 mg, 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (s, 9H), 2.14−2.18 (m, 1H), 2.25−2.30 (m, 2H), 2.42−2.45 (m, 1H), 3.57 (q, 1H, J = 8.0 Hz), 3.73 (t, 1H, J = 8.0 Hz), 5.78 (brs, 1H), 6.82 (s, 1H), 6.08 (brs, 1H), 8.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 29.4, 32.0, 34.6, 50.4, 57.8, 98.8, 135.7, 141.5, 162.6, 164.4, 165.9. ESI-MS: 343 (M + Na). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{15}H_{21}N_4O_2S$, 321.1385; found, 321.1376.

(*S*)-2-(1-(4-Phenylthiazol-2-yl)pyrrolidin-2-yl)oxazole-4-carboxamide (9g). A white powder: 13.5 mg, 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16−2.20 (m, 1H), 2.27−2.32 (m, 2H), 2.41−2.45 (m, 1H), 3.57−3.63 (dd, 1H, J^1 = 9.2 Hz, J^2 = 7.6 Hz), 3.77−3.81 (m, 1H), 5.18−5.21 (q, 1H, J = 8.0 Hz), 5.65 (brs, 1H), 6.71 (s, 1H), 6.81 (brs, 1H), 7.25 (d, 1H, J = 5.2 Hz), 7.33 (t, 2H, J = 7.2 Hz), 7.73 (d, 2H, J = 7.2 Hz), 8.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 32.1, 50.2, 57.7, 101.4, 126.0, 127.6, 128.5, 134.9, 135.8, 152.1, 162.6, 164.6, 166.4. ESI-MS: 363 (M + Na). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{17}H_{17}N_4O_2S$, 341.1072; found, 341.1065.

(*S*)-2-(1-(4-(3,4-Dihydroxyphenyl)thiazol-2-yl)-pyrrolidin-2-yl)oxazole-4-carboxamide (9h). A white powder: 15.4 mg, 72% yield. ^{1}H NMR (400 MHz, MeOH-d_4): δ 2.12 (m, 3H), 2.15 (m, 1H), 3.51 (m, 1H), 3.67 (m, 1H), 5.10 (dd, 1H, J^1 = 8.0 Hz, J^2 = 3.2 Hz), 6.68 (d, 1H, J = 8.4 Hz), 6.83 (s, 1H), 7.04 (dd, 1H, J^1 = 8.0 Hz, J^2 = 2.0 Hz), 7.17 (s, 1H), 7.45 (s, 1H), 7.59 (s, 1H), 8.50 (s, 1H), 8.86 (brs, 1H), 8.95 (brs, 1H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 24.4, 32.4, 50.6, 57.8, 99.8, 113.9, 115.9, 117.7, 127.6, 136.8, 142.4, 145.4, 145.6, 151.7, 162.3, 164.6, 166.1. ESI-MS: 373 (M + H). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{17}H_{17}N_4O_4S$, 373.0971; found, 373.0966.

(*S*)-2-(1-(4-Adamantylthiazol-2-yl)pyrrolidin-2-yl)-oxazole-4-carboxamide (9i). A white powder: 15.3 mg, 67% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75 (m, 12H), 1.99 (s, 3H), 2.14 (m, 1H), 2.26 (m, 2H), 2.41 (m, 1H), 3.52 (q, 1H, J = 7.2 Hz), 3.68 (m, 1H), 5.09 (m, 1H), 5.67 (brs, 1H), 6.01 (s, 1H), 6.82 (brs, 1H), 8.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.4, 28.6, 28.7, 32.0, 36.6, 37.0, 50.1, 57.6, 98.3, 135.6, 141.4, 162.7, 164.0, 165.0, 165.8. ESI-MS: 421 (M + Na). HRMS (ESI-TOF) m/z: (M+ H) calcd for $C_{21}H_{27}N_4O_2S$, 399.1855; found, 399.1850.

(*S*)-2-(1-(4-*tert*-Butylthiazol-2-ylamino)-2-methylpropyl)oxazole-4-carboxamide (10f). A white powder: 13.1 mg, 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (d, 3H, J = 6.8 Hz), 1.07 (d, 3H, J = 6.8 Hz), 1.17 (s, 9H), 2.28 (m, 1H), 4.78 (d, 1H, J = 7.2 Hz), 6.11 (s, 1H), 8.29 (s, 1H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 17.8, 17.9, 28.5, 32.3, 34.0, 58.9, 98.0, 135.6, 141.6, 161.2, 163.9, 164.9, 168.0. ESI-MS: 345 (M + Na). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{15}H_{23}N_4O_2S$, 323.1542; found, 323.1532.

(*S*)-2-(2-Methyl-1-(4-phenylthiazol-2-ylamino)propyl)-oxazole-4-carboxamide (10g). A white powder: 12.6 mg, 64% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (d, 3H, J = 6.8 Hz), 1.07 (d, 3H, J = 6.8 Hz), 2.35 (q, 1H, J = 6.8 Hz), 4.83 (brs, 1H), 5.66 (brs, 1H), 5.74 (brs, 1H), 6.71 (s, 1H), 6.78 (brs, 1H), 7.28 (d, 1H, J = 7.2 Hz), 7.36 (t, 2H, J = 7.2 Hz), 7.77 (d, 2H, J = 7.2 Hz), 8.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 18.7, 32.9, 59.3, 101.7, 126.0, 127.8, 128.5, 134.6, 135.6, 141.8, 151.4, 162.4, 163.7, 167.8. ESI-MS: 365 (M + Na). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{17}H_{19}N_4O_2S$, 343.1229; found, 343.1221.

(*S*)-2-(1-(4-(3,4-Dihydroxyphenyl)thiazol-2-ylamino)-2-methylpropyl)oxazole-4-carboxamide (10h). A white powder: 13.1 mg, 61% yield. ^{1}H NMR (400 MHz, MeOH-d_4): δ 0.89 (d, 3H, J = 6.8 Hz), 1.04 (d, 3H, J = 6.8 Hz), 2.26 (t, 1H, J = 6.8 Hz), 4.87 (t, 1H, J = 7.6 Hz), 6.69 (d, 1H, J = 8.4 Hz), 6.71 (s, 1H), 7.04 (dd, 1H, J^1 = 8.0 Hz, J^2 = 2.0 Hz), 7.18 (s, 1H), 7.45 (brs, 1H), 7.52 (brs, 1H), 8.13 (t, 1H, J = 6.8 Hz), 8.52 (s, 1H), 8.85 (s, 1H), 8.92 (s, 1H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 19.4, 19.5, 32.3, 58.5, 99.2, 113.8, 115.9, 117.5, 127.1, 136.5, 142.2, 145.4, 150.4, 162.3, 163.5, 164.4, 167.4. ESI-MS: 397 (M + Na). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{17}H_{19}N_4O_4S$, 375.1127; found, 375.1117.

(*S*)-2-(1-(4-Adamantylthiazol-2-ylamino)-2-methylpropyl)oxazole-4-carboxamide (10i). A white powder: 13.6 mg, 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, 3H, J = 6.8 Hz), 1.05 (d, 3H, J = 6.8 Hz), 1.74 (m, 6H), 1.86 (d, 6H, J = 2.8 Hz), 2.03 (brs, 3H), 2.29 (m, 1H), 4.61 (d, 1H, J = 6.0 Hz), 5.71 (brs, 2H), 6.03 (s, 1H), 6.80 (brs, 1H), 8.17 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 18.7, 28.5, 32.9, 36.5, 36.8, 41.8, 59.7, 98.7, 135.6, 141.7, 162.4, 163.1, 163.8, 167.7. ESI-MS: 423 (M + Na). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{21}H_{29}N_4O_2S$, 401.2011; found, 401.1998.

(*S*)-2-(1-(4-*tert*-Butylthiazol-2-ylamino)-2-phenylethyl)oxazole-4-carboxamide (11f). A white powder: 17.4 mg, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 9H), 3.35 (d, 2H, J = 5.2 Hz), 5.22 (brs, 1H), 5.78 (brs, 1H), 5.92 (brs, 1H), 6.07 (s, 1H), 6.78 (brs, 1H), 7.05 (d, 2H, J = 7.6 Hz), 7.24 (d, 3H, J = 7.2 Hz), 8.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.5, 34.6, 54.5, 98.7, 126.9, 128.5, 129.2, 135.8, 136.0, 141.3, 162.5, 162.6, 163.7, 166.1. ESI-MS: 393 (M + Na). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{19}H_{23}N_4O_2S$, 371.1542; found, 371.1531.

(*S*)-2-(2-Phenyl-1-(4-phenylthiazol-2-ylamino)ethyl)-oxazole-4-carboxamide (11g). A white powder: 15.9 mg, 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.39 (d, 2H, J = 6.4 Hz), 5.38 (t, 1H, J = 6.4 Hz), 6.19 (brs, 1H), 6.40 (brs, 1H), 6.72 (s, 1H), 6.85 (brs, 1H), 7.10 (d, 2H, J = 6.0 Hz), 7.26 (t, 3H, J = 7.2 Hz), 7.35 (t, 3H, J = 7.2 Hz), 7.77 (d, 2H, J = 7.2 Hz), 8.15 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.3, 101.7, 125.9, 127.0, 127.6, 128.4, 128.5, 129.2, 134.7, 135.8, 141.5, 151.1, 162.4, 163.6, 166.7. ESI-MS: 413 (M + Na). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{21}H_{19}N_4O_2S$, 391.1229; found, 391.1218.

(*S*)-2-(1-(4-(3,4-Dihydroxyphenyl)thiazol-2-ylamino)-2-phenylethyl)oxazole-4-carboxamide (11h). A white powder: 20.6 mg, 85% yield. ^{1}H NMR (400 MHz, MeOH-d_4): δ 3.29 (d, 2H, J = 7.6 Hz), 5.25 (q, 1H, J = 7.6 Hz), 6.69 (d, 1H, J = 8.4 Hz), 6.72 (s, 1H), 7.05 (dd, 1H, J^1 = 8.0 Hz, J^2 = 2.4 Hz), 7.19 (m, 2H), 7.25 (m, 4H), 7.45 (brs, 1H), 7.52 (brs, 1H), 8.31 (d, 1H, J = 8.0 Hz), 8.50 (s, 1H), 8.86 (s, 1H), 8.93 (s, 1H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 54.3, 99.4, 113.9, 116.0, 117.5, 127.0, 127.1, 128.8, 129.6, 136.6, 137.6, 142.3, 145.4, 145.5, 150.6, 162.2, 163.5, 164.2, 166.8. ESI-MS: 423 (M + H^+). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{21}H_{19}N_4O_4S$, 423.1127; found, 423.1115.

(*S*)-2-(1-(4-Adamantylthiazol-2-ylamino)-2-phenylethyl)oxazole-4-carboxamide (11i). A white pow-

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der: 16.2 mg, 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 1.72 (s, 6H), 1.85 (s, 6H), 2.01 (s, 3H), 3.35 (d, 2H, J = 7.2 Hz), 5.17 (d, 1H, J = 7.2 Hz), 6.03 (s, 1H), 6.14 (brs, 1H), 6.82 (brs, 1H), 7.06 (d, 2H, J = 6.8 Hz), 7.23 (m, 3H), 7.32 (d, 1H, J = 6.8 Hz), 8.13 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ 28.5, 36.5, 36.8, 41.7, 54.7, 98.7, 127.0, 128.5, 129.2, 135.8, 135.8, 141.5, 162.5, 163.6, 166.3. ESI-MS: 471 (M + Na). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{25}H_{29}N_4O_2S$, 449.2011; found, 449.1997.

(*S*)-2-(1-(4-*tert*-Butylthiazol-2-ylamino)-2-(4-hydroxyphenyl)ethyl)oxazole-4-carboxamide (12f). A white powder: 18.0 mg, 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 9H), 3.24 (d, 2H, J = 4.8 Hz), 5.10 (t, 1H, J = 5.2 Hz), 6.06 (s, 1H), 6.14 (brs, 1H), 6.71 (d, 2H, J = 6.8 Hz), 6.84 (d, 2H, J = 6.8 Hz), 7.34 (s, 1H), 8.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.5, 34.6, 38.9, 54.8, 98.7, 115.6, 126.2, 130.2, 135.7, 141.3, 156.2, 162.5, 163.9, 166.4. ESI-MS: 409 (M + Na). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{19}H_{23}N_4O_3S$, 387.1491; found, 387.1480.

(*S*)-2-(2-(4-Hydroxyphenyl)-1-(4-phenylthiazol-2-ylamino)ethyl)oxazole-4-carboxamide (12g). A white powder: 14.9 mg, 64% yield. ^{1}H NMR (400 MHz, MeOH-d_4): δ 3.25 (dd, 2H, J^1 = 7.6 Hz, J^2 = 2.6 Hz), 5.29 (t, 1H, J = 7.2 Hz), 6.66 (d, 2H, J = 8.4 Hz), 6.82 (s, 1H), 6.98 (d, 2H, J = 8.4 Hz), 7.22 (t, 1H, J = 7.2 Hz), 7.31 (t, 2H, J = 7.2 Hz), 7.72 (d, 2H, J = 7.2 Hz). ^{13}C NMR (100 MHz, MeOH-d_4): δ 38.4, 54.6, 101.2, 114.9, 125.6, 127.1, 127.2, 128.0, 129.9, 134.9, 135.6, 141.7, 150.7, 156.0, 163.9, 164.7, 167.7. ESI-MS: 429 (M + Na). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{21}H_{19}N_4O_3S$, 407.1178; found, 407.1166.

(*S*)-2-(1-(4-(3,4-Dihydroxyphenyl)thiazol-2-ylamino)-2-(4-hydroxyphenyl)ethyl)oxazole-4-carboxamide (12h). A white powder: 19.2 mg, 76% yield. ^{1}H NMR (400 MHz, MeOH-d_4): δ 3.16 (d, 2H, J = 8.0 Hz), 5.15 (q, 1H, J = 7.6 Hz), 6.64 (d, 1H, J = 8.4 Hz), 6.69 (d, 1H, J = 8.0 Hz), 6.71 (s, 1H), 7.00−7.06 (m, 3H), 7.18 (s, 1H), 7.44 (brs, 1H), 7.52 (brs, 1H), 8.25 (d, 1H, J = 7.2 Hz), 8.48 (s, 1H), 8.86 (s, 1H), 8.93 (s, 1H), 9.23 (s, 1H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 38.6, 54.6, 99.3, 113.8, 115.6, 115.9, 117.5, 127.1, 127.5, 130.5, 136.5, 142.2, 145.4, 150.6, 156.5, 162.3, 163.5, 164.4, 166.8. ESI-MS: 439 (M + Na). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{21}H_{19}N_4O_5S$, 439.1076; found, 439.1072.

(*S*)-2-(1-(4-Adamantylthiazol-2-ylamino)-2-(4-hydroxyphenyl)ethyl)oxazole-4-carboxamide (12i). A white powder: 18.1 mg, 68% yield. ^{1}H NMR (400 MHz, MeOH-d_4): δ 1.74 (m, 6H), 1.83 (s, 6H), 1.97 (s, 3H), 3.21 (m, 2H), 511 (t, 1H, J = 7.2 Hz), 6.04 (s, 1H), 6.64 (d, 2H, J = 8.4 Hz), 6.94 (d, 2H, J = 8.4 Hz), 8.24 (s, 1H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 28.7, 36.2, 36.6, 38.5, 41.5, 54.9, 98.0, 114.8, 127.3, 129.9, 135.6, 141.6, 156.0, 162.2, 163.9, 164.8, 167.3. ESI-MS: 487 (M + Na). HRMS (ESI-TOF) m/z: (M + H) calcd for $C_{25}H_{29}N_4O_3S$, 465.1960; found, 465.1943.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General information and copies of ^{1}H and ^{13}C NMR spectra and LC-MS and HR-MS chromatograms for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*A. Nefzi. adeln@tpims.org.

Notes

The authors declare no competing financial interest.

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(18) Because Hydrofluoric acid (HF) is an extremely corrosive acid, we used a well-designed HF manifold while protecting ourselves with lab coats, gloves, chemical splash goggles and face shields. People who handle HF must receive documented training on the hazards of HF and what to do in the event of an exposure or a spill. A material safety data sheet (MSDS) on HF should always be followed before planning any experiment with HF.