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Parallel synthesis of bis-oxazole peptidomimetics

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ABSTRACT

The parallel synthesis of bis-oxazole peptidomimetics starting from Boc-aminoacids and Serine-methyl ester is described. This work presents the synthesis of oxazole aminoacid building blocks in solution phase and their utilization for the solid phase peptide synthesis of a library of diverse bis-oxazole peptidomimetics in good overall yields.

Proteins and peptides play an essential role in almost all physiological processes, which makes them an attractive starting point for drug discovery programs.[1] The potential utilities of peptides as therapeutics are limited because of their inherent instability toward proteolytic cleavage by peptidases in the gastrointestinal tract, lack of oral bioavailability, inability to cross the blood–brain barrier due to their high molecular weight, and rapid excretion through the liver and kidneys.[2] These limitations have generated an intensive search for peptidomimetics. The alteration of peptides to peptidomimetics has included peptide side chain manipulation, amino acid extensions, deletions, substitutions and most recently backbone modification. A wide variety of peptide mimetic strategies have been described in recent years,[2c,d] ranging in complexity from single atom substitution in the amide group to motivated de novo design of multiple-residue mimetics.[3] Continuing with our work toward the synthesis of peptidomimetics and small molecule compounds from modified peptides,[4] we report the synthesis of bis-oxazole peptidomimetics starting from Boc-aminoacids and Serine-methyl ester.

A large number of oxazole-containing natural products,[5] particularly from the marine environment, have been isolated and found to exhibit a wide range of biological activities[6] such as antibacterial, antiviral, and cytotoxicity. Other oxazole derivatives are also found to be associated with antifungal, antitubercular, and anti-inflammatory activities.[7] In addition to a number of complex molecules containing a single oxazole, many natural products contain two or more oxazole rings that are either directly linked (2,4′-bis-oxazoles) or separated by at least three atoms.[8] Known bis-oxazole compounds include muscoride A,[9] diazonamide A,[10] and hennoxazole A.[11] Considering the potential of the oxazole moiety, there has been a rising interest in the use of oxazole precursors in preparing bioactive molecules and peptidomimetic structures.[12]

Small molecules containing an oxazole moiety have been demonstrated to possess drug like properties against varieties of diseases resulting in many FDA-approved drugs containing the oxazole ring. Known drugs include the anti-inflammatory drug "Oxaprozin" and the streptogramin antibiotic "Dalfopristin".

A few methods have been reported for the preparation of oxazole aminoacid precursors;[13] however, their utilization is limited to macrocyclic peptide syntheses.[14] Herein, we report the oxazole aminoacids as building blocks for the solid phase synthesis of diverse bis-oxazole peptides. Similar to the biosynthetic pathway,[15] our approach to oxazole aminoacids is based on the cyclodehydration of β-hydroxy peptides to oxazolines followed by ring oxidation and ester hydrolysis (Scheme 1). Our approach toward the parallel synthesis of bis-oxazole peptidomimetics is outlined in Scheme 2. Starting from five oxazole aminoacid building blocks (**5A**–**E**), we performed the parallel synthesis of 25 (5×5) bis-oxazole peptidomimetics. The Serine methylester **1** was coupled with different amino acids **2** to give the corresponding β-hydroxy peptides **3**. The hydroxyl peptide was then converted into oxazoline using DAST, followed by ring oxidation using BTCM/DBU to yield the desired oxazole aminoacid esters **4**. Base mediated hydrolysis of the oxazole ester gave the corresponding oxazole aminoacids (**5A**–**E**) in good overall yields (Scheme 1).

Having oxazole aminoacid building blocks in hand, a library of bis-oxazole peptides was synthesized. The parallel solid phase organic synthesis (SPOS)[16] of the diverse bis-oxazole dipeptidomimetics was performed using the tea-bag approach[16c,17] (Fig. 1).

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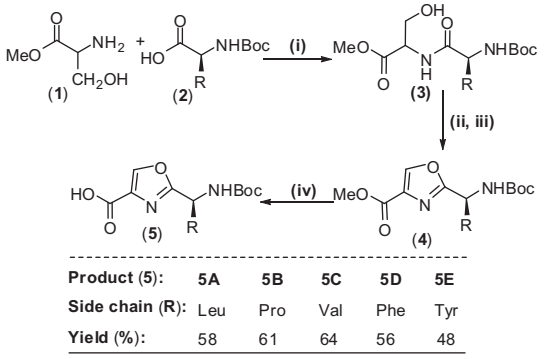
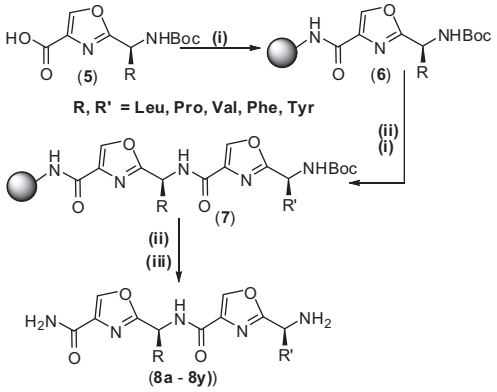


Scheme 1. Synthesis of chiral oxazole amino acid building blocks starting from serine methylester to amino acid. Reaction conditions: (i) HOBt, DIC, DIEA, DMF, 0 °C → RT; (ii) DAST, DCM, −78 °C; (iii) BTCM, DBU, DCM, 0 °C; (iv) 1 N aq NaOH, dioxane/H_2O.



Scheme 2. Solid phase parallel synthesis of bis-oxazole peptidomimetics from oxazole aminoacid building blocks. Reaction conditions: (i) DIC (1 equiv), HOBt (1 equiv), DMF, 8–12 h. (ii) 55% TFA in DCM, 30 min. (iii) HF-cleavage.

Starting from *p*-methyl benzhydrylamine (MBHA), the Boc protected oxazole aminoacid **5**, was coupled using standard coupling conditions (DIC and HOBt in DMF). The completion of the coupling reaction was confirmed by the Kaiser test.[18] Following Boc-deprotection with 55% TFA in DCM and neutralization with 5% DIEA in DCM, the second aminoacid **5** was coupled using the same conditions as mentioned above.

After Boc-deprotection, compounds were cleaved from the resin and the desired 25 diverse bis-oxazole peptides were obtained in good yields and high purity (Scheme 2, Table 1). The integrity of all compounds was confirmed by LC–MS and NMR.

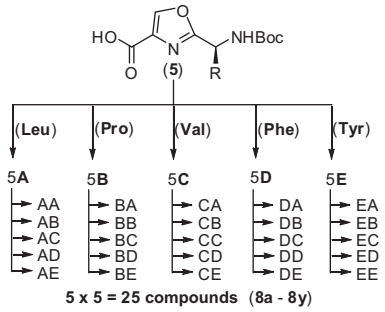


Figure 1. Parallel synthesis of bis-oxazole peptidomimetics (**8a–y**) from oxazole aminoacid building blocks (**5A–E**).

Table 1
Synthesis of bis-oxazole peptidomimetics from oxazole aminoacid building blocks[a]

Product	Corresponding aminoacid		Yield[b] (%)	Purity[c] (%)
	R^1	R^2		
8a	Leu	Leu	78	92
8b	Leu	Pro	86	96
8c	Leu	Val	92	88
8d	Leu	Phe	83	91
8e	Leu	Tyr	87	89
8f	Pro	Leu	75	92
8g	Pro	Pro	68	94
8h	Pro	Val	72	96
8i	Pro	Phe	76	87
8j	Pro	Tyr	67	93
8k	Val	Leu	85	95
8l	Val	Pro	76	93
8m	Val	Val	74	92
8n	Val	Phe	81	89
8o	Val	Tyr	78	91
8p	Phe	Leu	82	86
8q	Phe	Pro	75	93
8r	Phe	Val	80	95
8s	Phe	Phe	83	92
8t	Phe	Tyr	89	96
8u	Tyr	Leu	77	87
8v	Tyr	Pro	73	94
8w	Tyr	Val	82	91
8x	Tyr	Phe	86	93
8y	Tyr	Tyr	91	88

[a] Obtained via solid-phase parallel synthesis approach.
[b] Based on the product obtained after resin cleavage.
[c] Based on integration of LC–MS chromatogram.

It should be mentioned here that we obtained a set of distinct heterocyclic peptides (all B-series), from proline oxazole (**B**), containing two oxazoles and one pyrrolidine similar to another bioactive peptide Muscoride A.[9] Some of the bis-oxazole peptides from proline oxazole, containing a pyrrolidine side chain, exist as *cis–trans* isomers which were confirmed by ^{1}H NMR.

The synthesized bis-oxazole peptides were screened in competitive radioligand receptor binding assays for opioid affinity for mu and kappa receptors. Compounds with moderate affinity for mu receptors were identified (Fig. 2). These initial screening results indicate the high probability of finding new class of analgesics.

We have developed an approach for the parallel synthesis of pharmacologically relevant bis-oxazole peptides. This methodology can be extended to incorporate bis-oxazole moiety into peptides and peptidomimetics to generate combinatorial libraries for the purpose of drug discovery. We are in the process of preparing a large library of bis-oxazole peptidomimetics to screen for their biological activities. The synthesis of the libraries and results from their screening for the identification of biologically active compounds will be reported elsewhere.

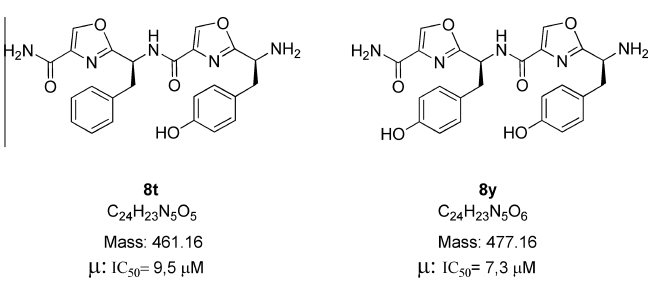


Figure 2. Opioid activity of oxazole dipeptides.

Acknowledgment

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Supplementary data

Supplementary data (general information, spectral data, copies of ^{1}H and/or ^{13}C NMR spectra for all products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.078.

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17. *General procedure for the solid-phase parallel synthesis of bis-oxazole peptides (**8a–y**):* A set of twenty 50 mg bags containing *p*-methyl benzhydrylamine hydrochloride salt (MBHA) resin (1.15 m equiv/g, 100–200 mesh) was prepared.[16c] Reactions were carried out by placing all the bags in polyethylene bottles. Following neutralization of the resin with 5% diisopropylethylamine (DIEA) in dichloromethane (DCM), Boc-Oxazole amino acid (**5**) (2 equiv) was coupled using the conventional reagents hydroxybenzotriazole (HOBt, 2 equiv) and diisopropylcarbodiimide (DIC, 2 equiv) in anhydrous DMF shaken overnight. Completion of the coupling was monitored by the ninhydrin test.[18]
Following the removal of the Boc group with 55% TFA/DCM for 30 min, the bags were neutralized with 5% DIEA/DCM. The resin-bound amino acid was treated with another Boc-oxazole amino acid (**5**) to yield Boc-protected bis-oxazole peptides connected to resin (**7**). Following the Boc-deprotection with 55% TFA/DCM, the product was cleaved from resin under HF conditions to provide the desired bis-oxazole peptides. All the products were confirmed by LC–MS and NMR analysis.
*2-((S)-1-Amino-2-(4-hydroxyphenyl)ethyl)-N-((S)-1-(4-carbamoyl oxazol-2-yl)-3-methylbutyl) oxazole-4-carboxamide (**8e**):* ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, 7H, J = 6.4 Hz), 1.66–1.71 (m, 1H), 1.82–1.87 (m, 2H), 2.15 (br s, 2H), 3.03–2.97 (m, 1H), 3.15–3.11 (m, 1H), 4.27–4.34 (m, 1H), 5.43 (q, 1H, J = 8.0 Hz), 5.77–5.86 (m, 1H), 6.72 (d, 2H, J = 8.4 Hz), 6.80 (br s, 1H), 6.94 (d, 2H, J = 8.4 Hz), 8.15 (s, 1H), 8.17 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.6, 24.7, 41.5, 42.5, 45.3, 51.6, 115.6, 128.1, 130.3, 135.2, 141.5, 141.8, 155.0, 160.2, 162.6, 163.8, 166.4. LC–MS (ESI): 450 (M+Na).
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