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Synthesis of Azole-Enriched Cyclic Peptides by A Clean Solid-Phase-Based Cyclization-Cleavage Strategy

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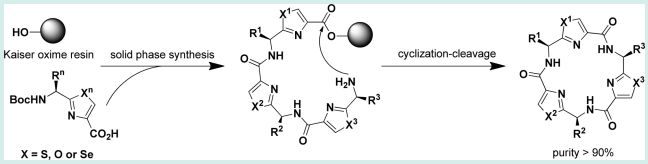
Supporting Information

ABSTRACT: Naturally occurring azole-enriched cyclic peptides have broad biological and pharmacological activities. Previous synthetic efforts have mainly concentrated on the preparation of individual target molecules in solution phase. A solid-phase-based cyclitive cleavage strategy was deployed here for efficient library synthesis of azole cyclopeptide derivatives, which is part of our continuous efforts for the characterization of potent modulators of multidrug resistance efflux proteins. Procedures were optimized to afford the azole cyclopeptides at high yield and purity, eliminating the need for any chromatographic purification steps. This development is ideal for high throughput library synthesis and screening and will facilitate the ultimate discovery of novel azole cyclopeptides with potent biological activities.



KEYWORDS: *cyclic peptides, cyclitive cleavage, solid-phase synthesis*

A large class of cyclic peptides biosynthesized in bacteria is characterized by macrocyclic backbones with high content of five-membered azole heterocycles.[1] These azole cycles, derived by enzyme-mediated post-translational modification of natural amino acid residues (serine, threonine, and cysteine), include oxazole, oxazoline, thiazole, and thiazoline.[2] Azole rings in the cyclic peptide framework confer novel features, such as structural rigidity, conformational constraint, hydrolytic stability, and proteolytic resistance. Many azole-based cyclic peptides, such as dendroamides,[3] patellamides,[4] tenuecyclamides,[5] and bistratamides[6] exhibit pharmaceutically useful biological activities. Considerable efforts have been devoted to the synthesis of individual target molecules.[7,8] The rigid azole cyclopeptide scaffold also provides an excellent platform for structural and functional optimization not only in drug discovery[9] but in other applications such as molecular recognition,[10−13] G-quadruplex ligand design,[14,15] and materials science.[16] While the naturally occurring azole cyclopeptides may evolve via selection among countless random mutations in vivo,[1,2,17] endeavors in library synthesis and screening of synthetic derivatives may facilitate the discovery of new and better compounds.

We have identified several azole-based cyclic peptides as effective modulators of the multidrug resistance efflux pump P-glycoprotein (P-gp).[18,19] Two selenazole-containing cyclopeptides, QZ59Se-*RRR* and QZ59Se-*SSS* (Figure 1), in which selenium replaces sulfur and oxygen atoms in the thiazole/oxazole rings of dendroamide A, were successfully cocrystallized with P-gp, yielding cocrystal structures that revealed the polyspecific drug binding sites of P-gp at moderate resolution.[18] In light of this initial study, we have set out to develop more potent modulators and map the drug binding sites of P-gp in greater detail through library synthesis and screening.

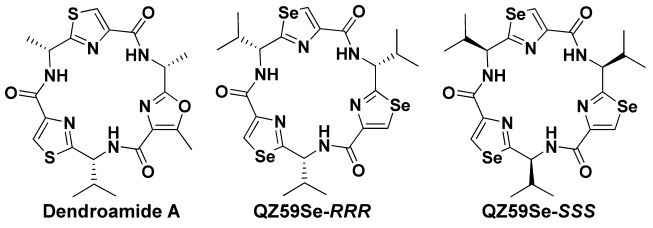


Figure 1. Natural product dendroamide A and its selenium-labeled analogs QZ59Se-*RRR* and QZ59Se-*SSS*. The latter two molecules have been cocrystallized with multidrug resistance transporter P-glycoprotein.

Earlier reports of the synthesis of azole cyclopeptides usually involved stepwise coupling of the building blocks in solution, followed by macrocyclization (Scheme 1A) often under dilute conditions (e.g., using large reaction volumes and with slow addition of linear peptide precursors) to avoid competitive intermolecular coupling.[7,8,20−22] One-pot fragment coupling and macrocyclization of single azole-containing amino acids is efficient and most appropriate for the synthesis of homotriazole or tetra-azole cyclic peptides (Scheme 1B),[11,23,24] whereas multicomponent one-pot cyclization in solution phase usually resulted in complex mixtures.[25,26] There have been several examples of solid-phase procedures used to build a linear precursor which was then cleaved from the resin and cyclized in

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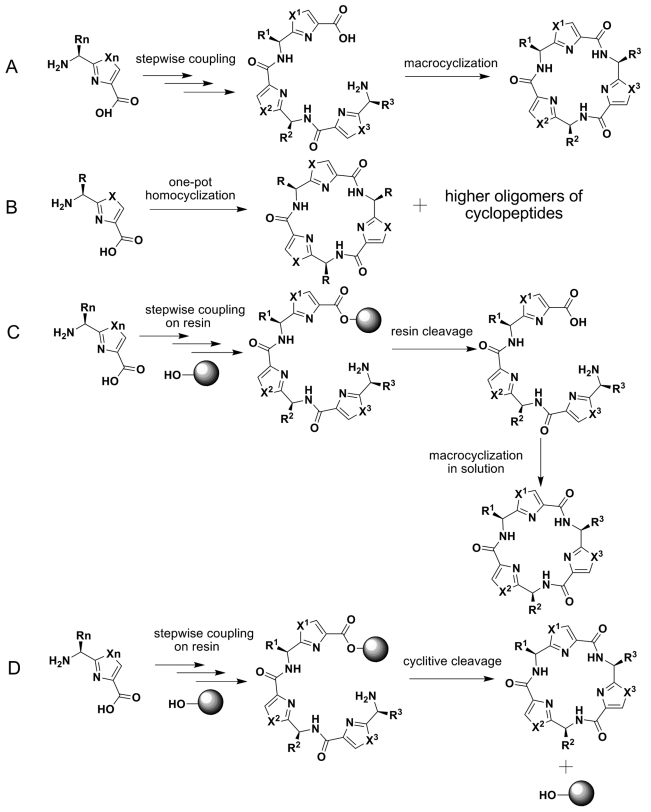
Scheme 1. Various Approaches to Synthesizing Azole Cyclopeptides[a]



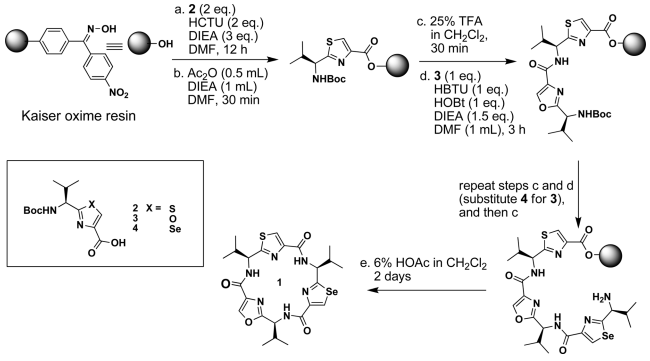
[a](A) Stepwise peptide elongation and macrocyclization in solution phase. (B) One-pot homocyclization of a single azole amino acid in solution. (C) Hybrid solid- and solution-phase synthesis. (D) Solid-phase synthesis involving head-to-tail cyclization with concurrent cleavage from resin. Amino acid protection and deprotection in A, C, and D is omitted for clarity.

solution (Scheme 1C).[20,27,28] These approaches are nevertheless too cumbersome for library synthesis because of the tediously long workup and chromatographic purification steps needed, often with only moderate yield in the final macrocyclization step. A cyclitive cleavage strategy involving concurrent peptide cyclization and cleavage from the solid phase (Scheme 1D) that we deployed in this report is obviously appealing. Most significantly, we have adapted respective procedures to generate azole cyclopeptides at high yield and purity which are sufficient for screening assays even without chromatographic purification. Of note, the same cyclitive cleavage strategy has been utilized in many cyclopeptide syntheses, but the selection of resin-peptide linker with proper stability and reactivity, and sometimes premature and difficult macrocyclization must be taken into consideration and often limit the broad application of this approach.[29] An excellent example of using this strategy is the synthesis of cyclic decapeptide tyrocidine A and analogs, in which macocyclization was strongly facilitated by the conformation-driven self-cyclization of linear precursors.[30]

We chose Kaiser oxime resin[31,32] and its compatible *t*-Boc (*N*-*tert*-butyloxycarbonyl) chemistry to elaborate the solid-phase synthesis and final cyclitive cleavage conditions. The use of oxime resin is generally limited to synthesis of short peptides because of sensitivity of the *p*-nitrobenzophenone oxime ester linkage to hydrolysis under strongly acidic conditions. Here, most syntheses will have three to four coupling steps for the construction of hexameric/octameric azole cyclopeptides (trimers/tetramers of azole-containing dipeptides), as we considered these small and conformationally rigid cyclopeptides advantageous for projected P-gp cocrystallization studies.[19] We found that the oxime linkage was sufficiently stable and peptide cleavage could be controlled in these syntheses.

We first deployed the cyclitive cleavage strategy to synthesize cyclopeptide **1**, which is analogous to QZ59Se-*SSS* but contains mixed thiazole/oxazole/selenazole units (Scheme 2). *t*-Boc-

Scheme 2. Solid-Phase Synthesis of Azole Cyclopeptide 1[a]



[a]Equivalents of other reagents were relative to the resin's oxime content.

protected fragments, including the thiazole[21,33] (**2**), oxazole[21,34] (**3**) and selenazole[19] (**4**), were readily prepared according to literature procedures.[19,21] Loading of the first fragment (**2**) onto the Kaiser oxime resin was attempted under several conditions (HBTU/HOBt, HCTU, HATU, and DIC/DMAP), and most gave ∼40−50% yield. Calculation of coupling yield was based on the maximum resin loading capacity (0.8 mmol/g, according to vendor) and HPLC quantification of **2** (ethyl ester form) cleaved by DBU-catalyzed ethanolysis. HCTU was selected as the coupling reagent for this step, as it has given consistent results in our experience. Residual oxime groups on the resin were blocked by acetylation. After treatment with 25% TFA to remove *t*-Boc from **2**-bound resin, TFA was removed by repetitive washing using dry solvents and additional treatment with 5% diisopropylethylamine (DIEA) to avoid tight binding of TFA to free amines that would reduce yield in subsequent reactions. Sequential couplings of fragments **3** and **4** were performed and monitored by ninhydrin test and MS analysis. The final cyclitive cleavage was realized in the presence of 6% acetic acid, a condition that activated the oxime ester bond for nucleophilic attack by free amines.[32,35] Cyclization was conducted for 2 days to ensure complete reaction, and no linear peptide precursors were detected by MS analysis after resin cleavage. Finally, simple filtration and solvent removal gave the product (**1**). Very interestingly, we found this product, without further purification, to be of high purity upon HPLC (93% area percentage, excluding solvent peak) and ^{1}H NMR analysis (Figure 2). By comparison of ^{1}H NMR spectra between the nonpurified product and HPLC-purified **1** (75% yield based on **2**-loaded resin), we found little impurities in the crude and some impurity peaks in the upfield region (<3 ppm) were ascribed to residual solvent (e.g., two singlet peaks ∼2.8 ppm from DMF).

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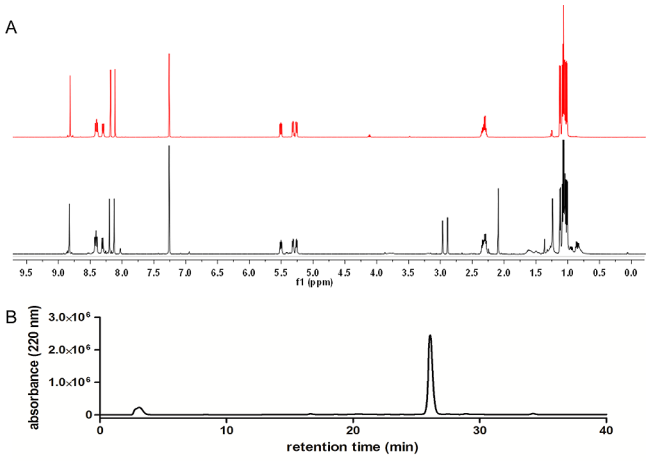
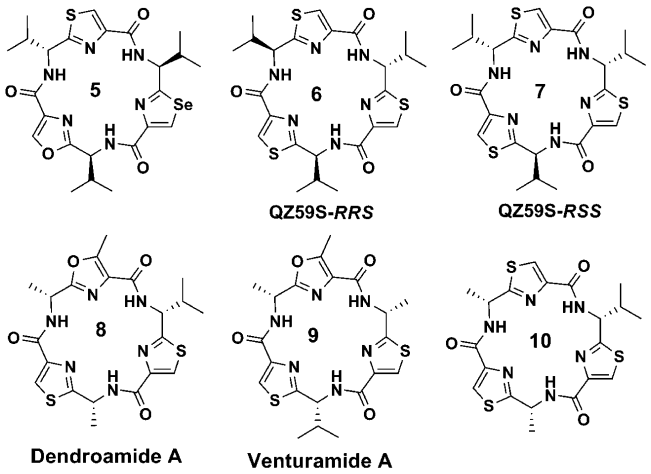


Figure 2. ^{1}H NMR spectrum (A, bottom spectrum in black) and HPLC chromatogram (B) of nonpurified cyclopeptide **1** as cleaved from resin. ^{1}H NMR spectrum for HPLC-purified **1** (top spectrum in red) is shown in panel A for comparison.

We applied the same procedure described above to the synthesis of other hexameric triazole cyclopeptides shown in Figure 3, including a diastereomer of **1** (**5**), two natural



Compd.	5	6	7	8	9	10
Yield[a]	76%	70%	70%	66%	60%	65%
Purity[b]	>98%	>98%	>98%	94%	>98%	>98%

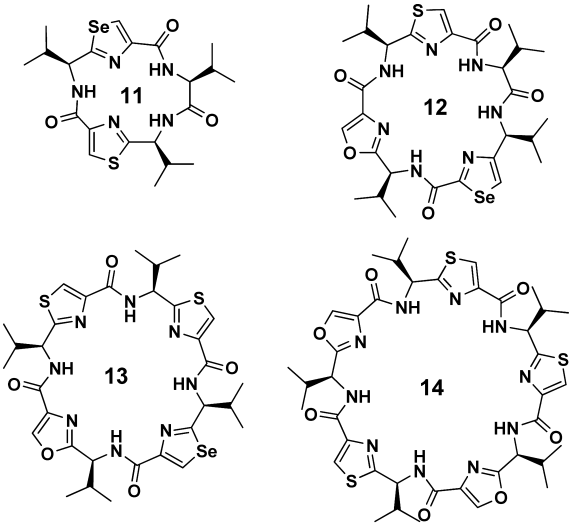
[a] All yields are based on *ent*-**2** preloaded resin and HPLC purified product.
[b] Crude purity based on HPLC calculation

Figure 3. Hexameric triazole cyclopeptides synthesized according to the procedure described in Scheme 2. The table portion shows the yields and purities of each cyclopeptide.

products dendroamide A (**8**)[3,21,22,25] and venturamide A (**9**),[36] the all-thiazole analog of **9** (**10**), together with QZ59S-*RRS* (**6**) and QZ59S-*RSS* (**7**) that we have prepared previously in solution phase.[19] All syntheses commenced from *ent*-**2**-preloaded oxime resin, which was split for reaction with different fragments to generate diverse cyclopeptide structures. Comparable to the synthesis of compound **1**, these cyclopeptides were obtained in good yields (60−76%, Figure 3), and at high purity (>90%) after resin cleavage and simple evaporation of solvents (HPLC spectra for the crude peptides are in Supporting Information). In addition, NMR spectroscopic analysis showed no or negligible occurrence of racemization at chiral centers in these cyclopeptides.

The clean cyclitive cleavage of the above hexameric cyclopeptides off the solid phase could be attributed to several factors: (1) shorter fragments, if any, generated by incomplete coupling reactions would be unable to cyclize because of ring strain; (2) incomplete cyclization of linear peptide precursors would not interfere with product purity, because in principal the cyclitive cleavage approach would release only cyclized products from the resin; and (3) H-bonding between amide N−H and azole ring nitrogen atoms may prearrange the linear precursor into a conformation that facilitates efficient macrocyclization.[10,30] In this regard, azole-based amino acids similar to **2**−**4** have been recognized as β-turn inducing motifs.[11,37]

We also applied the same solid-phase procedures to the synthesis of azole cyclopeptides of ring size smaller or larger than hexameric (Figure 4). For example, replacement of the



Compd.	11	12	13	14
Yield[a]	22%	35%	56%	48%
Purity[b]	76%	84%	94%	92%

[a] All yields are based on *ent*-**2** preloaded resin and HPLC purified product.
[b] Crude purity based on HPLC analysis.

Figure 4. Synthesized azole cyclopeptides of ring size smaller or larger than hexameric (yield and purity shown in the accompanying table).

(*S*)-Val-oxazole unit in **1** with (*S*)-valine to form a smaller cyclopeptide (pentamer **11**) significantly lowered the synthetic yield, with uncyclized peptides remaining even after 4 days of cyclization-cleavage. In this case, sluggish cyclization may be ascribed to the elevated strain built into the small cyclopeptide. The synthesis of heptamer **12**, in which one (*S*)-valine residue was added to **1**, also had a comparatively low yield. Interestingly, introducing one or two additional azole-containing amino acids in the synthesis of octamer (**13**) and decamer (**14**) gave moderate yields, although still noticeably less than in the corresponding hexamer synthesis. Of note, the octamer and decamer cleaved from solid phase have sufficient

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purity (>90%) for preliminary assay screening. Moreover, further purification of all these cyclopeptides was nevertheless convenient since the individual product predominated by HPLC analysis (Supporting Information).

In summary, we describe efficient solid-phase synthesis of azole-enriched cyclopeptides utilizing the cyclitive cleavage strategy, with enhanced product purity. The unique structural features of azole fragments appeared to facilitate cyclitive cleavage on the resin. It is interesting that most of the azole cyclopeptides eluted directly from the resin at sufficiently high purity for most functional assays. This communication outlines the methodology with example structures to demonstrate its potential application in library synthesis of azole-enriched cyclopeptides for various studies. In our laboratory, we have employed the method to quickly assemble >100 azole cyclopeptides, among which highly potent P-gp modulators have been identified and are currently under investigation for P-gp binding properties.

EXPERIMENTAL PROCEDURES

The solid-phase synthesis of azole-enriched cyclopeptides was conducted in open air at room temperature on an 8-armed Burrell Wrist-Action shaker. A batch of Kaiser oxime resin (Acros, 150 mg, capacity 0.8 mmol/g) was added to a 25 mL cylindrical glass vessel having a coarse porosity fritted filter at the bottom. The resin was first swollen in organic solvents (DCM for 0.5 h, then DMF for 1 h). After the solvent was drained, the first fragment (2 equiv, 0.24 mmol), HCTU (2 equiv, 0.24 mmol), DIEA (3 equiv, 0.36 mmol), and 1.5 mL of DMF were added. The vessel was agitated for 12 h to complete the first coupling. Then the solution was drained; the resin was rinsed exhaustively with DMF (5×), DCM (5×), and DMF (1×). Then 1 mL of DMF, 1.5 mL of DIEA, and 0.75 mL of Ac_2O were added to the resin. The vessel was agitated for 0.5 h to allow complete blocking of unreacted oxime sites by acetylation. Then the solution was drained and the resin was rinsed as before. To remove *t*-Boc protective groups, 3 mL of 25% TFA in DCM was added, and the vessel was agitated for 1 min before the solution was drained; 3 mL of 25%TFA in DCM was added again, and the vessel was agitated for 0.5 h. The solution was drained, and the resin was rinsed with DCM (5×), DMF (2×), and 5% DIEA in DMF (1×) to remove residual TFA. Then another acid fragment (1 equiv, 0.12 mmol), HBTU (1 equiv, 0.12 mmol), HOBt (1 equiv, 0.12 mmol), and DIEA (1.5 equiv, 0.18 mmol) were added. The vessel was agitated for 3 h to complete the second coupling reaction. Resin washing, *t*-Boc deprotection, and further fragment couplings were conducted in the same manner. Lastly, 3 mL of 6% HOAc in DCM was added and the vessel was agitated for 2 days to complete the cyclization-cleavage reaction. The filtered solution was combined with DCM solutions used to wash the resin. Organic solvents were removed in vacuo to give the products, which were analyzed or purified by reverse phase HPLC (Shimadzu) (analytical column, Phenomenex Jupiter 4 μm Protea 90 Å, 150 mm ×4.6 mm; flow rate, 1 mL/min; solvent, acetonitrile−water, 0−100% v/v acetonitrile linear gradient over 36 min). The cleavage of linear peptide fragments from resin for intermediate MS/HPLC analysis was carried out by agitating the resin in 3 mL of THF/MeOH or THF/EtOH (1:1) solution containing 20 μL of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).

ASSOCIATED CONTENT

Supporting Information

Analytical characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

P-gp, P-glycoprotein

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