



Synthesis of sansalvamide A peptidomimetics: triazole, oxazole, thiazole, and pseudoproline containing compounds

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ABSTRACT

Peptidomimetic-based macrocycles typically have improved pharmacokinetic properties over those observed with peptide analogs. Described are the syntheses of 13 peptidomimetic derivatives that are based on active sansalvamide A structures, where these analogs incorporate heterocycles (triazoles, oxazoles, thiazoles, or pseudoprolines) along the macrocyclic backbone. The syntheses of these derivatives employ several approaches that can be applied to convert a macrocyclic peptide into its peptidomimetic counterpart. These approaches include peptide modifications to generate the alkyne and azide for click chemistry, a serine conversion into an oxazole, a Hantzsch reaction to generate the thiazole, and protected threonine to generate the pseudoproline derivatives. Furthermore, we show that two different peptidomimetic moieties, triazoles, and thiazoles, can be incorporated into the macrocyclic backbone without reducing cytotoxicity: triazole and thiazole.

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1. Introduction

Recent work describing the synthesis and biological activity of pentapeptide derivatives that are based on the natural product sansalvamide A (San A), has brought attention to this compound class.^{1–4} San A was isolated from a marine fungus of the genus *Fusarium* by Fenical and co-workers.³ The pentapeptide structure (San A-amide, compound A, Fig. 1) has been used extensively as a template for the synthesis of compounds, where a number of these molecules exhibit cytotoxicity.^{1,2,5,6} We have discovered that in addition to San A-amide, three derivatives (compounds B, C, and D, Fig. 1) are cytotoxic against numerous cancer cell lines, and these compounds inhibit a key protein that enables many proteins involved in tumor progression: Heat shock protein 90 (Hsp90).^{1,7}

Hsp90 is a well-established chemotherapeutic target that modulates client proteins involved in cellular growth, angiogenesis, and apoptosis.^{8–13} The redundancy of pathways involved in cancer cell growth means targeting multiple mechanisms simultaneously improves its chances as a successful therapy. Hsp90

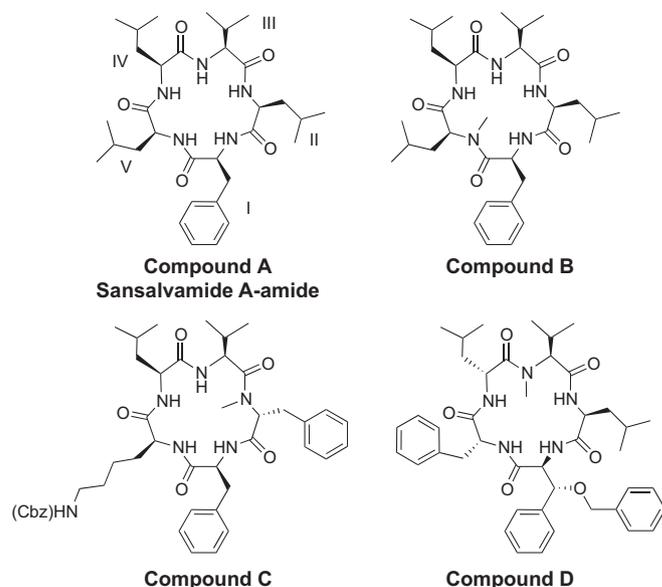


Fig. 1. San A compounds.

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controls approximately 200 client proteins and co-chaperones, many of which are involved in multiple cancer-related cell signaling pathways.^{14–16} There are currently fifteen Hsp90 inhibitors in development, with two of these in phase III clinical trials.^{17–22} We have previously reported that San A-amide (**A**, Fig. 1) is a cytotoxic molecule that modulates the activity of Hsp90. This modulation of Hsp90 acts via an allosteric effect, where San A-amide binds to the *N*-middle region and inhibits C-terminal client proteins.⁷ This mechanism of action is unique to Hsp90 inhibitors, making San A and its derivatives valuable molecular tools and potential lead structures for future chemotherapeutic studies.

In order to prepare these compounds to move into the next stage of development (mice models) the pharmacokinetic (PK) properties of these molecules should be improved as they are relatively poor.¹ One mechanism for improving PK is to introduce peptidomimetic features, or structural motifs that mimic the peptide backbone, where these mimics often improve the solubility and stability of the molecule without impacting the cytotoxicity.^{23,24} Introduction of these motifs into the macrocyclic backbone has been shown to rigidify the macrocycles, as well as improve the absorption, distribution, metabolism, and excretion (ADME) properties.^{25–28} Some common heterocycles that are known to improve stability of the peptide backbone include: triazoles, oxazoles, thiazoles, and pseudoproline.^{29–32}

The inclusion of a triazole, particularly in cyclic peptide backbone, has demonstrated an improvement in biological activity.^{26,31} Further, triazoles induce a rigid conformation by mimicking trans amide bonds.^{26,29} Studies have shown that a single *N*-methyl, *D*-aa or *N*-methyl *D*-aa play a critical role in locking the San A-amide macrocyclic analogs into a single conformation.^{1,2,4–6,33–35} If this conformation induces an advantageous presentation of the side chains to their biological target, locking it into place via one of these structural features will likely improve binding between the compound and the protein target. Likewise, there is also precedence for oxazole and thiazole peptidomimetic moieties improving biological stability when substituted within peptide backbones.²⁶ Similarly to triazoles, pseudoproline induce a rigid conformation by mimicking *cis* amide bonds, and thus make structurally interesting comparisons to triazoles.^{25,36,37}

Herein we describe the synthesis of 13 peptidomimetics that are based on San A-amide and the potent analogs **B–D** (Fig. 1). These compounds were chosen because they have demonstrated appropriate cytotoxicity, and they inhibit Hsp90.^{1,7} The synthesis of compounds that incorporate a triazole, oxazole, thiazole, or pseudoproline involved both solution and solid-phase approaches. These peptidomimetic residues are substituted for different features within the San A structure. The triazole replaces an amide bond, whereas the oxazole and thiazole replace both an amide bond as well as the adjacent amino acid side chain, and the pseudoproline replaces only the amino acid side chain. We discuss a series of synthetic strategies for these four unique classes of sansalvamide peptidomimetics, where these methods can be applied as general approaches for the conversion of macrocyclic peptides into peptidomimetic compounds. Further, biological testing of our peptidomimetic compounds allowed us to evaluate, which of these heterocyclic features are ideal for incorporation into future potent analogs and how their position in the macrocycle affects their cytotoxicity.

2. Results and discussion

Two triazole peptidomimetics (Tri), compounds **1** and **2** (Fig. 2), were synthesized via a convergent solution phase approach. Forming the triazole at the cyclization step has been reported as a successful strategy to synthesize cyclic triazole peptidomimetics.^{32,38–40} The synthetic strategy involved making

two fragments, a tri- and dipeptide; conversion of the amine moiety of the tripeptide to an azide yielded fragment 1, and formation of an alkyne on the dipeptide yielded fragment 2. Both fragments were coupled via a peptide bond to form the linear molecule between residues I and V, and the macrocycle was then clicked shut to generate a single 1,4-disubstituted triazole analog.³⁹

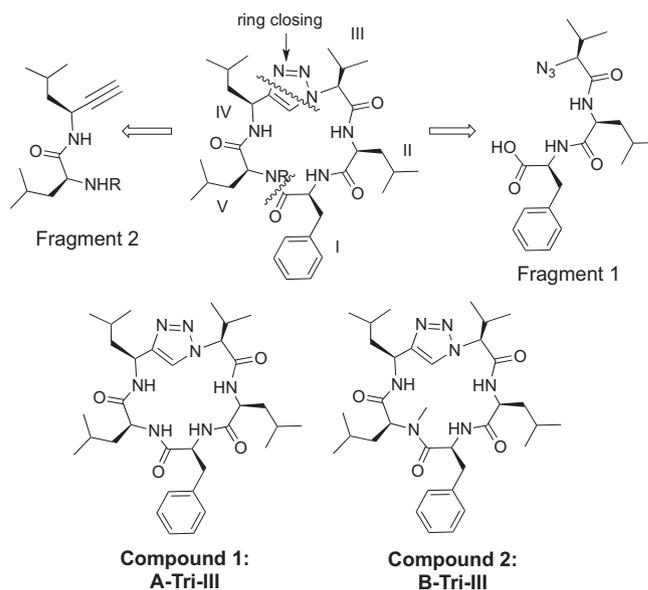


Fig. 2. Triazole synthetic strategy and compounds synthesized.

We made six oxazole peptidomimetics (Ox) (Fig. 3), which were templated from molecules **A–D** (Fig. 1). Compounds **3–6** were designed with the inclusion of an oxazole at position III based on the macrocycles **A–D**, whereas compounds **6–8** were only based on molecule **D** with the oxazole moiety placed at positions I, II, and III. These six oxazole-derived molecules were made using two different approaches, which utilized both a solid and solution phase approach. Initially our synthetic strategy involved oxazole formation after cyclization, whereupon the cyclic peptide was synthesized, and the serine was cyclized and oxidized after the formation of the macrocycle. However, the yield for this approach was extremely low for the oxazole formation (3% final yield for **8**) versus an average of 74% yield for oxazole formation prior to cyclization. Presumably this was due to the rigidity of the macrocycle inhibiting the formation of an inflexible heterocycles within the backbone. Thus, the synthetic strategy for the oxazole derivatives **3–7** involved the synthesis of two fragments; fragment 1 consisted of a tripeptide, while fragment 2 incorporated the oxazole moiety. The oxazole was synthesized by coupling a serine to a leucine or valine (compounds **3–6** and **7**, respectively). The oxazole was then formed via cyclodehydration upon treatment with DAST and potassium carbonate, then subsequent oxidation using bromochloroform and DBU.^{25,31,35} Coupling fragments 1 and 2, followed by peptide macrocyclization furnished the desired oxazole peptidomimetic derivatives.

Three thiazole (Th) derivatives were synthesized using two different approaches (Fig. 4). The first approach involved the synthesis of fragment 1, which incorporated a bromoketone moiety, while fragment 2 included a thioamide (Fig. 4, approach 4a). A linear precursor was formed via the Hantzsch-thiazole reaction⁴⁰ (Compound **9**, A-Th-III), and macrocyclization was performed via peptide bond formation to yield compound **9**. Given

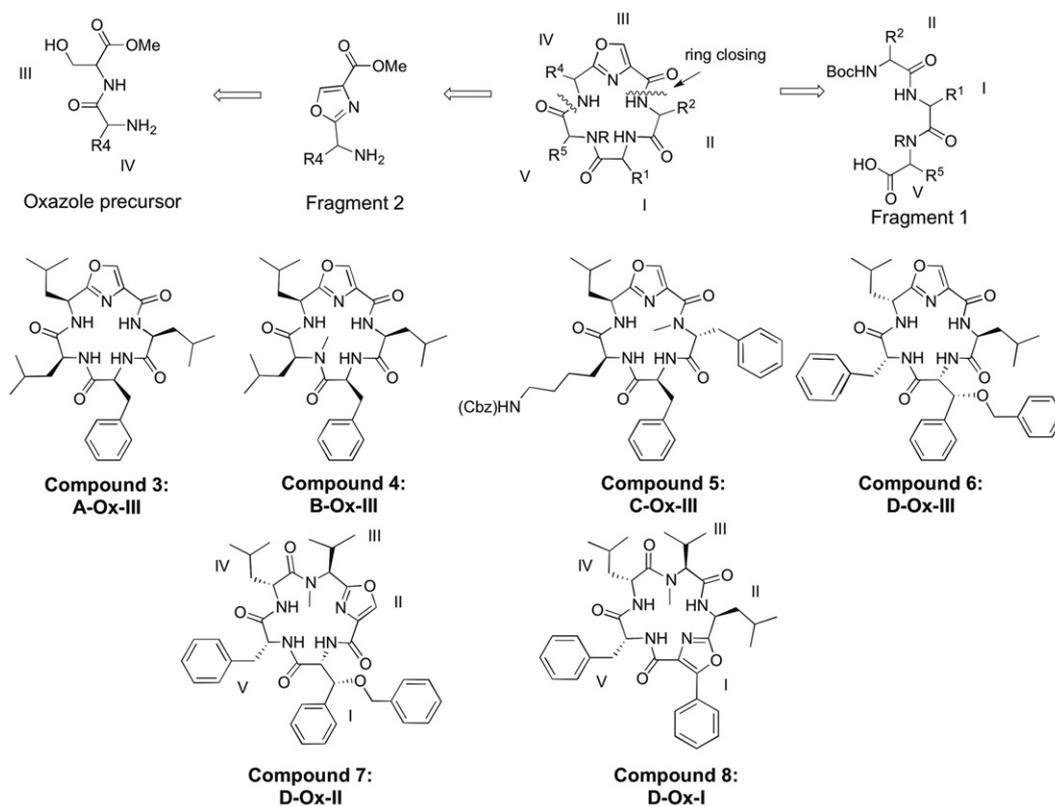


Fig. 3. Oxazole peptidomimetic compounds.

that the thiazole linear precursor had an extremely low yield (15% for thiazole formation), an alternative synthetic route was used for compounds **10** and **11** (Fig. 4, approach 4b). The alternative route involved the same general synthetic approach as the oxazoles, where a solution-phase procedure was used to form tripeptide fragment 1. The thiazole moiety was synthesized from two precursors, ethyl-bromopyruvate and a thioamide, via the Hantzschthiazole reaction to yield fragment 2.⁴¹ This proved to be a successful means of synthesizing the thiazole moiety with an average of 62% yield for this reaction.

Upon synthesis of these two fragments, amide bond formation between residues IV and V furnished the linear precursor followed by deprotection of the acid and amine and subsequent peptide cyclization between residues II and III generated compounds **10** and **11**.

We synthesized two pseudoproline (PP) derivatives based on the compound **A** scaffold, where the pseudoproline was placed at positions II and III, respectively (**12** and **13**, Fig. 5). These compounds were made via Fmoc solid-phase synthesis through sequential peptide coupling from chlorotriptylchloride resin loaded with the appropriate pseudoproline dipeptides.⁴⁰ Upon formation of the linear pentapeptide, the compounds were cleaved, cyclized, and purified.

3. Synthesis

3.1. Synthesis of triazole compound 1

Aldehyde **14** was converted to an alkyne by treatment with *p*-toluenesulfonyl azide and di-methyl (2-oxopropyl) phosphonate (Scheme 1). Removal of the Boc protecting group with TFA

furnished alkyne **15** in a 43% yield over two steps. Alkyne **15** was coupled to amino acid **16** and the Boc group was removed to yield **17**, fragment 2 (74% yield over two steps). Standard coupling of amino acids **18** and **19** and deprotection methods produced **20** (87% yield over two steps). Dipeptide **20** was then coupled to azide **21** and subsequently deprotected using lithium hydroxide to yield free acid **22**, fragment 1 (62% yield over two steps). Amine **17** and acid **22** were coupled using peptide coupling conditions to produce linear precursor **23** (52% yield). Treatment of **23** with catalytic amounts of copper produced **1** in 7.5% purified yield of cyclized compound.

3.2. Synthesis of triazole compound 2

Compound **2** was synthesized using a linear approach. The yield from this linear approach was then compared to the yield using the convergent approach used for compound **1** (Scheme 2). Aldehyde **24** was converted into an alkyne with the treatment of *p*-toluenesulfonyl azide and di-methyl (2-oxopropyl) phosphonate in acetonitrile and methanol. The Boc protecting group was removed to produce **25** (53% yield for two steps). Alkyne **25** was coupled to amino acid **26** upon treatment with *O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) and *N,N'*-diisopropylethylamine (DIPEA). The Boc protecting group was removed to furnish **27** (70% yield for two steps). This was coupled to amino acid **28**, and deprotected to generate alkyne **29** (60% yield over two steps). Coupling **29** to **30** and subsequent deprotection furnished tetrapeptide **31** in good yields (80% yield over two steps). Linear precursor **33** was produced by coupling tetrapeptide **31** to **32** (29% yield). Finally, the macrocyclization step used a copper catalyst to click the 1,4-disubstituted triazole

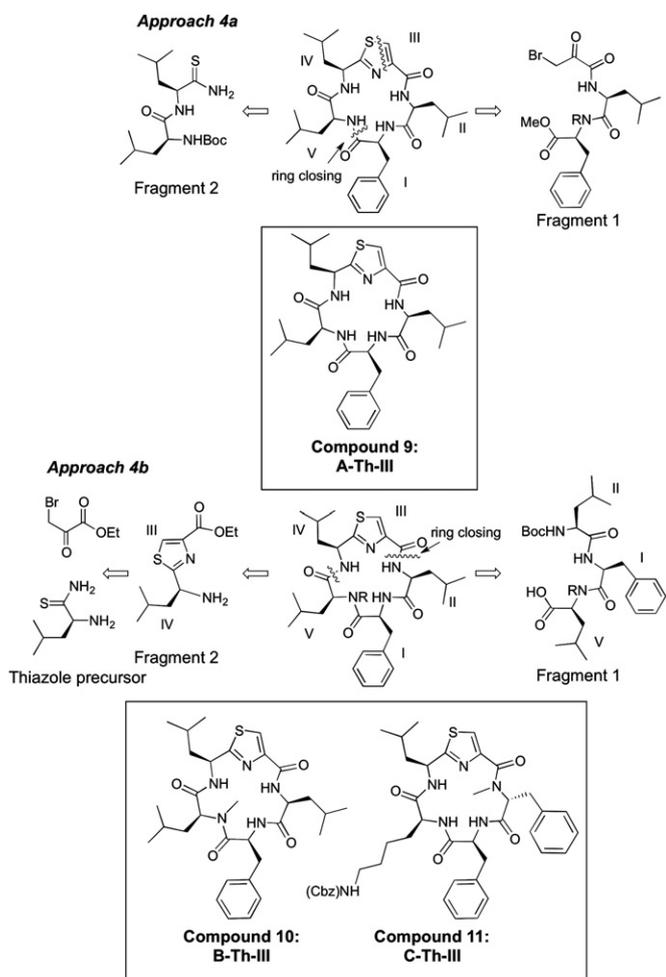


Fig. 4. Thiazole peptidomimetic compounds: 2 approaches.

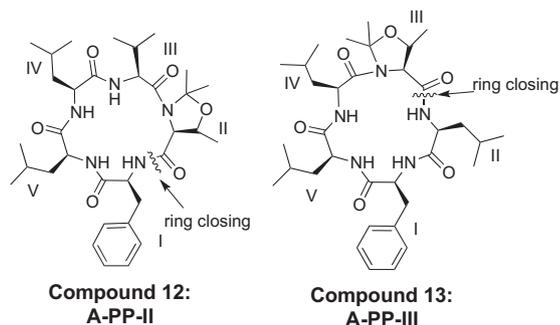
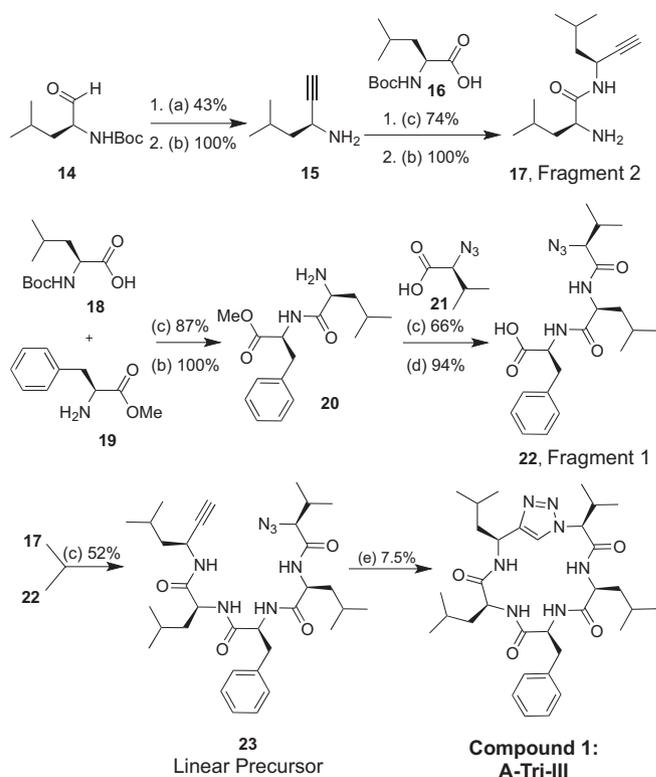


Fig. 5. Pseudoproline compounds.

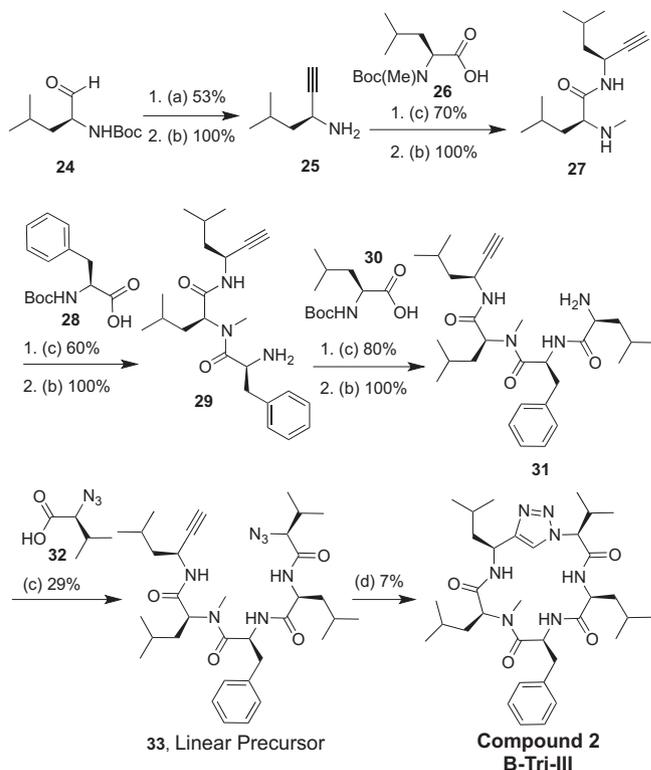
heterocycle and close the macrocyclic ring (7% yield for compound 2).

3.3. Optimal synthesis strategy for oxazole derivatives

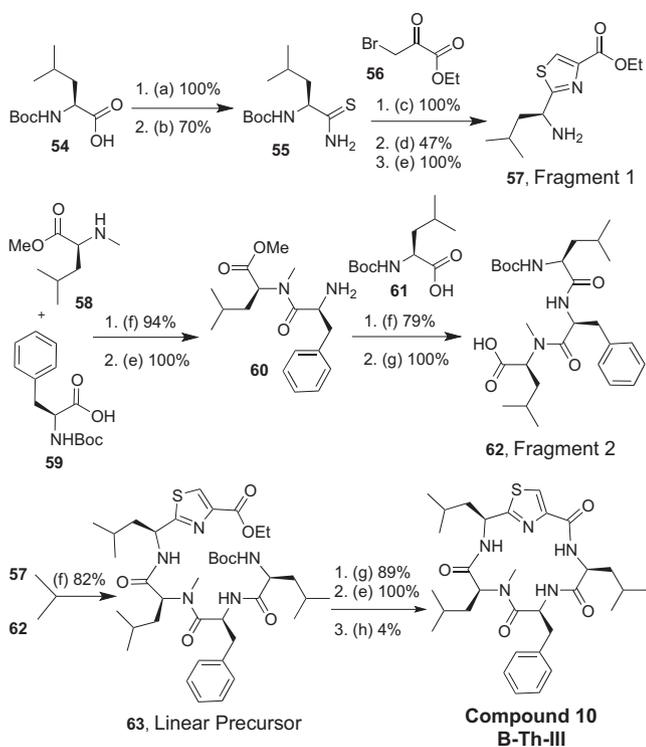
The most optimal synthesis for the oxazole derivatives is described. This approach was used on compounds 3–7 and described is the synthesis of analog 3 where the oxazole is formed prior to closing the macrocycle (Scheme 3). Amino acid 34 was coupled to 35 and then underwent methyl ester hydrolysis to furnish 36 (82% yield over two steps). Coupling 36 and 37 generated a tripeptide, whereupon treatment with lithium hydroxide and hydrogen



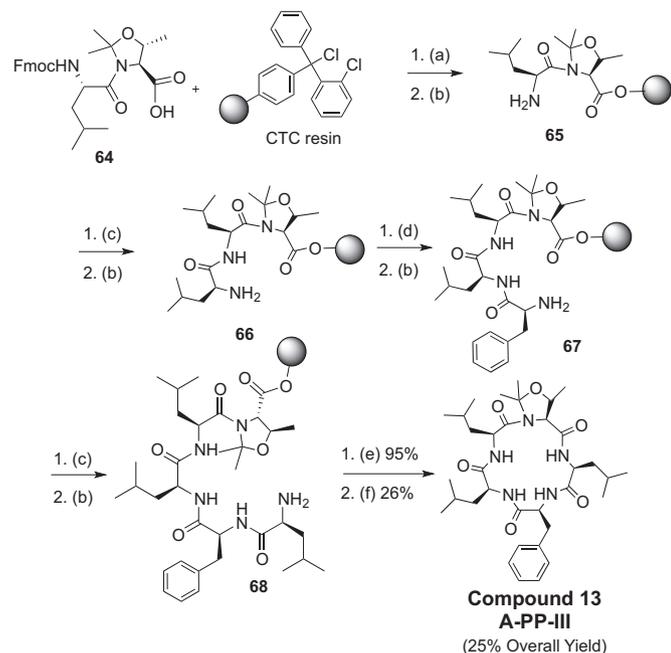
Scheme 1. Synthesis of 1. (a) *p*-Toluenesulfonyl azide (3 equiv), di-methyl (2-oxopropyl) phosphonate (3 equiv), potassium carbonate (3 equiv), 0.25 M in acetonitrile/methanol (1:1); (b) 20% trifluoroacetic acid/dichloromethane (0.1 M); (c) TBTU (1.2 equiv), DIPEA (8 equiv), methylene chloride (0.1 M); (d) LiOH (2 equiv), H₂O₂ (3.4 equiv), methanol (0.1 M), 0 °C; (e) L-ascorbic acid (9 equiv), NaHCO₃ (9 equiv), CuSO₄·H₂O (0.3 equiv), 0.007 M in methanol/water (1:1).



Scheme 2. Synthesis of 2. (a) *p*-Toluenesulfonyl azide (3 equiv), di-methyl (2-oxopropyl) phosphonate (3 equiv), potassium carbonate (3 equiv), 0.25 M in acetonitrile/methanol (1:1); (b) 20% trifluoroacetic acid/dichloromethane (0.1 M); (c) TBTU (1.2 equiv), DIPEA (8 equiv), methylene chloride (0.1 M); (d) L-ascorbic acid (9 equiv), NaHCO₃ (9 equiv), CuSO₄·H₂O (0.3 equiv), 0.007 M in methanol/water (1:1).



Scheme 5. Synthesis of **10**. (a) (1:1) Ammonium hydroxide/methanol (0.1 M); (b) Lawesson's reagent (1 equiv), 1,2-dimethoxyethane (0.15 M); (c) KHCO_3 (8 equiv), 1,2-dimethoxyethane (0.1 M); (d) pyridine (9 equiv), TFAA (4 equiv), TEA (2 equiv), 1,2-dimethoxyethane (0.1 M) 0 °C; (e) 20% trifluoroacetic acid/methylene chloride (0.1 M); (f) TBTU (1.1 equiv), DIPEA (4 equiv), methylene chloride (0.1 M); (g) LiOH (2 equiv), H_2O_2 (3.4 equiv), methanol (0.1 M), 0 °C; (h) TBTU (0.7 equiv), HATU (0.7 equiv), DEPBT (0.7 equiv), DIPEA (6 equiv), methylene chloride (0.007 M).



Scheme 6. Synthesis of **13**. (a) 3 mL/g resin of *N*-Methylpyrrolidone (NMP), DIPEA (6 equiv), methylene chloride (10 mL/g AA); (b) 20% piperidine/dimethylformamide (0.2 M); (c) Fmoc-Leu-OH (1.2 equiv), HOBT (3 equiv), DIC (6 equiv), dimethylformamide (0.2 M); (d) Fmoc-Phe-OH (1.2 equiv), HOBT (3 equiv), DIC (6 equiv), dimethylformamide (0.2 M); (e) TFE/methylene chloride (1:1) (0.2 M); (f) HATU (0.7 equiv), TBTU (0.7 equiv), DEPBT (0.6 equiv), DIPEA (8 equiv), methylene chloride/acetonitrile (1:1) (0.007 M).

providing the double deprotected peptide in an overall yield of 95%. The linear precursor was cyclized to produce the final compound **13** in 25% overall yield from the starting compound **64**. Synthesis of compound **12** utilizes this strategy and is described in the [Supplementary data](#).

4. Biological and modeling data

In order to evaluate, which of the heterocycles would be ideal for incorporation into the macrocyclic backbone, cytotoxicity data for molecule a peptidomimetic functional group was generated and compared to parent compound **A** (Fig. 6). All four classes of peptidomimetic features and compound **A** were evaluated for their ability to inhibit growth in HeLa cervical cancer cell lines. The bar graph indicates that potency is maintained with the inclusion of a triazole or thiazole at position III. Interestingly, inclusion of an oxazole or pseudoproline in the peptide backbone decreases cytotoxicity compared to the parent compound. These data likely represent the consequence of altering the macrocyclic backbone, whereby the trans conformation, that is, induced by the triazole is favorable, and the cis conformation induced by the pseudoproline is not. Further, oxazoles are known to be more rigid than thiazoles, and the additional flexibility of the thiazole must be critical for the macrocycle to maintain its binding affinity with Hsp90.^{1,20,42}

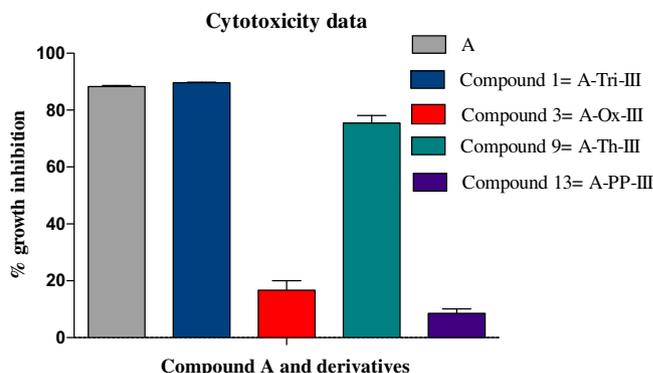


Fig. 6. Peptidomimetic compounds run at 25 μM against HeLa cervical cancer cell lines. Each data point is an average of four wells run in three separate assays using HeLa cancer cell lines. Inhibition is relative to 1% DMSO control.

Given the unique biological data, models of the four molecules were completed using ChemBio3D Ultra. The lowest energy structures for each peptidomimetic molecule are shown in Fig. 7. Although caution should be employed when drawing conclusions from relatively simple model systems, these models are useful tools in developing a hypothesis to explain the highly divergent cytotoxicity data we have generated. The inclusion of the triazole provides an additional atom to the macrocycle, and this appears to allow a large ring, that is, significantly less puckered than the pseudoproline large macrocycle structure, compare **1** versus **13**. This is logical given that the triazole induces a trans conformation, while the pseudoproline induces a cis conformation. Although structurally similar, the oxazole places the side chains at orientations that are different from the thiazole, perhaps allowing a compound–protein interaction with residue II, that is, unique to the thiazole compound (**9**) versus oxazole analog (**3**). Indeed, the modeling data below suggestion that compounds **1** and **9** have a conformation that places residues I and II in a similar orientations, whereas **3** and **13** have very different presentations of both residues. Although difficult to visualize, it is also possible that residues IV and V play a role in the improved cytotoxicity observed for compounds **1** and **9** by allowing an improved binding affinity for

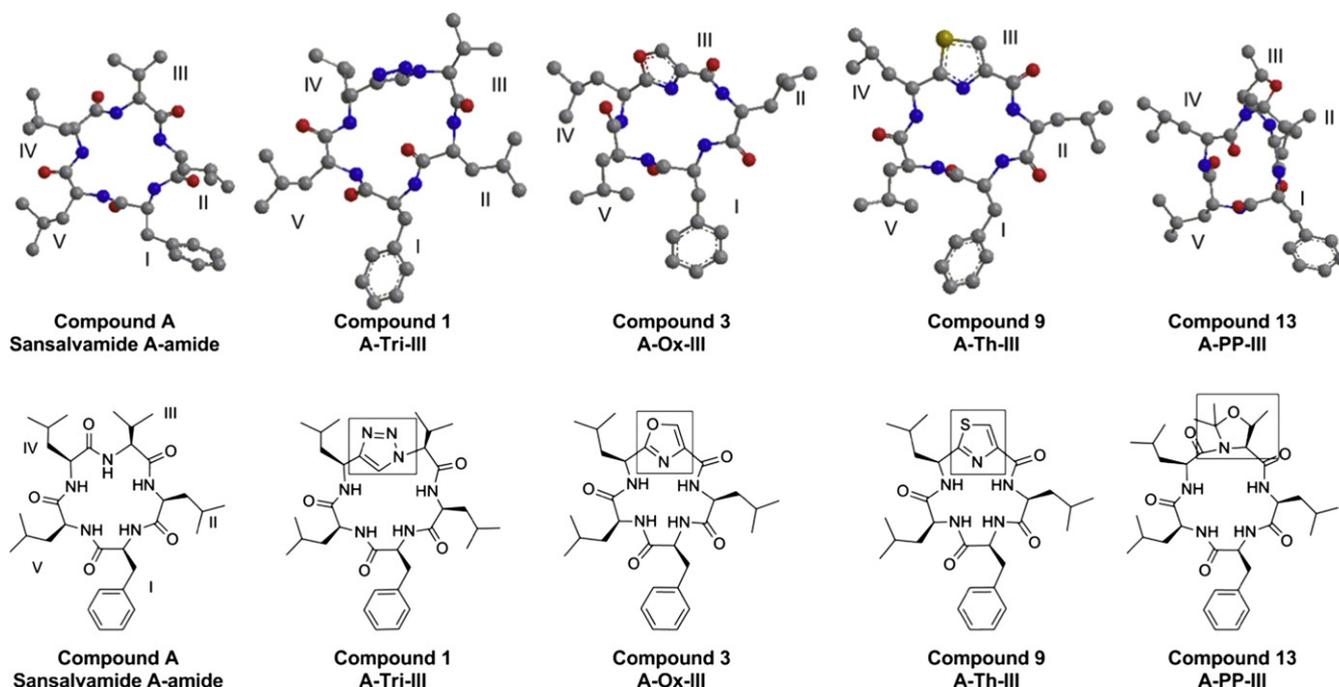


Fig. 7. Molecular models of peptidomimetic compounds. Energy was minimized using the Merck Molecular Force Field 94 (MMFF94) with ChemBio3D Ultra (version 12.0) available from CambridgeSoft. Convergence criteria: atomic root mean square force 0.01 kcal/mol; static energy 82.250–115.726 kcal/mol; 500 iterations.

Hsp90 over that of compounds **3** and **13**. Docking studies involving these molecules and Hsp90's crystal structure are on going and will be published in due course.

5. Conclusion

In summary, we have outlined the synthesis of thirteen peptidomimetics, all of which are related to a class of sansalvamide cytotoxic agents, with the anticipation that several moieties will have potency equal to that observed with the natural product. Two derivatives A-Tri-III (**1**) and A-Th-III (**9**) exhibited cytotoxicity at the same level as the parent San A-amide **A**. Although it is hard to predict how these peptidomimetic moieties affect the overall macrocyclic conformation, it appears that the triazole, which incorporates an additional carbon into the macrocyclic backbone as well as maintaining the side chain at position III is a favorable option. This is likely due to its ability to induce a trans-amide conformation, versus a cis amide conformation induced by the pseudoproline.^{23,26,30,35} The thiazole moiety is also promising, presumably because it is a more flexible heterocycle relative to the oxazole and thus able to accommodate a favorable conformation for binding to Hsp90. Based on modeling, both compounds **1** and **9** may have improved cytotoxicity because of their similar orientation of residues I and II. Future work involves the development of compounds with triazoles and thiazoles in the backbone, with the anticipation that they will maintain their biological activity, while having enhanced PK and ADME properties. Further, docking studies using these two moieties in their backbone will provide insight into the induced conformation, and will be reported in due course.

6. Experimental section

6.1. Cytotoxicity assays

Proliferation of HeLa cells was tested in the presence and absence of the compounds using CCK-8 assays (Dojindo, catalog# CK04–13). Cells were cultured in 96 well plates at a concentration

of 2000 cells/well in DMEM (Gibco) supplemented with L-glutamine, 10% fetal bovine serum, and 1% penicillin-streptomycin antibiotic. After overnight incubation, the compounds were added. The compounds were dissolved in DMSO and tested at the concentrations indicated in the manuscript with a final DMSO concentration of 1.0%. The DMSO control was also at 1.0%. The cells were incubated with compound or DMSO for 24 h upon which 10 μ L of CCK-8 solution was added to each well and allowed to incubate at 37 °C for an additional 2.5 h. The absorbance at 450 nm was measured using a 56 Genios Fluorimeter (Tecan). Percent growth inhibition was calculated as 1 minus the absorbance of compound-treated cells over DMSO-treated cells. All calculations including mean and SEM were performed using Prism software. Each data point is an average of four wells run in three separate assays.

6.2. General solution-phase peptide synthesis

All peptide coupling reactions were carried out under argon with dry solvent, using methylene chloride and/or acetonitrile for dipeptide, tripeptide, and pentapeptide couplings. The amine (1.1 equiv) and acid (1 equiv) were weighed into a dry flask along with 4–8 equiv of DIPEA and 1.1 equiv of TBTU. *Anhydrous methylene chloride and/or acetonitrile were added to generate a 0.1 M solution. The solution was stirred at room temperature and reactions were monitored by TLC. Reactions were run for 1 h before checking via TLC. If reaction was not complete an additional 0.25 equiv of TBTU was added. If reaction was complete then work-up was done by washing with 10% aqueous hydrochloric acid and saturated sodium bicarbonate. After back extraction of aqueous layers with methylene chloride, organic layers were combined, dried over sodium sulfate, filtered, and concentrated. Flash column chromatography using a gradient of ethyl acetate/hexane gave our desired peptide.

*Some coupling reactions would not go to completion using only TBTU and therefore 0.2–0.5 equiv of HATU, and/or DEPBT were used. In a few cases up to 0.7 equiv of all three coupling reagents were used.

6.3. General solution-phase amine deprotection

Amines were deprotected using 20% trifluoroacetic acid in methylene chloride (0.1 M) with 2 equiv of anisole. The reactions were monitored by TLC. Reactions were allowed to run for 1–2 h and then concentrated in vacuo.

6.4. General solution-phase acid deprotection

Acids were deprotected using 2 equiv of lithium hydroxide with 3.4 equiv of hydrogen peroxide in methanol (0.1 M). The peptide was dissolved in methanol and cooled to 0 °C. Hydrogen peroxide was added followed by lithium hydroxide. The reaction was monitored by TLC and usually done in 1–2 h. Sodium thiosulfate (3.8 equiv) was added to neutralize the peroxide and 5% hydrochloric acid was added till the solution pH was 1. The aqueous solution was extracted five times with methylene chloride, and the combined organic layer was dried, filtered, and concentrated in vacuo.

6.5. General solid-phase synthesis remarks

Stepwise solid-phase peptide synthesis was performed in a polypropylene solid-phase extraction cartridge fitted with a 20 µM polyethylene frit purchased from Applied Separations (Allentown, PA). 2-chlorotrityl resins were purchased in pre-loaded form with L-Leu, D-Leu, or D-Phe. In the case of compounds **12** and **13**, a commercially available pseudoproline moiety was loaded onto a 2-chlorotrityl resin. Resins were swelled in dimethylformamide for 30 min prior to assembly of the linear five-residue peptide sequence. Solid-phase syntheses were performed on a 0.5 mmol scale based on resin-loading. All operations were performed at room temperature under open atmosphere unless stated otherwise.

6.6. General solid-phase peptide synthesis

Fmoc-protected amino acids were coupled using 3 equiv of amino acid, 3 equiv of HOBt, and 6 equiv of DIC. Couplings were performed in dimethylformamide at 0.2 M with respect to the incoming Fmoc-protected amino acid. Couplings were allowed to proceed for a minimum of 2 h, and were assayed via ninhydrin test to verify completion. Once complete, the coupling reaction solution was drained, and the resin subjected to Fmoc deprotection. (Note: Fmoc and *N*-methyl amino acids are coupled according to the cycle above, however for subsequent coupling onto the secondary amino terminus, HOBt was substituted with HOAt and the coupling was allowed to proceed overnight).

6.7. General solid-phase amine deprotection

Following coupling completion, the peptide–resin was treated as follows for removal of the Fmoc protecting group: dimethylformamide wash (3×1 min), 20% piperidine/dimethylformamide (1×5 min), 20% piperidine/dimethylformamide (1×10 min), dimethylformamide wash (2×1 min), 2-propanol wash (1×1 min), dimethylformamide wash (1×1 min), 2-propanol (1×1 min), dimethylformamide (3×1 min). A ninhydrin test was performed to verify completion.

6.8. General N-terminal solid-phase deprotection

Once the final N-terminal amino acid residue had been coupled, the peptide–resin was treated as follows for removal of the Fmoc protecting group: dimethylformamide wash (3×1 min), 20% piperidine/dimethylformamide (1×5 min), 20% piperidine/dimethylformamide (1×10 min), dimethylformamide wash (3×1 min),

2-propanol wash (3×1 min), methanol (3×1 min). The fully-assembled peptide–resin was then drained and dried in vacuo overnight.

6.9. Cleavage of linear peptide from solid support

The full-length, linear peptide was cleaved from the resin by swelling and shaking the peptide–resin for 24 h in a 1:1 (v:v) TFE/methylene chloride (10 vol/g of dried resin). The cleavage solution was filtered through a Buchner filter, and the drained resin was washed with additional methylene chloride (5 vol/g of initial dried peptide–resin) to fully extract the cleaved peptide from the resin. Solvents in the combined filtrates were evaporated by rotary evaporation and the solids dried in vacuo overnight. The solids were then reconstituted in methylene chloride, evaporated by rotary evaporation and dried in vacuo overnight again to remove residual entrapped TFE.

6.10. Macrocyclization procedure (with syringe pump)

Three coupling agents (DEPBT, HATU, and TBTU) were used at ~0.5 to 0.75 equiv each. These coupling agents were dissolved in $\frac{3}{4}$ of a calculated volume of dry methylene chloride that would give a 0.001 M–0.0007 M overall concentration when included in the volume used for the deprotected peptide. The crude, dry, double deprotected peptide (free acid and free amine) was dissolved in the other $\frac{1}{4}$ solvent volume of methylene chloride. DIPEA (8 equiv) was then added to the solution containing coupling reagents dissolved in methylene chloride. The double deprotected peptide was then added to the bulk solution dropwise using a syringe pump at a rate of 30 mL/h. The reaction was monitored via LCMS and generally complete in 1–2 h. Upon completion, the reaction was worked up by washing with aqueous hydrochloric acid (pH 1) and saturated sodium bicarbonate. After back extraction of aqueous layers with large quantities of methylene chloride, the organic layers were combined, dried, filtered, and concentrated. All macrocycles were first purified by flash column chromatography using an ethyl acetate/hexane gradient on silica gel. Finally, when necessary, reverse phase-HPLC was used for additional purification using a gradient of acetonitrile and deionized water with 0.1% TFA.

6.11. Alkyne formation (Seyferth–Gilbert)^{43,44}

Dry K₂CO₃ (3.0 equiv) was weighed into the flask under argon atmosphere. Calculated volume of acetonitrile was added to bring the final concentration of 0.125 M *p*-tosyl azide (3.0 equiv) and dimethyl (2-oxypropyl) phosphonate (3.0 equiv) were added to the reaction mixture to generate the Bestmann–Ohira reagent. The reaction mixture stirred at room temperature and was monitored via TLC. After 2 h aldehyde (1.0 equiv dissolved in calculated amount of dry methanol to bring total reaction concentration to 0.25 M) was added. The reaction mixture was left stirring at room temperature overnight. The reaction was usually complete on the next day. Upon completion, confirmed by TLC, the reaction was concentrated in vacuo. The crude dried product was dissolved in 200 mL of ethyl acetate and washed with 150 mL of saturated sodium bicarbonate (× two times) and then by 100 mL of saturated sodium chloride (one time). The organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. Flash chromatography with a gradient of ethyl acetate/hexane was performed to purify the desired alkyne.

6.12. Cu(I)-catalyzed alkyne–azide cycloaddition

Sodium ascorbate was dissolved in 0.5 mL of water and put into round bottom flask. Copper sulfate was dissolved in 0.5 mL of water

and added to the flask. The peptide (with azide and alkyne) was dissolved in a mixture of solvents methanol/water (1:1) at a concentration of 0.005 M 10% of this solvent mixture was added to the flask. The remaining solvent mixture was added dropwise via syringe pump to the reaction flask mixture overnight. The concentration of copper was 1.5 mM and concentration of sodium ascorbate was 45 mM for the overall reaction. Upon completion of the reaction, methanol was removed under reduced pressure and the reaction mixture was diluted with 100 mL of methylene chloride. The organic layer was collected and concentrated in vacuo. Flash chromatography with a gradient of ethyl acetate/hexane was performed to purify the desired derivative. Finally, when necessary reverse phase-HPLC was used for additional purification using a gradient of Acetonitrile and distilled water with 0.1% trifluoroacetic acid.

6.13. General oxazole synthesis

DAST (1.1 equiv) was added (0.1 mL/min) to a solution of peptidyl-Ser or peptidyl-Phenylserine (1.0 equiv) in methylene chloride (0.1 M) cooled to $-78\text{ }^{\circ}\text{C}$ under argon atmosphere. The reaction mixture was stirred for 1 h and anhydrous K_2CO_3 (2.0 equiv) was added to the reaction mixture to stir at $-78\text{ }^{\circ}\text{C}$ for 1 h. The reaction mixture warmed to room temperature and stirred for an additional 1.5 h. Upon reaction completion, confirmed by TLC, the organic solution was poured into saturated aqueous sodium bicarbonate and extracted with methylene chloride. After back extraction of the aqueous layer with methylene chloride and/or ethyl acetate, the organic layers were combined, dried over sodium sulfate, filtered, and concentrated in vacuo to give the oxazoline as an oil. The oxazoline was used without further purification for the oxidation of the oxazoline to yield the desired oxazole. DBU (2.0 equiv) was added (0.1 mL/min) to a solution of oxazoline (1.0 equiv) in methylene chloride (0.1 M) at $-47\text{ }^{\circ}\text{C}$ under argon. The reaction was stirred for 20 min and BrCCl_3 (2.0 equiv) was added to the reaction mixture (0.1 mL/min). The reaction continued to stir at $-47\text{ }^{\circ}\text{C}$ for an additional 2 h and then warmed to room temperature to stir an additional 12 h, or until complete by TLC. Upon reaction completion, a work-up was done by extracting with 10% aqueous hydrochloric acid. After back extraction of aqueous layers with large quantities of methylene chloride and/or ethyl acetate, organic layers were combined, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography using a gradient of ethyl acetate/hexane gave our desired peptidyl-oxazole. Finally, when necessary, reversed phase-HPLC was used for additional purification using a gradient of acetonitrile and deionized water with 0.1% trifluoroacetic acid.

6.14. General amide formation

Boc-protected amino ester (1 equiv) was dissolved in 50% ammonium hydroxide and 50% methanol (0.05 M). The reaction mixture was stirred overnight or until complete by TLC. Upon completion, the solvent was concentrated in vacuo.

6.15. General thioamide formation

Boc-protected amide (1 equiv) was converted into Boc-protected thioamide using Lawesson's reagent (0.8 equiv) in 0.4 M 1,2-dimethoxyethane at room temperature under argon. The mixture was stirred overnight or until complete by TLC. Upon completion, the solvent was concentrated in vacuo. Boc-protected thioamide was purified by flash column chromatography using an ethyl acetate/methylene chloride gradient on silica gel.

6.16. General bromoketal acid formation

Trimethyl orthoformate (3 equiv) and sulfuric acid (0.25 equiv) were used to dissolve bromopyruvic acid (1 equiv) under argon. The mixture is stirred overnight for less than 24 h. Acid work-up was done by extracting with 10% aqueous hydrochloric acid. After back extraction of aqueous layers with methylene chloride and/or ethyl acetate, the organic layers were combined, dried over sodium sulfate, filtered, and concentrated in vacuo.

6.17. General ketone deprotection

Ketones were deprotected using formic acid (0.1 M), heated to $60\text{ }^{\circ}\text{C}$. The reaction was monitored by TLC and usually done within 30 min. Upon completion, the reaction was washed with saturated aqueous sodium bicarbonate. After back extraction of aqueous layers with methylene chloride, organic layers were combined, dried over sodium sulfate, filtered, and concentrated in vacuo.

6.18. General thiazole synthesis (modified Hantzsch)

Thiazole synthesis reaction was carried out under argon with anhydrous 1,2-dimethoxyethane. KHCO_3 (8 equiv) was added to the dry flask containing peptidyl thioamide (1.0 equiv). Anhydrous 1,2-dimethoxyethane (0.15 M) was added to the reaction, and it was stirred at room temperature for 15 min. α -Bromo ketone residue (3.0 equiv) was added (0.1 mL/min) and the reaction mixture was stirred overnight. Upon reaction completion, confirmed by TLC, the organic solution was poured into pre-primed Celite with ethyl acetate. The filtrate was concentrated in vacuo to give the thiazoline intermediate as an oil to be used without further purification. Next, pyridine (9.0 equiv) was added (0.1 mL/min) to a solution of thiazoline in 1,2-dimethoxyethane (0.05 M) at $0\text{ }^{\circ}\text{C}$ under argon for the dehydration of the thiazoline to yield the desired thiazole. The reaction was stirred for 15 min and then TFAA (4.0 equiv) was added to the reaction mixture (0.1 mL/min). After 3 h, TEA (2.0 equiv) was added to the reaction mixture (0.1 mL/min) and the reaction continued to stir at room temperature for an additional 2–3 h, or until complete by TLC. Upon completion, the reaction was extracted with 10% aqueous hydrochloric acid. After back extraction of aqueous layers with methylene chloride and/or ethyl acetate, the organic layers were combined, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography using a gradient of ethyl acetate/methylene chloride gave our desired peptidyl-thiazole. Finally, when necessary, reverse phase-HPLC was used for additional purification using a gradient of acetonitrile and deionized water with 0.1% trifluoroacetic acid.

6.19. Benzylation procedure

The cyclized peptide was dissolved in 50% tetrahydrofuran and 50% dimethylformamide to make a 0.1 M solution. The 60% NaH was used at 1.1 equiv and dissolved in the 0.1 M solution. Benzyl bromide (2 equiv) was then added to the reaction. After 2 h, LC/MS indicated the reaction was developing. The reaction was completed in about 5 h and then worked up by washing with deionized water. After that, the organic layer was collected, dried, and preliminarily purified by flash column chromatography. Finally, reverse phase-HPLC was used for further purification by using a gradient of acetonitrile and deionized water with 0.1% trifluoroacetic acid.

6.20. Synthesis of compound 1 (A-tri-III)

6.20.1. Dipeptide MeO-Phe-Leu-NHBoc. Dipeptide MeO-Phe-Leu-NHBoc was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 1.50 g (6.96 mmol) of amine **19** MeO-Phe-NH₂·HCl, 1.46 g (6.32 mmol) of acid **18** HO-Leu-NHBoc, 3.95 mL (27.8 mmol) of DIPEA, 2.44 g (7.58 mmol) of TBTU, in 66.0 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the dipeptide (2.26 g, 87% yield). *R_f*: 0.6 (EtOAc/Hex 1:1). Physical and spectroscopic data are consistent with those reported in the literature.²⁹

6.20.2. Dipeptide MeO-Phe-Leu-NH₂ (20). Dipeptide MeO-Phe-Leu-NH₂ was synthesized following the 'General solution-phase amine deprotection'. This dipeptide was taken on to the next reaction without further purification or characterization (445 mg, 100% yield).

6.20.3. Monomer HO-Val-N₃ (21). Monomer **21** HO-Val-N₃ was synthesized utilizing 500 mg (4.27 mmol) of HO-Val-NH₂, 2.82 g (8.54 mmol) of triflic anhydride, 2.78 g (42.7 mmol) of sodium azide, 885 mg (6.41 mmol) of potassium carbonate, 10.6 mg (42.5 μmol) of CuSO₄·5H₂O, in 48 mL of DCM/MeOH/H₂O (2:1:1) solvent system. The crude reaction was purified using an aqueous acidic wash to yield the pure monomer (600 mg, 97% yield).

6.20.4. Tripeptide MeO-Phe-Leu-Val-N₃. Tripeptide MeO-Phe-Leu-Val-N₃ was synthesized following the 'General solution-phase peptide synthesis'. Utilizing 444 mg (1.53 mmol) of amine **20** MeO-Phe-Leu-NH₂, 200 mg (1.39 mmol) of acid **21** HO-Leu-N₃, 1.80 mL of DIPEA, 534 mg (1.66 mmol) of TBTU, in 66.0 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the tripeptide (420 mg, 66% yield). *R_f*: 0.5 (EtOAc/Hex 1:2); ¹H NMR (400 MHz, CDCl₃): δ 0.83–0.91 (9H, m, CH(CH₃)₂), 1.08 (3H, d, *J* 6.6 Hz, CH(CH₃)₂), 1.47–1.51 (2H, m, CHCH₂(CH₃)₂), 2.24–2.33 (1H, m, CH(CH₃)₂), 3.02–3.20 (2H, dq, *J* 86.5, 14.2, 5.5 Hz, CHCH₂Ph), 3.72 (3H, s, OCH₃), 3.73 (1H, d, *J* 4.1 Hz, αCH), 4.37–4.42 (1H, m, αCH), 4.90–5.02 (1H, m, αCH), 6.43 (1H, d, *J* 7.7 Hz, NH), 6.62 (1H, d, *J* 7.7 Hz, NH), 7.09–7.32 (5H, m, Ph).

6.20.5. Tripeptide HO-Phe-Leu-Val-N₃ (22). Tripeptide HO-Phe-Leu-Val-N₃ was synthesized following the 'General solution-phase acid deprotection'. This tripeptide was taken on to the next reaction without further purification or characterization (382 mg, 94% yield).

6.20.6. Monomer alkyne-Leu-NHBoc. Monomer alkyne-Leu-NHBoc was synthesized following 'Alkyne formation'. Utilizing 165 mg (0.787 mmol) of **14** Leucinial-NHBoc, 0.353 mL (2.30 mmol) of pTsN₃, 0.310 mL (2.30 mmol) of di-methyl (2-oxopropyl) phosphonate, and 317 mg (2.30 mmol) K₂CO₃ in 3.22 mL of ACN/MeOH (1:1). The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the monomer (70.0 mg, 43% yield). *R_f*: 0.5 (EtOAc/Hex 1:9).

6.20.7. Monomer alkyne-Leu-NH₂ (15). Monomer **15** alkyne-Leu-NH₂ was synthesized following the 'General solution-phase amine deprotection'. This monomer was taken on to the next reaction without further purification or characterization (83 mg, 100% yield).

6.20.8. Dipeptide alkyne-Leu-Leu-NHBoc. Dipeptide alkyne-Leu-Leu-NHBoc was synthesized following the 'General solution-phase

peptide synthesis' procedure. Utilizing 83.0 mg (0.743 mmol) of amine **15** alkyne-Leu-NH₂, 204 mg (0.817 mmol) of acid **16** HO-Leu-NHBoc, 1.00 mL (6.53 mmol) of DIPEA, 286 mg (0.896 mmol) of TBTU, in 7.40 mL of methylene chloride. The crude reaction was by column chromatography (silica gel, EtOAc/Hex) to yield the dipeptide (241 mg, 74% yield). *R_f*: 0.6 (EtOAc/Hex 1:4); ¹H NMR (400 MHz, CDCl₃): δ 0.85–0.90 (12H, m, CH(CH₃)₂), 1.37 (9H, s, OC(CH₃)₃), 1.45–1.50 (1H, m, CH₂CH(CH₃)₂), 1.57–1.64 (4H, m, CHCH₂CH), 1.64–1.74 (1H, m, CH₂CH(CH₃)₂), 2.17 (1H, s, C≡CH), 3.91–4.02 (1H, br m, αCH), 4.65–4.78 (1H, m, αCH), 4.72 (1H, br s, CHNHCOOtBu), 7.72 (1H, br d, *J* 6.19 Hz, NH).

6.20.9. Dipeptide alkyne-Leu-Leu-NH₂ (17). Dipeptide alkyne-Leu-Leu-NH₂ was synthesized following the 'General solution-phase amine deprotection'. This dipeptide was taken on to the next reaction without further purification or characterization (145 mg, 100% yield).

6.20.10. Pentapeptide alkyne-Leu-Leu-Phe-Leu-Val-N₃ (23). Pentapeptide alkyne-Leu-Leu-Phe-Leu-Val-N₃ was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 145 mg (0.649 mmol) of amine **17** alkyne-Leu-Leu-NH₂, 237 mg (0.591 mmol) of acid **22** HO-Phe-Leu-Val-N₃, 0.82 mL (4.73 mmol) of DIPEA, 189 mg (0.591 mmol) of TBTU, 67.0 mg (0.177 mmol) of HATU, and 34.2 mg (0.118 mmol) of DEPBT, in 5 mL of methylene chloride and 2 mL acetonitrile. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the pentapeptide (186 mg, 52% yield). *R_f*: 0.5 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CD₃OD): δ 0.88–0.96 (24H, m, CH(CH₃)₂), 1.26–1.36 (1H, m, CHCH(CH₃)₂), 1.47–1.65 (6H, m, CHCH₂CH), 1.72–1.83 (1H, m, CH₂CH(CH₃)₂), 2.05–2.19 (1H, m, CH₂CH(CH₃)₂), 2.63 (1H, s, C≡CH), 2.89–3.16 (2H, dq, *J* 80.6, 8.3, 5.6 Hz, CHCH₂Ph), 3.55 (1H, d, *J* 6.9 Hz, N₃CHC=O), 4.32–4.44 (2H, m, αCH), 4.57–4.70 (2H, m, αCH), 7.17–7.26 (5H, m, Ph), 8.01 (1H, d, *J* 8.05 Hz, NH), 8.07 (1H, d, *J* 7.7 Hz, NH), 8.11 (1H, d, *J* 7.8 Hz, NH), 8.21 (1H, d, *J* 8.4 Hz, NH). LCMS: *m/z* calcd for C₃₃H₅₁N₇O₄ (M+1)=610.8, found 611.6.

6.20.11. Macrocycle Phe-Leu-Val-Triazole-Leu-Leu (1). Macrocycle Phe-Leu-Val-Triazole-Leu-Leu was synthesized following the 'Cu(I)-catalyzed alkyne-azide cycloaddition'. Utilizing 150 mg (0.252 mmol) of linear pentapeptide **23**, 389 mg (2.21 mmol) of L-ascorbic acid, 185 mg (2.21 mmol) of NaHCO₃, and 18.4 mg (74.2 μmol) CuSO₄·5H₂O in 35.0 mL MeOH/H₂O (1:1). The crude reaction was purified by reverse phase-HPLC to yield the macrocycle (12.3 mg, 7.5% yield). *R_f*: 0.25 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CD₃OD): δ 0.89–1.0 (24H, m, CH(CH₃)₂), 1.49–1.54 (2H, m, CHCH₂CH), 1.58–1.63 (2H, m, CHCH₂CH), 1.65–1.69 (1H, m, CH₂CH(CH₃)₂), 1.75–1.80 (2H, m, CHCH₂CH), 1.98–2.06 (1H, m, CH₂CH(CH₃)₂), 2.15–2.22 (1H, m, CH₂CH(CH₃)₂), 3.02–3.16 (2H, m, CH₂Ph), 3.60–3.69 (1H, m, αCH), 3.80–3.87 (1H, m, αCH), 4.02–4.09 (1H, m, αCH), 4.19–4.27 (1H, m, αCH), 5.18–5.24 (1H, m, αCH), 7.19–7.32 (5H, m, Ph), 8.04 (1H, s, NCH=C). LCMS: *m/z* calcd for C₃₃H₅₁N₇O₄ (M+1)=611.8, found 611.9; HRMS (ESI-TOF): MH⁺, found 610.4078, requires 610.4075 >95% pure by HPLC.

6.21. Synthesis of compound 2 (B-tri-III)

6.21.1. Monomer HO-Val-N₃ (32). Monomer HO-Val-N₃ was synthesized utilizing 500 mg (4.27 mmol) of HO-Val-NH₂, 2.82 g (8.54 mmol) of triflic anhydride, 2.78 g (42.7 mmol) of sodium azide, 885 mg (6.41 mmol) of potassium carbonate, 10.6 mg (42.5 μmol) of CuSO₄·5H₂O, in 48.0 mL of DCM/MeOH/H₂O (2:1:1) solvent system. The crude reaction was purified using an

aqueous acidic wash to yield the pure monomer (600 mg, 97% yield).

6.21.2. Monomer alkyne-Leu-NHBoc. Monomer alkyne-Leu-NHBoc was synthesized following 'Alkyne formation'. Utilizing 310 mg (1.39 mmol) of **24** Leucinal-NHBoc, 0.635 mL (4.18 mmol) of pTsn₃, 0.572 mL (4.18 mmol) of dimethyl (2-oxopropyl) phosphonate, and 577 mg (4.18 mmol) of K₂CO₃, in 5.50 mL of ACN/MeOH (1:1). The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the monomer (160 mg, 53% yield). *R*_f: 0.5 (EtOAc/Hex 1:9).

6.21.3. Monomer alkyne-Leu-NH₂ (25). Monomer alkyne-Leu-NH₂ was synthesized following the 'General solution-phase amine deprotection'. This monomer was taken on to the next reaction without further purification or characterization (83.2 mg, 100% yield).

6.21.4. Dipeptide alkyne-Leu-Leu-N(Me)Boc. Dipeptide alkyne-Leu-Leu-N(Me)Boc was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 83.2 mg (0.748 mmol) of amine **25** alkyne-Leu-NH₂, 169 mg (0.689 mmol) of acid **26** HO-Leu-N(Me)Boc, 0.902 mL (5.51 mmol) of DIPEA, 265 mg (0.823 mmol) of TBTU, in 7.05 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the dipeptide (245 mg, 70% yield). *R*_f: 0.6 (EtOAc/Hex 1:4); ¹H NMR (400 MHz, CDCl₃): δ 0.77–0.84 (12H, m, CH(CH₃)₂), 1.36 (9H, s, COOC(CH₃)₃), 1.37 (2H, br m, CH(CH₃)₂), 1.50–1.66 (4H, br m, CHCH₂CH), 2.15 (1H, s, C≡CH), 2.61 (3H, s, MeNCH), 4.40–4.52 (1H, br s, αCH), 4.55–4.67 (1H, q, J 7.3 Hz, αCH).

6.21.5. Dipeptide alkyne-Leu-Leu-N(Me)H (27). Dipeptide alkyne-Leu-Leu-N(Me)H was synthesized following the 'General solution-phase amine deprotection'. This dipeptide was taken on to the next reaction without further purification or characterization (173 mg, 100% yield).

6.21.6. Tripeptide alkyne-Leu-Leu-N(Me)-Phe-NHBoc. Tripeptide alkyne-Leu-Leu-N(Me)-Phe-NHBoc was synthesized following the 'General solution-phase peptide synthesis'. Utilizing 302 mg (1.13 mmol) of acid **28** HO-Phe-NHBoc, 299 mg (1.25 mmol) of amine **27** Alkyne-Leu-Leu-N(Me)H, 1.54 mL (9.04 mmol) of DIPEA, 362 mg (1.13 mmol) of TBTU, and 128 mg (0.339 mmol) of HATU in 11.0 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the tripeptide (328 mg, 60% yield). *R*_f: 0.5 (EtOAc/Hex 1:3); ¹H NMR (400 MHz, CDCl₃): δ 0.80–0.92 (12H, m, CH(CH₃)₂), 1.39 (9H, s, COOC(CH₃)₃), 1.48–1.58 (2H, m, CHCH₂CH), 1.63–1.72 (2H, m, CHCH₂CH), 1.81–1.90 (1H, m, CH₂CH(CH₂)₃), 1.81 (1H, s, C≡CH), 2.71 (3H, s, CH₃N), 2.84–2.96 (2H, m, CHCH₂Ph), 4.64–4.74 (1H, m, αCH), 5.05–5.11 (1H, m, αCH), 5.31–5.51 (1H, dd, J 50.8, 7.7 Hz, αCH), 5.95 (1H, d, J 8.17 Hz, NH), 7.23–7.32 (5H, m, Ph), 7.92 (1H, d, J 8.4 Hz, NH).

6.21.7. Tripeptide alkyne-Leu-Leu-N(Me)-Phe-NH₂ (29). Tripeptide alkyne-Leu-Leu-N(Me)-Phe-NH₂ was synthesized following the 'General solution-phase amine deprotection'. This tripeptide was taken on to the next reaction without further purification or characterization (262 mg, 100% yield).

6.21.8. Tetrapeptide alkyne-Leu-Leu-N(Me)-Phe-Leu-NHBoc. Tetrapeptide alkyne-Leu-Leu-N(Me)-Phe-Leu-NHBoc was synthesized following the 'General solution-phase peptide synthesis'. Utilizing 262 mg (0.674 mmol) of amine **29** Alkyne-Leu-Leu-N(Me)-Phe-NH₂, 152 mg (0.612 mmol) of acid **30** HO-Leu-NHBoc, 0.805 mL

(4.89) of DIPEA, 235 mg (0.734 mmol) of TBTU, in 6.70 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the tetrapeptide (332 mg, 80% yield). *R*_f: 0.4 (EtOAc/Hex 1:3); ¹H NMR (400 MHz, CDCl₃): δ 0.86–0.95 (18H, m, CH(CH₃)₂), 1.42 (9H, s, COOC(CH₃)₃), 1.46–1.56 (2H, m, CHCH₂CH), 1.56–1.68 (2H, m, CHCH₂CH), 1.69–1.80 (1H, m, CH(CH₃)₂), 2.84–2.93 (2H, m, CHCH₂Ph), 2.99 (3H, s, NCH₃), 3.04–3.12 (1H, m, CH(CH₃)₂), 3.28 (1H, d, C≡CH), 4.02–4.16 (1H, m, αCH), 4.59–4.69 (1H, m, αCH), 4.92 (1H, m, αCH), 5.09 (1H, m, αCH), 7.17–7.30 (5H, m, Ph), 7.94 (1H, d, J 8.2 Hz, NH), (1H, d, J 8.13 Hz, NH).

6.21.9. Tetrapeptide alkyne-Leu-Leu-N(Me)-Phe-Leu-NH₂ (31). Tetrapeptide alkyne-Leu-Leu-N(Me)-Phe-Leu-NH₂ was synthesized following the 'General solution-phase amine deprotection'. This tripeptide was taken on to the next reaction without further purification or characterization (233 mg, 100% yield).

6.21.10. Pentapeptide alkyne-Leu-Leu-N(Me)-Phe-Leu-Val-N₃ (33). Pentapeptide alkyne-Leu-Leu-N(Me)-Phe-Leu-Val-N₃ was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 326 mg (0.655 mmol) of amine Alkyne-Leu-Leu-N(Me)-Phe-Leu-NH₂ (**31**), 237 mg (0.594 mmol) of acid HO-Val-N₃ (**32**), 0.852 mL (4.75 mmol) of DIPEA, 199 mg (0.623 mmol) of TBTU, and 71.2 mg (0.193) of HATU in 6 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the pentapeptide (110 mg, 29% yield). *R*_f: 0.5 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CD₃OD): δ 0.88–0.98 (24H, m, CH(CH₃)₂), 1.40–1.49 (1H, m, CH(CH₃)₂), 1.51–1.61 (6H, br m, CHCH₂CH), 1.70–1.81 (1H, m, CH(CH₃)₂), 2.10–2.14 (1H, m, CH(CH₃)₂), 2.64 (1H, s, C≡CH), 2.91 (2H, m, CH₂Ph), 3.31 (3H, s, MeNC=O), 3.50–3.57 (1H, m, αCH), 4.42–4.48 (1H, m, αCH), 4.60–4.69 (1H, m, αCH), 4.80–4.89 (1H, m, αCH), 7.18–7.31 (5H, m, Ph). LCMS: *m/z* calcd for C₃₄H₅₃N₇O₄ (M+1)=624.9, found 646.5.

6.21.11. Macrocycle Phe-Leu-Val-Triazole-Leu-Leu-N(Me) (2). Macrocycle Phe-Leu-Val-Triazole-Leu-Leu-N(Me) was synthesized following the 'Cu(I)-catalyzed alkyne-azide cycloaddition'. Utilizing 110 mg (0.176 mmol) of linear pentapeptide (**33**), 1.75 g (8.79 mmol) of L-ascorbic acid, 730 mg (8.79 mmol) of NaHCO₃, and 124 mg (0.502 mmol) CuSO₄·H₂O in 35 mL MeOH/H₂O (1:1). The crude reaction was purified by reverse phase-HPLC to yield the macrocycle (8.20 mg, 7% yield). *R*_f: 0.4 (EtOAc/Hex 1:1) ¹H NMR (400 MHz, CD₃OD): δ 0.71–0.80 (3H, m, CH(CH₃)₂), 0.83–1.12 (18H, m, CH(CH₃)₂), 1.19–2.01 (1H, m, CH(CH₃)₂), 1.30–1.35 (1H, m, CH(CH₃)₂), 1.50–1.57 (2H, m, CHCH₂CH), 1.64–1.68 (2H, m, CHCH₂CH), 1.69–1.73 (2H, m, CHCH₂CH), 1.84–1.88 (1H, m, CH(CH₃)₂), 2.52–2.56 (1H, CH(CH₃)₂), 2.89–2.95 (2H, m, CH₂Ph), 2.99 (s, 3H, MeNC=O), 3.45–3.50 (1H, m, αCH), 3.70–3.80 (1H, m, αCH), 4.90–4.98 (1H, m, 1H, m, αCH), 5.01–5.12 (1H, m, 1H, m, αCH), 7.15–7.31 (5H, m, Ph), 7.99 (1H, d, J 7.7 Hz, O=CNHCH), 8.06 (1H, s, NCH=C), 8.37 (1H, d J 8.1 Hz, O=CNHCH). LCMS: *m/z* calcd for C₃₄H₅₃N₇O₄ (M+1)=624.8, found 625.3; HRMS (ESI-TOF): MH⁺, found 624.4257, C₃₄H₅₃N₇O₄ requires 624.4232 >95% pure by HPLC.

6.22. Synthesis of compound 3 (A-Ox-III)

6.22.1. Dipeptide MeO-Ser(Bzl)-Leu-NHBoc. Dipeptide MeO-Ser(Bzl)-Leu-NHBoc was synthesized following the 'General solution-phase peptide synthesis' procedure utilizing 756 mg (3.39 mmol) of amine MeO-Ser(Bzl)-NH₂ (**39**), 713 mg (3.08 mmol) of acid HO-Leu-NHBoc (**40**), 2.10 mL (12.3 mmol) of DIPEA, 1.19 g (3.70 mmol) of TBTU, in 31.0 mL of methylene chloride. This dipeptide was taken on to the next reaction without further purification (1.31 g, 98% yield). *R*_f: 0.73 (EtOAc/Hex 1:1); ¹H NMR

(400 MHz, CDCl₃): δ 0.85 (6H, d, *J* 8.0 Hz, CHCH₃), 1.36 (9H, s, CCH₃), 1.41–1.48 (1H, m, CHCH₃), 1.55–1.65 (2H, m, CH₂CH), 3.56 (1H, d, *J* 4.0 Hz, CH₂O), 3.65 (3H, s, OCH₃), 3.76 (1H, dd, *J* 4.0, 7.8 Hz, CH₂O), 4.22 (1H, br s, NH), 4.38 (2H, m, PhCH₂O), 4.66–4.72 (1H, m, α CH), 5.49 (1H, d, *J* 7.8 Hz, α CH), 7.14–7.21 (5H, m, Ph).

6.22.2. Dipeptide MeO-Ser-Leu-NHBoc (41). Dipeptide MeO-Ser-Leu-NHBoc was synthesized by dissolving 1.31 g (3.01 mmol) of dipeptide MeO-Ser(OBn)-Leu-NHBoc in 30 mL of ethyl alcohol, after purging the reaction vessel several times with hydrogen gas, the reaction was run overnight. Upon completion by TLC, this dipeptide was taken on to the next reaction without further purification or characterization (902 mg, 89% yield).

6.22.3. Dipeptide MeO-Oxazole-Leu-NHBoc. Dipeptide MeO-Oxazole-Leu-NHBoc was synthesized following the 'General oxazole synthesis' procedure utilizing 0.902 g (2.70 mmol) of dipeptide MeO-Ser-Leu-NHBoc, 0.390 mL (2.97 mmol) of DAST, 746 mg (5.40 mmol) of K₂CO₃, in 40 mL of methylene chloride. The intermediate was oxidized into product by using 0.810 mL of DBU (5.40 mmol), 0.53 mL of CBrCl₃ (5.40 mmol), in 14 mL of methylene chloride. This dipeptide was taken on to the next reaction without further purification (649 mg, 77% yield). *R*_f: 0.55 (EtOAc/Hex 1:1). Physical and spectroscopic data are consistent with those reported in the literature.⁴⁵

6.22.4. Dipeptide MeO-Oxazole-Leu-NH₂ (42). Dipeptide MeO-Oxazole-Leu-NH₂ was synthesized following the 'General solution-phase amine deprotection'. This dipeptide was taken on to the next reaction without further purification or characterization (210 mg, 100% yield).

6.22.5. Dipeptide MeO-Phe-Leu-NHBoc. Dipeptide MeO-Phe-Leu-NHBoc was synthesized following the 'General solution-phase peptide synthesis' procedure utilizing 850 mg (4.76 mmol) of amine MeO-Phe-NH₂ (35), 1.00 g (4.32 mmol) of acid HO-Leu-NHBoc (34), 2.90 mL (17.3 mmol) of DIPEA, 1.66 g (5.18 mmol) of TBTU, in 43.0 mL of methylene chloride. This dipeptide was taken on to the next reaction without further purification (1.64 g, 97% yield). *R*_f: 0.85 (EtOAc/Hex 1:1). Physical and spectroscopic data are consistent with those reported in the literature.⁴⁵

6.22.6. Dipeptide HO-Phe-Leu-NHBoc (36). Dipeptide HO-Leu-D-Leu-NHBoc was synthesized following the 'General solution-phase acid deprotection'. This tripeptide was taken on to the next reaction without further purification or characterization (1.40 g, 85% yield).

6.22.7. Tripeptide MeO-Leu-Phe-Leu-NHBoc. Tripeptide MeO-Leu-Phe-Leu-NHBoc was synthesized following the 'General solution-phase peptide synthesis' procedure utilizing 757 mg (2.00 mmol) of acid HO-Phe-Leu-NHBoc, 320 mg (2.20 mmol) of amine MeO-Leu-NH₂ (37), 1.40 mL (8.00 mmol) of DIPEA, 706 mg (2.40 mmol) of TBTU, in 20 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the tripeptide (890 mg, 88% yield). *R*_f: 0.55 (EtOAc/Hex 1:1). Physical and spectroscopic data are consistent with those reported in the literature.⁴⁶

6.22.8. Tripeptide HO-Leu-Phe-Leu-NHBoc (38). Tripeptide HO-Leu-D-Leu-NHBoc was synthesized following the 'General solution-phase acid deprotection'. This tripeptide was taken on to the next reaction without further purification or characterization (709 mg, 82% yield).

6.22.9. Pentapeptide MeO-Oxazole-Leu-Leu-Phe-Leu-NHBoc (43). Pentapeptide MeO-Oxazole-Leu-Leu-Phe-Leu-NHBoc was synthesized following the 'General solution-phase peptide synthesis'

procedure utilizing 469 mg (0.952 mmol) of acid HO-Leu-Phe-Leu-NHBoc (38), 223 mg (1.05 mmol) of amine MeO-Oxazole-Leu-NH₂ (42), 0.700 mL (3.81 mmol) of DIPEA, 366 mg (1.08 mmol) of TBTU, in 11.0 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the pentapeptide (468 mg, 72% yield). *R*_f: 0.35 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CDCl₃): δ 0.70–0.97 (18H, m, CHCH₃), 1.40 (9H, s, CCH₃), 1.47–1.68 (9H, m, CHCH₃, CH₂-CH), 2.98–3.24 (2H, m, CH₂O), 3.84 (3H, s, OCH₃), 4.50–4.78 (2H, m, α CH), 4.96–5.02 (1H, m, α CH), 5.17–5.31 (1H, m, α CH), 7.07–7.28 (5H, m, Ph), 8.09 (1H, s, OCH=C).

6.22.10. Macrocycle Phe-Leu-Oxazole-Leu-Leu (3). Macrocycle Phe-Leu-Oxazole-Leu-Leu was synthesized following the 'Macrocyclization procedure' utilizing 349 mg (0.611 mmol) of linear pentapeptide (43), 1.10 mL (6.11 mmol) of DIPEA, 138 mg (0.431 mmol) of TBTU, 141 mg (0.375 mmol) of HATU, and 129 mg (0.432 mmol) of DEPBT, in 9.20 mL methylene chloride and 9.00 mL acetonitrile. The crude reaction was purified by reverse phase-HPLC to yield the macrocycle (1.3 mg, 0.4% yield). *R*_f: 0.21 (EtOAc/Hex 1:1); ¹H NMR (600 MHz, CD₃OD): δ 0.69–0.96 (18H, m, CHCH₃), 1.18–1.65 (9H, m, CHCH₃, CH₂CH), 2.97–3.27 (2H, m, CH₂O), 3.52–3.77 (2H, m, α CH), 4.03–4.19 (1H, m, α CH), 4.38–4.57 (1H, m, α CH), 6.63 (1H, br s, NH), 7.03 (1H, br s, NH), 7.17–7.23 (5H, m, Ph), 7.79 (1H, s, OCH=C). LCMS: *m/z* calcd for C₃₀H₄₃N₅O₅ (M+1)=554.6, found 554.3; HRMS (ESI-TOF): MH⁺, found 554.3313, requires 554.3337 >90% pure by HPLC.

6.23. Synthesis of compound 4 (B-Ox-III)

6.23.1. Dipeptide MeO-Phe-Leu-NHBoc. Dipeptide MeO-Phe-Leu-NHBoc was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 850 mg (4.80 mmol) of amine MeO-Phe-NH₂, 1.00 g (4.30 mmol) of acid HO-Leu-NHBoc, 2.90 mL (17.2 mmol) of DIPEA, 1.66 g (5.20 mmol) of TBTU, in 43.2 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the dipeptide (1.64 g, 97% yield). *R*_f: 0.3 (EtOAc/Hex 1:3); ¹H NMR (400 MHz, CDCl₃): δ 0.78–0.84 (6H, m, CH(CH₃)₂), 1.33 (9H, s, C(CH₃)₃), 1.35–1.40 (1H, m, CH(CH₃)₂), 1.45–1.60 (2H, m, β CH₂), 2.90–3.05 (2H, m, β CH₂), 3.59 (3H, s, OCH₃), 4.00–4.10 (1H, br, α CH), 4.70–4.78 (1H, m, α CH), 5.25–5.35 (1H, br, NH), 6.86–6.96 (1H, d, *J* 7.8 Hz, NH), 7.00–7.20 (5H, m, Ph).

6.23.2. Dipeptide HO-Phe-Leu-NHBoc. Dipeptide HO-Phe-Leu-NHBoc was synthesized following the 'General solution-phase acid deprotection'. This dipeptide was taken on to the next reaction without further purification or characterization (1.35 g, 85% yield).

6.23.3. Tripeptide MeO-Leu-N(Me)-Phe-Leu-NHBoc. Tripeptide MeO-Leu-N(Me)-Phe-Leu-NHBoc was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 338 mg (2.10 mmol) of amine MeO-Leu-N(Me)H, 731 mg (1.90 mmol) of acid HO-Phe-Leu-NHBoc, 1.35 mL (5.70 mmol) of DIPEA, 744 mg (2.30 mmol) of TBTU, in 19.3 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the tripeptide (602 mg, 60% yield). *R*_f: 0.22 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CDCl₃): δ 0.84–0.98 (12H, m, CH(CH₃)₂), 1.34–1.42 (2H, m, CH(CH₃)₂), 1.47 (9H, s, C(CH₃)₃), 1.54–1.75 (4H, m, β CH₂), 2.80 (3H, s, NCH₃), 2.94–3.20 (2H, m, β CH₂), 3.68 (3H, s, OCH₃), 4.05–4.15 (1H, br, NH), 4.76–4.84 (1H, br, NH), 4.84–4.88 (1H, m, α CH), 5.10–5.20 (1H, m, α CH), 5.25–5.32 (1H, m, α CH), 7.10–7.33 (5H, m, Ph).

6.23.4. Tripeptide HO-Leu-N(Me)-Phe-Leu-NHBoc. Tripeptide HO-Leu-N(Me)-Phe-Leu-NHBoc was synthesized following the 'General

solution-phase acid deprotection. This tripeptide was taken on to the next reaction without further purification or characterization (470 mg, 80% yield).

6.23.5. Dipeptide MeO-Ser(Bzl)-Leu-NHBoc. Dipeptide MeO-Ser(Bzl)-Leu-NHBoc was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 756 mg (3.40 mmol) of amine MeO-Ser(Bzl)-NH₂, 713 mg (3.10 mmol) of acid HO-Leu-NHBoc, 2.10 mL (12.4 mmol) of DIPEA, 1.19 g (3.70 mmol) of TBTU, in 30.8 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the dipeptide (1.31 g, 97% yield). *R_f*: 0.76 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CDCl₃): δ 0.95–0.96 (3H, d, *J* 3.5 Hz, (CHCH₃)₂), 0.96–0.97 (3H, d, *J* 3.5 Hz, (CHCH₃)₂), 1.43 (9H, s, C(CH₃)₂), 1.61–1.63 (1H, m, CH(CH₃)₂), 1.63–1.78 (2H, m, βCH₂), 3.66–3.70 (1H, dd, *J* 6.9, 1.5 Hz, βCH), 3.75 (3H, s, OCH₃), 3.88–3.92 (1H, dd, *J* 7.1, 1.5 Hz, αCH), 4.14–4.21 (1H, br, αCH), 4.46–4.59 (2H, q, CH₂OBn), 4.72–4.76 (1H, m, αCH), 4.84–4.91 (1H, br, NH), 6.76–6.80 (1H, br, NH), 7.26–7.40 (5H, m, Ph).

6.23.6. Dipeptide MeO-Ser-Leu-NHBoc. Dipeptide MeO-Ser-Leu-NHBoc was synthesized by dissolving 1.28 g (3.03 mmol) of dipeptide MeO-Ser(Bzl)-Leu-NHBoc in 30.0 mL EtOH (0.1 M). The reaction mixture was hydrogenated using a catalytic amount of Pd/C and excess H₂ for 24 h. The reaction was filtered over Celite to yield pure dipeptide (900 mg, 89% yield). *R_f*: 0.28 (EtOAc/Hex 1:1).

6.23.7. Dipeptide MeO-Oxazole-Leu-NHBoc. Dipeptide MeO-Oxazole-Leu-NHBoc was synthesized following the 'General oxazole synthesis' procedure. The oxazoline intermediate was synthesized utilizing 900 mg (2.72 mmol) of dipeptide MeO-Ser-Leu-NHBoc, 0.390 mL (2.97 mmol) of DAST, 746 mg (5.40 mmol) of K₂CO₃ in 40.0 mL of methylene chloride. The resulting oxazoline was oxidized utilizing 0.810 mL (5.40 mmol) of DBU, 0.530 mL (5.40 mmol) of CBrCl₃ in 40.0 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the desired peptidyl-oxazole (649 mg, 77% yield over two steps). *R_f*: 0.5 (EtOAc/Hex 7:13); ¹H NMR (400 MHz, CDCl₃): δ 0.94–0.96 (3H, d, *J* 3.5 Hz, CHCH₃), 0.96–0.98 (3H, d, *J* 3.5 Hz, CHCH₃), 1.43 (9H, s, C(CH₃)₃), 1.58–1.64 (1H, m, CH(CH₃)₂), 1.64–1.80 (2H, m, βCH₂), 3.93 (3H, s, OCH₃), 4.94–5.04 (1H, br, αCH), 5.04–5.10 (1H, br, NH), 8.18 (1H, s, OCH=C).

6.23.8. Dipeptide MeO-Oxazole-Leu-NH₂. Dipeptide MeO-Oxazole-Leu-NH₂ was synthesized following the 'General solution-phase amine deprotection'. This dipeptide was taken on to the next reaction without further purification or characterization (212 mg, 100% yield).

6.23.9. Pentapeptide MeO-Oxazole-Leu-Leu-N(Me)-Phe-Leu-NHBoc. Pentapeptide MeO-Oxazole-Leu-Leu-N(Me)-Phe-Leu-NHBoc was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 210 mg (0.990 mmol) of amine MeO-Oxazole-Leu-NH₂, 470 mg (0.930 mmol) of acid HO-Leu-N(Me)-Phe-Leu-NHBoc, 0.650 mL (3.72 mmol) of DIPEA, 353 mg (1.10 mmol) of TBTU, in 10.0 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the pentapeptide (281 mg, 43% yield). *R_f*: 0.47 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CDCl₃): δ 0.80–1.02 (18H, m, CH(CH₃)₂), 1.22–1.57 (6H, m, βCH₂), 1.35–1.44 (9H, m, C(CH₃)₃), 1.57–1.73 (2H, m, CH(CH₃)₂), 1.73–1.94 (1H, m, CH(CH₃)₂), 2.69 (3H, m, NCH₃), 2.84–3.23 (2H, m, βCH₂), 3.91 (3H, m, OCH₃), 4.04–4.15 (2H, br, NH), 4.60–4.70 (1H, br, NH), 4.78–4.96 (2H, m, αCH), 5.14–5.28 (1H, m, αCH), 5.28–5.38 (1H, m, αCH), 7.08–7.30 (5H, m, Ph),

8.08–8.20 (1H, m, OCH=C). LCMS: *m/z* calcd for C₃₇H₅₇N₅O₈ (M+1)=699.88, found 699.8.

6.23.10. Macrocycle Phe-Leu-Oxazole-Leu-Leu-N(Me) (4). Macrocycle Phe-Leu-Oxazole-Leu-Leu-N(Me) (4) was synthesized following the 'Macrocyclization procedure'. Utilizing 281 mg (0.400 mmol) of linear pentapeptide, 0.420 mL (2.4 mmol) of DIPEA, 90.0 mg (0.280 mmol) of TBTU, 107 mg (0.280 mmol) HATU, and 83.8 mg (0.280 mmol) of DEPBT in 571 mL methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) and reverse phase-HPLC to yield the macrocycle (17.3 mg, 6.4% yield). *R_f*: 0.42 (EtOAc/Hex 1:1) ¹H NMR (400 MHz, CDCl₃): δ 0.75–0.80 (3H, d, *J* 3.5 Hz, CH(CH₃)₂), 0.84–0.89 (3H, d, *J* 3.5 Hz, CH(CH₃)₂), 0.90–1.00 (21H, br m, C(CH₃)₃ and CH(CH₃)₂), 1.08–1.20 (1H, m, CH(CH₃)₂), 1.43–1.50 (2H, m, CH(CH₃)₂), 1.50–1.64 (2H, m, βCH₂), 1.65–1.80 (4H, m, βCH₂), 2.56–2.66 (3H, m, NCH₃), 2.98–3.15 (2H, m, βCH₂), 4.15–4.45 (3H, br, NH and 2αCH), 4.88–4.98 (1H, br, NH), 4.99–5.10 (2H, m, αCH Leu-Ox and αCH Phe), 6.93–7.03 (1H, m, Ph), 7.33–7.38 (4H, m, Ph), 8.15 (1H, s, OCH=C). LCMS: *m/z* calcd for C₃₁H₄₅N₅O₅ (M)=567.72, found 567.8; HRMS (ESI-TOF): MH⁺, found 568.3520, C₃₁H₄₅N₅O₅ requires 568.3493 >90% pure by HPLC.

6.24. Synthesis of compound 5 (C-Ox-III)

6.24.1. Dipeptide MeO-Lys(Cbz)-Phe-NHBoc. Dipeptide MeO-Lys(Cbz)-Phe-NHBoc was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 294 mg (1.00 mmol) of amine MeO-Lys(Cbz)-NH₂, 241 mg (0.910 mmol) of acid HO-Phe-NHBoc, 1.30 mL (7.28 mmol) of DIPEA, 235 mg (0.730 mmol) of TBTU, 209 mg (0.550 mmol) of HATU, in 9.00 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the dipeptide (380 mg, 77% yield). *R_f*: 0.37 (EtOAc/Hex 1:1) ¹H NMR (400 MHz, CDCl₃): δ 1.11–1.49 (2H, m, γCH₂ Lys), 1.30–1.36 (9H, s, C(CH₃)₃), 1.36–1.64 (2H, m, δCH₂ Lys), 1.51–1.81 (2H, m, βCH₂ Lys), 2.93–3.03 (2H, m, εCH₂ Lys), 3.03–3.16 (2H, m, βCH₂), 3.60–3.65 (3H, s, OCH₃), 4.21–4.35 (1H, m, αCH), 4.42–4.52 (1H, m, αCH), 4.85–4.93 (1H, br, NH), 5.00–5.05 (2H, s, CH₂Ph), 6.39–6.47 (1H, br, NH), 7.08–7.32 (10H, m, Ph).

6.24.2. Dipeptide MeO-Lys-Cbz-Phe-NH₂. Dipeptide MeO-Lys(Cbz)-Phe-NH₂ was synthesized following the 'General solution-phase amine deprotection'. This dipeptide was taken on to the next reaction without further purification or characterization (309 mg, 100% yield).

6.24.3. Tripeptide MeO-Lys(Cbz)-Phe-D-Phe-N(Me)Boc. Tripeptide MeO-Lys(Cbz)-Phe-D-Phe-N(Me)Boc was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 309 mg (0.700 mmol) of amine MeO-Lys(Cbz)-Phe-NH₂, 215 mg (0.770 mmol) of acid HO-D-Phe-N(Me)Boc, 0.980 mL (4.9 mmol) of DIPEA, 180 mg (0.560 mmol) of TBTU, 133 mg (0.350 mmol) of HATU, in 7.00 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the tripeptide (454 mg, 93% yield). *R_f*: 0.38 (EtOAc/Hex 7:13); ¹H NMR (400 MHz, CDCl₃): δ 1.10–1.22 (2H, m, γCH₂ Lys), 1.22–1.30 (9H, s, C(CH₃)₃), 1.35–1.48 (2H, m, δCH₂ Lys), 1.51–1.83 (2H, m, βCH₂ Lys), 2.51–2.73 (3H, s, NCH₃), 2.82–3.02 (2H, m, βCH₂), 3.02–3.15 (2H, m, CH₂ε Lys), 3.16–3.34 (2H, m, βCH₂), 3.59–3.70 (3H, s, OCH₃), 4.34–4.46 (1H, br, αCH), 4.47–4.68 (2H, m, 2αCH), 4.98–5.08 (2H, s, CH₂Ph), 6.22–6.61 (2H, br m, NH), 6.98–7.34 (15H, m, Ph).

6.24.4. Tripeptide HO-Lys(Cbz)-Phe-D-Phe-N(Me)Boc. Tripeptide HO-Lys(Cbz)-Phe-D-Phe-N(Me)Boc was synthesized following the 'General solution-phase acid deprotection'. This tripeptide was taken

on to the next reaction without further purification or characterization (448 mg, 100% yield).

6.24.5. Dipeptide MeO-Ser(Bzl)-Leu-NHBoc. Dipeptide MeO-Ser(Bzl)-Leu-NHBoc was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 383 mg (1.83 mmol) of amine MeO-Ser(Bzl)-NH₂, 414 mg (1.66 mmol) of acid HO-Leu-NHBoc, 1.20 mL (6.64 mmol) of DIPEA, 588 mg (1.83 mmol) of TBTU, in 17.0 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the dipeptide (701 mg, 100% yield). *R_f*: 0.76 (EtOAc/Hex 1:1). ¹H NMR (400 MHz, CDCl₃): δ 0.95–0.96 (3H, d, *J* 3.5 Hz, CHCH₃), 0.96–0.97 (3H, d, *J* 3.5 Hz, CHCH₃), 1.42–1.46 (9H, s, C(CH₃)₃), 1.61–1.63 (1H, m, CH(CH₃)₂), 1.63–1.78 (2H, m, βCH₂), 3.66–3.70 (1H, dd, *J* 7.2, 1.5 Hz, βCH Ser), 3.73–3.76 (3H, s, OCH₃), 3.88–3.92 (1H, dd, *J* 7.9, 1.5 Hz, βCH), 4.14–4.21 (1H, br, αCH), 4.46–4.59 (2H, m, CH₂OBn), 4.72–4.76 (1H, m, αCH), 4.84–4.91 (1H, br, NH), 6.76–6.80 (1H, br, NH), 7.26–7.40 (5H, m, Ph).

6.24.6. Dipeptide MeO-Ser-Leu-NHBoc. Dipeptide MeO-Ser-Leu-NHBoc was synthesized by dissolving 701 mg (1.66 mmol) of dipeptide MeO-Ser(Bzl)-Leu-NHBoc in 4.00 mL EtOH (0.48 M). The reaction mixture was hydrogenated using a catalytic amount of Pd/C and excess H₂ for 24 h. The reaction was filtered over Celite to yield pure dipeptide (521 mg, 95% yield). *R_f*: 0.28 (EtOAc/Hex 1:1).

6.24.7. Dipeptide MeO-Oxazole-Leu-NHBoc. Dipeptide MeO-Oxazole-Leu-NHBoc was synthesized following the 'General oxazole synthesis' procedure. The oxazoline intermediate was synthesized utilizing 421 mg (1.27 mmol) of dipeptide MeO-Ser-Leu-NHBoc, 0.170 mL (1.40 mmol) of DAST, 351 mg (2.54 mmol) of K₂CO₃ in 12.7 mL of methylene chloride. The resulting oxazoline was oxidized utilizing 0.380 mL (2.54 mmol) of DBU, 0.250 mL (2.54 mmol) of CBrCl₃ in 12.7 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the desired peptidyl-oxazole (298 mg, 76% yield over two steps). *R_f*: 0.5 (EtOAc/Hex 7:13); ¹H NMR (400 MHz, CDCl₃): δ 0.94–0.96 (3H, d, *J* 3.5 Hz, CHCH₃), 0.96–0.98 (3H, d, *J* 3.5 Hz, CHCH₃), 1.42–1.46 (9H, s, C(CH₃)₃), 1.58–1.64 (1H, m, CH(CH₃)₂), 1.64–1.80 (2H, m, βCH₂), 3.93 (3H, s, OCH₃), 4.94–5.04 (1H, br, αCH), 5.04–5.10 (1H, br, NH), 8.18 (1H, s, OCH=C).

6.24.8. Dipeptide MeO-Oxazole-Leu-NH₂. Dipeptide MeO-Oxazole-Leu-NH₂ was synthesized following the 'General solution-phase amine deprotection'. This dipeptide was taken on to the next reaction without further purification or characterization (202 mg, 100% yield).

6.24.9. Pentapeptide MeO-Oxazole-Leu-Lys(Cbz)-Phe-D-Phe-N(Me)Boc. Pentapeptide MeO-Oxazole-Leu-Lys(Cbz)-Phe-D-Phe-N(Me)Boc was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 152 mg (0.720 mmol) of amine MeO-Oxazole-Leu-NH₂, 447 mg (0.650 mmol) of acid HO-Lys(Cbz)-Phe-D-Phe-N(Me)Boc, 0.910 mL (5.2 mmol) of DIPEA, 167 mg (0.520 mmol) of TBTU, 148 mg (0.390 mmol) of HATU in 7.00 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the pentapeptide (274 mg, 48% yield). *R_f*: 0.2 (EtOAc/Hex 1:1) ¹H NMR (400 MHz, CDCl₃): δ 0.78–0.92 (6H, m, CH(CH₃)₂), 1.10–1.31 (2H, m, γCH₂ Lys), 1.23–1.27 (9H, s, C(CH₃)₃), 1.33–1.48 (2H, m, δCH₂ Lys), 1.48–1.60 (2H, m, βCH₂ Lys), 1.64–1.87 (3H, m, CH(CH₃)₂, CH₂β Leu), 2.35 (3H, m, NCH₃), 2.85–3.05 (2H, m, βCH₂), 3.05–3.19 (2H, m, εCH₂ Lys), 3.19–3.32 (2H, m, βCH₂), 3.75 (3H, s, OCH₃), 4.21–4.43 (1H, br, αCH), 4.33–4.55 (1H, br, αCH), 4.46–4.70 (1H, m, αCH), 4.95–5.06 (2H, m, CH₂Ph), 5.06–5.26 (2H, m, αCH, NH), 6.28–6.78 (2H, m, NH),

6.91–7.44 (15H, m, Ph), 8.09 (1H, s, OCH=C). LCMS: *m/z* calcd for C₄₈H₆₂N₆O₁₀ (M)=883.04, found 883.

6.24.10. Macrocycle Phe-D-Phe-N(Me)-Oxazole-Leu-Lys(Cbz) (5). Macrocycle Phe-D-Phe-N(Me)-Oxazole-Leu-Lys(Cbz) (5) was synthesized following the 'Macrocyclization procedure'. Utilizing 238 mg (0.310 mmol) of linear pentapeptide, 0.430 mL (2.48 mmol) of DIPEA, 80.0 mg (0.250 mmol) of TBTU, 95.0 mg (0.250 mmol) HATU, and 75.0 mg (0.250 mmol) of DEPBT in 44.3 mL methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) and reverse phase-HPLC to yield the macrocycle (19.8 mg, 8.5% yield). *R_f*: 0.18 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CDCl₃): δ 0.82–0.88 (3H, d, *J* 15.7 Hz, CH(CH₃)₂), 0.89–0.94 (3H, d, *J* 15.7 Hz, CH(CH₃)₂), 1.03–1.19 (2H, br, γCH₂ Lys), 1.33–1.58 (2H, m, δCH₂ Lys), 1.58–1.70 (2H, m, βCH₂ Lys), 1.86–2.03 (2H, m, βCH₂), 2.17–2.33 (1H, m, CH(CH₃)₂), 2.62–2.67 (3H, s, NCH₃), 2.82–3.21 (2H, m, βCH₂), 3.01–3.11 (2H, m, εCH₂ Lys), 3.35–3.44 (1H, dd, *J* 8.85, 2.92 Hz, CH_αH_β Phe), 3.46–3.56 (1H, br, αCH), 4.58–4.65 (1H, dd, *J* 8.85, 2.94 Hz, βCH_αH_β Phe), 4.65–4.78 (2H, m, 2αCH), 5.01–5.06 (2H, m, CH₂Ph), 5.14–5.24 (1H, m, αCH), 6.76–6.93 (3H, m, NH), 7.07–7.33 (15H, m, Ph), 8.00–8.08 (1H, s, OCH=C). LCMS: *m/z* calcd for C₄₂H₅₀N₆O₇ (M)=750.88, found 751; HRMS (ESI-TOF): MH⁺, found 751.3821, C₄₂H₅₀N₆O₇ requires 751.3814 >95% pure by HPLC.

6.25. Synthesis of compound 6 (D-Ox-III)

6.25.1. Dipeptide NH₂-(2R,3R)/(2S,3S)-β-OH-Phe-D-Phe-O-Resin. A mixture of NH₂-D-Phe-O-Resin (2.00 g, 1.44 mmol), (2R,3R)/(2S,3S)-racemic Fmoc-β-OH-Phe-OH (1.74 g, 4.32 mmol), HOBt (661 mg, 4.32 mmol), and DIC (1.34 mL, 8.64 mmol) were stirred at room temperature for 3 h following the 'General solid-phase peptide synthesis' procedure. Completion of the coupling reaction was verified by a negative ninhydrin test. The reaction mixture was then drained to leave the amine-protected resin-bound dipeptide. Deprotection of amine was performed following the 'General solid-phase amine deprotection' procedure. A positive ninhydrin test served to verify Fmoc removal and gave the *title compound*.

6.25.2. Tripeptide Boc-Leu-(2R,3R)/(2S,3S)-β-OH-Phe-D-Phe-OH. A mixture of NH₂-(2R,3R)/(2S,3S)-β-OH-D-Phe-O-Resin (1.44 mmol), Boc-Leu-OH residue (1.00 g, 4.32 mmol), HOBt (661 mg, 4.32 mmol), and DIC (1.34 mL, 8.64 mmol) were stirred at room temperature for 3 h following the 'General solid-phase peptide synthesis' procedure. Completion of the coupling reaction was verified by a negative ninhydrin test. The reaction mixture was then drained and dried in vacuo overnight to leave the amine-protected resin-bound tripeptide. The tripeptide was cleaved from the resin following the 'Cleavage of linear peptide from solid support' procedure. A resin slurry of Boc-Leu-(2R,3R)/(2S,3S)-β-OH-Phe-D-Phe-O-Resin (2.50 g), 2,2,2-trifluoroethanol (12.5 mL) and of methylene chloride (12.5) was stirred for 24 h, after which it was filtered, washed with additional methylene chloride, and dried in vacuo for 24 h (596 mg, 76% yield).

6.25.3. Dipeptide MeO-Ser(Bzl)-D-Leu-NHBoc. A mixture of amine MeO-Ser(Bzl)-NH₂ (709 mg, 3.39 mmol), acid HO-D-Leu-NHBoc (767 mg, 3.08 mmol), DIPEA (4.30 mL, 2.46 mmol), TBTU (1.19 g, 3.94 mmol) in methylene chloride (30.8 mL) was stirred at room temperature under an argon atmosphere for 2.5 h following the 'General solution-phase peptide synthesis' procedure. The crude reaction was purified by column chromatography (20% EtOAc/Hex) to yield the *title compound* (1.24 g, 96% yield). *R_f*: 0.78 (50% EtOAc/Hex); ¹H NMR (200 MHz, CDCl₃): δ 0.9–0.95 (6H, m,

CH(CH₃)₂), 1.43 (9H, s, C(CH₃)₃), 1.63–1.73 (2H, m, CHCH₂CH), 3.65–3.70 (1H, dd, *J* 2.8, 8.9 Hz, OCH_aH_b), 3.73 (3H, s, OCH₃), 3.86–3.91 (1H, dd, *J* 3.0, 9.0 Hz, OCH_aH_b), 4.18–4.26 (1H, br, α CH), 4.45–4.54 (2H, q, *J* 11.9 Hz, CH₂Ph), 4.70–4.75 (1H, m, α CH), 4.95–5.07 (1H, br, NH), 7.01 (1H, br, NH), 7.23–7.36 (5H, m, Ph).

6.25.4. Dipeptide MeO-Ser-D-Leu-NHBoc. A mixture of dipeptide MeO-Ser(Bzl)-D-Leu-NHBoc (1.24 g, 2.94 mmol) and a catalytic amount of Pd/C in ethanol (29.4 mL) was stirred under a hydrogen atmosphere for 24 h. Upon completion, confirmed by TLC, the reaction mixture was filtered over Celite to yield the *title compound* (839 mg, 86% yield), *R*_f: 0.44 (50% EtOAc/Hex). Physical and spectroscopic data are consistent with those reported in the literature.⁴⁷

6.25.5. Dipeptide MeO-Oxazole-D-Leu-NHBoc. Dipeptide MeO-Oxazole-D-Leu-NHBoc was synthesized following the 'General oxazole synthesis' procedure. The oxazoline intermediate was synthesized utilizing dipeptide MeO-Ser-D-Leu-NHBoc (819 mg, 2.46 mmol), DAST (357 μ L, 2.71 mmol), K₂CO₃ (664 mg, 4.92 mmol) in methylene chloride (24.6 mL). The resulting oxazoline was oxidized utilizing DBU (746 μ L, 4.92 mmol), CBrCl₃ (489 μ L, 4.92 mmol) in methylene chloride (12.3 mL). The crude reaction was purified by column chromatography (40% EtOAc/Hex) to yield the desired *title compound* (516 mg, 70% yield over two steps). *R*_f: 0.80 (50% EtOAc/Hex); ¹H NMR (200 MHz, CDCl₃): δ 0.86 (3H, d, *J* 1.6 Hz, CHCH₃), 0.87 (3H, d, *J* 1.8 Hz, CHCH₃), 1.35 (9H, s, C(CH₃)₃), 1.53–1.61 (1H, m, CH(CH₃)₂), 1.63–1.71 (2H, m, CHCH₂CH), 3.83 (3H, s, OCH₃), 4.87–4.95 (1H, br, α CH), 5.08–5.14 (1H, br, NH), 8.11 (1H, s, CCHO).

6.25.6. Dipeptide MeO-Oxazole-D-Leu-NH₂. A mixture of peptidyl MeO-Oxazole-D-Leu-NHBoc (516 mg, 1.65 mmol) in TFA (3.30 mL) and methylene chloride (13.2 mL) was stirred at room temperature under open atmosphere for 30 min following the 'General solution-phase amine deprotection'. Reaction completion was confirmed by TLC and the mixture was concentrated in vacuo with several washes with methylene chloride. This dipeptide was taken on to the next reaction without further purification or characterization (350 mg, quantitative yield).

6.25.7. Pentapeptide MeO-Oxazole-D-Leu-D-Phe-(2R,3R)/(2S,3S)- β -OH-Leu-NHBoc. A mixture of amine MeO-Oxazole-D-Leu-NH₂ (257 mg, 1.21 mmol), acid Boc-Leu-(2R,3R)/(2S,3S)- β -OH-Phe-D-Phe-OH (596 mg, 1.1 mmol), TBTU (424 mg, 1.32 mmol), HATU (301 mg, 7.92 mmol), and DIPEA (2.11 mL, 12.1 mmol) in methylene chloride (12.1 mL) was stirred at room temperature under an argon atmosphere for 3 h following the 'General solution-phase peptide synthesis' procedure. Upon completion, confirmed by TLC, the reaction mixture was diluted with methylene chloride (200 mL), quenched by the addition of 10% hydrochloric acid solution (200 mL), and further washed with sodium bicarbonate solution (500 mL, satd aq) and then brine (200 mL). The organic layer was dried (Na₂SO₄) and the solvent was evaporated in vacuo. The crude reaction was purified by column chromatography (90% EtOAc/Hex) to yield the *title compound* (490 mg, 61% yield). *R*_f: 0.40 (50% EtOAc/Hex); ¹H NMR (400 MHz, CDCl₃): δ 0.76–0.81 (9H, m, 3CHCH₃), 0.84 (3H, d, *J* 4.0 Hz, CHCH₃), 0.89 (6H, d, *J* 3.4 Hz, 2CHCH₃), 0.91 (3H, d, *J* 3.5 Hz, CHCH₃), 1.38–1.42 (4H, m, buried, 2CH(CH₃)₂), 1.39 (9H, s, C(CH₃)₃), 1.40 (9H, s, C(CH₃)₃), 1.63 (2H, m, CHCH₂CH), 1.74 (2H, m, CHCH₂CH), 2.75 (1H, dd, *J* 6.6, 13.9 Hz, PhCH_aH_b), 3.10 (2H, m, PhCH_aH_b), 3.21 (1H, dd, *J* 7.7, 13.8 Hz, PhCH_aH_b), 3.63 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 4.53 (1H, m, α CH), 4.63 (2H, m, 2 α H), 4.80 (1H, m, α CH), 4.88 (1H, m, α CH), 4.99 (2H, m, 2 α CH), 5.20 (1H, q, *J* 7.8 Hz, CHO), 5.30 (1H, q, *J* 7.9 Hz, CHO), 6.55 (1H, br, NH), 6.64 (1H, d, *J*

8.8 Hz, NH), 6.95 (2H, m, 2NH), 7.01 (1H, d, *J* 8.5 Hz, NH), 7.07 (1H, d, *J* 6.1 Hz, NH), 7.12–7.18 (6H, m, 4CCHCH, 2CHCHCH), 7.22–7.34 (10H, m, Ph), 7.4 (4H, m, 4CHCHCH), 7.60 (2H, d, *J* 7.2 Hz, NH), 8.19 (2H, s, CCHO). LCMS (ESI): *m/z* called for C₃₉H₅₃N₅O₉ (M⁺)=735.4, found 735.8.

6.25.8. Deprotected pentapeptide HO-Oxazole-D-Leu-D-Phe-(2R,3R)/(2S,3S)- β -OH-Leu-NH₂. A mixture of pentapeptide MeO-Oxazole-D-Leu-D-Phe-(2R,3R)/(2S,3S)- β -OH-Leu-NHBoc (100 mg, 0.136 mmol), lithium hydroxide (17.0 mg, 0.408 mmol), and 30% hydrogen peroxide (14.0 μ L) in methanol (340 μ L) was stirred at room temperature under open atmosphere for 12 h following the 'General solution-phase acid deprotection'. Upon completion, the reaction was diluted with methylene chloride (50 mL) and quenched with sodium thiosulfate (154 mg) in pH 1 hydrochloric acid solution (200 mL). The organic layer was separated and the aqueous layer was back extracted with ethyl acetate. The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to yield the deprotected acid HO-Oxazole-D-Leu-D-Phe-(2R,3R)/(2S,3S)- β -OH-Leu-NHBoc. Deprotection of the amine resulted from a mixture of acid HO-Oxazole-D-Leu-D-Phe-(2R,3R)/(2S,3S)- β -OH-Leu-NHBoc (76.0 mg, 0.105 mmol), anisole (23.0 μ L, 0.211 mmol) in TFA (211 μ L) and methylene chloride (842 μ L) stirred at room temperature for 40 min under open atmosphere following the 'General solution-phase amine deprotection'. Reaction completion was confirmed by TLC and the mixture was concentrated in vacuo with several washes with methylene chloride. This deprotected pentapeptide HO-Oxazole-D-Leu-D-Phe-(2R,3R)/(2S,3S)- β -OH-Leu-NH₂ was taken on to the next reaction without further purification or characterization (65.0 mg, 77% yield over two steps). LCMS (ESI): *m/z* called for C₃₃H₄₃N₅O₇ (M+2H⁺)=623.7, found 623.8.

6.25.9. Macrocycle (2R,3R)- β -benzoxy-Phe-Leu-Oxazole-D-Leu-D-Phe (6). A mixture of TBTU (41.0 mg, 0.126 mmol), HATU (36.0 mg, 0.948 μ mol), and DIPEA (147 μ L, 0.842 mmol) in methylene chloride (6.77 mL) and acetonitrile (4.53 mL) stirred at room temperature in a round bottom flask under an argon atmosphere following the 'Macrocyclization procedure'. The deprotected pentapeptide HO-Oxazole-D-Leu-D-Phe-(2R,3R)/(2S,3S)- β -OH-Leu-NH₂ (65.0 mg, 0.105 mmol) was dissolved in methylene chloride (2.26 mL) and acetonitrile (1.49 mL) and added to the reaction flask via syringe pump at the rate of 15 mL/h. After 12 h, the reaction was diluted with methylene chloride (200 mL) and quenched with ammonium chloride solution (200 mL, satd aq). The organic layer was separated, dried (Na₂SO₄), and concentrated in vacuo. The crude reaction was semi-purified by reverse phase-HPLC to yield the macrocycle (2R,3R)/(2S,3S)- β -OH-Phe-Leu-Oxazole-D-Leu-D-Phe (19 mg, 29% yield). *R*_f: 0.2 (65% EtOAc/Hex); LCMS: *m/z* called for C₃₃H₄₁N₅O₆ (M+1)=604.7, found 603.9. Finally, a mixture of macrocycle (2R,3R)- β -benzoxy-Phe-Leu-Oxazole-D-Leu-D-Phe (18.0 mg, 0.298 μ mol), NaH (1.50 mg, 0.596 μ mol), and benzyl bromide (14.0 μ L, 0.0119 mmol) in THF (1.19 mL) stirred at room temperature for 12 h under an atmosphere of argon following the 'Benzylation procedure'. The crude reaction was purified by reverse phase-HPLC to yield the *title compound 6* (1.0 mg, 0.4%); stereochemistry was assigned previously.¹ *R*_f: 0.40 (65% EtOAc/Hex); >90% pure by HPLC ¹H NMR (600 MHz, CD₃OD): δ 0.79 (3H, d, *J* 6.6 Hz, CHCH₃), 0.82 (3H, d, *J* 6.5 Hz, CHCH₃), 0.90 (3H, d, *J* 6.4 Hz, CHCH₃), 1.05 (3H, d, *J* 6.6 Hz, CHCH₃), 1.27–1.34 (2H, m, 2CH(CH₃)₂), 1.57–1.63 (4H, m, 2CH₂CH), 3.19 (1H, m, CH_aH_bPh), 3.43 (1H, m, CH_aH_bPh), 3.75–3.80 (2H, m, OCH₂Ph), 4.34–4.38 (2H, m, 2 α CH), 4.70 (1H, d, *J* 5.3 Hz, α CH), 4.83 (1H, m, α CH), 5.06 (1H, d, *J* 5.2 Hz, PhCHO), 6.81 (1H, d, *J* 8.7 Hz, NH), 7.14–7.34 (10H, m, 2Ph), 7.37–7.47 (5H, m, Ph), 7.58 (1H, d, *J* 4.3 Hz, NH), 7.59 (1H, d, *J* 4.7 Hz, NH), 8.42 (1H, s, CCHO), 8.52 (1H, m, NH), 8.77 (1H, m, NH). LCMS: *m/z* called for C₄₀H₄₇N₅O₆

(M+1)=694.8, found 694.4; HRMS (ESI-TOF): MH⁺, found 694.3592, C₄₀H₄₇N₅O₆ requires 694.3599.

6.26. Synthesis of compound 7 (D-Ox-II)

6.26.1. Dipeptide NH₂-D-Phe-D-Leu-O-Resin. A mixture of NH₂-D-Leu-O-Resin (1.50 g, 1.10 mmol), Fmoc-D-Phe-OH (1.27 g, 3.29 mmol), HOBt (503 mg, 3.29 mmol), and DIC (1.02 mL, 6.57 mmol) were stirred at room temperature for 3 h following the 'General solid-phase peptide synthesis' procedure. Completion of the coupling reaction was verified by a negative ninhydrin test. The reaction mixture was then drained to leave the amine-protected resin-bound dipeptide. Deprotection of amine was performed following the 'General solid-phase amine deprotection' procedure. A positive ninhydrin test served to verify Fmoc removal and gave the *title compound*.

6.26.2. Tripeptide Boc-(2R,3R)/(2S,3S)-β-OH-Phe-D-Phe-D-Leu-OH. A mixture of NH₂-D-Phe-D-Leu-O-Resin (1.10 mmol), (2R,3R)/(2S,3S)-racemic Boc-β-OH-Phe-OH residue (923 mg, 3.29 mmol), HOBt (503 mg, 3.29 mmol), and DIC (1.02 mL, 6.57 mmol) were stirred at room temperature for 3 h following the 'General solid-phase peptide synthesis' procedure. Completion of the coupling reaction was verified by a negative ninhydrin test. The reaction mixture was then drained and dried in vacuo overnight to leave the amine-protected resin-bound tripeptide. The tripeptide was cleaved from the resin following the 'Cleavage of linear peptide from solid support' procedure. A resin slurry of Boc-(2R,3R)/(2S,3S)-β-OH-Phe-D-Phe-D-Leu-O-Resin (2.07 g), 2,2,2-trifluoroethanol (10.3 mL), and of methylene chloride (10.3) was stirred for 24 h, after which it was filtered, washed with additional methylene chloride, and dried in vacuo for 24 h to yield the *title compound* (534 mg, 90% yield).

6.26.3. Dipeptide MeO-Ser(Bzl)-Val-N(Me)Boc. A mixture of amine MeO-Ser(Bzl)-NH₂ (709 mg, 3.39 mmol), acid HO-Val-N(Me)-Boc (712 mg, 3.09 mmol), DIPEA (5.16 mL, 2.46 mmol), TBTU (1.19 g, 3.69 mmol) in methylene chloride (30.8 mL) was stirred at room temperature under an argon atmosphere for 2.5 h following the 'General solution-phase peptide synthesis' procedure. The crude reaction was purified by column chromatography (20% EtOAc/Hex) to yield the *title compound* (1.22 g, 97% yield). *R*_f: 0.80 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CDCl₃): δ 0.82 (3H, d, *J* 6.7 Hz, CHCH₃), 0.95 (3H, d, *J* 6.1 Hz, CHCH₃), 1.41 (9H, s, C(CH₃)₃), 2.19–2.30 (1H, m, CH(CH₃)₂), 2.74 (3H, s, NCH₃), 3.58–3.62 (1H, dd, *J* 3.6, 9.4 Hz, CHCH₂H₂O), 3.70 (3H, s, OCH₃), 4.10 (1H, br, αCH), 3.77–3.82 (1H, d, *J* 7.7 Hz, CHCH₂H₂O), 4.40–4.56 (2H, q, *J* 13.0 Hz, CH₂Ph), 4.67 (1H, m, αCH), 6.93 (1H, br, NH), 7.20–7.30 (5H, m, Ph).

6.26.4. Dipeptide MeO-Ser-Val-N(Me)Boc. A mixture of dipeptide MeO-Ser(Bzl)-Val-N(Me)-Boc (1.22 g, 3.01 mmol) and a catalytic amount of Pd/C in ethanol (30.1 mL) was stirred under a hydrogen atmosphere for 24 h. Upon completion, confirmed by TLC, the reaction mixture was filtered over Celite to yield the *title compound* (723 mg, 75% yield). *R*_f: 0.5 (EtOAc/Hex 1:1). Physical and spectroscopic data are consistent with those reported in the literature.⁴⁸

6.26.5. Dipeptide MeO-Oxazole-Val-N(Me)Boc. Dipeptide MeO-Oxazole-Val-N(Me)-Boc was synthesized following the 'General oxazole synthesis' procedure. The oxazoline intermediate was synthesized utilizing dipeptide MeO-Ser-Val-N(Me)-Boc (700 mg, 2.11 mmol), DAST (306 μL, 2.32 mmol), K₂CO₃ (569 mg, 4.21 mmol) in methylene chloride (21.1 mL). The resulting oxazoline was oxidized utilizing DBU (420 μL, 4.21 mmol), CBrCl₃ (420 μL, 4.21 mmol) in methylene chloride (21.1 mL). The crude reaction was purified by column chromatography (40% EtOAc/Hex) to yield

the desired *title compound* (494 mg, 75% yield over two steps). *R*_f: 0.82 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CDCl₃): δ 0.87 (3H, d, *J* 6.7 Hz, CHCH₃), 0.93 (3H, d, *J* 5.6 Hz, CHCH₃), 1.43 (9H, s, C(CH₃)₃), 2.41–2.52 (1H, m, CH(CH₃)₂), 2.76 (3H, s, NCH₃), 3.40 (1H, s, OH), 3.84 (3H, s, OCH₃), 4.86 (1H, d, *J* 10.5 Hz, αCH), 5.12 (1H, d, *J* 10.9 Hz, NH), 8.19 (1H, s, CCHO).

6.26.6. Dipeptide MeO-Oxazole-Val-N(Me)H. A mixture of peptidyl MeO-Oxazole-Val-N(Me)-NBoc (494 mg, 1.58 mmol) in TFA (3.16 mL) and methylene chloride (12.6 mL) was stirred at room temperature under open atmosphere for 30 min following the 'General solution-phase amine deprotection'. Reaction completion was confirmed by TLC and the mixture was concentrated in vacuo with several washes with methylene chloride. This dipeptide was taken on to the next reaction without further purification or characterization (335 mg, quantitative yield).

6.26.7. Pentapeptide MeO-Oxazole-Val-N(Me)-D-Leu-D-Phe-(2R,3R)/(2S,3S)-β-OH-Phe-NHBoc. A mixture of amine MeO-Oxazole-Val-N(Me)H (230 mg, 1.09 mmol), acid Boc-(2R,3R)/(2S,3S)-β-OH-Phe-D-Phe-D-Leu-OH (534 mg, 0.986 mmol), TBTU (189 mg, 0.592 mmol), HATU (375 mg, 0.986 mmol), and DIPEA (1.38 mL, 7.89 mmol) in acetonitrile (9.86 mL) was stirred at room temperature under an argon atmosphere for 1.5 h following the 'General solution-phase peptide synthesis' procedure. Upon completion, confirmed by TLC, the reaction mixture was diluted with ethyl acetate (300 mL), quenched by the addition of 10% hydrochloric acid solution (200 mL), and further washed with sodium bicarbonate solution (500 mL, satd aq) and then brine (200 mL). The organic layer was dried (Na₂SO₄) and the solvent was evaporated in vacuo. The crude reaction was purified by column chromatography (85% EtOAc/Hex) to yield the *title compound* (158 mg, 22% yield). *R*_f: 0.30 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CDCl₃): δ 0.76 (6H, *J* 2.7 Hz, CH(CH₃)₂), 0.78 (6H, *J* 1.7 Hz, CH(CH₃)₂), 0.81–0.79 (6H, *J* 3.5 Hz, CH(CH₃)₂), 0.87–0.83 (6H, m, 2CH(CH₃)₂), 1.14 (9H, s, C(CH₃)₃), 1.22 (9H, s, C(CH₃)₃), 1.32–1.44 (2H, br, CH(CH₃)₂), 2.32–2.44 (4H, m, 2CHCH₂CH), 2.73 (2H, m, CH(CH₃)₂), 2.84–2.90 (6H, m, 2NCH₃), 3.78 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 3.82 (4H, br, 2CH₂Ph), 4.09–4.21 (2H, m, 2αCH), 4.44–4.52 (1H, q, *J* 6.4 Hz, αCH), 4.51–4.65 (1H, m, αCH), 4.78 (2H, br, 2αCH), 4.86 (1H, m, αCH), 4.90 (1H, m, αCH), 5.32 (1H, d, *J* 8.6 Hz, CHOH), 5.42 (1H, t, *J* 12.3 Hz, CHOH), 6.00 (2H, d, *J* 6.7 Hz, 2NH), 6.59 (2H, d, *J* 8.4 Hz, 2NH), 6.83–6.87 (2H, m, 2NH), 7.02–7.32 (20H, m, 4Ph), 8.05 (1H, s, CCHO), 8.10 (1H, s, CCHO).

6.26.8. Deprotected pentapeptide HO-Oxazole-Val-N(Me)-D-Leu-D-Phe-(2R,3R)/(2S,3S)-β-OH-Phe-NH₂. A mixture of pentapeptide MeO-Oxazole-Val-N(Me)-D-Leu-D-Phe-(2R,3R)/(2S,3S)-β-OH-Phe-NHBoc (158 mg, 0.215 mmol), lithium hydroxide (18.0 mg, 0.429 mmol), and 30% hydrogen peroxide (70.0 μL) in water (134 μL) and THF (403 μL) was stirred at room temperature under open atmosphere for 3 h following the 'General solution-phase acid deprotection'. Upon completion, the reaction was diluted with ether (100 mL) and quenched with sodium thiosulfate (175 mg) in pH 1 hydrochloric acid solution (200 mL). The organic layer was separated and the aqueous layer was back extracted with ether (240 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo to yield the deprotected acid HO-Oxazole-D-Leu-D-Phe-(2R,3R)/(2S,3S)-β-OH-Phe-NHBoc. Deprotection of the amine resulted from a mixture of acid HO-Oxazole-D-Leu-D-Phe-(2R,3R)/(2S,3S)-β-OH-Phe-NHBoc (155 mg, 0.215 mmol), anisole (50.0 μL, 0.429 mmol) in TFA (537 μL) and methylene chloride (1.61 mL) stirred at room temperature for 40 min under open atmosphere following the 'General solution-phase amine deprotection'. Reaction completion was confirmed by TLC and the mixture was concentrated in vacuo with several washes with methylene

chloride. This deprotected pentapeptide HO-Oxazole-Val-N(Me)-D-Leu-D-Phe-(2R,3R)/(2S,3S)- β -OH-Phe-NH₂ was taken on to the next reaction without further purification or characterization (135 mg, quantitative yield). LCMS (ESI): *m/z* called for C₃₃H₄₃N₅O₇ (M+H⁺)=621.7, found 621.8.

6.26.9. Macrocycle (2R,3R)- β -benzoxy-Phe-Oxazole-Val-N(Me)-D-Leu-D-Phe (7). A mixture of TBTU (69.0 mg, 0.215 mmol), HATU (82.0 mg, 0.215 μ mol), and DIPEA (375 μ L, 2.15 mmol) in methylene chloride (7.70 mL) and acetonitrile (7.70 mL) stirred at room temperature in a round bottom flask under an argon atmosphere following the 'Macrocyclization procedure'. The deprotected pentapeptide HO-Oxazole-Val-N(Me)-D-Leu-D-Phe-(2R,3R)/(2S,3S)- β -OH-Phe-NH₂ (134 mg, 0.215 mmol) was dissolved in methylene chloride (7.7 mL) and acetonitrile (7.7 mL) and added to the reaction flask via syringe pump at the rate of 15 mL/h. After 12 h, the reaction was diluted with ethyl acetate (500 mL), quenched with pH 1 hydrochloric acid solution (200 mL, satd aq), washed with sodium bicarbonate solution (200 mL, satd aq), and then brine (200 mL). The organic layer was separated, dried (Na₂SO₄), and concentrate in vacuo. The crude reaction was semi-purified by reverse phase-HPLC to yield the macrocycle (2R,3R)- β -OH-Phe-Oxazole-Val-N(Me)-D-Leu-D-Phe (29 mg, 23% yield). *R_f*: 0.21 (65% EtOAc/Hex); LCMS: *m/z* called for C₃₃H₄₁N₅O₆ (M+1)=604.7, found 604.3. Finally, a mixture of macrocycle (2R,3R)- β -OH-Phe-Oxazole-Val-N(Me)-D-Leu-D-Phe (18.0 mg, 0.298 μ mol), NaH (1.50 mg, 0.596 μ mol), and benzyl bromide (14.0 μ L, 0.0119 mmol) in THF (1.19 mL) stirred at room temperature for 12 h under an atmosphere of argon following the 'Benzylation procedure'. The crude reaction was purified by reverse phase-HPLC to yield the *title compound 7* (1.3 mg, 0.6%); stereochemistry was assigned previously.¹ *R_f*: 0.37 (65% EtOAc/Hex); >90% pure by HPLC ¹H NMR (600 MHz, CD₃OD): δ 0.79 (3H, d, *J* 6.7 Hz, CHCH₃), 0.82 (3H, d, *J* 6.4 Hz, CHCH₃), 1.04 (3H, d, *J* 6.8 Hz, CHCH₃), 1.37 (3H, d, *J* 7.3 Hz, CHCH₃), 1.49 (1H, m, CH(CH₃)₂), 1.93 (2H, m, CH₂CH), 2.92 (1H, m, CH(CH₃)₂), 3.18 (1H, m, CH₂H_bPh), 3.32 (3H, s, NCH₃), 3.42 (1H, m, CH₂H_bPh), 3.74 (2H, m, OCH₂Ph), 4.69 (1H, d, *J* 5.6 Hz, OCH), 4.90 (1H, m, α CH), 5.04 (1H, m, α CH), 6.64 (1H, m, α CH), 6.81 (1H, m, α CH), 7.12–7.20 (5H, m, CH₂Ph), 7.23–7.31 (10H, m, 2Ph), 7.43 (1H, d, *J* 8.8 Hz, NH), 7.71 (1H, d, *J* 8.8 Hz, 1H, NH), 8.41 (1H, s, CCHO), 8.70 (1H, d, *J* 10.3 Hz, NH). LCMS: *m/z* called for C₄₀H₄₇N₅O₆ (M+1)=694.8, found 694.0; HRMS (ESI-TOF): MH⁺, found 694.3570, C₄₀H₄₇N₅O₆ requires 694.3599.

6.27. Synthesis of compound 8 (D-Ox-I)

6.27.1. Dipeptide NH(Me)-Val-Leu-O-Resin. Dipeptide Fmoc-N(Me)-Val-Leu-O-Resin was synthesized following the 'General solid-phase peptide synthesis' procedure. Using 1.01 g (0.815 mmol) of NH₂-Leu-O-Resin, the residue N(Me)-Val residue was incorporated using 864 mg of Fmoc-N(Me)-Val-OH (2.44 mmol), 374 mg (2.44 mmol, 3 equiv) of HOBt, and 0.756 mL (4.88 mmol) of DIC. Completion of the coupling reaction was verified by a negative ninhydrin test. The reaction mixture was then drained to leave the amine-protected resin-bound dipeptide. Deprotection of amine was performed following the 'General solid-phase amine deprotection' procedure. A positive ninhydrin test served to verify Fmoc removal and gave the *title compound*.

6.27.2. Tripeptide NH₂-D-Leu-N(Me)-Val-Leu-O-Resin. Tripeptide Fmoc-D-Leu-N(Me)-Val-Leu-O-resin was synthesized following the 'General solid-phase peptide synthesis' procedure. Using the NH(Me)-Val-Leu-O-Resin prepared above, the D-Leu residue was incorporated using 864 mg (2.44 mmol) of Fmoc-D-Leu-OH, 374 mg (2.44 mmol) of HOAt, and 0.756 mL (4.88 mmol) of DIC. Completion of the coupling reaction was verified by a negative ninhydrin test.

The reaction mixture was then drained to leave the amine-protected resin-bound tripeptide. Deprotection of amine was performed following the 'General solid-phase amine deprotection' procedure. A positive ninhydrin test served to verify Fmoc removal and gave the *title compound*.

6.27.3. Tetrapeptide NH₂-D-Phe-D-Leu-N(Me)-Val-Leu-O-Resin. Tetrapeptide Fmoc-D-Phe-D-Leu-N(Me)-Val-Leu-O-Resin was synthesized following the 'General solid-phase peptide synthesis' procedure. Using the NH₂-D-Leu-N(Me)-Val-Leu-O-Resin prepared above, the D-Phe residue was incorporated using 947 mg (2.44 mmol) of Fmoc-D-Phe-OH, 374 mg (2.44 mmol) of HOBt, and 0.756 mL of DIC (4.88 mmol). Completion of the coupling reaction was verified by a negative ninhydrin test. The reaction mixture was then drained to leave the amine-protected resin-bound tetrapeptide. Deprotection of amine was performed following the 'General solid-phase amine deprotection' procedure. A positive ninhydrin test served to verify Fmoc removal and gave the *title compound*.

6.27.4. Pentapeptide NH₂- β -OH(2R,3R)(2S,3S)-Phe-D-Phe-D-Leu-N(Me)-Val-Leu-O-Resin. Pentapeptide Fmoc- β -OH(2R,3R)(2S,3S)-Phe-D-Phe-D-Leu-N(Me)-Val-Leu-O-Resin was synthesized following the 'General solid-phase peptide synthesis' procedure. Using the NH₂-D-Phe-D-Leu-N(Me)-Val-Leu-O-Resin prepared above, the β -OH(2R,3R)(2S,3S)-Phe residue was incorporated using 657 mg (1.63 mmol) of Fmoc- β -OH(2R,3R)(2S,3S)-Phe-OH, 374 mg (2.44 mmol) of HOBt, 0.756 mL of DIC (4.88 mmol). Completion of the coupling reaction was verified by a negative ninhydrin test. The reaction mixture was then drained to leave the amine-protected resin-bound pentapeptide. Deprotection of amine was performed following the 'General solid-phase amine deprotection' procedure. A positive ninhydrin test served to verify Fmoc removal and gave the *title compound*.

6.27.5. Double deprotected pentapeptide NH₂- β -OH(2R,3R)(2S,3S)-Phe-D-Phe-D-Leu-N(Me)-Val-Leu-OH. Double deprotected pentapeptide NH₂- β -OH(2R,3R)(2S,3S)-Phe-D-Phe-D-Leu-N(Me)-Val-Leu-OH was synthesized following the 'Cleavage of linear peptide from solid support' procedure. Utilizing the 1.32 g of dried NH₂- β -OH(2R,3R)(2S,3S)-Phe-D-Phe-D-Leu-N(Me)-Val-Leu-O-Resin, 6.59 mL of 2,2,2-trifluoroethanol and 6.59 mL of methylene chloride. The resin slurry was stirred for 24 h, after which it was filtered, washed with additional methylene chloride, and dried in vacuo for 24 h (242 mg, 45% yield).

6.27.6. Macrocycle β -OH(2R,3R)(2S,3S)-Phe-D-Phe-D-Leu-N(Me)-Val-Leu (8). Macrocycle β -OH(2R,3R)(2S,3S)-Phe-D-Phe-D-Leu-N(Me)-Val-Leu was synthesized following the 'Macrocyclization procedure'. Utilizing 242 mg (0.363 mmol) of linear pentapeptide, 0.580 mL (3.63 mmol) of DIPEA, 109 mg (0.338 mmol) of TBTU, 128 mg (0.338 mmol) HATU, and 58.0 mg (0.193 mmol) of DEPBT. The crude reaction was purified by reverse phase-HPLC to yield the macrocycle (69.0 mg, 29% yield). ¹H NMR (600 MHz, CD₃OD): δ 0.84 (3H, d, *J* 6.7 Hz, CHCH₃), 0.85 (12H, dd, *J* 8.4, 6.7 Hz CHCH₃), 0.93 (3H, d, *J* 6.7 Hz, CHCH₃), 1.42–1.51 (2H, m, CH₂CH(CH₃)₂), 1.74 (2H, m, CHCH₂CH), 1.81 (2H, m, CHCH₂CH), 2.05 (1H, m, CHCH(CH₃)₂), 2.83 (3H, s, NCH₃), 3.02 (1H, m, CHCH₂C), 3.11 (1H, m, CHCH₂C), 3.85 (1H, m, α CH), 4.08 (1H, m, α CH), 4.15 (1H, m, α CH), 4.56 (1H, m, 1H, m, α CH), 4.65 (1H, m, α CH), 4.91 (1H, d, *J* 4.6 Hz, HOCH), 7.01–7.45 (10H, m, Ph). LCMS: *m/z* called for C₃₆H₅₁N₅O₆ (M+1)=649.82, found 650.1.

6.27.7. Macrocycle Phe-Oxazole-D-Phe-D-Leu-N(Me)-Val-Leu (8). Macrocycle Phe-Oxazole-D-Phe-D-Leu-N(Me)-Val-Leu was synthesized following the 'General oxazole synthesis' procedure. The oxazoline intermediate was synthesized utilizing 42.7 mg (66.5 μ mol)

of macrocycle β -OH(2R,3R)-Phe-D-Phe-D-Leu-N(Me)-Val-Leu, 11.2 μ L (72.0 μ mol) of DAST, 11.3 μ L (0.131 mmol) of pyridine in 0.660 mL of methylene chloride. The resulting oxazoline was oxidized utilizing 20.1 μ L (0.130 mmol) of DBU, 0.130 mL (0.130 mmol) of CBrCl_3 in 0.331 mL of methylene chloride. The crude reaction was purified by HPLC to yield the desired Phe-Oxazole-D-Phe-D-Leu-N(Me)-Val-Leu macrocycle (1.30 mg, 3.1% yield over two steps). ^1H NMR (600 MHz, CDCl_3): δ 0.64 (3H, d, J 7.3 Hz CHCH_3), 0.79 (3H, d, J 6.7 Hz CHCH_3), 0.82 (3H, d, J 7.3 Hz CHCH_3), 0.88 (3H, d, J 4.9 Hz CHCH_3), 0.91 (3H, d, J 6.5 Hz CHCH_3), 0.92 (3H, d, J 6.4 Hz CHCH_3), 1.41–1.50 (2H, m, CHCH_2CH), 1.75 (2H, m, CHCH_2CH), 1.86 (1H, m, $\text{CHCH}(\text{CH}_3)_2$), 2.40 (1H, m, $\text{CHCH}(\text{CH}_3)_2$), 2.53 (1H, m, $\text{CHCH}(\text{CH}_3)_2$), 3.04 (1H, m, CHCH_2C), 3.69 (3H, s, NCH_3), 4.09 (1H, m, CHCH_2C), 4.15 (1H, m, αCH), 4.22 (1H, m, αCH), 4.35 (1H, m, αCH), 5.31 (1H, m, αCH), 6.78 (1H, d, J 8.8 Hz, NH), 6.83 (1H, m, NH), 6.95 (1H, d, J 8.8 Hz, NH) 7.01–7.38 (10H, m, Ph) LCMS: m/z called for $\text{C}_{36}\text{H}_{47}\text{N}_5\text{O}_5$ ($M+1$)=629.79, found 630.7; HRMS (ESI-TOF): MH^+ , found 630.3646, $\text{C}_{36}\text{H}_{47}\text{N}_5\text{O}_5$ requires 630.3650 >75% pure by HPLC.

6.28. Synthesis of compound 9 (A-Th-III)

6.28.1. *HO-Pyruvic-Ketal-Br (47)*. HO-Pyruvic-Ketal-Br was synthesized following the 'General bromoketal acid formation' procedure. Utilizing bromopyruvic acid 806 mg (4.86 mmol) and 0.120 mL (0.122 mmol) of sulfuric acid in 1.60 mL (14.6 mmol) of trimethyl orthoformate. This *title compound 47* was taken on to the next reaction without further purification or characterization (700 mg, 67% yield).

6.28.2. *Dipeptide MeO-Phe-Leu-NHBoc*. Dipeptide MeO-Phe-Leu-NHBoc was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 700 mg (3.90 mmol) of amine MeO-Phe-NH₂ (**45**), 886 mg (3.55 mmol) of acid HO-Leu-NHBoc (**44**), 2.50 mL (14.2 mmol) of DIPEA, 1.26 g (3.90 mmol) of TBTU, in 35.5 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the dipeptide (1.44 g, 99% yield). R_f : 0.3 (EtOAc/Hex 1:3); ^1H NMR (400 MHz, CDCl_3): δ 0.78–0.84 (6H, m, $\text{CH}(\text{CH}_3)_2$), 1.30–1.35 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.35–1.40 (1H, m, $\text{CH}(\text{CH}_3)_2$), 1.45–1.60 (2H, m, CHCH_2CH), 2.90–3.05 (2H, m, CHCH_2CH), 3.58–3.60 (3H, d, J 1.8 Hz, OCH_3), 4.00–4.10 (1H, br, αCH), 4.70–4.78 (1H, m, αCH), 5.25–5.35 (1H, br, NH), 6.86–6.96 (1H, m, NH), 7.00–7.20 (5H, m, Ph).

6.28.3. *Dipeptide MeO-Phe-Leu-NH₂ (46)*. Dipeptide MeO-Phe-Leu-NH₂ was synthesized following the 'General solution-phase amine deprotection'. This dipeptide was taken on to the next reaction without further purification or characterization (1.09 g, 100% yield).

6.28.4. *Tripeptide MeO-Phe-Leu-Ketal-Br*. Tripeptide MeO-Phe-Leu-Ketal-Br was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 1.09 g (3.52 mmol) of amine MeO-Phe-Leu-NH₂ (**46**), 688 mg (3.20 mmol) of acid HO-Pyruvic-Ketal-Br (**47**), 2.46 mL (12.8 mmol) of DIPEA, 1.13 g (3.52 mmol) of TBTU, in 35.0 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the tripeptide (1.33 g, 82% yield). R_f : 0.55 (EtOAc/Hex 1:1).

6.28.5. *Tripeptide MeO-Phe-Leu-Ketone-Br (48)*. Tripeptide MeO-D-Phe-Leu-Ketone-Br was synthesized following the 'General ketone deprotection' procedure. Utilizing 507 mg (1.00 mmol) of MeO-Phe-Leu-Ketal-Br in 26.0 mL of formic acid. The reaction mixture was refluxed. This tripeptide was taken on to the next reaction without further purification (405 mg, 92% yield). R_f : 0.56 (EtOAc/Hex 1:1); ^1H NMR (200 MHz, CDCl_3): δ 0.88–0.96 (6H, m, $\text{CH}(\text{CH}_3)_2$), 1.55–1.65 (2H, m, CHCH_2CH), 1.55–1.76 (1H, m, $\text{CH}(\text{CH}_3)_2$),

3.05–3.20 (2H, dq, J 86.5, 14.2, 5.5 Hz, CH_2Phe), 3.78 (3H, s, OCH_3), 4.35–4.45 (1H, m, αCH), 4.39–4.50 (2H, m, CH_2Br), 4.82–4.90 (1H, m, $\alpha\text{CH}\alpha$), 6.32–6.38 (1H, m, NH), 7.04–7.10 (2H, m, Ph), 7.20–7.30 (3H, m, Ph).

6.28.6. *Monomer amide-Leu-NHBoc*. Monomer Amide-Leu-NHBoc was synthesized following the 'General amide formation' procedure. Utilizing 471 mg (1.79 mmol, 1.0 equiv) of MeO-Leu-NHBoc (**49**) in 36.0 mL of ammonium hydroxide and 36.0 mL of methanol. The *title compound* was taken on to the next reaction without further purification (444 mg, 100% yield). R_f : 0.05 (EtOAc/Hex 1:1).

6.28.7. *Monomer thioamide-Leu-NHBoc*. Monomer thioamide-Leu-NHBoc was synthesized following the 'General thioamide formation' procedure. Utilizing 444 mg (1.79 mmol) of amide-Leu-NHBoc and 724 mg (1.79 mmol) of Lawesson's reagent in 12.0 mL of dimethoxyethane. This thioamide was purified by column chromatography (silica gel, EtOAc/DCM) to yield the thioamide-Leu-NHBoc (322 mg, 68% yield). R_f : 0.74 (EtOAc/Hex 1:1).

6.28.8. *Monomer thioamide-Leu-NH₂ (50)*. Monomer thioamide-Leu-NH₂ was synthesized following the 'General solution-phase amine deprotection'. This thioamide-Leu-NH₂ was taken on to the next reaction without further purification or characterization (200 mg, 100% yield).

6.28.9. *Dipeptide thioamide-Leu-Leu-NHBoc (52)*. Dipeptide thioamide-Leu-Leu-NHBoc was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 199 mg (1.22 mmol) of amine thioamide-Leu-NH₂, 274 mg (1.10 mmol) of acid HO-Leu-NHBoc, 0.801 mL (4.40 mmol) of DIPEA, 391 mg (1.22 mmol) of TBTU, in 11.0 mL methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the dipeptide (265 mg, 61% yield). R_f : 0.6 (EtOAc/Hex 1:1); ^1H NMR (400 MHz, CDCl_3): δ 0.90–0.95 (6H, d, J 3.5 Hz, $\text{CH}(\text{CH}_3)_2$), 0.95–1.00 (6H, d, J 3.5 Hz, $\text{CH}(\text{CH}_3)_2$), 1.46 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.62–1.76 (4H, m, CHCH_2CH), 1.76–1.92 (2H, m, $\text{CH}(\text{CH}_3)_2$), 4.02–4.12 (1H, m, αCH), 4.75–4.83 (1H, m, αCH), 4.90–4.98 (1H, d, J 13.3 Hz, NH), 6.70–6.78 (1H, d, J 13.3 Hz, NH), 7.48–7.56 (1H, br, CSNH), 8.04–8.12 (1H, br, CSNH).

6.28.10. *Pentapeptide MeO-Phe-Leu-Thiazole-Leu-Leu-NHBoc (53)*. Pentapeptide MeO-Phe-Leu-Thiazole-Leu-Leu-NHBoc was synthesized following the 'General thiazole synthesis' procedure. Thioamide-Leu-Leu-NHBoc (**52**) 265 mg (0.670 mmol) and 537 mg (5.36 mmol) of potassium bicarbonate were dissolved in 6.00 mL dimethoxyethane. MeO-Phe-Leu-Ketone-Br (**48**) 413 mg (0.940 mmol) was dissolved in 7.50 mL dimethoxyethane and added dropwise to the thioamide mixture to yield thiazoline intermediate. Thiazoline was dehydrated using 0.400 mL (2.68 mmol) of trifluoroacetic acid, 0.490 mL (6.03 mmol) of pyridine, 0.190 mL (1.34 mmol) triethylamine in 13.5 mL dimethoxyethane. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the pentapeptide (71.0 mg, 15% yield). R_f : 0.37 (EtOAc/Hex 2:3); ^1H NMR (400 MHz, CDCl_3): δ 0.86–1.02 (18H, m, $\text{CH}(\text{CH}_3)_2$), 1.46 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.60–1.82 (8H, br m, $3\text{CHCH}_2\text{CH}$ and $2\text{CH}(\text{CH}_3)_2$), 1.88–2.00 (1H, m, $\text{CH}(\text{CH}_3)_2$), 3.02–3.18 (2H, m, CH_2Phe), 3.74 (3H, s, OCH_3), 4.05–4.15 (1H, m, αCH), 4.55–4.62 (1H, m, αCH), 4.80–4.88 (1H, m, αCH), 5.30–5.38 (1H, m, αCH), 6.66–6.70 (1H, d, J 13.3 Hz, NH), 6.74–6.82 (1H, br, NH), 7.05–7.32 (5H, m, Ph), 7.45–7.52 (1H, d, J 13.3 Hz, NH), 8.00 (1H, s, $\text{SCH}=\text{C}$). LCMS: m/z calcd for $\text{C}_{36}\text{H}_{55}\text{N}_5\text{O}_7\text{S}$ ($M+23$)=724.92, found 724.3.

6.28.11. *Macrocycle Phe-Leu-Thiazole-Leu-Leu (9)*. Macrocycle Phe-Leu-Thiazole-Leu-Leu (**9**) was synthesized following the

'*Macrocyclization procedure*'. Utilizing 40.0 mg (70.1 μmol) of linear pentapeptide (**53**), 0.070 μL (0.420 mmol) of DIPEA, 15.5 mg (50.4 μmol , 0.7 equiv) of TBTU, 18.2 mg (50.4 μmol) HATU, and 15.0 mg (50.2 μmol) of DEPBT in 97.6 mL methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) and reverse phase-HPLC to yield the macrocycle (2.30 mg, 6% yield). *R_f*: 0.1 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CD₃OD): δ 0.84–1.05 (18H, m, CH(CH₃)₂), 1.26–1.42 (9H, m, C(CH₃)₃), 1.46–1.85 (8H, m, 3CHCH₂CH and 2CH(CH₃)₂), 1.95–2.05 (1H, m, CH(CH₃)₂), 3.02–3.18 (2H, m, CHCH₂CH), 4.38–4.45 (1H, m, αCH), 4.52–4.55 (1H, m, αCH), 4.80–4.88 (1H, m, αCH), 5.23–5.27 (1H, m, αCH), 7.05–7.32 (5H, m, Ph), 8.03 (1H, s, SCH=C). LCMS: *m/z* calcd for C₃₀H₄₃N₅O₄S (M+1)=570.76, found 570.30; HRMS (ESI-TOF): MH⁺, found 570.3102, requires 570.3108 >95% pure by HPLC.

6.29. Synthesis of compound 10 (B-Th-III)

6.29.1. *Dipeptide MeO-Leu-N(Me)-Phe-NHBoc*. Dipeptide MeO-Leu-N(Me)-Phe-NHBoc was synthesized following the '*General solution-phase peptide synthesis*' procedure. Utilizing 325 mg (2.04 mmol) of amine MeO-Leu-N(Me)H (**58**), 494 mg (1.86 mmol) of acid HO-Phe-NHBoc (**59**), 1.30 mL (7.44 mmol) of DIPEA, 655 mg (2.04 mmol) of TBTU, in 18.6 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the dipeptide (711 mg, 94% yield). *R_f*: 0.79 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CDCl₃): δ 0.88–0.92 (6H, m, CH(CH₃)₂), 1.22–1.25 (1H, m, CH(CH₃)₂), 1.34–1.50 (9H, s, C(CH₃)₃), 1.58–1.74 (3H, m, CHCH₂CH), 2.79–2.82 (3H, s, NCH₃), 2.94–3.14 (2H, m, CH₂Phe), 3.65–3.72 (3H, d, *J* 2.5 Hz, OCH₃), 4.55–4.62 (1H, br, NH), 4.80–4.88 (1H, m, αCH), 4.94–5.00 (1H, br, NH), 5.25–5.32 (1H, m, αCH), 7.10–7.33 (5H, m, Ph).

6.29.2. *Dipeptide MeO-Leu-N(Me)-Phe-NH₂* (**60**). Dipeptide MeO-Leu-N(Me)-Phe-NH₂ was synthesized following the '*General solution-phase amine deprotection*'. This dipeptide was taken on to the next reaction without further purification or characterization (536 mg, 100% yield).

6.29.3. *Tripeptide MeO-Leu-N(Me)-Phe-Leu-NHBoc*. Tripeptide MeO-Leu-N(Me)-Phe-Leu-NHBoc was synthesized following the '*General solution-phase peptide synthesis*' procedure. Utilizing 536 mg (1.75 mmol) of amine MeO-Leu-N(Me)-Phe-NH₂ (**60**), 400 mg (1.60 mmol) of acid HO-Leu-NHBoc (**61**), 1.10 mL (6.40 mmol) of DIPEA, 562 mg (1.75 mmol) of TBTU, in 16.0 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the tripeptide (683 mg, 79% yield). *R_f*: 0.22 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CDCl₃): δ 0.84–0.98 (12H, m, 2CH(CH₃)₂), 1.34–1.42 (2H, m, 2CH(CH₃)₂), 1.42–1.50 (9H, s, C(CH₃)₃), 1.54–1.75 (4H, m, 2CHCH₂CH), 2.79–2.82 (3H, s, NCH₃), 2.94–3.20 (2H, m, CH₂Phe), 3.65–3.72 (3H, s, OCH₃), 4.05–4.15 (1H, br, NH), 4.76–4.84 (1H, br, NH), 4.84–4.88 (1H, m, αCH), 5.10–5.20 (1H, m, αCH), 5.25–5.32 (1H, m, αCH), 7.10–7.33 (5H, m, Ph).

6.29.4. *Tripeptide HO-Leu-N(Me)-Phe-Leu-NHBoc* (**62**). Tripeptide HO-Leu-N(Me)-Phe-Leu-NHBoc was synthesized following the '*General solution-phase acid deprotection*'. This tripeptide was taken on to the next reaction without further purification or characterization (665 mg, 100% yield).

6.29.5. *Monomer amide-Leu-NHBoc*. Monomer amide-Leu-NHBoc was synthesized following the '*General amide formation*' procedure. Utilizing 463 mg (1.76 mmol) of MeO-Leu-NHBoc (**54**) in 35.0 mL of ammonium hydroxide and 35.0 mL of methanol. This amide was

taken on to the next reaction without further purification (437 mg, 100% yield). *R_f*: 0.05 (EtOAc/Hex 1:1).

6.29.6. *Monomer thioamide-Leu-NHBoc* (**55**). Monomer thioamide-Leu-NHBoc was synthesized following the '*General thioamide formation*' procedure. Utilizing 437 mg (1.76 mmol) of amide-Leu-NHBoc and 712 mg (1.76 mmol) of Lawesson's reagent in 12.0 mL of dimethoxyethane. The title compound **55** was purified by column chromatography (silica gel, EtOAc/DCM) to yield the thioamide-Leu-NHBoc (324 mg, 70% yield). *R_f*: 0.74 (EtOAc/Hex 1:1).

6.29.7. *Dipeptide EtO-Thiazole-Leu-NHBoc*. Dipeptide EtO-Thiazole-Leu-NHBoc was synthesized following the '*General thiazole synthesis*' procedure. Thioamide-Leu-NHBoc (**55**) 324 mg (1.23 mmol) and 981 mg (9.80 mmol) of potassium bicarbonate were dissolved in 24.6 mL dimethoxyethane. Ethyl-Br-pyruvate (**56**) 0.310 mL (2.46 mmol) was added dropwise to the thioamide mixture to yield thiazoline intermediate. Thiazoline was dehydrated using 0.680 mL (4.92 mmol) of trifluoroacetic acid, 0.890 mL (11.1 mmol) of pyridine, 0.340 mL (2.46 mmol) triethylamine in 24.6 mL dimethoxyethane. The crude reaction was purified by column chromatography (silica gel, EtOAc/DCM) to yield the pentapeptide (198 mg, 47% yield). *R_f*: 0.47 (EtOAc/Hex 1:3); ¹H NMR (400 MHz, CDCl₃): δ 0.88–0.90 (3H, d, *J* 4.3 Hz, CHCH₃), 0.90–0.92 (3H, d, *J* 4.3 Hz, CHCH₃), 1.29–1.35 (3H, t, OCH₂CH₃), 1.34–1.39 (9H, s, C(CH₃)₃), 1.60–1.74 (1H, m, CH(CH₃)₂), 1.77–1.98 (2H, m, CH₂CH(CH₃)₂), 4.29–4.39 (2H, q, OCH₂CH₃), 4.85–5.14 (1H, br, CONHCH), 7.98–8.00 (1H, s, SCH=C).

6.29.8. *Dipeptide EtO-Thiazole-Leu-NH₂* (**57**). Dipeptide EtO-Thiazole-Leu-NH₂ was synthesized following the '*General amine deprotection*'. This dipeptide was taken on to the next reaction without further purification or characterization (140 mg, 100% yield).

6.29.9. *Pentapeptide EtO-Thiazole-Leu-Leu-N(Me)-Phe-Leu-NHBoc* (**63**). Pentapeptide EtO-Thiazole-Leu-Leu-N(Me)-Phe-Leu-NHBoc was synthesized following the '*General solution-phase peptide synthesis*' procedure. Utilizing 140 mg (0.580 mmol) of amine EtO-Thiazole-Leu-NH₂ (**57**), 276 mg (0.530 mmol) of acid HO-Leu-N(Me)-Phe-Leu-NHBoc (**62**), 0.370 mL (2.12 mmol) of DIPEA, 186 mg (0.580 mmol) of TBTU, in 5.30 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the pentapeptide (317 mg, 82% yield). *R_f*: 0.63 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CDCl₃): δ 0.74–1.00 (18H, m, CH(CH₃)₂), 1.24–1.30 (3H, t, *J* 4.2 Hz, OCH₂CH₃), 1.35–1.44 (13H, m, C(CH₃)₃, 2CHCH₂CH), 1.46–1.66 (2H, m, CHCH₂CH), 1.66–1.88 (2H, m, CH(CH₃)₂), 1.90–2.04 (1H, m, CH(CH₃)₂), 2.64–2.90 (3H, m, NCH₃), 2.90–3.23 (2H, m, CH₂Phe), 4.04–4.15 (1H, br, NH), 4.09–4.15 (2H, m, OCH₂CH₃), 4.30–4.44 (2H, m, αCH , NH), 4.60–4.70 (1H, br, NH), 4.85–5.01 (1H, m, αCH), 5.01–5.21 (1H, m, αCH), 5.25–5.40 (1H, br, αCH), 7.08–7.30 (5H, m, Ph), 7.95–8.05 (1H, m, SCH=C). LCMS: *m/z* calcd for C₃₈H₅₉N₅O₇S (M+1)=730.41, found 730.10.

6.29.10. *Macrocycle Phe-Leu-Thiazole-Leu-Leu-N(Me)* (**10**). Macrocycle Phe-Leu-Thiazole-Leu-Leu-N(Me) (**10**) was synthesized following the '*Macrocyclization procedure*'. Utilizing 170 mg (0.280 mmol) of linear pentapeptide (**63**), 0.290 mL (1.68 mmol) of DIPEA, 64.2 mg (50.2 μmol) of TBTU, 76.0 mg (50.5 μmol) HATU, and 60.0 mg (50.2 μmol) of DEPBT in 300 mL methylene chloride and 100 mL acetonitrile. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) and reverse phase-HPLC to yield the macrocycle (6.50 mg, 4% yield). *R_f*: 0.35 (EtOAc/Hex 1:1); ¹H NMR (400 MHz, CDCl₃): δ 0.81–0.84 (3H, d, *J* 3.5 Hz, CH(CH₃)₂), 0.86–0.89 (3H, d, *J* 3.5 Hz, CH(CH₃)₂), 0.98–1.08 (12H, m, CH(CH₃)₂),

1.25–1.36 (2H, m, $\text{CH}(\text{CH}_3)_2$), 1.58–1.80 (6H, m, $3\text{CHCH}_2\text{CH}$), 2.10–2.30 (1H, m, $\text{CH}(\text{CH}_3)_2$), 2.53–2.63 (3H, m, NCH_3), 3.03–3.18 (2H, m, CH_2Phe), 4.65–4.79 (1H, m, αCH), 4.90–4.98 (1H, m, αCH), 5.10–5.20 (1H, m, αCH), 5.23–5.32 (1H, m, αCH), 6.42–6.50 (1H, m, NH), 6.92–7.00 (1H, m, NH), 7.20–7.33 (5H, m, Ph), 7.42–7.50 (1H, m, NH), 8.15 (1H, s, $\text{SCH}=\text{C}$). LCMS: m/z calcd for $\text{C}_{31}\text{H}_{45}\text{N}_5\text{O}_4\text{S}$ (M) = 584.3265, found 583.80; HRMS (ESI-TOF): MH^+ , found 584.3253, $\text{C}_{31}\text{H}_{45}\text{N}_5\text{O}_4\text{S}$ requires 610.4075 >95% pure by HPLC.

6.30. Synthesis of compound 11 (C-Th-III)

6.30.1. Dipeptide MeO-Lys-Cbz-Phe-NHBoc. Dipeptide MeO-Lys(Cbz)-Phe-NHBoc was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 392 mg (1.30 mmol) of amine MeO-Lys(Cbz)- NH_2 , 379 mg (1.43 mmol) of acid HO-Phe-NHBoc, 1.80 mL (10.4 mmol) of DIPEA, 334 mg (1.04 mmol) of TBTU, 297 mg (0.780 mmol) of HATU, in 13.0 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the dipeptide (578 mg, 80% yield). R_f : 0.37 (EtOAc/Hex 1:1); ^1H NMR (400 MHz, CDCl_3): δ 1.11–1.49 (2H, m, γCH_2), 1.30–1.36 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.36–1.64 (2H, m, δCH_2), 1.51–1.81 (2H, m, βCH_2), 2.93–3.03 (2H, m, ϵCH_2), 3.03–3.16 (2H, m, CH_2Phe), 3.60–3.65 (3H, s, OCH_3), 4.21–4.35 (1H, m, $\alpha\text{CH}\alpha$), 4.42–4.52 (1H, m, αCH), 4.85–4.93 (1H, br, NH), 5.03 (2H, s, CH_2Ph), 6.39–6.47 (1H, br, NH), 7.08–7.32 (10H, m, Ph).

6.30.2. Dipeptide MeO-Lys(Cbz)-Phe-NH₂. Dipeptide MeO-Lys(Cbz)-Phe-NH₂ was synthesized following the 'General solution-phase amine deprotection'. This dipeptide was taken on to the next reaction without further purification or characterization (459 mg, 100% yield).

6.30.3. Tripeptide MeO-Lys(Cbz)-Phe-D-Phe-N(Me)Boc. Tripeptide MeO-Lys(Cbz)-Phe-D-Phe-N(Me)Boc was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 459 mg (1.04 mmol) of amine MeO-Lys(Cbz)-Phe-NH₂, 320 mg (1.14 mmol) of acid HO-D-Phe-N(Me)Boc, 1.50 mL (8.32 mmol) of DIPEA, 267 mg (0.830 mmol) of TBTU, 198 mg (0.520 mmol) of HATU, in 10.4 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the tripeptide (731 mg, 100% yield). R_f : 0.38 (EtOAc/Hex 7:13); ^1H NMR (400 MHz, CDCl_3): δ 1.10–1.22 (2H, m, γCH_2), 1.22–1.30 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.35–1.48 (2H, m, δCH_2), 1.51–1.83 (2H, m, βCH_2), 2.51–2.73 (3H, s, NCH_3), 2.82–3.02 (2H, m, CH_2Phe), 3.02–3.15 (2H, m, ϵCH_2), 3.16–3.34 (2H, m, CH_2Phe), 3.59–3.70 (3H, s, OCH_3), 4.34–4.46 (1H, br, αCH), 4.47–4.68 (2H, m, $2\alpha\text{CH}$), 4.98–5.08 (2H, s, CH_2Ph), 6.22–6.61 (2H, br, NH), 6.98–7.34 (15H, m, Ph).

6.30.4. Tripeptide HO-Lys(Cbz)-Phe-D-Phe-N(Me)Boc. Tripeptide HO-Lys(Cbz)-Phe-D-Phe-N(Me)Boc was synthesized following the 'General solution-phase acid deprotection'. This tripeptide was taken on to the next reaction without further purification or characterization (716 mg, 100% yield).

6.30.5. Monomer amide-Leu-NHBoc. Monomer amide-Leu-NHBoc was synthesized following the 'General amide formation' procedure. Utilizing 353 mg (1.34 mmol) of MeO-Leu-NHBoc in 27.0 mL of ammonium hydroxide and 27.0 mL of methanol. This amide was taken on to the next reaction without further purification (333 mg, 100% yield). R_f : 0.05 (EtOAc/Hex 1:1).

6.30.6. Monomer thioamide-Leu-NHBoc. Monomer thioamide-Leu-NHBoc was synthesized following the 'General thioamide formation' procedure. Utilizing 333 mg (1.34 mmol) of amide-Leu-NHBoc and 542 mg (1.34 mmol) of Lawesson's reagent in 9.00 mL of

dimethoxyethane. This thioamide was purified by column chromatography (silica gel, EtOAc/DCM) to yield the thioamide-Leu-NHBoc (240 mg, 68% yield). R_f : 0.74 (EtOAc/Hex 1:1).

6.30.7. Dipeptide EtO-Thiazole-Leu-NHBoc. Dipeptide EtO-Thiazole-Leu-NHBoc was synthesized following the 'General thiazole synthesis' procedure. Thioamide-Leu-NHBoc 240 mg (0.910 mmol) and 729 mg (7.30 mmol) of potassium bicarbonate were dissolved in 18.2 mL dimethoxyethane. Ethyl-Br-pyruvate 0.230 mL (2 equiv) was added dropwise to the thioamide mixture to yield thiazoline intermediate. Thiazoline was dehydrated using 0.510 mL (3.64 mmol) of trifluoroacetic acid, 0.660 mL (8.19 mmol) of pyridine, 0.250 mL (1.82 mmol) triethylamine in 18.2 mL dimethoxyethane. The crude reaction was purified by column chromatography (silica gel, EtOAc/DCM) to yield the pentapeptide (404 mg, 77% yield). R_f : 0.81 (EtOAc/Hex 1:1); ^1H NMR (400 MHz, CDCl_3): δ 0.88–0.90 (3H, d, J 4.3 Hz, CHCH_3), 0.90–0.92 (3H, d, J 4.3 Hz, CHCH_3), 1.29–1.35 (3H, t, J 4.3 Hz, OCH_2CH_3), 1.36 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.60–1.74 (1H, m, $\text{CH}(\text{CH}_3)_2$), 1.77–1.98 (2H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 4.29–4.39 (2H, q, J 2.1 Hz, OCH_2CH_3), 4.85–5.14 (1H, br, CONHCH), 7.99 (1H, s, $\text{SCH}=\text{C}$).

6.30.8. Dipeptide EtO-Thiazole-Leu-NH₂. Dipeptide EtO-Thiazole-Leu-NH₂ was synthesized following the 'General amine deprotection'. This dipeptide was taken on to the next reaction without further purification or characterization (287 mg, 100% yield).

6.30.9. Pentapeptide EtO-Thiazole-Leu-Lys(Cbz)-Phe-D-Phe-N(Me)Boc. Pentapeptide EtO-Thiazole-Leu-Lys(Cbz)-Phe-D-Phe-N(Me)Boc was synthesized following the 'General solution-phase peptide synthesis' procedure. Utilizing 266 mg (1.10 mmol) of amine EtO-Thiazole-Leu-NH₂, 688 mg (1.00 mmol) of acid HO-Lys(Cbz)Phe-D-Phe-N(Me)Boc, 1.05 mL (6 mmol) of DIPEA, 257 mg (0.802 mmol) of TBTU, 190 mg (0.501 mmol) of HATU in 11.0 mL of methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) to yield the pentapeptide (497 mg, 49.5% yield). R_f : 0.16 (EtOAc/Hex 1:1); ^1H NMR (400 MHz, CDCl_3): δ 0.79–0.91 (6H, m, $\text{CH}(\text{CH}_3)_2$), 1.09–1.30 (12H, m, $\text{C}(\text{CH}_3)_3$ and OCH_2CH_3), 1.34–1.60 (2H, m, γCH_2), 1.66–1.87 (6H, m, $2\beta\text{CH}_2$ and δCH_2), 1.88–2.01 (1H, m, $\text{CH}(\text{CH}_3)_2$), 2.26–2.44 (3H, m, NCH_3), 2.86–3.04 (2H, m, ϵCH_2), 3.04–3.19 (3H, m, CH_2Phe and CH_2HbPhe), 3.19–3.33 (1H, m, βCHaHb), 3.71–3.91 (2H, m, OCH_2CH_3), 4.21–4.70 (2H, m, $2\alpha\text{CH}$), 4.96–5.04 (2H, m, CH_2Ph), 5.06–5.23 (2H, m, $2\alpha\text{CH}$), 6.29–6.79 (2H, br, 2NH), 6.89–7.36 (15H, m, Ph), 8.02–8.13 (1H, m, $\text{SCH}=\text{C}$). LCMS: m/z calcd for $\text{C}_{49}\text{H}_{64}\text{N}_6\text{O}_9\text{S}$ (M) = 913.13, found 913.00.

6.30.10. Macrocyclic Phe-D-Phe-N(Me)-Thiazole-Leu-Lys(Cbz) (11). Macrocyclic Phe-D-Phe-N(Me)-Thiazole-Leu-Lys(Cbz) (**11**) was synthesized following the 'Macrocyclization procedure'. Utilizing 418 mg (0.530 mmol) of linear pentapeptide, 0.750 mL (4.24 mmol) of DIPEA, 138 mg (0.430 mmol) of TBTU, 164 mg (0.430 mmol) HATU, and 129 mg (0.430 mmol) of DEPBT in 533 mL methylene chloride. The crude reaction was purified by column chromatography (silica gel, EtOAc/Hex) and reverse phase-HPLC to yield the macrocycle (50.3 mg, 12.3% yield). R_f : 0.53 (EtOAc/Hex 9:1); ^1H NMR (400 MHz, CDCl_3): δ 0.79–0.87 (3H, d, J 11.4 Hz, $\text{CH}(\text{CH}_3)_2$), 0.87–0.92 (3H, d, J 11.4 Hz, $\text{CH}(\text{CH}_3)_2$), 1.08–1.30 (4H, m, γCH_2 and δCH_2), 1.34–1.68 (3H, m, CHCH_2CH and CHCH_2HbCH), 1.83–2.00 (1H, m, CH_2HbCH), 2.21–2.36 (1H, m, $\text{CH}(\text{CH}_3)_2$), 2.49–2.72 (3H, m, NCH_3), 2.87–3.24 (2H, m, CH_2Phe), 3.00–3.12 (2H, m, ϵCH_2), 3.29–3.39 (1H, d, J 9.75 Hz, CH_2HbPhe), 3.50–3.64 (1H, br, NH), 3.98–4.10 (1H, m, αCH), 4.35–4.42 (1H, d, J 9.75 Hz, CH_2HbPhe), 4.76–4.87 (2H, m, $2\alpha\text{CH}\alpha$), 4.97–5.08 (2H, m, CH_2Ph), 5.24–5.34 (1H, m, αCH), 6.66–6.85 (2H, m, NH), 6.97–7.34 (15H, m, Ph), 7.52–7.64 (1H, m, NH), 7.94–8.02 (1H, m, $\text{SCH}=\text{C}$). LCMS: m/z calcd

for $C_{42}H_{50}N_6O_6S$ (M)=766.95, found 767; HRMS (ESI-TOF): MH^+ , found 767.3583, $C_{42}H_{50}N_6O_6S$ requires 767.3585 >95% pure by HPLC.

6.31. Synthesis of compound 12 (A-PP-II)

6.31.1. Fmoc-Val-Thr(Ψ Me,Me-Pro)-O-Resin. A mixture of 2-chlorotriptyl-chloride resin (100 mg, 0.100 mmol), dipeptide Fmoc-Val-Thr(Ψ Me,Me-Pro)-OH (96.0 mg, 0.200 mmol), and DIPEA (3.00 mL) in anhydrous methylene chloride (0.400 M) was stirred under argon at room temperature for 12 h. The reaction mixture was filtered and the collected resin was washed with a solution of $CH_2Cl_2/CH_3OH/DIPEA$ (30.0 mL 17:4:1, v:v:v), followed by methylene chloride (20.0 mL), dimethylformamide (20.0 mL), and finally methylene chloride (30 mL). The resin was drained well and dried in vacuo overnight to give the resin-bound dipeptide. Resin loading was determined via RP-HPLC to be 0.250 mmol/g.

6.31.2. Dipeptide NH_2 -Val-Thr(Ψ Me,Me-Pro)-O-Resin. Dipeptide NH_2 -Val-Thr(Ψ Me,Me-Pro)-O-Resin was synthesized using Fmoc-Val-Thr(Ψ Me,Me-Pro)-O-Resin synthesized above and followed the 'General solid-phase amine deprotection' procedure. A positive ninhydrin test served to verify Fmoc removal.

6.31.3. Tripeptide NH_2 -Leu-Val-Thr(Ψ Me,Me-Pro)-O-Resin. Following the 'General solid-phase peptide synthesis' procedure, a mixture of NH_2 -Val-Thr(Ψ Me,Me-Pro)-O-Resin (0.250 mmol), Fmoc-Leu-OH (177 mg, 0.500 mmol), HBTU (190 mg, 0.500 mmol), and DIPEA (3.00 mL, 0.400 M) in DMF was stirred at room temperature for 2 h. Completion of the coupling reaction was verified by a negative ninhydrin test. The reaction mixture was drained and washed with DMF (30 mL) to give the resin-bound tripeptide. The Fmoc was then removed following the 'General solid-phase amine deprotection' procedure to give the title tripeptide. A positive ninhydrin test served to verify Fmoc removal.

6.31.4. Tetrapeptide NH_2 -Leu-Leu-Val-Thr(Ψ Me, Me-Pro)-O-Resin. Following the 'General solid-phase peptide synthesis' procedure, a mixture of NH_2 -Leu-Val-Thr(Ψ Me,Me-Pro)-O-Resin prepared above (0.250 mmol), Fmoc-Leu-OH (177 mg, 0.500 mmol), HBTU (190 mg, 0.500 mmol), and DIPEA (3 mL, 0.400 M) in dimethylformamide was stirred at room temperature for 12 h. Completion of the coupling reaction was verified by a negative ninhydrin test. The reaction mixture was drained and washed with DMF (30 mL) to give the resin-bound tetrapeptide. The Fmoc was then removed following the 'General solid-phase amine deprotection' procedure to give title tetrapeptide. A positive ninhydrin test served to verify Fmoc removal.

6.31.5. Pentapeptide NH_2 -Phe-Leu-Leu-Val-Thr(Ψ Me,Me-Pro)-O-Resin. Following the 'General solid-phase peptide synthesis' procedure, a mixture of NH_2 -Leu-Leu-Val-Thr(Ψ Me,Me-Pro)-O-Resin prepared above (0.250 mmol), Fmoc-Phe-OH (194 mg, 0.500 mmol), HBTU (190 mg, 0.500 mmol), and DIPEA (3.00 mL, 0.400 M) in dimethylformamide was stirred at room temperature for 12 h. Completion of the coupling reaction was verified by a negative ninhydrin test. The reaction mixture was drained and washed with DMF (30 mL) to give the resin-bound pentapeptide. The Fmoc was then removed following the 'General solid-phase amine deprotection' procedure to give the title pentapeptide. A positive ninhydrin test served to verify Fmoc removal. The resin was then dried in vacuo for 24 h in a vacuum desiccator.

6.31.6. Double deprotected pentapeptide NH_2 -Phe-Leu-Leu-Val-Thr(Ψ Me,Me-Pro)-OH. Double deprotected pentapeptide NH_2 -Phe-Leu-Leu-Val-Thr(Ψ Me,Me-Pro)-OH was synthesized following the

'Cleavage of linear peptide from solid support' procedure. Utilizing the 250 mg of dried Resin-O-Thr(Ψ Me,Me-Pro)-Val-Leu-Leu-Phe- NH_2 , 1 mL of hexafluoroisopropanol and 4 mL of methylene chloride. The resin slurry was stirred for 30 min, after which it was filtered, washed with additional methylene chloride, and dried in vacuo to give the double deprotected pentapeptide (150 mg, 95% yield).

6.31.7. Macrocycle Phe-Thr(Ψ Me,Me-Pro)-Val-Leu-Leu (12). Macrocycle Phe-Thr(Ψ Me,Me-Pro)-Val-Leu-Leu was synthesized following the 'Macrocyclization procedure'. Utilizing linear pentapeptide (59.0 mg, 90.0 μ mol), DIPEA (80.0 μ L), and DMTMM BF_4^- (87.0 mg, 0.270 mmol), the linear peptide and coupling reagent were dissolved in dimethylformamide (10 mL) and added dropwise via syringe pump (0.5 mL/h) to a vigorously stirred solution of DIPEA and dimethylformamide (1 mM) under N_2 . The reaction mixture was stirred for 3 days, after which time the solvent was removed under reduced pressure and the crude reaction was purified by reverse phase-HPLC to yield the macrocycle **12** (14.5 mg, 26% yield). 1H NMR (CD_3CN , 400 MHz): δ 0.80–1.03 (18H, m, 3CH(CH_3) $_2$), 1.19 (3H, d, J 5.6 Hz, $CHCH_3$), 1.39–1.78 (12H, m, $CH_2CH_2CH_3$), 2.88 (1H, m, $CHMe_2$), 3.30–3.40 (2H, m, CH_2Ph), 3.67 (1H, m, αCH), 3.85 (1H, m, αCH), 3.91–4.04 (2H, m, $2\alpha CH$), 4.21–4.46 (2H, m, $2\alpha CH$), 6.59 (1H, m, NH), 6.69 (1H, m, NH), 6.87 (1H, m, NH), 7.12–7.41 (5 h, m, Ph), 7.48 (1H, d, J 8.0 Hz, NH) >95% pure by HPLC. HRMS (ESI-TOF): MH^+ , found 614.3887, $C_{33}H_{51}N_5O_6$ requires 614.3912.

6.32. Synthesis of compound 13 (A-PP-III)

6.32.1. Fmoc-Leu-Thr(Ψ Me,Me-Pro)-O-Resin. A mixture of 2-chlorotriptyl-chloride resin (3.00 g, 4.74 mmol), dipeptide **64** Fmoc-Leu-Thr(Ψ Me,Me-Pro)-OH (4.68 g, 9.48 mmol), *N*-methyl-2-pyrrolidone (14.04 mL or 3.00 mL per gram of dipeptide), and DIPEA (4.90 mL, 28.4 mmol) in anhydrous methylene chloride (46.8 mL) was stirred under argon at room temperature for 12 h. The reaction mixture was filtered and the collected resin was washed with a solution of $CH_2Cl_2/CH_3OH/DIPEA$ (30.0 mL 17:4:1, v:v:v), followed by methylene chloride (20.0 mL), dimethylformamide (20.0 mL), and finally methylene chloride (30 mL). The resin was drained well and dried in vacuo overnight to give the resin-bound dipeptide. Resin loading was determined via RP-HPLC to be 0.400 mmol/g.

6.32.2. Dipeptide NH_2 -Leu-Thr(Ψ Me,Me-Pro)-O-Resin (65). Title compound **65** was synthesized utilizing Fmoc-Leu-Thr(Ψ Me,Me-Pro)-O-Resin from above and followed the 'General solid-phase amine deprotection' procedure. A positive ninhydrin test served to verify Fmoc removal.

6.32.3. Tripeptide NH_2 -Leu-Leu-Thr(Ψ Me,Me-Pro)-O-Resin (66). Following the 'General solid-phase peptide synthesis' procedure, a mixture of NH_2 -Leu-Thr(Ψ Me,Me-Pro)-O-Resin **65** (1.00 g, 0.400 mmol), Fmoc-Leu-OH (420 mg, 1.20 mmol), HOBT (180 mg, 1.20 mmol), and DIPEA (0.370 mL, 2.40 mmol) in DMF was stirred at room temperature for 2 h. Completion of the coupling reaction was verified by a negative ninhydrin test. The reaction mixture was drained and washed with DMF (30 mL) to give the resin-bound tripeptide. The Fmoc was then removed following the 'General solid-phase amine deprotection' procedure to give title compound **66**. A positive ninhydrin test served to verify Fmoc removal.

6.32.4. Tetrapeptide NH_2 -Phe-Leu-Leu-Thr(Ψ Me, Me-Pro)-O-Resin (67). Following the 'General solid-phase peptide synthesis' procedure, a mixture of NH_2 -Leu-Leu-Thr(Ψ Me,Me-Pro)-O-Resin **66** prepared above, Fmoc-Phe-OH (460 mg, 0.120 mmol), HOBT (180 mg, 1.20 mmol), and DIPEA (0.370 mL, 2.40 mmol) in DMF was

stirred at room temperature for 12 h. Completion of the coupling reaction was verified by a negative ninhydrin test. The reaction mixture was drained and washed with DMF (30 mL) to give the resin-bound tetrapeptide. The Fmoc was then removed following the 'General solid-phase amine deprotection' procedure to give *title compound 67*. A positive ninhydrin test served to verify Fmoc removal.

6.32.5. Pentapeptide NH₂-Leu-Phe-Leu-Leu-Thr(Ψ Me,Me-Pro)-O-Resin (68**).** Following the 'General solid-phase peptide synthesis' procedure, a mixture of NH₂-Phe-Leu-Leu-Thr(Ψ Me,Me-Pro)-O-Resin **67** prepared above, Fmoc-Leu-OH (420 mg, 1.20 mmol), HOBt (180 mg, 1.20 mmol), and DIPEA (0.370 mL, 2.40 mmol) in DMF was stirred at room temperature for 12 h. Completion of the coupling reaction was verified by a negative ninhydrin test. The reaction mixture was drained and washed with DMF (30 mL) to give the resin-bound pentapeptide. The Fmoc was then removed following the 'General solid-phase amine deprotection' procedure to give *title compound 68*. A positive ninhydrin test served to verify Fmoc removal. The resin was then dried in vacuo for 24 h in a vacuum desiccator.

6.32.6. Double deprotected pentapeptide NH₂-Leu-Phe-Leu-Leu-Thr(Ψ Me,Me-Pro)-OH. Dried **68** (206 mg) in a solution of 2,2,2-trifluoroethanol (3.00 mL) and methylene chloride (3.00 mL) was stirred at room temperature for 24 h, after which it was filtered, washed with additional methylene chloride, and the resulting eluent was dried in vacuo for 24 h to give resin-free double-deprotected linear pentapeptide NH₂-Leu-Phe-Leu-Leu-Thr(Ψ Me,Me-Pro)-OH (65.0 mg, 25%). LCMS: *m/z* called for C₃₄H₅₅N₅O₇ (M+1)=646.4, found 646.3.

6.32.7. Macrocycle Leu-Phe-Leu-Leu-Thr(Ψ Me,Me-Pro) (13**).** Following the 'Macrocyclization procedure', a mixture of TBTU (23.0 mg, 0.0707 mmol), HATU (27.0 mg, 0.0707 mmol), DEPBT (18.0 mg, 0.0606 mmol), and DIPEA (0.140 mL, 0.808 mmol) were dissolved in 7.20 mL of anhydrous methylene chloride and acetonitrile (1:1, v:v) and stirred under argon at room temperature. Linear double-deprotected pentapeptide (65.0 mg, 0.101 mmol) was dissolved in 7.20 mL of anhydrous methylene chloride and acetonitrile (1:1, v:v) under argon and placed in a 10.0 mL syringe with 15.96 mm diameter and injected into the mixture of coupling reagents and allowed to run at room temperature for 4 h. The reaction was diluted in methylene chloride and quenched with saturated ammonium chloride (100 mL). The organic layer was then washed with brine (200 mL), dried over sodium sulfate, and the solvent evaporated in vacuo to give the crude product, which was then purified by flash chromatography (75% ethyl acetate/hexanes) and reverse phase-HPLC to yield macrocycle **13** (1.01 mg, 1.60% yield). *R_f*: 0.48 (EtOAc/Hex 3:1) ¹H NMR (400 MHz, CD₃OD): δ 0.83–1.00 (18H, m, CH₂CH(CH₃)₂), 1.44–1.46 (3H, d, *J* 7.3 Hz, CHCH₃), 1.56 (6H, s, CH₃), 1.56–1.78 (9H, m, CH₂CH(CH₃)₂), 2.98 (1H, m, CH_aH_bPh), 3.19 (1H, m, CH_aH_bPh), 3.63 (1H, m, CHCH₃), 3.95 (1H, m, α CH), 4.18 (1H, m, α CH), 4.30 (1H, m, α CH), 4.40 (1H, m, α CH), 7.19–7.35 (m, 5H). HRMS (ESI-TOF): MH⁺, found 628.4040, C₃₄H₅₃N₅O₆ requires 628.4068.

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Supplementary data

Supplementary data can be associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.11.089.

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