Title
New Methods to Prepare Complex Macro cyclic Peptidomimetics Directly from Unprotected Peptides

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New Methods to Prepare Complex Macrocyclic Peptidomimetics Directly from Unprotected Peptides

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Chemistry

by

Kenneth Victor Lawson

2014
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2014
ABSTRACT OF THE DISSERTATION

New Methods to Prepare Complex Macrocyclic Peptidomimetics Directly from Unprotected Peptides

by

Kenneth Victor Lawson

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2014

Professor Patrick G. Harran, Chair

Chapter one provides a brief overview of existing methods to prepare template-constrained macrocyclic peptides. This includes precedent from our laboratory describing a multi-functional electrophile which, in three conserved steps, forms composite macrocycles directly from unprotected oligopeptides. This lipophilic reagent was designed to offset the limiting characteristics of peptides, while imparting favorable conformational definition and an ability to passively diffuse through cellular membranes. This chapter also describes a new route to synthesize the processing reagent on scale, which enabled further study of the electrophilic reactivity of this species with two prototypical peptides.

Using the asymmetric synthesis described in chapter 1 we prepared a pilot library of composite macrocyclic peptidomimetics and screened it for antibacterial activity in a high-throughput format. Chapter 2 described preparation of a library consisting of 383 compound pools from which single compounds that inhibit S. aureus and B. subtilis were isolated. Moreover, we were
able to successfully establish an initial structure-activity relationship profile of the active constituent and moderately improve its antibacterial activity through iterative re-synthesis, purification and re-screening.

Chapter three describes the utility of a simplified, readily prepared lipophilic reagent to synthesize template constrained macrocyclic peptides via palladium catalyzed cinnamylolation of imidazoles, carboxylates, amines, and phenols present in natural amino acids. This strategy is uniquely powerful. No protecting groups were used and subtle changes in reaction conditions had a marked effect the chemoselectivity of cyclization. This allowed the selective, divergent synthesis of isomeric macrocyclic peptides. We showed that conformation constraints, imparted by the template stabilized the secondary structure of longer peptide sequences (10 to 12 amino acids) and enhanced in vitro proteolytic stability relative their acyclic congeners.

Chapter four describes the utility of our lipophilic reagent, harboring a latent cinnamyl cation, to participate in Friedel-Crafts macrocyclization with tripeptide Trp-Trp-Tyr. In a single reaction eight unique macrocycles were generated from electrophilic substitution of tryptophan and tyrosine. The product distribution as a function of multiple Lewis- and Brønsted acids was investigated, as well as rearrangements induced from ionization of the corresponding tyrosine-linked macrocyclic ether. A bridged macrocyclic pyrroloindoline was isolated and the solution conformation was determined by two-dimensional NMR methods and molecular mechanics simulations. Chapter five expands the scope of this method. Using our processing reagent, a pilot library composed of thirty composite macrocycles was prepared from functionally diverse tryptophan containing oligopeptides. We anticipate this method to prepare diverse composite macrocycles has the potential to target surfaces involved in protein-protein interaction.
The dissertation of Kenneth Victor Lawson is approved.

Neil K. Garg

Curtis D. Eckhert

Patrick G. Harran, Committee Chair

University of California, Los Angeles

2014
For my family and friends who have been extraordinarily supportive of my academic pursuits.
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<table>
<thead>
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<tbody>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
</tr>
<tr>
<td>Cbz</td>
<td>benzyloxycarbonyl</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation Spectroscopy</td>
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<tr>
<td>DBU</td>
<td>1,8-Diazobicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
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<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>equiv</td>
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<tr>
<td>ESI</td>
<td>Electrospray ionization</td>
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<td>Heteronuclear Multiple Bond Correlation</td>
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<td>Heteronuclear Multiple Quantum Coherence</td>
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<td>HPLC</td>
<td>High performance liquid chromatography</td>
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<td>High resolution mass spectrometry</td>
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<tr>
<td>LCMS</td>
<td>Liquid chromatography – mass spectrometry</td>
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<tr>
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<tr>
<td>NMR</td>
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</tr>
<tr>
<td>NOE</td>
<td>Nuclear Overhauser Effect</td>
</tr>
<tr>
<td>pHPLC</td>
<td>Preparative High performance liquid chromatography</td>
</tr>
<tr>
<td>Abbreviation</td>
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<td>--------------</td>
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<tr>
<td>quant.</td>
<td>Quantitative</td>
</tr>
<tr>
<td>ROESY</td>
<td>Rotating frame Nuclear Overhauser Effect Spectroscopy</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBTU</td>
<td>O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
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<tr>
<td>TFE</td>
<td>2,2,2-Trifluoroethanol</td>
</tr>
<tr>
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<td>Tetrahydrofuran</td>
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<tr>
<td>TLC</td>
<td>Thin-layer chromatography</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
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Chapter 1 - Towards synthetic emulations of natural product biosynthesis

1.1. Introduction

Advances in pharmaceutical and biological research have revealed numerous protein-protein interactions underlying poorly treated diseases.\textsuperscript{1,2,3} The relatively large, shallow, solvent exposed surfaces involved in these interactions are difficult to modulate using traditional 'drug-like' small molecules. Consequently, there is considerable need for new synthetic methods to prepare complex molecules able to modulate protein-protein interactions for therapeutic intervention or to interrogate their biological roles. Peptides presenting complimentary recognition motifs represent a logical starting point to develop molecules able to bind these surfaces avidly and selectively. However the poor pharmacological properties of peptides have precluded their application in vivo.\textsuperscript{4} Nature has evolved numerous strategies to mitigate these problems, including the incorporation of recognition domains into complex, conformationally constrained macrocyclic scaffolds (Figure 1A). These macrocyclic natural products are abundant and often feature sophisticated biological activity which is not present in their acyclic progenitors.\textsuperscript{5,6} Synthetic methods to systematically access comparable 'macrocycle space' could be uniquely valuable.\textsuperscript{7,8}

Numerous methods have been developed to prepare peptide macrocycles, including: head-to-tail lactamization\textsuperscript{9,10}, internal disulfide bonding\textsuperscript{11}, ring-closing metathesis\textsuperscript{12}, azide-alkyne cycloaddition\textsuperscript{13,14}, and others. Many of these methods have been applied to the discovery of biological active compounds and pharmaceutical leads, however each relies on a unique set of reactive amino acid monomers and protecting group strategies. The direct modification of unprotected, unmodified peptides is significantly less developed.

An alternative strategy is to incorporate short peptides into macrocyclic scaffolds through the use of templates or scaffolds. Degrado\textsuperscript{15,16} Boger\textsuperscript{17}, and others\textsuperscript{18,19,20,21} have demonstrated the utility of so-called 'template-constrained' macrocyclic peptides (Figure 1B).
Their work established that conformation can be controlled by the template, which can have a marked affect on the polarity, geometry, and overall function of the peptide domain. Recently these strategies have been coupled with biosynthetic techniques, including phage display and...
DNA templated synthesis\textsuperscript{21} (Figure 1B), to prepare large libraries of macrocyclic peptidomimetics.

Our templates (e.g. E, Figure 1C) were designed to mimic post-translational peptide modification and secondary metabolism.\textsuperscript{23} These templates incorporate multiple latent reactive sites able to sequentially engage peptides; first bi-molecularly to form a stable peptide-template linkage, then multiple times intramolecularly to form structurally complex template-constrained macrocycles in a conserved reaction sequence. The end-result would be a \textit{sequence dependent} remodeling of synthetic peptides. The goal from each polymer is not one product, but rather a mixture of isolable isomeric shape variants, each poised to display recognition elements in a unique ensemble of three dimensional conformations. These products would ideally possess characteristics making them valuable as biological probes and leads for drug development, including the ability to traverse lipid membranes and resist metabolic degradation.

\subsection{1.2. Background}

Two embodiments of E have been reported by Harran and co-workers previously. The first, compound 1, featured two electrophilic motifs designed to react in series with functional groups common to peptides and related polyamides. For example the aldehyde of 1 is able to form a Schiff base with the N-terminus of Gly-Tyr-NHBu (Figure 2A). Following conditions developed by Van Leusen, condensation of the incipient imine with p-fluorophenyltosylmethyl isocyanide 3 in the presence of base affords 2,3,4-trisubstituted imidazole 4 - effectively incorporating the aldehyde of 1 and peptide N-terminus into a stable heterocycle. The vinylnaryl carbinol is now poised to engage nucleophiles intramolecularly via intermediate metal π-allyl species.\textsuperscript{24} Ideally a variety of nucleophiles presented by peptides could participate; namely phenols, imidazoles, indoles, and amines. These studies found the phenol of tyrosine to react selectively (e.g. 5).\textsuperscript{25} This two-step process proved general with numerous macrocyclic ethers prepared in good yield.
A second-generation reagent was envisioned to build added functionality within the core design of 1. Post cyclization, the goal was to unveil additional reactive intermediates to further diversify and stabilize products. Inspired by terpene biosynthesis, reagent 2 harbors an unsaturated hydrocarbon motif which can be activated following the two-step macrocyclization

**Figure 2.** A. The earliest design for E was compound 1, a molecule having two reactive positions. This substance can be incorporated into a range of unprotected peptides to form macrocyclic composites. B. Template 2 retains the reactive functionality, of 1 but also harbors a dieneyne appendage. This substance is able to transform linear peptides into diverse sets of polycyclic products (e.g. 7 - 11) in three steps.
process. The diene-yne appendage was designed to react divergently with the peptide domain to provide an array of composite macrocycles from a single reaction. These isomers would vary in shape and uniquely display recognition groups in three dimensions. Furthermore this reactivity would ideally be dependent on the constitution of the starting oligomer, with bonding dependent on the proximity and nature of the functional groups present in the peptide.

An example of this process is depicted in Figure 2B. The product obtained from Van Leusen imidazole synthesis of 2 and Gly-Trp-Tyr-NHBu was converted to cinnamyl ether 6 by treatment with Pd-Xantphos complex. Exposure of 6 to anhydrous methanesulfonic acid in nitromethane promoted a series of carbocationic rearrangements within the hydrocarbon template, generating products 7 - 11. In each, the cinnamyl ether had rearranged to form stable C-C bonded macrocycles. This likely occurs via an intermediate cinnamyl cation which undergoes Friedel-Crafts alkylation with adjacent aryl residues. Concomitantly, protonation of the diene-yne appendage promotes skeletal rearrangements (Figure 2B, inset). Notably, product 9 is derived from transannular electrophilic aromatic substitution of the proximal tryptophan residue. This \textit{ansa} bridge imparts further conformational definition the peptide.

As a pilot study three oligopeptides, GWY, WWY and GGY were processed using reagent 2. Product mixtures were synthesized as described above and fractionated by preparative HPLC. An average of 10-12 product fractions were separated from each sequence and reconstituted in DMSO to provide 10mM stock solutions (total isomer concentration). Fractions were assayed for hippocampal neurogenesis \textit{in vivo}.

A description of assay protocols and resulting data are described below - adapted from Zhao, H. D.; Negash, L.; Wei, Q.; LaCour, T. G.; Estill, S. J.; Capota, E.; Pieper, A. A.; Harran, P. G. \textit{J. Am. Chem. Soc.} 2008, 130, 13864 (Reference 23):

Isolated HPLC fractions were diluted (10³ fold) in artificial cerebrospinal fluid and infused intracerebroventricularly at a constant rate into the left lateral ventricle of adult C57BL/J6 mice by means of an implanted Alzet osmotic minipump. Mice were awake and unconstrained during
the infusion, and administered daily intraperitoneal injections of bromo deoxyuridine (BrdU, 50 mg/kg) as a marker of cell divisions. After infusion was complete (7 days), mice were transcardially perfused and brain tissue stained with antibodies against BrdU. Hippocampal neurogenesis was evaluated by light microscopy contralateral to the side of pump implantation (Fig. 3A) to avoid artifacts from tissue damage. Every fifth section through the rostral-caudal extent of the hippocampus was analyzed, and the total number of BrdU+ cells was normalized against the volume of the dentate gyrus. Similarly infused recombinant fibroblast growth factor (FGF – 0.04 mg/ Kg / day) served as a positive control (Fig. 3B).

Figure 3. A) Normally proliferating cells (anti BrdU, black dots) in the subgranular zone of the mouse hippocampal dentate gyrus (DG, lower left). B) Magnified DG from a mouse infused with FGF (0.04 mg/kg/d for 7d) showing increased BrdU incorporation. C) In vivo screening of products derived from processing GGY with 6 identified a chromatography fraction (5) that elicits BrdU incorporation comparably to FGF. HPLC analysis of this fraction (D) showed it contained several products. These were divided into three pools by HPLC and re-screened in vivo. The active fraction (E) was resolved into components, one of which (F) retained the majority of neurogenesis activity and was assigned structure 17. (~1:1 mixture of isomers, stereochemistry at C9 and C38 unassigned). Isolated 12 elicits market BrdU incorporation in the DG when infused at 0.1 mg/kg/d for 7d (G) and its activity is dose dependent (H).

Pools derived from each of the processed peptides displayed activity in this format. Fractions derived from GGY elicited the most robust and selective response (Fig 3C). This fraction contained several products (Fig. 3D) which were fractionated into three pools and re-screened. A single fraction retained the observed activity. HPLC analysis showed it was composed of four major products (Figure 3E). Each was chromatographed to homogeneity. A single fraction (Figure 3F) retained the majority of neurogenesis activity. The structure of the active constituent was subsequently assigned as meta-cyclophane 12. Pure 12 reproducibly
elicited marked (Figure 3G) and selective neural cell proliferation in the hippocampal dentate gyrus and its activity was dose dependent in a dilution series (Figure 3H).

Isolation of 12 was a milestone for the project, showing that we could track and purify a trace constituent from our chemistry. Iterative purification and re-screening of increasingly homogenous product fractions minimized the probability of isolating false positives. Time-intensive structure determination was limited to active components.

1.3. Asymmetric synthesis of processing reagent on scale.26

Inspired by the utility of the initial screening library, our attention turned to expanding the screening sets derived from the second generation processing reagent. This required us to further our understanding of the reactivity and scope of the acid-promoted carbocationic rearrangements. The studies performed above utilized scalemic 2 (~60% ee) and required separation of diastereomers following ligation with peptides. A more scalable, selective synthesis of 2 was desirable.

The initial synthesis of 2 relied upon copper promoted 1,4-addition of homopropargylic organozinc species 17 to cinnamaldehyde 15 (Scheme 1).27 The resultant trimethylsilyl enol ether was parlayed (1. PhSeCl; 2. HF/pyridine; 3. CCl₃C(Me)₂CO₂Cl, DMAP, pyridine; 4. NaIO₄) into isomeric enals 21. Subsequent chiral imidazolidinone-catalyzed conjugate reduction28 afforded 2. The conjugate reduction required high catalyst loads to proceed at a useful rate and provided 2 in moderate enantiomeric excess (60% ee). This was inconvenient because oily substance 2 could not be further resolved via crystallization.29 Furthermore, attempts to selectively monosilate diol 14 were unsuccessful. The nearly statistical mixtures of starting material and mono-/di-silyl ethers required chromatographic separation which reduced the scalability of the route at an early stage.
To circumvent these limitations and to provide flexible, scalable access to optically active 
2 and congeners, an alternate synthesis was developed. Commercial isophthalaldehyde was 
desymmetrized via controlled olefination employing (R)-(−)-phenylglycine derived 
phosphonoacetyl oxazolidinone 22 (Scheme 1). Adduct 23 was then treated with vinyl 
magnesium chloride to generate a mixture of diastereoisomeric aryl vinyl carbinols 24. MeReO₃ 
catalyzed allylic alcohol transposition followed by in situ silylation with TBSCI afforded a single 
isomer of cinnamyl ether 25. Homopropargylic Grignard reagent 26 was added conjugately to 
the acrylimide in 25 affording 27 in high yield and diastereomeric excess. After degradation of 
the silicon groups in 27 with TBAF, the terminal alkyne in 28 participated smoothly in a
Sonogashira cross-coupling reaction with methylheptenone derived enol triflate 29. The resultant diene-yne containing imide 30 was reduced with a 2-fold excess of (i-Bu)₂AlH in toluene to afford aldehyde 31, from which target 2 was derived via acylation with 2,2,2-trichloro-1,1-dimethylethyl chloroformate.

The above route entailed eight linear steps, proceeded in 17 % overall yield and provided 2 in 91% e.e. It gave access to our target in up to 10 g batches without incident and had the added benefit of introducing the diene-yne appendage incrementally in two segments, wherein both could be controllably varied in future iterations. To simplify its use, aldehyde 2 was stored a 0.3M solution in DMF at -20 °C. Under these conditions only slight decomposition, comparable to that of a neat sample, was observed after storage for over six months.
1.4. Investigation of scope and reactivity of acid-promoted rearrangements.

With a scalable route to 2 established, we further investigated the cationic rearrangements that occur as the final step in our processing sequence. Moreover, electronic and steric properties of arene nucleophiles that would effecting participate in the chemistry were ill defined. We first attempted to simultaneously probe these two issues.

Peptides 32 and 33 we chosen for study. These sequences harbored pi-basic aromatics, namely thiophene, anisole, oxazole, and 5-hydroxindole that had not been examined. Furthermore, we anticipated the 3-oxazoyl-indole motif present in 32 would reduce available conformation degrees of freedom in the substrate. The resulting product distribution would be informative.

Following protocols described above, condensation of 32 and 33 with aldehyde 2 followed by cycloaddition with TosMIC reagent 3 provided N-terminal imidazole ligation products. These cyclized upon treatment with catalytic amounts of Pd/xantphos complex.27 Notable, cyclic ethers derived 33 were isolated as a 2:1 mixture of branched and linear alkylation products 35 and 36. Branched ethers had not been observed from Pd-catalyzed cinnamylation of tyrosine. Branched regiochemistry was confirmed by COSY correlations between H\(^1\)-H\(^1\)\(^\prime\) (\(^2J_{gem}= 1.0 \text{ Hz}\)), H\(^2\)-H\(^3\) (\(^3J_{HH}= 6.3 \text{ Hz}\)), and H\(^1\)/H\(^1\)\(^\prime\)-H\(^2\) (\(^3J_{cis}= 10.5 \text{ Hz}, ^3J_{trans}= 17.0 \text{ Hz}\)) indicative of a terminal olefin (Figure 3C). The macrocyclic ether linkage was assigned by a diagnostic HMBC correlation between the methine H\(^3\) and the phenolic carbon (C\(^6\)) resonance observed at \(\delta 153 \text{ ppm}\) (Figure 4D). The macrocyclic linkages in 34 and 35 were assigned analogously.

A mixture of branched and linear alkylation products would be inconsequential in subsequent acidolysis reactions. Interestingly, however 36 slowly underwent thermal aryl Claisen rearrangement selectively to the indole 4-position forming stable C-C bonded macrocycle 37.37 This process was complete, as observed by NMR, at 70 °C within 12 hours in MeCN-\(d_3\) (Figure 5B). This rearrangement was also accelerated under the macrocyclization
conditions leading to considerable degradation of 36 at extended reaction times. Catalyst poisoning with aqueous NaCN and cold-storage was essential to halt this process.
Treatment of \(35/36\) with anhydrous MeSO\(_3\)H (25 eq.) in nitromethane at 0 °C afforded a complex mixture of isomeric compounds (Figure 5 inset). Products were fractionated manually by iterative preparative HPLC. The major products were purified to homogeneity and characterized by NMR spectroscopy. Four compounds, \(37\) - \(40\), were fully characterized and demonstrate the propensity for intraresidue O\(_\text{ortho}\) cinnamyl migration. As shown previously the diene is prone to 6-exo cyclization forming \(39\) and \(40\) as a ~3:1 mixture of olefin regioisomers.\(^{23}\) Products \(37\) and \(38\) likely derived from \(39\) and \(40\), respectively, wherein a second annulation occurred to form a conjugated dihydronaphthalene. Mechanistically these products are likely derived from alkyne protonation and capture of the incipient vinyl cation with the adjacent aromatic ring. An additional five compounds, comprising smaller percentages of the overall mixture, were isolated in insufficient quantities for \(^1\)H-\(^{13}\)C correlation spectroscopy, precluding complete structure assignment. For each, analysis of TOCSY and COSY spectra revealed the thiophenylalanine and tryptophan residues were not substituted, indicating

![Figure 5](image-url)
rearrangements were limited to aromatic substitutions of the 5-hydroxyindole and rearrangements within the framework of 2.

![Figure 5](image_url)

**Figure 5.** A. Treatment of 35 and 36 with dry acid promotes a series of cationic rearrangements. Nine compounds including 37 - 40 were purified to homogeneity by preparative HPLC (C18, MeCN/H2O, 0.1% HCOOH). Inset: HPLC chromatogram of reaction mixture at 2 hours. **Conditions:** MeSO3H (25 eq.), MeNO2 (5 mM), 0 °C, 2h. B. Acidolysis of macroether 34 afforded isomeric macrocycles 41 - 45. Numerous additional products were observed by HPLC, but were not present in sufficient quantity for characterization or could not be purified to homogeneity. **Conditions:** MeSO3H (25 eq.), MeNO2 (5 mM), 0 °C, 2h.

Novel reactivity was observed from acidolysis of indole-oxazole 34. Indole N-alkylation proceeded to form 24-membered macrocycles 41 and 43 wherein the diene-yne had cyclized to form cyclohexene and dihydronapthalene groups respectively. These products were the first examples of cinnamyl ion migration to form larger ring macrocycles. Products 42 and 44 provide
insight into the relative kinetics of cinnamyl and diene-yne isomerization. meta-Cyclophane 44 is derived from nucleophilic addition of the trisubstituted olefin to the cinnamyl cation. Conversely, product 42 retained an intact cinnamyl ether and cyclized diene-yne, suggesting cyclohexene formation and cinnamyl ionization occur at similar rates.

1.5. Discussion and Conclusion

A scalable route to 2 was developed which enabled further study of its electrophilic reactivity in the context peptide macrocycles. All acidolysis products isolated had undergone 6-exo cyclization of the diene-yne appendage. Previous studies, processing Trp-Trp-Tyr, identified a single example of the cyclohexene reacting further to alkylate Trp$_2$ to form an ansa-bridged macrocycle. No analogous transannular Friedel-Crafts alkylations were observed from acidolysis of macrocycles 34 and 35/36 demonstrating the limited scope of this diene-yne reactivity. Further cyclization to form the dihydronaphthalene motif, likely prevents additional engagement with the peptide domain due to geometrical constraints. Modification of this reactive appendage to mitigate rapid, small-ring formations would likely be beneficial.

The entropic cost associated with the large-ring forming cationic rearrangements observed in these systems is potentially offset by starting from macrocyclic precursors. This is evidenced by the unresolvable reaction mixtures obtained from acidolysis of the acyclic carbonates which are presumably able to access analogous carbocationic intermediates following carbonate decomposition. The novel indole N-alkylated macrocycles 41 and 43 uniquely demonstrate the ability of cinnamyl cation migration to form ring-expanded macrocycles. Ionization of the ether C-O bond likely proceeds conformational relaxation in these systems. The presence of ring expanded products suggest intermediate cinnamyl cations may be poised to engage aromatic nucleophiles in large-ring forming reactions directly from acyclic material. This observation greatly influenced the direction of our subsequent research (see chapters 4 and 5).
Chapter 1 - Supporting Information

General Experimental Procedures. All reactions were performed in flame-dried glassware under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Analytical thin-layer chromatography was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore size, 230-400 mesh, Silicycle Inc.) impregnated with a fluorescent indicator and visualized by exposure to ultraviolet light (254 nm) and/or stained by submersion in basic aqueous KMnO$_4$, acidic $p$-anisaldehyde in ethanol, or aqueous ceric ammonium molybdate followed by heating with a heat gun. Flash-column chromatography was performed employing silica gel (60-Å pore size, 40-60 μm, Silicycle Inc.) or utilizing pre-packed silica gel cartridges (60-Å pore size, 40-60 μm, Silicycle Inc.) with an automated flash chromatography system equipped with a binary gradient pump, UV-Vis detector, and fraction collector. Commercial reagents were used as received. Tetrahydrofuran (THF), toluene, and acetonitrile were dried by passing through alumina towers according to Pangborn, et al.$^1$ The concentration of commercial solution $n$-butyllithium was determined by titration against standard solutions of diphenylacetic acid.$^2$

Experimental Procedures.

![Diethyl {2-[(4R)-4-Phenyl-2-oxo-1,3-oxazolidin-3-yl]-2-oxoethyl}-phosphonate (20) reaction](image)

Diethyl {2-[(4R)-4-Phenyl-2-oxo-1,3-oxazolidin-3-yl]-2-oxoethyl}-phosphonate (20). To a solution of (R)-(-)-5,5-dimethyl-4-phenyl-2-oxazolidinone (62.09 g, 324.7 mmol) in THF (1.3 L) at -78 °C was added $n$-BuLi (2.5 M in hexane, 132.5 mL, 331.2 mmol) dropwise over 30 minutes. The resulting solution was stirred 30 min at this temperature prior to the addition of bromoacetylbromide (65.5 g, 325 mmol) over 3 minutes via syringe. After stirring an additional 45 minutes the solution was allowed to slowly warm to 0 °C and sat. NH$_4$Cl (300 mL) is added. The organic layer is separated and washed with sat. NH$_4$Cl and brine, dried over Na$_2$SO$_4$ and concentrated. This material was taken up in triethylphosphite (670 mL) and heated to 60 °C for 2 h then concentrated under reduced pressure. The resulting dark viscous oil was taken up in ethyl acetate (2.0 L) and washed sequentially with water and brine, dried over Na$_2$SO$_4$ and concentrated to give an amber oil. This material is used without further purification.$^1$ $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.28-7.39 (m, 3H), 7.16-7.22 (m, 2H), 5.07 (s, 1H), 4.09-4.17 (m, 4H), 3.98 (dd, $J_{HP} = 22.5$ Hz, $J_{HH} = 13.7$ Hz, 1H), 3.66 (dd, $J_{HP} = 22.5$ Hz, $J_{HH} = 13.7$ Hz, 1H), 1.62 (s, 3H), 1.30 (t, $J = 7.1$ Hz, 1H), 1.27 (t, $J = 7.1$ Hz, 1H), 0.99 (t, $J = 7.1$ Hz, 1H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 164.6 (d, $J_{CP} = 6.8$ Hz), 153.2,
135.8, 128.8, 128.6, 126.5, 82.7, 67.3, 62.8 (d, $J_{CP} = 6.0$ Hz), 34.6 (d, $J_{CP} = 129$ Hz), 28.8, 23.6, 16.32 (d, $J_{CP} = 1.7$ Hz), 16.26 (d, $J_{CP} = 1.7$ Hz).

(R,E)-3-(3-(5,5-dimethyl-2-oxo-4-phenyloxazolidin-3-yl)-3-oxoprop-1-en-1-yl)benzaldehyde (23). Diisopropylethylamine (62.2 mL, 357 mmol) was added to a solution of keto-phosphonate 20 (119 g, 324 mmol) and LiCl (15.1 g, 357.2 mmol) at room temperature. This mixture was stirred for 5 minutes prior to the addition of isophthalaldehyde (87.1 g, 649.4 mmol) in one portion. After stirring overnight, water (500 mL) was added and the mixture was extracted with EtOAc (1.0 L). The organic phase was washed with sat. NH$_4$Cl, sat. NaHCO$_3$, and brine, dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash chromatography (SiO$_2$, gradient 70:15:10 $\rightarrow$ 45:15:40 hexanes:CHCl$_3$:Et$_2$O) gave aldehyde 23 (83.5 g, 74% over 3 steps) as a white solid. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 10.05 (s, 1H), 8.10 (d, $J = 15.7$ Hz, 1H), 8.05 (d, $J = 0.6$, 1H), 7.92 (dd, $J = 7.6$, 1.3 Hz, 1H), 7.86 (d, $J = 7.8$ Hz, 1H), 7.80 (d, $J = 15.7$ Hz, 1H) 7.57 (app t, $J = 7.7$ Hz, 1H), 7.30-7.45 (m, 3H), 7.15-7.25 (m, 2H), 5.21 (s, 1H), 1.66 (s, 3H), 1.04 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 191.7, 164.6, 153.3, 144.5, 136.9, 136.2, 135.5, 133.9, 131.0, 129.9, 129.7, 128.9, 128.7, 126.4, 119.0, 82.7, 67.3, 29.0, 23.8. HRMS (ESI) Calculated for C$_{21}$H$_{19}$NO$_4$ [M+Na$^+$]: 372.1206, found 372.1207.

(4R)-3-((E)-3-(1-hydroxyallyl)phenyl)acryloyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (24). To a solution of aldehyde 23 (5.0 g, 14.3 mmol) in toluene (190 mL) at -78 °C was added dropwise vinylmagnesium chloride (1.6 M in THF, 10.3 mL, 16.47 mmol) over 45 minutes maintaining an internal temperature < -65 °C. The mixture was stirred an additional 4h at this temperature and quenched with saturated NH$_4$Cl (50 mL). The organic layer was separated, diluted with ethyl acetate (100 mL) and washed sequentially with sat. NH$_4$Cl, water, and brine. The solution was dried over Na$_2$SO$_4$, filtered and concentrated to give a crude yellow foam which was used in the next step without further purification. An analytically pure sample was obtained by flash chromatography (SiO$_2$, gradient 15 $\rightarrow$ 40%
EtOAc/hexanes). 

$^1$H NMR (CDCl$_3$, 400 MHz): δ 8.00 (d, $J = 15.7$ Hz, 1H), 7.76 (d, $J = 15.7$ Hz, 1H), 7.58 (s, 1H), 7.53 (dd, $J = 7.2,1.6$ Hz, 1H), 7.30-7.45 (m, 5H), 7.25-7.05 (m, 2H), 6.03 (ddd, $J = 16.8, 10.3, 5.9$ Hz, 1H), 5.36 (ddd, $J = 16.8, 1.2, 1.2$ Hz, 1H) 5.15-5.25 (m, 3H), 2.09 (s, 1H), 1.64 (s, 3H), 1.03 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): δ 165.1, 153.3, 146.4, 143.4, 140.0, 136.3, 134.8, 129.1, 128.9, 128.7, 128.6, 127.9, 126.6, 117.4, 115.6, 82.5, 75.0, 74.9, 67.3, 29.0, 23.8. HRMS (ESI) Calculated for C$_{23}$H$_{23}$NO$_4$ [M+Na]$^+$: 400.1519, found 400.1521.

(R)-3-((E)-3-((E)-3-((tert-butyldimethylsilyloxy)prop-1-en-1-yl)phenyl)acryloyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (25). Methyltrioxorhenium (107 mg, 0.430 mmol) was added in one portion to a solution of allylic alcohol 24 (5.40 g, 14.32 mmol) in toluene (115 mL). After complete consumption of starting material (typically 12 h), as monitored by HPLC, imidazole (2.92 g, 43.0 mmol) was added followed by TBSCl (2.59 g, 17.2 mmol). After 1h the mixture was diluted with EtOAc (200 mL) and washed sequentially with sat. NH$_4$Cl, NaHCO$_3$, and brine, dried over Na$_2$SO$_4$ and concentrated. Cinnamyl silyl ether 25 (5.56 g, 79 % from 23) was obtained as an off-white foam. 

$^1$H NMR (CDCl$_3$, 400 MHz): δ 8.01 (d, $J = 15.7$ Hz, 1H), 7.76 (d, $J = 15.7$ Hz, 1H), 7.58 (s, 1H), 7.30-7.50 (m, 6H), 7.20 (d, $J = 6.8$ Hz, 2H), 6.61 (dt, $J = 15.8, 1.6$ Hz, 1H), 6.33 (dt, $J = 15.8, 4.9$ Hz, 1H), 5.21 (s, 1H), 4.37 (dd, 4.9, 1.6 Hz, 2H), 1.65 (s, 3H), 1.03 (s, 3H), 0.95 (s, 9H), 0.12 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): 165.1, 153.3, 146.5, 137.9, 136.3, 134.8, 130.4, 129.1, 129.0, 128.9, 128.6, 128.5, 127.4, 126.7, 117.3, 82.5, 67.3, 63.7, 29.0, 26.0, 23.8, 18.5. HRMS (ESI) Calculated for C$_{29}$H$_{37}$NO$_4$Si [M+Na]$^+$: 514.2384, found 514.2394.

(R)-3-((R)-3-((E)-3-((tert-butyldimethylsilyloxy)prop-1-en-1-yl)phenyl)-7-(trimethylsilyl)hept-6-ynoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (27). Grignard reagent 26 was prepared by addition of 4-bromo-1-trimethylsilyl-1-butyne (16.4 g, 80 mmol) in THF (80 mL) to magnesium filings (2.92 g, 120 mmol); initial addition of 8 mL followed by dropwise addition of the remainder via syringe pump over 1 h. The solution was warmed to reflux for 15 min, cooled to room temperature, diluted with 80 mL THF and
titrated against a standard solution of menthol in THF containing 1,10-phenanthroline as an indicator (c = 0.50 M). Copper(I) Iodide (10.11 g, 53.1 mmol) was dissolved in THF (90 mL) and dimethylsulfide (22 mL), cooled to -78 °C and stirred for 15 min. The Grignard reagent (101 mL) was added via cannula over 10 minutes, and the mixture was stirred for 10 minutes at -78 °C, then 10 minutes at -40 °C. A pre-cooled solution of 25 (22.53 g, 45.8 mmol) in THF (60 mL) was added over 10 minutes, and stirring continued at -40 °C for 30 min and then at -20 °C for 4 h. The reaction was quenched with saturated NH₄Cl (25 mL) and diluted with H₂O (150 mL). The aqueous phase was extracted with EtOAc, and the combined organic phase was washed with H₂O, brine, dried over MgSO₄, and concentrated. The residue was freed from copper salts by repeated trituration with 1:1 hexane:EtOAc and filtration through short plugs of silica gel. Compound 27 (27.30 g, 96%, single diastereoisomer by ¹H NMR) was used without purification. ¹H NMR (CDCl₃, 400 MHz): δ 7.28-7.38 (m, 3H), 7.18-7.24 (m, 3H), 7.05-7.10 (m, 3H), 6.55 (dt, J = 15.8, 1.7 Hz, 1H), 6.27 (dt, J = 15.8, 5.0 Hz, 1H), 4.87 (s, 1H), 4.35 (dd, J = 5.0, 1.7 Hz, 2H), 3.67 (dd, J = 16.2, 9.6 Hz, 1H), 3.27 (ddd, J = 10.0, 9.6, 5.4, 4.9 Hz, 1H), 3.09 (dd, J = 16.2, 5.4 Hz, 1H), 1.75-2.12 (m, 4H), 1.34 (s, 3H), 0.95 (s, 9H), 0.90 (s, 3H), 0.12 (brs, 15H). ¹³C NMR (CDCl₃, 100 MHz): δ 171.5, 153.4, 143.1, 137.4, 136.4, 129.5, 129.4, 129.0, 128.8, 128.7, 126.9, 126.1, 124.9, 106.7, 85.1, 82.5, 69.1, 66.9, 63.3, 41.5, 41.2, 28.7, 26.1, 25.8, 23.7, 18.6, 18.1, 0.3, -5.0. HRMS (ESI) Calculated for C₃⁶H₅₁NO₄Si₂ [M+Na]^+: 640.3249, found 640.3243.

(R)-3-((R)-3-((E)-3-hydroxyprop-1-en-1-yl)phenyl)hept-6-ynoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (28). To a solution of 27 (24.40 g, 39.48 mmol) in THF (400 mL) at -10 °C was added tetrabutylammonium fluoride (1.0M/THF, 98.70 mL, 98.71 mmol) over 15 min. The resulting orange solution was stirred for 1 h at this temperature then diluted with EtOAc (500 mL) and washed with sat. NH₄Cl, and brine, dried over Na₂SO₄ and concentrated by rotary evaporation. The crude oil was taken up in chloroform (100 mL) and filtered through a plug of silica gel and 1:1 ethyl acetate:hexanes (1.0 L). The filtrate was concentrated to give 28 (16.25 g, 95%) as an orange foam. ¹H NMR (CDCl₃, 400 MHz): δ 7.24-7.34 (m, 3H), 7.14-7.24 (m, 3H), 7.02-7.1 (m, 3H), 6.54 (dt, J = 15.9, 1.4 Hz, 1H), 6.31 (dt, J = 15.9, 5.6 Hz, 1H), 4.86 (s, 1H), 4.24 (dd, J = 5.6, 1.4 Hz, 2H), 3.63 (dd, J = 16.2, 9.3 Hz, 1H), 3.24-3.34 (m, 1H), 3.08 (dd, J = 16.2, 5.7 Hz, 1H), 2.65 (brs, 1H), 1.70-2.05 (m, 5H), 1.30 (s, 3H), 0.88 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 171.3, 153.3, 143.0, 137.1, 136.2, 130.5, 129.1, 128.9, 128.8, 128.7, 128.6, 127.0, 126.0, 124.9, 83.7, 82.5, 69.1, 66.9, 63.3, 41.5, 40.8, 35.0, 28.5, 23.5, 16.5. HRMS (ESI) Calculated for C₂₇H₂₉NO₄ [M+Na]^+: 454.1989, found 454.1992.
(R)-3-((R)-3-(3-(E)-3-hydroxyprop-1-en-1-yl)phenyl)-12-methyl-8-methylenetridec-11-en-6-ynoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (30). A mixture of PdCl$_2$(PPh$_3$)$_2$ (641 mg, 0.913 mmol), Cul (349 mg, 1.83 mmol), diisopropylamine (12.8 mL, 91.3 mmol) and vinyl triflate 29 (11.31 g, 43.8 mmol) in argon-sparged THF (40 mL) and DMF (10 mL) was cooled to 0 °C, and a solution of alkyne (28) (15.75 g, 36.5 mmol) in THF (50 mL) was added over 10 min. The reaction was allowed to warm to room temperature and stir an additional 1 h. The reaction mixture was diluted with EtOAc, washed with H$_2$O, brine, dried over MgSO$_4$ and concentrated. Purification by flash chromatography (SiO$_2$, gradient 0 → 50% EtOAc/hexanes) gave diene-yne 30 (12.04 g, 61%) as a light brown oil. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.28-7.38 (m, 3H), 7.20-7.24 (m, 3H), 7.04-7.14 (m, 3H), 6.57 (brd, J = 15.9 Hz, 1H), 6.34 (td, J = 15.9, 5.6 Hz, 1H), 5.19 (d, J = 1.3 Hz, 1H), 5.11 (d, J = 1.3 Hz, 1H), 5.05-5.10 (m, 1H), 4.87 (s, 1H), 4.29 (d, J = 5.6 Hz, 1H), 3.66 (dd, J = 16.1, 9.4 Hz, 1H), 3.23-3.36 (m, 1H), 3.10 (dd, J = 16.1, 5.4 Hz, 1H), 1.76-2.23 (m, 9H), 1.67 (s, 3H), 1.59 (s, 3H), 1.33 (s, 3H), 0.91 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 171.4, 153.3, 143.2, 137.0, 136.3, 132.1, 131.8, 131.1, 129.0, 128.9, 128.8, 128.7, 127.3, 126.6, 126.1, 124.9, 123.6, 119.9, 89.2, 82.5, 81.6, 67.0, 63.7, 41.6, 41.1, 37.7, 35.5, 28.6, 26.9, 25.8, 23.6, 17.8, 17.5. HRMS (ESI) Calculated for C$_{35}$H$_{41}$NO$_4$ [M+Na]$^+$: 562.2933, found 562.2912.

(R,E)-3-(3-(3-hydroxyprop-1-en-1-yl)phenyl)-12-methyl-8-methylenetridec-11-en-6-ynal (31). A solution of 1-acyl-oxazolidin-2-one 30 (8.84 g, 16.4 mmol) in toluene (160 mL) was cooled to -78 °C and diisobutylaluminum hydride (49 mL, 1.0 M/hexanes) was added. After stirring 20 min at this temperature, 10 % (w/v) aqueous Rochelle’s salt (100 mL) was added and the reaction was warmed to rt, stirred for 15 min, and filtered through Celite. The aqueous filtrate was extracted with EtOAc and the combined organic phase was washed with brine, dried over Na$_2$SO$_4$ and concentrated. The partially solidified residue was reconstituted in Et$_2$O and treated with pentane to induce crystallization. After chilling, the mixture was
filtered and the cake washed with cold 2:1 pentane:Et₂O to recover the chiral auxiliary (1.503 g, 48%) as colorless needles. The filtrate was concentrated to give 31 (5.49 g) as a light brown oil, which was used without purification. An aliquot was purified for characterization (preparative TLC eluent 1:1:1 hexane:DCM:EtOAc). ¹H NMR (CDCl₃, 400 MHz): δ 9.66 (t, J = 1.8 Hz, 1H), 7.30-7.24 (m, 3H), 7.23-7.20 (m, 1H), 6.60 (brd, J = 15.9 Hz, 1H), 6.36 (dt, J = 15.9, 5.6 Hz, 1H), 5.23 (d, J = 1.1 Hz, 1H), 5.16 (d, J = 1.1 Hz, 1H), 5.14-5.08 (m, 1H), 4.32 (dd, J = 5.6, 1.0 Hz, 2H), 3.40-3.30 (m, 1H), 2.75 (dt, J = 7.1, 1.8 Hz, 2H), 2.26-2.06 (m, 7H), 1.97-1.76 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 201.5, 143.1, 137.3, 132.2, 131.8, 131.0, 129.2, 129.0, 127.0, 125.9, 125.1, 123.5, 120.1, 89.0, 81.9, 63.7, 50.1, 39.0, 37.8, 35.4, 26.9, 25.8, 17.9, 17.4.

(R,E)-3-(3-(12-methyl-8-methylene-1-oxotridec-11-en-6-yn-3-yl)phenyl)allyl (1,1,1-trichloro-2-methylpropan-2-yl) carbonate (2). A solution of alcohol 31 (5.49 g, 15.7 mmol) in DCM (160 mL) was cooled to -40 ºC. A solution of pyridine (2.0 mL, 25 mmol) and DMAP (230 mg, 1.9 mmol) in DCM (50 mL) was added, followed by dropwise addition of 1,1-dimethyl-2,2,2-trichloroethyl chloroformate (5.25 g, 21.9 mmol) in DCM (50 mL). The reaction was stirred for 2 h, diluted with EtOAc (700 mL), washed with cold sat. NaHCO₃, H₂O, brine, dried over MgSO₄ and concentrated. Purification by flash chromatography (SiO₂, 15% EtOAc/hexanes) afforded 2 as a colorless oil (4.75 g, 52% from 30). ¹H NMR (CDCl₃, 500 MHz): δ 9.66 (t, J = 1.9 Hz, 1H), 7.10-7.32 (m, 4H), 6.67 (brd, J = 15.8 Hz, 1H), 6.30 (dt, J = 15.8, 6.6 Hz, 1H), 5.23 (s, 1H), 5.15 (s, 1H), 5.08-5.14 (m, 1H), 4.78 (d, J = 6.7 Hz, 2H), 3.33-3.42 (m, 1H), 2.75 (dt, J = 7.5, 1.9 Hz, 2H), 2.07-2.29 (m, 6H), 1.96 (s, 6H), 1.75-1.95 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H). ¹³C NMR (CDCl₃, 125 MHz): δ 201.3, 152.4, 143.2, 136.6, 135.1, 132.2, 131.8, 129.2, 127.6, 126.1, 125.4, 123.5, 122.7, 120.2, 105.6, 90.1, 88.9, 81.9, 68.6, 50.1, 39.0, 37.8, 35.4, 26.9, 25.8, 21.3 (2), 17.9, 17.4. [α]D²⁰ = +29.0 (c 0.56, CHCl₃).

Indole-oxazole composite macrocycles 41-45:
All work related contained within the oxazole-indole series was performed by Tristan E. Rose. Tabulated spectroscopic data and synthetic methods related to these compounds will be described elsewhere.
Synthesis of composite macrocycles of Gly-Thi-Trp-5HTA:

Peptide Synthesis:
H-Gly-Trp-Thi-5-Hydroxytryptamine was prepared by attachment of Fmoc-5-hydroxytryptamine to 2-Chlorotriptylchloride resin (100-200 mesh, 0.84 mmol/g) via the phenolic oxygen as follows: A solution of Fmoc-5-hydroxytryptamine (398 mg, 1.00 mmol) in dichloromethane (10 ml) was added to a flask containing 2-Chlorotriptylchloride resin (840 mg, 1.00 mmol) followed by iPr₂NEt (174 ul, 1.00 mmol). The mixture was agitated for 10 minutes then an addition aliquot of iPr₂NEt (261 ul, 1.50 mmol) was added and the mixture was agitated for an addition 2 hours. Methanol (500 uL) was added and the resin was mixed for an addition 15 minutes, then filtered through a sintered glass funnel. The resin was washed with CH₂Cl₂ (3x), DMF (3x), CH₃OH (3x), and dried under high vacuum. The substitution was estimated by mass. Chain elongation was performed as described above. Fmoc-deprotection was achieved with 20% piperidine in DMF (2 x 30 min). The reaction vessel was washed with DMF (3x) and CH₂Cl₂ (2x). The vessel was then charged with the appropriate Fmoc-amino acid (4 equiv) and TBTU (4 equiv) followed by DMF (10-20 ml) and iPr₂NEt (10 eq). The resin was agitated for 2 hours, drained, and washed with DMF (3X). Cleavage from the resin was achieved with 1:1:8 AcOH:TFE:CH₂Cl₂ for 2 hours.

NMR methods:
NMR spectra were recorded on Bruker Avance (300, 500 or 600 MHz), DRX (500 MHz) and ARX (400 MHz) spectrometers. Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration), and are referenced to a residual protonated solvent peak. ¹³C resonances are reported in terms of chemical shift (δ ppm) as referenced to the residual DMSO peak. For mass-limited samples, solvent magnetic susceptibility matched Shigemi tubes were used with a sample volume of ~300 µL. Optimization of on-axis shims was accomplished using the TopShim automated tool within Bruker Topspin™ 2.1. Optimization of off-axis shims was performed manually. ¹H 90º transmitter pulse lengths were calibrated by back calculation from the 360º or 180º null. The pulse width or power level for soft pulses and shaped pulses were calculated using the Shape Tool within TopSpin™ 2.1. ¹H-¹H COSY spectra were recorded using a phase sensitive, gradient enhanced double-quantum-filtered experiment, using States-TPPI acquisition. TOCSY spectra were recorded using a sensitivity improved, phase sensitive experiment using a 60ms DIPSI-2 pulse train for homonuclear Hartman-Hahn transfer. NOESY spectra were recorded using a phase sensitive

experiment with selection gradients during the mixing time.\(^6\) ROESY spectra were recorded using a phase sensitive experiment with selection gradients and water suppression with excitation sculpting.\(^7\) Carbon chemical shifts were measured from 2D plots of either HSQC spectra for protonated carbons or HMBC spectra for non-protonated carbons. \(^1\)H-\(^13\)C HSQC spectra were recorded using a sensitivity improved phase sensitive experiment using an adiabatic shape pulse for \(^13\)C inversion, and \(^13\)C decoupling during acquisition.\(^8\) Experimental parameters were optimized for \(^1\)J\(_{\text{CH}}\) = 145Hz. \(^1\)H-\(^13\)C HMBC spectra were recorded using a gradient selected experiment with a two-fold J-filter optimized for \(^1\)J\(_{\text{CH}}\) = 125-165Hz. Experimental parameters were optimized for long range \(^\alpha\)J\(_{\text{CH}}\) = 8Hz.

**Imidazole S1**

To a solution of Gly-Thi-Trp-5HTA (1.36 g, 2.23 mmol, 1.2 eq.) in DMF (12.5 mL) was added Cs\(_2\)CO\(_3\) (1.94g, 5.95 mmol, 3.2 equiv) followed by a 0.3M solution of 1 in DMF (6.2 ml, 1.86 mmol, 1 eq.) and mixed for 4 hours to induce imine formation. Solid (para-fluorophenyl)tosylmethylisocyanate (445 mg, 2.23 mmol, 1.2 equiv) was added directly to the reaction vessel and the resulting solution was stirred overnight. The reaction was filtered and the DMF removed in vacuo. The crude residue purified by column chromatography (dry loading, SiO\(_2\), 0-10% MeOH/CHCl\(_3\)) to afford imidazole S1 (993 mg, 47%).

\(^1\)H NMR (MeOH-\(d_4\), 600 MHz): \(\delta\) 7.86 (s, 1H), 7.5 (d, \(J = 7.9\) Hz, 1H), 7.25-7.34 (m, 5H), 7.11-7.17 (m, 3H), 7.0-7.03 (m, 3H), 6.95-7.03 (m, 5H), 6.88 (d, \(J = 2.1\) Hz, 1H), 6.82-6.86 (m, 2H), 6.74-6.80 (m, 3H), 6.65 (dd, \(J = 8.6, 2.3\) Hz, 1H), 6.5 (d, \(J = 16\) Hz, 1H), 6.16 (dt, \(J = 15.9, 6.4\) Hz, 1H), 4.98-5.10 (m, 4H), 4.63-2.73 (m, 3H), 5.45-4.63 (m, 2H), 4.37 (d, \(J = 16.8\) Hz, 1H), 4.22 (d, \(J = 16.9\) Hz, 1H), 3.20-3.40 (m, 6H), 2.99-3.20 (m, 4H), 2.53-2.70 (m, 3H), 1.93-2.11 (m, 7H), 1.9 (s, 6H), 1.7-1.80 (m, 2H), 1.62 (s, 3H), 1.52 (s, 3H). \(^1\)H NMR (MeCN-\(d_3\), 150 MHz): 171.9, 170.9, 167.7, 167.1, 160.1, 152.3, 149.7, 142.8, 138.5, 137.5, 136.6, 136.2, 134.4, 131.8, 131.7, 131.7, 131.5, 131.0, 129.1, 128.4, 128.0, 127.5, 127.2, 126.6, 126.4, 126.3, 125.9, 124.9, 124.3, 123.4, 123.2, 122.9, 122.3, 121.2, 118.9, 118.6, 118.1, 114.8, 114.7, 111.3, 111.0, 110.9, 109.4, 105.4, 102.2, 89.5, 88.7, 81.2, 78.1, 68.2, 54.7, 54.5, 46.7, 44.3, 39.8, 37.4, 33.7, 31.4, 30.4, 27.7, 26.5, 24.7, 24.5, 20.2, 16.6. MS (ESI) Calculated for C\(_{67}\)H\(_{89}\)Cl\(_3\)FN\(_7\)O\(_4\)S [M+H]\(^+\): 1240.4, found 1240.8.

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To a solution of imidazole S1 (146 mg, 0.118 mmol) in degassed DMF (30 ml, 5 mM) was added catalyst solution (3.5 ml, 0.04 mol% [PdCl(C3H5)]2, 0.10 mol% xantphos). The reaction was allowed to stir at room temperature for two hours as monitored by HPLC-MS (C18, MeCN/H2O, 0.1% TFA). The reaction was diluted with EtOAc (200 ml) and washed with 0.1M NaCN (aq), H2O (3x) and brine. The organic layer was dried over Na2SO4, filtered and solvent removed in vacuo. The macrocyclic ethers were purified by preparative HPLC (Waters Sunfire C18, 30x150mm, MeCN/H2O, 0.1% TFA) and lyophilized to provide 35 and 36 (34 mg, 53%). For characterization analytical samples each isomer were isolated. For subsequent reactions a mixture of macrocyclic ether isomers 35 and 36 was employed.

The solution of catalyst was prepared as follows: An oven-dried, serum-topped vial was placed in a glove bag and charged with [PdCl(C3H5)]2 (14 mg, 0.038 mmol) and xantphos (55 mg, 0.095 mmol). The vial is sealed, removed from the glove bag, and degassed THF (7.0 ml) was added, followed by degassed DMF (7.0 ml). The resulting yellow solution was stirred under argon for 30 minutes.

Data for 35 - 1H NMR (MeCN-d3, 600 MHz): δ 9.12 (s, 1H), 8.93 (s, 1H), 7.67-7.71 (m, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.38 (br. s, 1H), 7.3 (d, J = 8.5 Hz, 1H), 7.24 (s, 1H), 7.22 (br. d, J = 7.9 Hz, 1H), 7.14-7.19 (m, 3H), 7.11-7.14 (m, 2H), 7.09 (d, J = 7.7 Hz, 1H), 7.06 (d, J = 6.8 Hz, 1H), 7.03 (d, J = 2.3 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.91 (br. d, J = 8.2 Hz, 1H), 6.86 (dd, J = 8.8, 2.4 Hz, 1H), 6.70-6.75 (m, 2H), 6.65-6.68 (m, 2H), 6.63 (br. d, J = 7.6 Hz, 1H), 6.51 (dt, J = 16.4, 5.2 Hz, 1H), 6.4 (d, J = 6.2 Hz, 1H), 5.11-5.13 (m, 1H), 5.05-5.07 (m, 1H), 5.01-5.05 (m, 1H), 4.88 (ddd, J = 14.8, 5.3, 1.5 Hz, 1H), 4.83 (ddd, J = 14.8, 5.4, 1.4 Hz, 1H), 4.54 (ddd, J = 8.1, 8.1, 5.6 Hz, 1H), 4.31 (ddd, J = 10.0, 5.7, 4.4 Hz, 1H), 4.21 (d, J = 17.6 Hz, 1H), 3.63 (d, J = 17.5 Hz, 1H), 3.41-3.48 (m, 1H), 3.32-3.40 (m, 1H), 3.25 (dd, J = 14.7, 5.4 Hz, 1H), 2.91 (dd, J = 15.4, 10.7, 5.6 Hz, 1H), 2.70-2.82 (m, 4H), 2.52 (dd, J = 15.6, 9.5 Hz, 1H), 1.99-2.10 (m, 6H), 1.91-1.95 (m, 2H), 1.82-1.90 (m, 2H), 1.73-1.82 (m, 1H), 1.66 (s, 3H), 1.56 (s, 3H). 1H NMR (MeCN-d5, 150 MHz): 171.5, 170.6, 169.8, 152.4, 144.3, 142.4, 139.6, 139.5, 138.4, 138.3, 137.4, 132.9, 132.8, 129.8, 129.3, 128.8, 128.6, 128.5, 128.0, 127.5, 127.0, 126.3, 125.9, 124.4, 124.2, 123.9, 122.5, 120.5, 119.9, 119.6, 116.6, 116.1, 115.9, 115.3, 113.1, 113.0, 112.3,
111.4, 104.7, 90.1, 82.4, 82.3, 57.4, 54.3, 48.0, 45.7, 40.1, 38.2, 34.7, 32.1, 31.0, 27.4, 25.8, 25.4, 17.9, 17.7. MS (ESI) Calculated for C_{62}H_{62}FN_{7}O_{4}S [M+H]^+: 1020.5, found 1020.6

Data for 36 - ^1^H NMR (MeCN-d$_3$, 600 MHz): δ 9.21 (s, 1H), 8.94 (s, 1H), 7.64 (d, J = 5.5 Hz, 1H), 7.63 (d, J = 5.7 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 7.4 Hz, 1H), 7.29 (d, J = 9.1 Hz, 1H), 7.14-7.24 (m, 6H), 7.04-7.12 (m, 4H), 6.99 (br. s, 1H), 6.86 (br. s, 1H), 6.82 (dd, J = 8.8, 2.2 Hz, 1H), 6.78 (d, J = 7.7 Hz, 1H), 6.66 (dd, J = 4.5, 4.5 Hz, 1H), 6.61 (br. s, 1H), 6.51-6.57 (m, 2H), 6.15-6.19 (m, 1H), 6.11 (ddd, J = 17.0, 10.6, 6.3 Hz, 1H), 5.79 (d, J = 6.4 Hz, 1H), 5.33 (d, J = 17.2 Hz, 1H), 5.19 (d, J = 10.2 Hz, 1H), 5.15 (br. s, 1H), 5.11 (br. s, 1H), 5.02-5.07 (m, 1H), 4.60-4.65 (m, 1H), 4.11-4.17 (m, 1H), 3.66 (d, J = 17.7 Hz, 1H), 3.56 (ddd, J = 18.0, 13.6, 6.9 Hz, 1H), 3.28-3.39 (m, 3H), 3.12 (dd, J = 14.9, 8.5 Hz, 1H), 2.86-2.97 (m, 4H), 2.75-2.81 (m, 3H), 2.72 (dd, J = 15.6, 2.6 Hz, 1H), 2.21-2.33 (m, 2H), 2.19 (ddd, J = 17.0, 6.1, 6.1 Hz, 1H), 2.07-2.13 (m, 3H), 2.02-2.05 (m, 3H), 1.83-1.90 (m, 2H), 1.66 (s, 3H), 1.56 (s, 3H). Spectra for the remaining branched diastereomer is below. Stereochemistry of the vinylphenyl methine was not determined. MS (ESI) Calculated for C_{62}H_{62}FN_{7}O_{4}S [M+H]^+: 1020.5, found 1020.6

**Ortho-Aryl Claisen product 37 -**

An analytical sample of 36 (~ 1 mg) in MeCN-d$_3$ was heated to 70 °C using the Bruker variable temperature unit. Slow conversion to 37 was observed by ^1^H NMR. The reaction was removed and heated to 70°C in an oil bath for 12 hours. The reaction was periodically monitored by NMR for conversion. The macrocyclic linkage was assigned by TOCSY/HMBC correlation. ^1^H NMR (MeCN-d$_3$, 600 MHz): δ 9.21 (s, 1H), 8.97 (s, 1H), 7.68-7.74 (m, 2H), 7.56 (d, J = 7.8 Hz, 1H), 7.42 (br. s, 1H), 7.4 (d, J = 8.2 Hz, 1H), 7.13-7.23 (m, 6H), 7.05-7.12 (m, 3H), 6.95-7.04 (m, 3H), 6.75-6.81 (m, 2H), 6.65-6.71 (m, 2H), 6.63 (d, J = 2.8 Hz, 1H), 6.57 (d, J = 7.7 Hz, 1H), 6.39 (d, J = 3.8 Hz, 1H), 6.13 (d, J = 16.3 Hz, 1H), 5.12 (d, J = 1.7 Hz, 1H), 5.06 (d, J = 1.7 Hz, 1H), 4.99-5.03 (m, 1H), 4.55 (ddd, J = 7.7, 7.7, 5.2 Hz, 1H), 4.18 (ddd, J = 9.7, 4.9, 4.0 Hz, 1H), 4.03 (d, J = 17.3, Hz, 1H), 3.92 (dd, J = 17.0, 3.2 Hz, 1H), 3.84 (dd, J = 16.8, 5.5 Hz, 1H), 3.42-3.53 (m, 1H), 3.35 (d, J = 17 Hz, 1H), 3.31 (dd, J = 14.9, 4.9 Hz, 1H), 3.19 (dd, J = 15.0, 7.7 Hz, 1H), 3.13 (dd, J = 15.3, 3.8 Hz, 1H), 3.01 (ddd, J = 15.1, 9.3, 6.0 Hz, 1H), 2.84-2.93 (m, 2H), 2.81 (dd, J = 15., 9.9 Hz, 1H), 2.74 (dd, J = 15.8, 4.8 Hz, 1H), 2.45 (dd, J = 15.6, 9.6 Hz, 1H), 2.13 (ddd, J = 17.1, 5.7 Hz, 1H), 1.82-1.95 (m, 2H), 1.74-1.82 (m, 1H), 1.65 (s, 3H), 1.54 (s, 3H). MS (ESI) Calculated for C_{62}H_{62}FN_{7}O_{4}S [M+H]^+: 1020.5, found 1020.5.
Acidolysis of 35 - 36 -

To a suspension of 35 and 36 (608 mg, 0.596 mmol) in CH$_3$NO$_2$ (150 mL) at 0 °C was added MeSO$_3$H (970 μL, 14.9 mmol, 25 eq.). The suspension rapidly dissolved and colored. After stirring 2 hours the reaction was quenched with saturated NaHCO$_3$ (25 ml), transferred to a separatory funnel and diluted with EtOAc (200 ml). The organic layer was washed with sat. NaHCO$_3$, brine, dried over Na$_2$SO$_4$ and evaporated. The product mixture was reconstituted in N,N-DMF and purified by semi-preparative RP-HPLC (Sunfire C18, 5 μ, 10x250 mm, MeCN/H$_2$O, 0.1% HCO$_2$H). Fractions were pooled and evaporated under reduced pressure.

Fraction numbers annotated on spectra below indicate relative compound retention of iterative purifications. For example, Fraction 2-3 (product 38) was contained in the second fraction of the first purification and purified a second time to reach homogeneity (Fraction 3 on second column). Products 37-40 were unambiguously characterized by a combination of hetero-/homonuclear correlation spectroscopy.

An addition six isomers were partially assigned as indicated on copies of the respective NMR. These partial assignments indicated no substitution the Thi and Trp amino acids and were therefore of limited interest. Compound 37 was characterized by John MacMillan and co-workers (UT Southwestern).

Tabulated data for 37 - $^1$H NMR (MeOD-d$_4$, 600 MHz): δ 8.72 (s, 1H), 7.88 (d, J = 7.7 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.29-7.35 (m, 2H), 7.17 (app t, J = 8.5 Hz, 2H), 7.16-7.12 (m, 4H), 6.96-7.01 (m, 3H), 6.85-6.88 (m, 3H), 6.7 (t, J = 4.9 Hz, 1H), 6.48-6.55 (m, 2H), 6.36 (br. s, 1H), 6.34 (d, J = 16.1 Hz, 1H), 5.52 (s, 1H), 4.74 (d, J = 16.6 Hz, 1H), 4.59-4.65 (m, 1H), 4.57 (dd, J = 9.2, 5.3 Hz, 1H), 4.5 (d, J = 6.8 Hz, 1H), 4.48 (d, J = 7 Hz, 1H), 3.74 (dd, J = 15.1, 5.4 Hz, 1H), 3.54-3.63 (m, 1H), 3.46 (dd, J = 14.9, 7.4 Hz, 1H), 3.21 (dd, J = 14.9, 5.4 Hz, 1H), 2.93-3.06 (m, 2H), 2.9 (dd, J = 15.5, 5.1 Hz, 1H), 2.79-2.85 (m, 1H), 2.63-2.76 (m, 2H), 2.55-2.46-2.52 (m, 1H), 2.13-2.21 (m, 1H), 1.75-1.85 (m, 1H), 1.63 (s, 3H), 1.62 (s, 3H), 1.32-1.43 (m, 4H). MS (ESI) Calculated for C$_{62}$H$_{62}$FN$_7$O$_4$S [M+H]$^+$: 1020.5, found 1020.4

Tabulated data for 38 - $^1$H NMR (MeOD-d$_4$, 600 MHz): δ 8.73 (s, 1H), 7.58 (br. t, J = 4.6 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.24 (dd, J = 5.2, 1.1 Hz, 1H), 7.07 (dd, J = 7.5, 7.5 Hz, 1H), 7.00-7.05 (m, 4H), 6.95 (br. d, J = 8.1 Hz, 1H), 6.92 (s, 1H), 6.87-6.92 (m, 2H), 6.85-6.87 (m, 1H), 6.83 (d, J = 8.1 Hz, 1H), 6.51 (dt, J = 15.5, 5.6 Hz, 1H), 6.18 (d, J = 15.7 Hz, 1H), 5.54 (s, 1H), 5.16-2.53 (m, 1H), 4.97 (s, 1H), 4.52 (dd, J = 7.2, 7.2 Hz, 1H), 4.47 (dd, J = 14.0, 7.2 Hz, 1H), 4.37
(dd, J = 10.0, 3.6 Hz, 1H), 3.88 (br. d, J = 4.9 Hz, 2H), 3.44-3.52 (m, 1H), 3.31-3.38 (m, 1H), 3.23 (dd, J = 14.6, 7.5 Hz, 1H), 3.09-3.11 (m, 1H), 2.93 (ddd, J = 15.4. 10.4, 5.2 Hz, 1H), 2.77-2.86 (m, 11H), 2.38 (d, J = 16.6 Hz, 1H), 2.09-2.18 (m, 2H), 1.96-2.06 (m, 1H), 1.93 (d, J = 13.4 Hz, 1H), 1.83 (d, J = 13.2 Hz, 1H), 1.55-1.64 (m, 2H), 0.76 (s, 3H), 0.73 (s, 3H). MS (ESI) Calculated for C_{62}H_{62}FN_{7}O_{4}S [M+H]^+: 1020.5, found 1020.2

Tabulated data for 39 - 3/1 mixture of olefin isomers - ^1H NMR (MeOD-d_4, 600 MHz): δ 8.34 (s, 1H), 7.52-7.58 (m, 2H), 7.22-7.29 (m, 4H), 7.14 (app t, J = 7.6 Hz, 1H), 7.02-7.07 (m, 2H), 6.99 (app t, J = 7.5 Hz, 1H), 6.92 (d, J = 4.7 Hz, 1H), 6.8 (s, 1H), 6.77 (br. t, J = 4.8 Hz, 1H), 6.54-6.62 (m, 2H), 6.41-6.48 (m, 3H), 5.67-5.71 (m, 0.65 H, major isomer), 5.49-5.51 (m, 0.35 H, minor isomer), 4.47-4.57 (m, 2H), 4.20-4.34 (m, 2H), 3.76 (dd, J = 15.4, 4.2 Hz, 1H), 3.48-3.54 (m, 2H), 3.45 (dd, J = 15.0, 7.5 Hz, 1H), 3.03 (dd, J = 14.9, 8.4 Hz, 1H), 2.73-2.85 (m, 3H), 2.56-2.68 (m, 2H), 2.48 (dd, J = 15.7, 8.3 Hz, 1H), 2.18 (dd, J = 14.6, 11.0 Hz, 1H), 2.02-2.07 (m, 1H), 1.91-1.98 (m, 1H), 1.72-1.82 (m, 2H), 1.54-1.58 (m, 1H), 1.34-1.44 (m, 2H), 1.24-1.31 (m, 2H), 0.93 (s, 1H, minor isomer), 0.92 (s, 1H, minor isomer), 0.86 (br. s, 4H, major isomer). MS (ESI) Calculated for C_{62}H_{62}FN_{7}O_{4}S [M+H]^+: 1020.5, found 1020.2

Tabulated data for 40 - 3/1 mixture of olefin isomers - ^1H NMR (MeOD-d_4, 600 MHz): δ 8.46 (br. s, 1H), 7.96 (s, 1H), 7.54 (m, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.53 (m, 1H), 7.44-7.51 (m, 2H), 7.28-7.33 (m, 2H), 7.19-7.25 (m, 3H), 7.05-7.09 (m, 2H), 7.02-7.05 (m, 2H), 7.01 (br. s, 1H), 6.96-7.01 (m, 2H), 6.92 (br. s, 1H), 6.87 (dd, J = 5.2, 3.7 Hz, 1H), 6.8 (br. d, J = 3 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 6.6 (br. d, J = 7.1 Hz, 1H), 6.53 (dt, J = 15.4, 5.9 Hz, 1H), 6.35 (d, J = 15.4 Hz, 1H), 5.66-5.70 (m, 0.75 H major isomer), 5.48-5.50 (m, 0.25 H minor isomer), 4.69 (d, J = 17 Hz, 1H), 4.46-4.51 (m, 1H), 4.38 (dd, J = 10.6, 3.6 Hz, 1H), 4.18-4.27 (m, 1H), 3.91 (dd, J = 15.9, 5.6 Hz, 1H), 3.87 (dd, J = 16.1, 5.2 Hz, 1H), 3.43-3.50 (m, 2H), 3.24-3.28 (m, 1H), 3.2 (dd, J = 14.8, 7.3 Hz, 1H), 3.14 (dd, J = 15.4, 3.5 Hz, 1H), 2.94-3.08 (m, 2H), 2.74-2.87 (m, 3H), 1.99-2.05 (m, 2H), 1.72-1.84 (m, 3H), 1.57-1.69 (m, 6H), 1.22-1.31 (m, 3H). MS (ESI) Calculated for C_{62}H_{62}FN_{7}O_{4}S [M+H]^+: 1020.5, found 1020.2
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**Chemical Structure:**

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D1  2.00000000 sec
P1  7.50 usec
SP1  400.1324008 MHz
NUCLEUS  1H

F2 - Processing parameters
SI  65536
SF  400.1300173 MHz
WDW  EM
SSB  0
LB  0.30 Hz
GB  0
PC  1.00
Current Data Parameters
NAME   KL-II-292_clf23_13c_meod
EXPNO   1
PROCNO  1

F2 - Processing parameters
SI       65536
SF      150.9028090 MHz
WDW    EM
SSB     0
LB      1.00 Hz
GB      0
PC      1.00
Current Data Parameters
NAME     KL-II-292_c1f23_2d_1h_nmoed
EXPNO                 3
PROCNO                1

F1 - Acquisition parameters
TD                  256
SFO1           600.1327 MHz
FIDRES        21.046606 Hz
SW                8.078 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                 2048
SF          600.1300000 MHz
MC1         States-TPPI
SSB      0
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2         States-TPPI
SF          600.1300000 MHz
WDW               QSINE
SSB      0
LB       0 Hz
GB       0
Current Data Parameters
NAME KL-II-292_c1f23_2d_1h_meod
EXPMO 4
PROCNO 1
F1 - Acquisition parameters
TD 256
SFO1 150.9179 MHz
FIDRES 117.903725 Hz
SW 199.999 ppm
FnMODE QF
F2 - Processing parameters
SI 2048
SF 600.130000 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 2048
MC2 QF
SF 150.9028090 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 2048
MC2 QF
SF 150.9028090 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F2 - Processing parameters
SI 2048
SF 600.130000 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
Current Data Parameters
NAME: KL-II-293_F4_13C_CD3CN
EXPNO: 1
PROCNO: 1

F2 - Processing parameters
SI: 65536
SF: 150.9026668 MHz
WDW: EM
SSB: 0
LB: 1.00 Hz
GB: 0
PC: 1.40
Current Data Parameters

NAME       KL-II-292_F4_2d_cd3cn
EXPNO       3
PROCNO      1

F1 - Acquisition parameters
TD          256
SP01        600.1332 MHz
FIDRES      24.660667 Hz
SW          10.520 ppm
FMODE       States-TPPI

F2 - Processing parameters
SI          2048
SF          600.1300000 MHz
WDW         SINE
SSB         0
LB          0 Hz
GB          0
PC          1.00

F1 - Processing parameters
SI          2048
MC2         States-TPPI
SF          600.1300000 MHz
WDW         TRAP
SSB         0
LB          0 Hz
GB          0
Current Data Parameters
NAME           KL-II-293_f5_1h_cd3cn
EXPNO                 6
PROCNO                1

F2 - Acquisition Parameters
Date_          20100923
Time              17.26
INSTRUM           AV600
PROBHD   5 mm TBI 1H-BB
PULPNOG            zg30
TD                65536
SOLVENT           CD3CN
NS                 121
DS                 0
SWH       12376.237 Hz
FIDRES          0.188846 Hz
AQ              2.6476543 sec
RG                 256
DW        40.400 usec
DE                6.00 usec
TE             294.0 K
DL         2.00000000 sec
TD0                   1

------- CHANNEL f1 -------
NUC1                 1H
P1               8.60 usec
PL1              -2.00 dB
PL1W     39.81071854 W
SF01          600.1300000 MHz

F2 - Processing parameters
SI                65536
SF          600.1300000 MHz
WDW                 EM
SSB                 0
LB                0.30 Hz
GR                 0
PC                 1.00
Current Data Parameters
NAME: KL-II-293_F4heat12h_1h_cd3cn
EXPNO: 2
PROCNO: 1
F2 - Acquisition Parameters
Date: 20100930
Time: 19.04
INSTRUM: AV600
PROBHD: 5 mm TBI 1H-BB
PULPROG: zg
TD: 65536
SOLVENT: CD3CN
NS: 16
DS: 0
SWH: 6009.615 Hz
FIDRES: 0.091699 Hz
AQ: 5.4529952 sec
RG: 228.1
DW: 83.200 usec
DG: 6.00 usec
TE: 293.9 K
D1: 2.00000000 sec
TDO: 1
---------- CHANNEL f1 ----------
NUC1: 1H
P1: 8.60 usec
PL1: -2.00 dB
PL1W: 39.81071854 W
SF01: 600.130006 MHz
F2 - Processing parameters
SI: 65536
SP: 600.130000 MHz
WDW: EM
SSB: 0
LB: 0.30 Hz
PC: 1.00
Current Data Parameters
NAME     KL-II-293_F4heat12h_1h_cd3cn
EXPGN    3
PROCNO   1

F1 - Acquisition parameters
TD                  256
SFO1            600.133 MHz
FIDRES        23.475060 Hz
SW               10.014 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                 2048
SF          600.1300000 MHz
WDW               SINE
SSB      0
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2         States-TPPI
SF          600.1300000 MHz
WDW               QSINE
SSB      0
LB       0 Hz
GB       0
Current Data Parameters
NAME     KL-II-293_F4heat12h_1h_cd3cn
EXPDNO    4
PROCNO    1

F1 - Acquisition parameters
TD                  256
SFO1           150.9179 MHz
FIDRES       117.904610 Hz
SM              200.000 ppm
FnMODE               QF

F2 - Processing parameters
SI                 2048
SF          600.1300000 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2                  QF
SF          150.9028090 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME     KL-III-108-2-1
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20110513
Time              18.32
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG            zg30
TD                65536
SOLVENT            MeOD
NS                   37
DS                    0
SWH           12376.237 Hz
FIDRES              0.188846 Hz
AQ                  2.6476543 sec
RG                362
DW               40.400 usec
DE                6.50 usec
TE                294.4 K
D1        2.00000000 sec
TD0                   1

-------- CHANNEL f1 --------
NUC1                 1H
F1                10.40 usec
PLL            -2.00 dB
PLLW           39.81071654 W
SPOL        600.1336008 MHz

F2 - Processing parameters
SI                65536
SF        600.1300273 MHz
WDH             EM
SB              0
LB                0.30 Hz
GB                    0
PC                  1.00
Fraction 2-1

Current Data Parameters
NAME       KL-III-108-2-1
EXFNO      3
PROCNO     1

F1 - Acquisition parameters
TD          600  
SFO1       600.1327 MHz
FIDRES     10.602201 Hz
SW         10.600 ppm
FmMODE     States-TPPI

F2 - Processing parameters
SI          2048
SF         600.1300273 MHz
WDW            QSINE
SSB          2
LB          0 Hz
GB           0
PC           1.00

F3 - Processing parameters
SI          2048
MC2      States-TPPI
SF          600.1300273 MHz
WDW          USER
SSB          2
LB          0 Hz
GB           0
Fraction 2-1

Current Data Parameters
NAME     KL-III-108-2-1
EXPN0    4
PROINO   1

F1 - Acquisition parameters
TD       600
SF01     600.1327 MHz
FIDRES   10.602203 Hz
SW       10.600 ppm
FnMODE   Echo-Antiecho

F2 - Processing parameters
SI       1024
SF       600.1300273 MHz
WDW      QSINE
SSB      2
LB       0 Hz
GB       0
PC       1.00

F1 - Processing parameters
SI       1024
MC2      echo-antiecho
SF       600.1300273 MHz
WDW      USER
SSB      2
LB       0 Hz
GB       0
Fraction 2-1

Current Data Parameters
NAME     KL-III-108-2-1
EXNO                 5
PROCNO                1
F1 - Acquisition parameters
TD                  256
SF01           150.9134 MHz
FIDRES       106.110962 Hz
SW              180.000 ppm
F1MODE     Echo-Antiecho

F2 - Processing parameters
SI                 2048
SF          600.1300273 MHz
WDW                QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.40

F1 - Processing parameters
SI                 2048
MC2       echo-antiecho
SF          150.9028800 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
Fractions 2-2, 2-3, and 2-3 exhibit nearly identical $^1$H NMR spectra (overlay below), but distinct by HPLC analysis. Fraction 2-3 was unambiguously assigned as dihydronaphthalene 38. The related fractions are likely olefin isomers featuring the same C-C connectivity.

**Figure:** $^1$H NMR (600 MHz, MeCN-$d_3$). Fraction 2-4 (green, top), Fraction 2-3 (product 39, red, middle) and Fraction 2-4 (blue, bottom).
Fraction 2-2

incomplete assignment

Current Data Parameters
NAME    KL-III-108-2-2_MeOD
EXPN0   1
PROCNO  1

F2 - Acquisition Parameters
Date     20110504
Time     18.02
INSTRUM  av600
PROBHD   5 mm TBI5
PULPROG  zg30
TD       65536
SOLVENT  MeOD
NS       837
DS       0
SWH      12376.237 Hz
FIDRES   0.188846 Hz
AQ       2.6476543 sec
RG       362
DW       40.400 usec
DE       6.50 usec
TE       295.8 K
D1       2.00000000 sec
TDO      1

--------- CHANNEL f1 ---------
NUC1   1H
P1     8.60 usec
PL1    -2.00 dB
PL1W   39.81071854 W
SFO1   600.1336008 MHz

F2 - Processing parameters
SI      65536
SF      600.1300273 MHz
WDW     EM
SSB     0
LB      0.30 Hz
PC      1.00
Current Data Parameters
NAME KL-III-108-2-2_MeOD
EXPNO 3
PROCNO 1
F1 - Acquisition parameters
TD 256
SFO1 600.1329 MHz
FIDRES 22.816883 Hz
SW 9.733 Ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 2048
SF 600.1300273 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 2048
MC2 States-TPPI
SF 600.1300273 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
Fraction 2-2

Current Data Parameters
NAME: KL-III-108-2-2 MeOD
EXPNO: 4
PROCNO: 1

F1 - Acquisition parameters
TD: 256
F01: 600.1329 MHz
FIDRES: 22.816883 Hz
SW: 9.733 ppm
FmMODE: Echo-Antiecho

F2 - Processing parameters
SI: 1024
SF: 600.1300273 MHz
WDW: QSINE
SSB: 2
LB: 0 Hz
GB: 0
PC: 1.00

F1 - Processing parameters
MC2: echo-antiecho
SF: 600.1300273 MHz
WDW: USER
SSB: 2
LB: 0 Hz
GB: 0
Fraction 2-3 (Product 38)
Fraction 2-3 (Product 38)
Fraction 2-3 (Product 38)
Fraction 2-3 (Product 38)
Fraction 2-3 (Product 38)
Fraction 2-4

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Current Data Parameters
NAME     KL-III-108-2-4_MeOD
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20110502
Time              21.03
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG            zg30
TD                65536
SOLVENT            MeOD
NS                  112
DS                0
SWH           12376.237 Hz
FIDRES            0.188846 Hz
AQ                  2.6476543 sec
RG                362
DW                40.400 usec
DE               6.50 usec
TE                294.8 K
D1                2.00000000 sec
TDO                1

----- CHANNEL f1 ------
NUC1                 1H
P1                8.60 usec
PL1               -2.00 dB
PL1W            39.81071854 W
SFO1      600.1336008 MHz

F2 - Processing parameters
SI                65536
SF            600.1336008 MHz
WDW        EM
SSB                0
LB                0.30 Hz
PC                1.00
Fraction 2-4

Current Data Parameters
NAME: KL-III-108-2-4_MeOD
EXPN0: 3
PROCNO: 1

F1 - Acquisition parameters
TD: 256
SFO1: 600.1328 MHz
FIDRES: 21.798269 Hz
SW: 9.299 ppm
FnMODE: States-TPPI

F1 - Processing parameters
SI: 2048
MC2: States-TPPI
SF: 600.1300273 MHz
WDW: TRAP
SSB: 2
GB: 0
LB: 0 Hz
PC: 1.00

F1 - Processing parameters
SI: 2048
MC2: States-TPPI
SF: 600.1300273 MHz
WDW: TRAP
SSB: 2
GB: 0
LB: 0 Hz
PC: 1.00
Fraction 2-4

Current Data Parameters
NAME: KL-III-108-2-4_MeOD
EXPNO: 4
PROCNO: 1

F1 - Acquisition parameters
TD: 256
SFO1: 600.1328 MHz
FIDRES: 21.798269 Hz
SW: 9.299 ppm
FnMODE: Echo-Antiecho

F2 - Processing parameters
SI: 1024
SF: 600.1300273 MHz
WDW: QSINE
SSB: 2
LB: 0 Hz
GB: 0
PC: 1.00

F1 - Processing parameters
SI: 1024
MC2: Echo-Antiecho
SF: 600.1300273 MHz
WDW: QSINE
SSB: 2
LB: 0 Hz
GB: 0
Fraction 2-4
Fraction 3-5-1

Current Data Parameters
NAME        K1-III-108-3-5-1
EXPNO       5
PROCNO      1

F2 - Acquisition Parameters
Date_       20110603
Time        9.49
INSTRUM      av600
PROBHD      5 mm TBI5
PULPROG      zg
TD           65536
SOLVENT      MeOD
NS           368
DS           0
SWH         12376.237 Hz
FIDRES      0.188846 Hz
AQ           2.6476543 sec
RG           362
DW           40.400 usec
DE           6.50 usec
TE           295.1 K
D1           2.00000000 sec
TDO          1

-------- CHANNEL f1 --------
NUC1          1H
P1            10.60 usec
PL1           -2.00 dB
PL1W      39.81071854 W
SPOL        600.1336008 MHz

F2 - Processing parameters
SI           65536
SF           600.1300273 MHz
WDM         EM
SSB          0
LB           0.30 Hz
GB           0
PC           1.00
Fraction 3-5-1

Current Data Parameters
NAME     Kl-III-108-3-5-1EXPNO                 2
PROCNO                1
F1 - Acquisition parameters
TD                  512
SFO1           600.1327 MHz
FIDRES        10.523297 Hz
SW                8.978 ppm
FnMODE      States-TPPI
F2 - Processing parameters
SI                 2048
SF          600.1300273 MHz
WDW                QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.00
F1 - Processing parameters
SI                 2048
MC2         States-TPPI
SF          600.1300273 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
Fraction 3-5-1

Current Data Parameters
NAME     KL-III-108-3-5-1
EXPNO                 3
PROCNO                1

F1 - Acquisition parameters
TD                  512
F1 - Processing parameters
SI                 1024
SF          600.1300273 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Acquisition parameters
TD                  512
SP01           600.1327 MHz
FIDRES        12.424457 Hz
SW               10.600 ppm
FmMODE     Echo-Antiecho

F2 - Processing parameters
SI                 1024
SF          600.1300273 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Acquisition parameters
TD                  512
SP01           600.1327 MHz
FIDRES        12.424457 Hz
SW               10.600 ppm
FmMODE     Echo-Antiecho

F2 - Processing parameters
SI                 1024
SF          600.1300273 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.00
Fraction 3-5-1
Fraction 3-5-1

Current Data Parameters
NAME: Kl-III-108-3-5-1
EXPCNO: 7
PROCNO: 1

F1 - Acquisition parameters
TD: 256
SFO1: 150.9149 MHz
FIDRES: 117.902252 Hz
SW: 200.000 ppm
FmMODE: QF

F2 - Processing parameters
SI: 1024
SF: 600.1300273 MHz
WDW: QSINE
SSB: 2
LB: 0 Hz
GB: 0
PC: 1.00

F1 - Processing parameters
SI: 1024
MC2: QF
SF: 150.9028090 MHz
WDW: TRAP
SSB: 2
LB: 0 Hz
GB: 0
Fraction 4-1 (Product 40)

Current Data Parameters
NAME       KL-III-108-4-1_MeOD
EXPNO      1
PROCNO     5

F2 - Acquisition Parameters
Date_       20110420
Time        21.14
INSTRUM     av600
PROBHD      5 mm TBI5
PULPROG     zg30
TD          65536
SOLVENT     MeOD
NS          179
DS          0
SWH         12376.237 Hz
FIDRES      0.188846 Hz
AQ          2.6476543 sec
RG          456.1
DW          40.400 usec
DE          6.50 usec
TE          294.6 K
D1         2.00000000 sec
TDD         1

--------- CHANNEL f1 ---------
NUCI        1H
P1          8.60 usec
PLL         -2.00 dB
PLLW        39.81071854 W
SF01        600.1336008 MHz

F2 - Processing parameters
SI          65536
SF          600.1300273 MHz
WDW         EM
LB          0
GR          0.30 Hz
PC          1.00
Fraction 4-1 (Product 40)
Fraction 4-1 (Product 40)
Fraction 4-1 (Product 40)

Current Data Parameters
NAME       KL-III-108-4-1_MeOD
EXPNO      8
PROCNO     1

F1 - Acquisition parameters
TD          256
SFO1        150.9134 MHz
FIDRES      106.110962 Hz
SW          180.000 ppm
FmMODE      Echo-Antiecho

F2 - Processing parameters
SI          2048
SF          600.1300273 MHz
WDW         Q-SINE
SSB         2
LB          0 Hz
GB          0
PC          1.40

F1 - Processing parameters
SI          2048
MC2         echo-antiecho
SP          150.9028800 MHz
WDW         Q-SINE
SSB         2
LB          0 Hz
GB          0
Fraction 5-2

Current Data Parameters
NAME     KL-III-108-5-2_MeOD
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20110415
Time              17.09
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG            zg30
TD                65536
SOLVENT            MeOD
NS                  128
DS                  0
SWH           12376.237 Hz
FIDRES        0.188846 Hz
AQ                2.6476543 sec
RG                  362
DW               40.400 usec
DE                6.50 usec
TE                293.6 K
D1           2.00000000 sec
D0                  1

-------- CHANNEL f1 --------
NUC1                 1H
P1                 8.60 usec
PL1               -2.00 dB
PL1W         39.81071854 W
SFO1       600.1336008 MHz

F2 - Processing parameters
SI                65536
SF     600.1300273 MHz
WDW                  EM
SSB                  0
LB                  0.30 Hz
PC                  1.00
Fraction 5-2 (Product 39)
Fraction 5-2 (Product 39)
Fraction 5-2 (Product 39)

Current Data Parameters
NAME     KL-III-106-5-2_MeOD_3
EXPNO                6
PROCNO                1

F1 - Acquisition parameters
TD                  248SFO1           150.9134 MHz
FIDRES       109.533897 Hz
SW              180.000 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 2048
SF          150.9028800 MHz
WDW                USERSSB                   2LB       0 Hz
GB       0
PC                 1.40

F1 - Processing parameters
SI                 2048
MC2       echo-antiecho
SF           600.1300273 MHz
WDW                QSINE                   2GB       0
LB       0 Hz
GC                 0
PC                 1.40

F1 - Processing parameters
SI                 2048
MC2       echo-antiecho
SF           150.9028800 MHz
WDW                USER
SSB                   2LB       0 Hz
GB       0
Fraction 5-2 (Product 39)
Fraction 6-2 (incomplete assignment)
Fraction 6-2

Current Data Parameters
NAME   KL-III-108-6-2
EXPNO  3
PROCNO 1

F1 - Acquisition parameters
TD      600
SFO1    600.1327 MHz
FIDRES  10.602201 Hz
SW      10.600 ppm
FnMODE  States-TPPI

F2 - Processing parameters
SI      2048
SF      600.1300273 MHz
WDW     QSINE
SSB     2
LB      0 Hz
GB      0
PC      1.00

F1 - Processing parameters
SI      2048
MC2     States-TPPI
SF      600.1300273 MHz
WDW     QSINE
SSB     2
LB      0 Hz
GB      0
Fraction 6-2

Current Data Parameters
NAME     KL-III-108-6-2
EXPN     4
PROCNO   1

F1 - Acquisition parameters
TD        600
SFO1      600.1327 MHz
FIDRES    10.602203 Hz
SW        10.600 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI        1024
SF        600.1300273 MHz
WDW       QSINE
SSB       2
LB        0 Hz
GB        0
PC        1.00

F1 - Processing parameters
SI        1024
MC2       echo-antiecho
SF        600.1300273 MHz
WDW       USER
SSB       2
LB        0 Hz
GB        0
References

Reactions of scalemic 1 with enantiopure polyamides generate diastereoisomeric product mixtures which are difficult to separate. This unnecessarily complicates analysis/characterization.

Material prepared in this work shows [α]D = +29.0 (c 0.56, CHCl3). This is signed opposite to previously synthesized 1, which was drawn incorrectly in our previous communication.

Chapter 2 - Composite macrocyclic peptidomimetics display antibacterial activity against *S. aureus*

2. Introduction

*Introduction adapted from Lawson, K.V; Rose, T.E.; Harran, P.G*

NIH Application Number: 1 R01 AI097490-01

Modern antibiotics have been an unparalleled success. So much so that our ability to treat infectious disease is often taken for granted. However, after decades of use, resistance is widespread, rendering numerous of these compounds obsolete. More than 70% of hospital-acquired infections are now recalcitrant to at least one class of small molecule antibiotic – and resistance is no longer confined to health care institutions. In the United States, community associated methicillin-resistant *Staphylococcus aureus* (MRSA) is the leading cause of soft tissue infections. Vancomycin (Figure 1), often a last line of defense against multi-drug resistant bacteria, has begun to lose potency. The need to develop new, broadly efficacious antibiotics is widely recognized. At the same time, the rate of new antimicrobials reaching the

![Non-ribosomal peptides](image)

*Figure 1.* Non-ribosomal peptides are a diverse family of clinically useful antimicrobial natural products. In general, the materials are characterized by large ring structures incorporating non-proteinogenic amino acid residues, imbedded and/or peripheral heterocycles and often harbor lipid and/or carbohydrate modifications.
clinic is in steady decline.\textsuperscript{8,9} This is, in part, due to a lack of innovative technology to address the structural complexity of current antibiotics – the majority of which derive from intricate natural products.\textsuperscript{10} Whether the commercial material is natural or a semi-synthetic derivative, fermentation-based production methods inherently limit the range of accessible chemical diversity.\textsuperscript{11,12,13,14}

A promising source of novel antibiotics are the non-ribosomal peptides (Figure 1). Many well-known antibiotics are derived biosynthetically from peptides, such as the $\beta$-lactams, the glycopeptides vancomycin, teicoplanin, and televancin, the lipopeptide daptomycin, as well as the cyclosporins, lantibiotics, and gramicidin.\textsuperscript{15} Inspired by how nature assembles these materials, we are developing synthetic processes that operate similarly. Using this technology, we are building a platform for antibiotic discovery. In short processing sequences, we transform machine-made peptides and related oligomers into complex polycyclic derivatives. These are rich in stereochemistry and diverse in shape. End-products retain molecular recognition elements in the biopolymer, yet display that functionality as part of stable, conformationally defined structures having improved pharmacological properties.

We have previously described the utility of aldehyde 1 to prepare diverse mixtures of conformationally constrained peptidomimetics which mirror the complexity of NRP natural products. This process involves three steps wherein electrophilic functionality present in 1 was sequentially promoted to react with unprotected peptide first bimolecularly, then intramolecularly to form constrained composites of 1 and the peptide. A typical example of this process is depicted in Figure 2A. Tripeptide WWY was ligated to 1 at the N-terminus using TosMIC methodology. Treatment of this adduct with catalytic Pd\textsuperscript{0} decomposes the cinnamyl carbonate and the resultant electrophilic Pd-cinnamyl is captured by the pendent tyrosyl phenol to afford macroether 2. Reagent 1 sheds its oxygenation during these events to become solely unsaturated hydrocarbon in the product. Compound 2 is a unique cyclopeptide, yet the value of 1 in assembling such structures is the options it makes available for further modifications.
Treatment with anhydrous acid initiates a number of competing/sequential isomerizations via carbocationic rearrangements. In the case of 2, we convert a 23-membered cyclic ether into polycycle 13 wherein non-canonical aryl Claisen rearrangement has occurred alongside...
installation of a novel *ansa* bridge - likely via a side-chain propargylic cation engaging the proximal tryptophan residue in a transannular electrophilic aromatic substitution. Additionally, structurally unique isomeric products having 21, 19 and 15-membered macrocycles (see chapter 1) are also obtained from this single reaction.

The power of this process lies in its ability to rapidly produce structurally diverse macrocyclic composite peptides. We have characterized thoroughly individual products from this synthetic sequence to gain understanding of the chemistry. In future iterations full structure elucidations will be guided by biological screening after iterative SAR of the peptide domain has identified refined lead compounds. A schematic of this process is shown in Figure 2C. This study aims to expand the library size and interface with high-throughput screening for antibacterial activity. We believe this therapeutic area is well matched to the structural types generated in this work.

**2.1. Materials and Methods**

2.2.1. Van Leusen imidazole synthesis

Reactions were conducted in disposable reaction vials and mixed with an oscillating platform. Each vessel was charged with ~0.25 mmol peptide (1.2 equiv), K$_2$CO$_3$ (1.0 mmol, 4 equiv.) and diluted with anhydrous DMF (1.66 mL, 0.15 M). To this solution was added a 0.3M solution of 1 in DMF (833 μL, 1 equiv.) and mixed for 4 hours to induce imine formation. Solid (para-fluorophenyl)tosylmethylisocyanate (0.3 mmol, 1.2 equiv) was added directly to the reaction vessel and the resulting solutions was mixed overnight. Each reaction was syringe filtered (0.45 μM) into 16x100mm tubes and the solvent removed by centrifugal evaporation. The crude products were reconstituted in DMF (1.5 mL) and purified by mass-guided automated HPLC/MS (Table 1). Fractions were evaporated to dryness, reconstituted in methanol, and appropriate

<table>
<thead>
<tr>
<th>Method</th>
<th>20-100%B (12min grad.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column</td>
<td>Sunfire C18 30x150mm</td>
</tr>
<tr>
<td>Solvent A</td>
<td>H$_2$O (0.1% TFA)</td>
</tr>
<tr>
<td>Solvent B</td>
<td>MeOH (0.1% TFA)</td>
</tr>
<tr>
<td>Injection Vol.</td>
<td>750 μL (2 injections)</td>
</tr>
</tbody>
</table>
Figure 3. Sample set of imidazole syntheses performed in a MiniBlock® 24-well reactor. A. Sample spreadsheet of reagent/stoichiometry calculations and yields. Yield denoted as 0% if desired product was not detected by LC/MS B. Sequences corresponding to A1-D6. C. Purity

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>MW (product)</th>
<th>Reinstr.</th>
<th>Purity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KL-IV-71-A1</td>
<td>1118.59</td>
<td>X</td>
<td>95A1</td>
</tr>
<tr>
<td>KL-IV-71-A2</td>
<td>1144.61</td>
<td>X</td>
<td>95A2</td>
</tr>
<tr>
<td>KL-IV-71-A3</td>
<td>1312.80</td>
<td>X</td>
<td>85A3</td>
</tr>
<tr>
<td>KL-IV-71-A4</td>
<td>1305.75</td>
<td>X</td>
<td>85A4</td>
</tr>
<tr>
<td>KL-IV-71-A5</td>
<td>1272.76</td>
<td>X</td>
<td>85A5</td>
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<tr>
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<td>1182.64</td>
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<td>90A6</td>
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<tr>
<td>KL-IV-71-B1</td>
<td>1213.65</td>
<td>X</td>
<td>80B1</td>
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<td>1253.70</td>
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<td>80B2</td>
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<td>95B3</td>
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<td>KL-IV-71-C1</td>
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<td>X</td>
<td>95C1</td>
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<td>1286.71</td>
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<tr>
<td>KL-IV-71-C3</td>
<td>1161.62</td>
<td>X</td>
<td>90C3</td>
</tr>
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<td>90C4</td>
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<td>85C5</td>
</tr>
<tr>
<td>KL-IV-71-C6</td>
<td>1196.66</td>
<td>X</td>
<td>90C6</td>
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<tr>
<td>KL-IV-71-D1</td>
<td>1200.65</td>
<td>X</td>
<td>90D1</td>
</tr>
<tr>
<td>KL-IV-71-D2</td>
<td>1196.66</td>
<td>X</td>
<td>90D2</td>
</tr>
<tr>
<td>KL-IV-71-D3</td>
<td>1250.72</td>
<td>X</td>
<td>60D3</td>
</tr>
<tr>
<td>KL-IV-71-D4</td>
<td>1253.73</td>
<td>X</td>
<td>90D4</td>
</tr>
<tr>
<td>KL-IV-71-D5</td>
<td>1253.72</td>
<td>X</td>
<td>90D5</td>
</tr>
<tr>
<td>KL-IV-71-D6</td>
<td>1166.64</td>
<td>X</td>
<td>95D6</td>
</tr>
</tbody>
</table>
fractions were combined into tared 16x100mm tubes and evaporated. The purity was re-analyzed via HPLC/MS. An example spreadsheet is shown in Figure 3.

2.1.2. Pd-catalyzed macrocyclization

Compounds purified by preparative HPLC were treated with silica bound tetraalkylaammonium carbonate (Si-CO$_3$, Silicycle, 0.59 mmol/g, 2 equiv.) for 30 minutes in DMF, and re-concentrated to remove residual TFA prior to cyclization. The Pd-catalyzed macrocyclizations were performed in 24-well format using a MiniBlock® fitted with an inert atmosphere manifold. Reactions were performed in 10 mL filter tubes as follows. To a solution of imidazole (0.05 mmol) in degassed DMF (10 mL, 5 mM) was added catalyst solution (735 uL, 0.04 mol% [PdCl(C$_3$H$_5$)$_2$], 0.10 mol% xanthphos). The reaction was allowed to stir at room temperature for two hours and 50 mg Si-Thiol (Silicycle) was added to the reaction tube and mixed for 5 minutes. The solutions were filtered and collected in 16x100mm tubes and evaporated. The crude solutions were used without further purification.

The solution of catalyst was prepared as follows: An oven-dried, serum-topped vial was placed in a glove bag and charged with [PdCl(C$_3$H$_5$)$_2$] (14 mg, 0.038 mmol) and xanthphos (55 mg, 0.095 mmol). The vial is sealed, removed from the glove bag, and degassed THF (7.0 mL) was added, followed by degassed DMF (7.0 mL). The resulting yellow solution was stirred under argon for 30 minutes.

2.1.3. Acid treatment

The crude macrocycles were dissolved in CH$_3$NO$_2$ (5 mM, based on mass of acyclic imidazole) and CH$_3$SO$_3$H (15 equiv.) was added via micropipette. The reaction was stirred for two hours then quenched with saturated NaHCO$_3$. The reaction was diluted with EtOAc and transferred to a separatory funnel. The organic layer was washed with water and brine then dried over Na$_2$SO$_4$ and evaporated in vacuo. The crude acidolysis mixture was reconstituted in
DMSO and fractionated by preparative HPLC. The fractions were evaporated, dissolved in methanol and transferred into pre-weighed 0.5dr vials and evaporated to dryness.

2.1.4. Antibacterial Screening

A detailed SOP for the primary screen is described in the appendix. Following fractionation the library was prepared as 10 mM stock solutions in DMSO and arrayed in 96-well plates. DMSO solutions were transferred into 384-well plates and diluted to 1.0 mM with DMSO. These solutions were pin tool transferred (0.5 μM) to plates containing sterile culture media for a final concentration of 10 μM with 1% DMSO present in final assay volume.

The primary library was initially assayed for antibacterial activity against *Burkholderia oklahomensis* (C6786), *Escherichia coli* (BW25113), *Staphalococcus aureus* at 10 μM final compound concentration. Each strain was grown in liquid culture to OD$_{600} = 0.6$, diluted 1000-fold, and seeded into assay plates in a class II biosafety cabinet. Microplates were sealed for biocontainment and incubated at 37°C. Optical density (OD$_{600}$) was measured every 60 minutes for 24 hours and data was obtained as growth curves. Growth inhibition was evaluated from the slope of growth within the logarithmic phase for each compound. Compounds displaying favorable activity were selected for further investigation. Chloramphenicol served as positive control for all screens. The dynamic range of the assay was confirmed using dilution series of doxycycline.

2.2. Results

2.2.1. Library Construction

Adapting our previous described protocols to parallel high-throughput synthesis required considerable optimization. Liquid-liquid extractions following the Van Leusen imidazole synthesis and Pd-catalyzed macrocyclization were readily obviated. Purification of the acyclic imidazoles was achieved via mass-guided automated preparative HPLC. A methanol/water
mobile phase was utilized to reduce cost. A set of 24 crude imidazole reaction mixtures (e.g. Figure 3) could be purified in 6 hours. Yields for the imidazole synthesis ranged from 0 to 30% and was highly dependent to amino acid at the terminal position. As a result, β-branched amino acids were typically not employed at the N-terminus. This compromise improved average yields to approximately 30%.

Catalyst removal following macrocyclization was achieved with thiol impregnated silica gel, obviating a second chromatographic purification. Aqueous work-up following acidolysis was required which proved technically challenging when conducted in parallel. Similarly, due to the complicated acidolysis reaction mixtures, manual preparative HPLC fraction collection was required.

The pilot library was derived from sequences composed of 3-5 amino acids. Peptides were prepared using Fmoc-based automated solid phase synthesis techniques. Assembly was performed Rink polystyrene resin, providing C-terminal carboxamides upon cleavage. Each sequences contained at least one phenol-presenting residue selected from those show in Figure 2B or a histidine residue. The remaining positions were filled randomly with residues chosen from the same set shown and natural and D-configured amino acids. Cysteine was not included due to its oxidative lability. The initial screening set consisted of 383 fractions derived from 35 sequences (Table 2). An average of 11 fractions were isolated from each peptide.
Table 2. List of peptides processed to construct primary screening library.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sequence</th>
<th>Entry</th>
<th>Sequence</th>
<th>Entry</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Val-Trp-Tyr-Phe</td>
<td>13</td>
<td>Phe-Tyr-Tyr</td>
<td>25</td>
<td>Tyr(OMe)-Trp-Tyr(o-NMe₂)</td>
</tr>
<tr>
<td>2</td>
<td>Val-Ala-Tyr-Val</td>
<td>14</td>
<td>Ala-Val-Tyr(o-OMe)</td>
<td>26</td>
<td>Gly-D-Leu-D-Tyr-Ala</td>
</tr>
<tr>
<td>3</td>
<td>Gly-Trp-Tyr-Trp</td>
<td>15</td>
<td>Leu-Phe-Tyr(o-OMe)</td>
<td>27</td>
<td>Ac-Gly-Orn(II)-Dap(CO₂C₆H₁₃)-Tyr</td>
</tr>
<tr>
<td>4</td>
<td>Ala-Phe-Trp-Tyr</td>
<td>16</td>
<td>Gly-MePhe-Tyr</td>
<td>28</td>
<td>Gly-Ser-Tyr-Trp</td>
</tr>
<tr>
<td>5</td>
<td>Ala-Phe-Tyr-Val</td>
<td>17</td>
<td>D-Leu-D-Tyr-D-His</td>
<td>29</td>
<td>D-Ile-Trp-Tyr-D-Ala</td>
</tr>
<tr>
<td>6</td>
<td>Ile-Trp-Tyr-5HTA</td>
<td>18</td>
<td>D-Leu-Phe(NMe₂)-Tyr(o-NMe₂)</td>
<td>30</td>
<td>Gly-Gly-Phg-Tyr(o-NMe₂)</td>
</tr>
<tr>
<td>7</td>
<td>Gly-Leu-SHTA</td>
<td>19</td>
<td>Gly-Phe-Tyr-D-His</td>
<td>31</td>
<td>Gly-Tyr-Leu-SHTA</td>
</tr>
<tr>
<td>8</td>
<td>Val-D-Val-D-Leu-Tyr-Thi</td>
<td>20</td>
<td>D-Ala-D-Phe-His-Phe</td>
<td>32</td>
<td>D-Leu-Ile-Tyr(o-OMe)</td>
</tr>
<tr>
<td>9</td>
<td>D-Val-D-Tyr-Tyr(o-OMe)-Tyr</td>
<td>21</td>
<td>B-Ala-Tyr(OMe)-Tyr-oxazole-indole</td>
<td>33</td>
<td>Phe(NMe₂)-Tyr(OMe)-Tyr</td>
</tr>
<tr>
<td>10</td>
<td>Tyr(OMe)-D-Leu-Tyr(o-NMe₂)-D-Ala</td>
<td>22</td>
<td>B-Ala-Pro(4-OAr)-Trp-Tyr</td>
<td>34</td>
<td>Val-Pro-Tyr(o-OMe)-Tyr</td>
</tr>
<tr>
<td>11</td>
<td>Ala-D-Val-D-Pro-His</td>
<td>23</td>
<td>Ser-Tyr(OMe)-Tyr-Ile-oxazole</td>
<td>35</td>
<td>D-Val-Pro-Tyr(o-NMe₂)</td>
</tr>
<tr>
<td>12</td>
<td>Ser-Tyr-D-Pro</td>
<td>24</td>
<td>Gly-Trp-Pro-Tyr-Leu-NHMe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Library Statistics:
- 383 member library
- 35 sequences (average ~11 fractions/peptide sequence)
- Fraction quantities:
  - average: 1.24 mg
  - median: 0.76 mg

2.2.2. Screening

The primary bacterial growth inhibition screen of the 383 compounds was performed against gram negative *B. oklahomensis*, *E. coli*, and gram positive *S. aureus* at 10 μM substrate concentration. No active fractions were identified against *B. oklahomensis* or *E. coli*. However, fractions derived from tetrapeptide Ala-D-Val-D-Pro-His, suppressed growth of *S. aureus* at 10 μM. The exponential growth phase was delayed 12 hours relative to vehicle (Figure 4C). The observed activity was confirmed in a repeat assays.
HPLC analysis of the active fraction revealed it was predominantly composed of 4 and 5 – unconsumed starting materials to the acidolysis reaction (Figure 4). These regioisomeric macrocycles differ in the position of cinnamyl linkage. The major and minor products arise from the cinnamylation of the imidazole Nτ and Nπ positions respectively. In contrast to the tyrosyl ethers derived from Pd-catalyzed macrocyclization, the cinnamyl-histidine C-N bond is not prone to acid-catalyzed ionization. Cationic isomerizations are thereby limited to the dien-yne moiety and a reduced rate starting material consumption was common for His-alkylated macrocycles.

To minimize potential false negatives associated with screening compound mixtures and confirm no additional fractions were active against *S. aureus*, Ala-D-Val-D-Pro-His was re-synthesized and processed with 1. Acidolysis products were fractionated to single components
and screened using an 8-point dilution series (range: 1.5 - 200 μM). Only fractions composed of 5 inhibited bacterial growth with an IC50 of ~12.5 μM. The major regioisomeric macrocycle 4, derived the Pd-catalysis, showed no growth inhibition up to 200 μM. Also, only the unreacted macrocycles were active indicating protolytic modification of the dien-yne appendage was not tolerated.

We next examined modifications of the peptide sequence. A set of 18 related sequences were prepared and processed with 1 (Table 3). Sequences were designed to systematically mutate single amino acid positions to build an initial SAR profile. Acidolysis products were fractionated to single components to minimize the need for re-purification and secondary screens. Isolated compounds were screened at 10 and 20 μm as described for the primary assay.

Only limited modification of the first residue was tolerated. Truncation, oxygenation, and stereochemical modification resulted no observed growth inhibition (entries 2-4). The A1G mutated sequence (entry 1) showed a moderate reduction in activity, delaying growth for 10 hours at 20 μM (Figure 4A). N-methylation and V2A mutation at position 2 was not tolerated (entries 7-9). Replacement of Val2 with (2,4-dimethoxy)phenylalanine resulted in multiple, sequential fractions which inhibited growth at 20 μM (entry 10 and Figure 5A). Replacement of D-Val with D-Thr at position 2 resulted in slightly improved activity with growth inhibition observed at 10 μM (entry 6, Figure 5B). All modifications of the proline residue resulted in reduced activity. Only replacement with α-aminoisobutyric acid displayed growth inhibition at 20 μM. Replacement of the His4 with histamine briefly delayed growth at 20 μM (entry 16). Stereochemical inversion at this position led to slightly enhanced activity with growth inhibition observed at 10 μM (entry 17). These compounds retained activity when screened in the same format against B. subtilis.
Table 3. Antibacterial activities of secondary screening set.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sequence</th>
<th>Inhib.</th>
<th>Entry</th>
<th>Sequence</th>
<th>Inhib.</th>
<th>Entry</th>
<th>Sequence</th>
<th>Inhib.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gly-D-Val-D-Pro-His</td>
<td>20 μM</td>
<td>7</td>
<td>Ala-Val-D-Pro-His</td>
<td>–</td>
<td>13</td>
<td>Ala-D-Val-Sar-His</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>D-Val-D-Pro-His</td>
<td>–</td>
<td>8</td>
<td>Ala-D-Ala-D-Pro-His</td>
<td>–</td>
<td>14</td>
<td>Ala-D-Val-D-Hyp-His</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Ser-D-Val-D-Pro-His</td>
<td>–</td>
<td>9</td>
<td>Ala-D-(NMe)Val-D-Pro-His</td>
<td>–</td>
<td>15</td>
<td>Ala-D-Val-Pro-His</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>D-Ala-D-Val-D-Pro-His</td>
<td>–</td>
<td>10</td>
<td>Ala-D-Phe(3,4-OMe)-D-Pro-His</td>
<td>20 μM</td>
<td>16</td>
<td>Ala-D-Val-D-Pro-Histamine</td>
<td>20 μM</td>
</tr>
<tr>
<td>5</td>
<td>Ac-Orn-D-Val-D-Pro-His</td>
<td>–</td>
<td>11</td>
<td>Ala-D-Val-Aib-His</td>
<td>20 μM</td>
<td>17</td>
<td>Ala-D-Val-D-Pro-D-His</td>
<td>10 μM</td>
</tr>
<tr>
<td>6</td>
<td>Ala-D-Thr-D-Pro-His</td>
<td>10 μM</td>
<td>12</td>
<td>Ala-D-Val-Hyp-His</td>
<td>–</td>
<td>18</td>
<td>Ala-D-Thr-D-Pro-D-Tyr</td>
<td>–</td>
</tr>
</tbody>
</table>

Modified residues depicted in blue. Fractions derived from each sequence were screened at 10 and 20 μM. The concentration at which the sequence inhibited growth of *S. aureus* relative to control is indicated.

Figure 5. Bacterial growth curve for select Table 3 entries. A. Growth curves at 20 μM substrate concentration. Repeat table entries represent unique fractions from acidolysis which exhibits growth inhibition. B. Growth curves at 10 μM substrate concentration.
With an initial SAR profile of the peptide domain established we sought to investigate activity relationships of the hydrophobic domain imparted from 1. As discussed above, an unmodified dien-yne appendage was a requisite for antibacterial activity. The $p$-fluorophenylimidazole motif was invariant within the screening library. To determine if this motif was essential for bioactivity we prepared an oxidized analog of our reagent (6, Figure 6). This allowed the imidazole motif to be replaced with an amide bond while retaining the core functionality of 1. Following a three-step amidation-macrocyclization-acidolysis sequence (Figure 6), purified fractions were arrayed and screened. No fractions inhibited S. aureus growth up to 200 μM, suggested the $p$-fluorophenylimidazole motif was a determinant for antibacterial activity.

2.3 Discussion and Conclusions

This initial follow-up set shows systematic modification of the peptidyl domain provides useful SAR data in the context of these discovery efforts. The hit-rate of the secondary library was greatly increased over that from random sequences. Multiple modifications aimed towards synergistic activity gains were not investigated, but would likely be beneficial. Of particular interest was the regiochemical dependence of cinnamyl alkylation on antibacterial activity. Although compounds derived from the secondary library were not fully characterized spectroscopically, the active component in each was derived from the minor product of the Pd-
catalyzed macrocyclization. Subsequent studies (chapter 3) reveal the ratio of \( N^T \) and \( N^{\text{III}} \) alkylation is consistent across numerous sequences. The marked activity relationship with this relatively minor structural variation suggests a general bacterial membrane poor-forming mechanism of action, common to amphipathic cationic antimicrobial peptides, may not be operative.\textsuperscript{18,19} Future work on the lead series identified in these studies is certainly warranted.
References


Chapter 3 - Preparation of template-constrained macrocyclic peptides via Palladium-catalyzed allylic alkylation of natural amino acids

adapted in part from

Template-constrained macrocyclic peptides prepared from native, unprotected precursors

Kenneth V. Lawson, Tristan E. Rose, Patrick G. Harran


3.1. Introduction

Synthetic peptides and peptidomimetics play wide ranging roles in pharmacology and drug discovery. Interest in these substances continues to grow, particularly as medicinal chemistry pushes further into control of cellular signaling events mediated by protein-protein interactions (PPIs).\(^1\),\(^2\),\(^3\) The subset of so-called ‘druggable’ PPIs include those mediated by consensus peptides, where binding determinants are localized within defined motifs.\(^4\),\(^5\),\(^6\),\(^7\),\(^8\) Experimental data as well as computational / bioinformatic efforts\(^9\),\(^10\),\(^11\) to identify ‘short linear motifs’ within signaling proteins suggest the number of druggable PPIs has been underestimated.\(^12\),\(^13\) Considerable opportunity exists for new chemistry in this area.\(^14\) Synthetic peptides that target ‘hot spots’ on protein surfaces are a logical entry to drug discovery programs.\(^15\),\(^16\),\(^17\),\(^18\),\(^19\) However, native peptides generally have poor pharmacological properties.\(^20\) Modifications that offset those limitations while stably recapitulating protein-binding conformations are of considerable interest.\(^14\),\(^21\),\(^22\),\(^23\)

Ring-forming reactions are prominent among alterations found to improve the stability and performance of peptides.\(^24\),\(^25\),\(^26\),\(^27\) Relative to their acyclic counterparts, cyclic peptides have more defined conformations and are less prone to aggregate.\(^28\) Head-to-tail lactamization is the most common method to synthesize cyclic peptides.\(^29\),\(^30\),\(^31\) Internal disulfide bonding is also used\(^32\),\(^33\), as are newer techniques such as ring-closing olefin metathesis\(^34\) and catalyzed
cycloaddition of azides to alkynes.\textsuperscript{35,36,37} These procedures rely on judicious use of protecting groups and/or tailored amino acid residues (Fig 1 A).\textsuperscript{38,39} Careful attention must be paid to substrate conformational biases to avoid competing oligomerization. Moreover, lactamization of peptides shorter than five residues can be particularly difficult.\textsuperscript{29,40}

A. Established Methods for Peptide Cyclization:

Peptide bond formation

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {peptide};
\node (b) at (1,0) {peptide};
\draw[->] (a) -- (b);
\end{tikzpicture}
\end{center}

\text{e.g. PyBOP}

\text{conformation/substrate dependent}

Ring closing olefin metathesis

\begin{center}
\begin{tikzpicture}
\node (c) at (0,0) {peptide};
\node (d) at (1,0) {peptide};
\draw[->] (c) -- (d);
\end{tikzpicture}
\end{center}

\text{e.g. Grubbs II}

\text{custom synthesized amino acids}

Azide-alkyne cycloaddition

\begin{center}
\begin{tikzpicture}
\node (e) at (0,0) {peptide};
\node (f) at (1,0) {peptide};
\draw[->] (e) -- (f);
\end{tikzpicture}
\end{center}

\text{e.g. Cul, base}

\text{Peptide bond formation}

\text{Ring closing olefin metathesis}

\text{Azide-alkyne cycloaddition}

B. Current Work: Templated Macrocyclization Catalyzed by Palladium(0)

\begin{center}
\begin{tikzpicture}
\node (g) at (0,0) {peptide};
\node (h) at (1,0) {peptide};
\draw[->] (g) -- (h);
\end{tikzpicture}
\end{center}

1. N-Acylation
2. Pd\textsuperscript{0}-catalyzed cyclization

\text{• unprotected peptide}

\text{X = AA side-chains:}

\begin{center}
\begin{itemize}
\item rapid/efficient macrocyclization
\item diverse macrocyclic linkages
\item utilizes natural AA side-chains
\item tunable chemoselectivity
\end{itemize}
\end{center}

\textbf{Figure 1. A.} Existing methods for peptide cyclization can be sensitive to substrate conformational preferences and/or require tailored amino acid residues. \textbf{B.} The template-based cyclizations described here are catalyzed allylic substitutions. They engage native peptide functionality and proceed largely independent of oligomer length and composition.

An alternate method to incorporate short epitopes into rings is through the use of scaffolds. Degrado\textsuperscript{41}, Boger\textsuperscript{42} and others have shown the utility of such template-constrained cyclic peptides\textsuperscript{43,44}, and how polarity and geometry of the template can the influence shape and
function of the peptide domain. Our laboratory has also explored templates for forming
macro cyclic peptides. In this work templates were designed as multiply reactive inserts.
Stepwise engagement with a variety of peptides gave novel composite products. The resultant
structures varied in shape, possessed defined conformations and increased solubility.

The large ring forming reaction in these processes was an allylic substitution catalyzed
by palladium(0). We observed that decomposition of a cinnamyl carbonate within the template
could capture pendant tryosine residues to form cyclic ethers. This result followed from
catalysis pioneered by Tsuji and Trost. Palladium catalyzed substitution of allylic leaving groups
(a.k.a. the ‘Tsuji-Trost reaction’) is a versatile and well-studied process. Mechanistically it
involves intermediate palladium π-allyl complexes that function as electrophiles. The chemistry
occurs under mild conditions and is amenable to ligand-induced regio- and stereocontrol. It has
been applied broadly, including in numerous instances to form large carbocyclic and
heterocyclic rings. That said, when we simplified our templates to further study the
catalysis in the context of cyclic peptide synthesis, we discovered a combination of scope and
functional group tolerance that was remarkable. We describe those results here.

We show that intramolecular palladium-catalyzed cinnamyl ation of heteroatom
nucleophiles can operate within highly functionalized native peptides. The nucleophile in the
macrocylization can be an amine, a carboxylic acid, a phenol, an imidazole and/or an aniline.
Chemoselectivity is predictable and in many cases switchable. With one type of exception (vide
infra), the reaction is catalyzed by a commercial complex of palladium(0), namely Pd(PPh\textsubscript{3})\textsubscript{4}. No
exotic or costly ligand sphere for the metal is necessary. No protecting groups are used in any
substrate. Reactions proceed rapidly and in high yield at room temperature and, thus far,
independent of product ring size and composition.

3.2. Results and Discussion
Template 1 (Figure 1B) is reminiscent of a lignan monomer. It is a simplified, achiral form of a structure we described previously.\textsuperscript{46} The intent was to study large ring-forming reactions involving palladium $\pi$-allyl intermediates generated from the cinnamyl carbonate in this molecule. Compound 1 was synthesized in six steps and 51% overall yield from commercial 3-(3-bromophenyl)propionic acid (Scheme 1). Multi-gram batches of solid 1 were prepared and stored at room temperature without incident. Procedures using this material were designed to be simple. It's active ester acylated peptidyl amines in neutral DMF at room temperature. The resultant adducts reacted with catalytic amounts of commercial Pd(PPh$_3$)$_4$ in argon-sparged DMF, also at room temperature.

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.png}
\end{center}

Scheme 1. Synthetic route to 1. (conditions: see supporting information).

$^1$H NMR (500 MHz, CDCl$_3$) of 1.

Initial experiments served to probe catalyzed cycloetherification of tyrosine residues (Figure 1B, XH = PhOH). Attention focused on how ring size, solvent, additives and substrate
concentration affected reaction rate and efficiency. As these experiments progressed, we observed a much greater functional group tolerance than expected. Moreover, residues such as aspartic acid, glutamic acid and histidine would participate as nucleophiles in the cyclization, as would a free carboxy or amino terminus under appropriate conditions. Chemoselectivity was both predictable and tunable. In two steps beginning with 1 and an unprotected peptide, we could achieve any one of several cyclization modes including head-to-tail, side chain-to-tail and side chain-to-side chain. Peptides up to eleven residues long were readily transformed into templated macrocycles.

3.2.1. Impact of solvent, substrate concentration and base additives on catalyzed cycloetherification of tyrosyl phenols.

Linear substrate 2 (Figure 2A) was chosen to evaluate affects of solvent and additives on catalyzed internal etherification of its tyrosyl phenol. N-Acylation of synthetic Ala-Trp-Thr-Tyr with N-hydroxysuccimidy1 ester 1 gave adduct 2 in 72% yield. Exposure of 2 to 5 mol % Pd(PPh$_3$)$_4$ in deoxygenated DMF (5 mM in 2) at room temperature caused rapid conversion to cyclic ether 4 in 91% HPLC assay yield (78% when isolated by preparative HPLC). Reaction monitoring showed complete conversion to product within 15 minutes (Figure 2B). No dimeric or oligomeric materials were detected in the experiment. As illustrated in Table 1, the catalysis proceeded efficiently in several polar aprotic solvents. The use of water as co-solvent was tolerated (entry 5), but it slowed the reaction rate ~30-fold and resulted in formation of an unidentified side-product (~15%).
In neat DMF, contact ion pairing of transient intermediates within the catalytic cycle may explain the rapid reaction rate and high product yield.\textsuperscript{54,55} Consistent with literature precedent, tert-butoxide formed from decomposition of the cinnamyl carbonate following oxidative addition of Pd\textsuperscript{0} to the allylic C-O sigma bond likely deprotonates the proximal phenol, resulting in a new, more product-like (i.e cyclic, Figure 2C) metal ion pair. Reductive elimination or displacement of palladium would follow, leading to product. Electrostatic pre-organization of amphoteric peptides has been discussed previously.\textsuperscript{56,57} The inner salts invoked here as intermediates formed at low concentration would likewise be expected to offset entropic costs associated with ring formation.\textsuperscript{57,58} It is also consistent with a general lack of oligomeric products formed in the catalysis (vide infra), which can limit other peptide cyclization methods.\textsuperscript{40,59,60} Increasing the concentration 20-fold to 0.1M (Table 1, entry 2) led to only a slight reduction in yield.

Figure 2. A. Catalyzed cycloetherification of substrates derived from templates 1 or S8 and model peptide Ala-Trp-Thr-Tyr. B. HPLC analyses (C18, 40→100% MeCN/H\textsubscript{2}O 0.1\%TFA, 10 min, monitoring @ 254 nm) of samples taken from reaction of 2 with 5 mol\% Pd(PPh\textsubscript{3})\textsubscript{4} (Table 1, entry 1) at the indicated time points. C. Partial schematic of internally ion-paired pi-allyl palladium(II) complex putatively generated from 2 via oxidative addition of Pd(0).
When cinnamyl acetate 3 (Figure 2) was subjected to identical cyclization conditions, conversion to 4 was not observed even upon prolonged heating (Table 1, entry 6). We speculated that, unlike the situation for 2, acetate ion liberated by oxidative addition of Pd$^0$ to 3 was insufficiently basic to propagate a catalytic cycle involving a tyrosyl phenoxide. Consistent with this hypothesis, addition of Cs$_2$CO$_3$ (2 equiv., Table 1, entry 7) rescued the reaction, promoting rapid conversion of 3 to cinnamyl ether 4. Under buffered aqueous conditions, the cyclization rate was pH dependent. No conversion of 2 to 4 was observed when an equal mixture of DMF and pH 5.5 phosphate buffer was used as solvent (entry 8). Increasing the buffer pH to 7.4 induced a sluggish reaction. Complete conversion to 4 required 16 hours. However, at pH 8.5 the reaction was complete within 2 hours and 4 was formed in 89% HPLC assay yield. Taken together, data in Fig. 2C suggested 5 mM solutions of carbonate substrate in neat DMF (no additives) would be the most convenient to further evaluate the scope of the macrocyclization. Substrate solubility and reaction rate would be generally highest.

### 3.2.2. Evaluating the scope of catalyzed cycloetherification.

To define the range of macrocycles available through catalyzed cinnamylation of phenols, a set of unprotected, L-amino acid derived peptides were prepared as C-terminal

---

**Table 1.** Media and additive effects on the palladium catalyzed synthesis of macrocyclic ether 4 from precursors 2 and 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent/additive</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>DMF (5 mM)</td>
<td>91 (78)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>DMF (100 mM)</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>THF (5 mM)</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>DMSO (5 mM)</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>1:1 DMF/H$_2$O (5 mM)</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>DMF (5 mM)$^b$</td>
<td>nr</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>DMF (5 mM), Cs$_2$CO$_3$ (2 equiv.)</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>1:1 DMF/100mM PBS (pH=5.5, 5mM)$^b$</td>
<td>nr</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>1:1 DMF/100mM PBS (pH=7.4, 5mM)$^b$</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>1:1 DMF/100mM PBS (pH=8.5, 5mM)</td>
<td>89</td>
</tr>
</tbody>
</table>

Reactions were run for 2h at room temperature in argon sparged media containing 5 mol % Pd(PPh$_3$)$_4$. $^a$Yield determined by HPLC assay. Isolated yield in parentheses. $^b$No conversion at 16h. $^c$16h reaction time. PBS = phosphate buffered solution. nr = no reaction
carboxamides. Peptides ranged from three to five residues long and each possessed a free N-terminus and a tyrosine residue in the sequence. All functional groups present in natural amino acids were represented in the set, with the exception of thiols (cysteine) to avoid complications from oxidative lability.

Table 2. Macrocyclic ethers obtained in two steps from template 1 and the indicated unprotected peptides (listed above product). Isolated yield of palladium catalyzed cyclization step indicated in parentheses. For conditions see Table 1, Entry 1. 5HTA = 5-hydroxytryptamine.

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Structure</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ser-Met-Tyr</td>
<td><img src="image" alt="Structure 5" /></td>
<td>(80 %)</td>
</tr>
<tr>
<td>Ile-Trp-Tyr</td>
<td><img src="image" alt="Structure 6" /></td>
<td>(72 %)</td>
</tr>
<tr>
<td>Ala-Val-Tyr</td>
<td><img src="image" alt="Structure 7" /></td>
<td>(78 %)</td>
</tr>
<tr>
<td>Trp-Ile-Gln-Tyr</td>
<td><img src="image" alt="Structure 8" /></td>
<td>(81 %)</td>
</tr>
<tr>
<td>Val-Met-Phe-Tyr</td>
<td><img src="image" alt="Structure 9" /></td>
<td>(73 %)</td>
</tr>
<tr>
<td>Gly-Thi-Trp-5HTA</td>
<td><img src="image" alt="Structure 10" /></td>
<td>(75 %)</td>
</tr>
<tr>
<td>Ile-Ala-Arg-Tyr</td>
<td><img src="image" alt="Structure 11" /></td>
<td>(84 %)</td>
</tr>
<tr>
<td>Ile-Met-Ser-Tyr-Trp</td>
<td><img src="image" alt="Structure 12" /></td>
<td>(73 %)</td>
</tr>
<tr>
<td>Ala-Phe-Thr-Ile-Tyr</td>
<td><img src="image" alt="Structure 13" /></td>
<td>(85 %)</td>
</tr>
<tr>
<td>Gly-Ser-Phe-Asn-Tyr</td>
<td><img src="image" alt="Structure 14" /></td>
<td>(74 %)</td>
</tr>
</tbody>
</table>

Acylation of each peptide with template 1 was achieved by mixing in DMF in the presence of (i-Pr)_2NEt (see Table S1). Treatment of these products with 5 mol % Pd(PPh_3)_4...
gave macrocyclic cinnamyl ethers 5-9 and 11-14 (Table 2) in high isolated yields (72-85%). No branched phenylallyl ethers were detected in these experiments. Polar functional groups including alcohols, amides and guanidines were well tolerated. Notably, efficient macroetherification was not restricted to tyrosine. 5-Hydroxyindole, incorporated as commercial 5-hydroxytryptamine, was equally competent as a nucleophile, affording macrocycle 10 in 75% yield. For each product, the macrocyclic ether linkage was assigned by NMR, wherein a diagnostic HMBC correlation between the cinnamyl methylene protons and the phenolic carbon resonance (~δ 155 ppm) was observed.

When the sequence Ala-Leu-Glu-Tyr was acylated with 1 and the product (15, Figure 3A) treated with Pd(PPh₃)₄, HMBC analysis of the resultant product did not reveal the anticipated cinnamyl ether. Rather, it indicated cyclization had formed macrolactone 16 (67% isolated yield) from cinnamylolation of glutamic acid. This connectivity was assigned based on HMBC correlation between the cinnamyl methylene protons (H1, Figure 3C) and Glu-C20 (δ 171.6 ppm). No other products were observed by HPLC (Figure 3B). We were cognizant that 16

![Diagram](image-url)
could form from 15, yet expected this compound to be susceptible to re-ionization by palladium(0). However, consistent with the inertness of cinnamyl acetate 3 to Pd(PPh₃)₄ in the absence of base (Figure 2C, entry 6), macro lactone 16 proved stable and isolable. Re-subjecting 16 to the reaction conditions did not result in isomerization to cyclic ether 17.

In contrast, when 15 was treated with 5 mol % Pd(PPh₃)₄ in the presence of Cs₂CO₃, macrocyclic ether 17 was formed exclusively and isolated in good yield (Figure 3B). Lactone 16 was not observable by HPLC during the course of the reaction. The absence or presence of Cs₂CO₃ was a convenient means to select for a 26-membered or 21-membered ring product. Such tunable outcomes bode well for preparing structurally distinct macrocycles from a single peptide sequence.

Catalyzed internal esterification proved an excellent method for head-to-tail macrolactonizations. Substrates prepared from 1 and peptides harboring a free carboxy terminus underwent the reaction readily. For example, treatment of Gly-Val-Trp-OH and Phe-Ile-Hyp-OH with 1 followed by Pd(PPh₃)₄ efficiently produced macrolactones 21 and 22 (Table 3), respectively. Branched allylic ester 22 was isolated as a ~1:1 mixture of diastereomers. No cinnamyl linkage was detected in this instance, an atypical outcome rationalized in terms of added geometric constraints imposed by the hydroxyproline residue.

Next examined were histidine containing substrates. Compound 18, derived from 1 and Val-Gln-Tyr-His, was recovered unchanged after exposure to Pd(PPh₃)₄ for extended reaction times. Stable ligation of palladium by histidine containing peptides has been reported. To mitigate suspected catalyst poisoning, we turned to a less labile/dynamic ligand sphere for the metal. When a pre-catalyst generated from [Pd(C₃H₅Cl)]₂ (4 mol%) and the chelating bis-phosphine xantphos (10 mol%) was employed, complete consumption of 18 was observed within 30 minutes (Figure 4A,B). Two regioisomeric products were obtained in a ~5:1 ratio and 75% combined yield. HMBC correlations from the cinnamyl methylene H1 to C28 and C30 confirmed the major product as histidine N29-alkylated macrocycle 20 (Figure 4C). The minor
product was determined to be its \( N31 \)-alkylated regioisomer. Neutral imidazole is a weak nucleophile in solution. A more nucleophilic imidazolate ion may be formed in this reaction. However, competition from the tyrosyl phenol was not observed despite possessing a similar pKa to the histidine imidazole. Alternatively, the propensity for azoles to ligate palladium may sustain proximity to the \( \pi \)-allyl complex, thereby favoring imidazole allylation. As observed for substrate 15, chemoselectivity was switchable upon the addition of base.

**Figure 4.** A. Cyclization chemoselectivity in sequences containing both tyrosine and histidine residues is high and base-dependent. B. HPLC analyses for the conversion of 18 to 19 or 20: (a) starting material 18, (b) after 30 min in the presence of \([\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2 (4 \text{ mol \%})/\text{xantphos} (10 \text{ mol \% in DMF})\) or (c) after 30 min in the presence of \([\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2 (4 \text{ mol \%})/\text{xantphos} (10 \text{ mol \% in DMSO})\) and \(\text{Cs}_2\text{CO}_3 (2 \text{ equiv.})\). C. Key HMBC correlations used to assign connectivity within 19 (left) and 20 (right). Note: 19 is formed as a ~5:1 mixture (see HPLC trace) of histidine \( N \)-alkylation regioisomers. The major isomer is drawn. Yields in parentheses refer to material isolated by preparative HPLC.

Treatment of 18 with \([\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2/\text{xantphos} \) and \( \text{Cs}_2\text{CO}_3 \) (2 equiv.) in DMF afforded macrocyclic ether 20 in a 5.7:1 ratio relative to regioisomers 19. Changing the reaction solvent to DMSO improved the selectivity to 10.2:1 (Figure 4), likely due to the increased solubility of \( \text{Cs}_2\text{CO}_3 \) in DMSO.

A set of peptides was prepared to examine the generality of histidine-based macrocyclization (Table 2). In each case, treatment with \([\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2/\text{xantphos} \) afforded
exclusively histidine alkylated macrocycles in high yield. Where possible, tyrosine alkyla-
tion was not detected regardless of resultant ring size or stereochemistry (e.g. Table 3 25a-c and 29). Histidine alkyla-
tion also occurred in preference to macrolactone formation in the presence of free carboxylic acids (see 23). The presence of an carboxylic acid would theoretically preclude an intermediate imidazolate species. It is possible initial macrolactone formation precedes allyl migration to form a more stable cinnamyl-imidazole. Other polar functional groups including amides, alcohols, and guanidines were well tolerated. Sequences containing both histidine and residues displaying primary amines (i.e. Lys or Orn) were unique in that cyclization was unselective and low yielding. Only the combination of histidine caused this result with amines, which likely could be managed using orthogonal protection schemes.
In other settings, amines were useful and competent reaction partners in Pd\textsuperscript{0}-catalyzed cinnamylation.\textsuperscript{68} Moreover, use of the xantphos ligand was no longer necessary. For example, acylation of Fmoc-Val-Orn-Met-Tyr with template 1 followed by treatment with piperidine gave adduct 31 (Figure 5A). Exposure of this material to 5 mol % Pd(PPh\textsubscript{3})\textsubscript{4} resulted in exclusive cinnamylation of the N-terminus to afford 33 (>95% HPLC peak area purity). This product was readily assigned by TOCSY correlations. Uniquely, 32 shows \textsuperscript{1}H-\textsuperscript{1}H correlations from the cinnamyl methylene to Val-H\textsuperscript{N}, H\textsuperscript{o}, and H\textsuperscript{b} (Figure 5B). Analogous to previous examples, chemoselectivity was sensitive to added base. The addition of 3 equiv.

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**Table 3.** Novel macrocycles obtained from templated cyclization of oligomers (drawn above product) containing carboxylic acids, imidazoles, and anilines. Isolated yield of palladium catalyzed cyclization step indicated in parentheses. For conditions see Table 1, Entry 1.

<table>
<thead>
<tr>
<th>Gly-Val-Trp-OH</th>
<th>Phe-Ile-Hyp-OH</th>
<th>D-Ala-D-Val-D-Pro-His-X</th>
<th>β-Ala-Pro(4-OAr)-His</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 21" /></td>
<td><img src="image" alt="Structure 22" /></td>
<td><img src="image" alt="Structure 23" /></td>
<td><img src="image" alt="Structure 26" /></td>
</tr>
<tr>
<td>21 (74 %)</td>
<td>22 (71 %)</td>
<td>23 X = OH (69 %)</td>
<td>24 X = NH\textsubscript{2} (77 %)</td>
</tr>
<tr>
<td>Ala-Ile-His-Phe</td>
<td>Gly-Thr-His-Tyr</td>
<td>Gly-Thr-(D)Tyr-His</td>
<td>Gly-Thr-Tyr-His</td>
</tr>
<tr>
<td><img src="image" alt="Structure 27" /></td>
<td><img src="image" alt="Structure 25a" /></td>
<td><img src="image" alt="Structure 25b" /></td>
<td><img src="image" alt="Structure 25c" /></td>
</tr>
<tr>
<td>27 (71 %)</td>
<td>25a (73 %)</td>
<td>25b (n.d.)</td>
<td>25c (n.d.)</td>
</tr>
<tr>
<td>Ala-Arg-His-Phe</td>
<td>Thr-Ala-Trp-Ile-Pro-Tyr-His-Asn-Val</td>
<td>Asn-Trp-Thr-Phe(4-NH\textsubscript{2})</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Structure 28" /></td>
<td><img src="image" alt="Structure 29" /></td>
<td><img src="image" alt="Structure 30" /></td>
<td></td>
</tr>
<tr>
<td>28 (76 %)</td>
<td>29 (69 %)</td>
<td>30 (77 %)</td>
<td></td>
</tr>
</tbody>
</table>
Cs$_2$CO$_3$ and use of DMSO as solvent provided cinnamyl ether 32 as the sole cyclization product. Under the same conditions, substrate 34 derived from 1 and Orn-Thr-Tyr gave macrocyclic ether 35 in 80% yield. The primary amine and secondary alcohol were unaffected.

We next examined a third type of nitrogen nucleophile in the cyclization reaction. Sequences were prepared containing the non-proteinogenic amino acid 4-aminophenylalanine, which is readily available and utilized as a tyrosine isostere.\textsuperscript{69,70} Peptides Ser-Phe-Phe(4-NH$_2$) and Asn-Trp-Thr-Phe(4-NH$_2$) were mixed independently with 1, which selectively acylated their N-termini. Exposure of the products to 5 mol % Pd(PPh$_3$)$_4$ rapidly formed macrocyclic aryl amines 37 and 30 in high yield (Figure 6 and Table 3). Aniline alkylated macrocycles showed
moderate oxidative lability upon storage. This could be alleviated by acetylation of the aniline N-H with Ac₂O. (37a, Figure 6C). Experiments are ongoing to determine selectivity in aniline-based macrocyclizations when other potentially competing functional groups are present.

### 3.2.3. Reversibility of Pd-catalyzed macrocyclization

As described above, Pd-catalyzed cyclization of VQYH in the absence of exogenous base affords only the histidine alkylated macrocycles. There is potential for His- and Tyr alkylation products to re-enter the catalytic cycle by oxidative insertion into the cinnamyl-N or O-bonds respectively. If this were to occur a thermodynamic distribution of products would be anticipated. Under these conditions equilibration was not observed. Re-subjecting 19 or 20 to [Pd(C₃H₅Cl)₂]/xantphos did not reveal any interconversion of macrocyclic products (Figure 7A).

Similarly, treatment of 4 with Pd(PPh₃)₄ (5 mol%) would irreversibly form 3 if oxidative...

**Figure 6.**

A. Sequences containing histidine and primary amines form non-isomeric mixtures up treatment with Pd⁰. B. In the presence of base, primary amines do not interfere with tyrosyl cyclizations. Conditions: Pd(PPh₃)₄ (5 mol %), Cs₂CO₃ (3 equiv.), DMSO (5 mM in 34). C. A sequence containing p-aminophenylalanine cyclizes readily in the absence of base. Conditions: Pd(PPh₃)₄ (5 mol %), DMF (5 mM in 36). Yields in parentheses refer to material isolated by preparative HPLC.
insertion/ionization of cinnamyl-tyrosyl C-O bond was operative (Figure 7B). These data suggest a kinetic product distribution formed when competitive tyrosine-histidine alkylation was possible.

Uniquely, the macrolactone C-O bond of 16 was isomerized to the more stable tyrosyl macrocyle upon treatment with Pd$^0$ in the presence of Cs$_2$CO$_3$ (2 equiv.). This isomerization was not reversible resulting in complete conversion to 17.

![Figure 7](https://example.com/figure7.png)

**Figure 7.** A. Resubjecting histidine or tyrosine alkylated macrocyclic products to Pd$^0$ does not result in isomeric macrocyclic products. Macrolactone 16 isomerizes to 17 when exposed to Pd$^0$ in the presence of Cs$_2$CO$_3$. B. Treatment of 4 with Pd(PPh$_3$)$_4$ (5 mol%) in the presence of AcOH (20 eq.) does not afford 3.
3.2.4. Longer sequences undergo efficient macrocyclization.

Nascent secondary structure elements in longer peptides can assist or hinder cyclization attempts, depending upon how they influence access to the transition state for intramolecular reaction. Hinderance is common and oligomeric by-products often form as a result. High dilution, pseudo-dilution on solid-support and conformationally restrained pseudoprolines are used to improve cyclization efficiency. Techniques such as helical peptide ‘stapling’, based on ring-closing olefin metathesis, require folding of the helical element for efficient cyclization.

To begin testing the utility of palladium π-allyl chemistry for cyclizing longer sequences, we prepared octa- and dodecapeptides WLQMTGFY and AFSVPGVWISYV. Acylation of these materials with template followed by treatment of the products with 5 mol % Pd(PPh₃)₄ gave macrocyclic cinnamyl ethers 39 and 38, respectively. As observed for shorter sequences, the cyclization reactions were rapid and efficient at room temperature. The 38- and 47-membered ring products were readily isolated by preparative HPLC and characterized. Competing dimerization or oligomerization was not observed.
These impressive results prompted us to investigate whether we had inadvertently chosen sequences poised to cyclize. Both 38 and 39 harbor potential turn inducing motifs centered at proline and glycine, respectively, which may accelerate the rate of ring closure. To explore this possibility, we utilized NMR to probe conformational preferences of macrocycles 38 and 39 relative to their linear precursors S32 and S33. Comparison of $^{13}$C$^\alpha$ shifts, expressed as $\Delta\delta_{\text{cyclic-linear}}$ in Figure 8C and E, revealed distinct differences in the backbone conformations of linear and cyclic structures. These data imply that the linear precursors do not tightly occupy a product-like conformation, perhaps sampling an ensemble of states under these conditions. Differences were further evidenced by changes in the temperature dependence of backbone H$^N$ chemical shifts following cyclization (Figure 9). Notably, Val$^7$ and Gly$^6$ in macrocycles 38 and 39, respectively, showed a temperature dependence of greater than -3 ppb/K, suggestive of
internal hydrogen bonding at these positions.\textsuperscript{75,81} Similar interactions were not observed in the linear precursors, wherein a smaller temperature dependence was measured at the same positions; these comparisons are illustrated in Figure 5C as $\Delta(\Delta\delta/\Delta T)_{cyclic-linear}$. It appears that a product-like conformation of the linear precursor need not predominate in order for the palladium catalyzed cyclization to occur. Also, the G6A mutant of 8 cyclized readily. (Figure 10)
**Figure 9.**

A. Temperature dependence of backbone $\delta^{H\text{N}}$ chemical shifts for $S_{32}$, $S_{33}$, $S_{38}$, and $S_{39}$ recorded in 9:1 DMSO-$d_6$/H$_2$O. Linear regression equation shown for residues exhibiting reduced chemical shift temperature dependence. B. Overlay of TOCSY and NOESY spectra of $S_{39}$ (DMSO-$d_6$/D$_2$O, 9/1, 600 MHz). For full NOESY assignment see supporting information.
3.2.5. Template 1 stabilizes secondary structure and enhances proteolytic stability in vitro.

Based on NMR evidence for internal hydrogen bonding, we next examined if templated macrocycle 39 exhibited a defined conformation in solution. Complete resonance annotations from NMR spectra acquired in 9:1 DMSO-\(d_6\):H\(_2\)O facilitated assignment of 80 intramolecular NOEs and 13 dihedral angle restraints. Sequential H\(^N\) NOEs within the triad Met\(^4\)-Thr-Gly\(^6\) indicated the presence of a beta turn. Transannular NOEs between Leu\(^2\) and Phe\(^7\), and between Gln\(^3\) and the C-terminus were indicative of the ring structure. Distance and angle constrained molecular mechanics calculations identified a tight ensemble of low energy conformers. The global energy minimum and an overlay of conformers of similar energy are shown Figure 5A and B. The region Gln\(^3\)-Met-Thr-Gly-Phe\(^7\) occupies a type I \(\beta\)-turn, consistent with the observed Gly\(^6\) H\(^N\) temperature coefficient (-2.4 ppb/K, Figure 9). These data indicate a well-ordered core macrocycle and stabilization of the peptide domain, despite potential flexibility of the template.

Restricted conformational mobility is one means by which folded polypeptides evade enzymatic degradation.\(^{82,83,84}\) Accordingly, we examined the extent to which macrocycles 38 and 39 were protected against proteolytic degradation by \(\alpha\)-chymotrypsin in vitro. As expected, linear compound S33 was degraded rapidly, with primary cleavage occurring between Phe\(^7\) and Tyr\(^8\). Corresponding macrocycle 39 was 8.7-fold more stable in this assay (Figure 8D), and was

![Figure 10. Cyclization of G6A mutant of 39 – Efficient cyclization can be achieved in the absence of turn-inducing residues.](image-url)
cleaved at the same site. Macrocycle 38 also exhibited resistance to proteolysis, although product inhibition precluded accurate determination of its half-life and comparison to linear counterpart S32. Enzymatic hydrolysis between Trp⁸ and Ile⁹ was invariant between cyclic 38 and the linear material. These preliminary results are encouraging and imply enhanced proteolytic stability observed for conventional cyclic peptides will be a feature of macrocycles derived from template 1 as well. Investigation of additional pharmocological properties of composite peptide macrocycles are ongoing.

3.2.6. Template-stabilized α-helical motifs

We are currently investigating whether palladium catalyzed allylation can be employed to stabilize other secondary structure elements. Methods to stabilize short alpha-helical domains present at protein-protein interfaces are of considerable interest, with numerous strategies having been employed. Recently all-hydrocarbon peptide stapling utilizing ring closing olefin metathesis of alpha-alkenyl alanine residues has been shown to stabilize known helical protein binding domains and confer favorable pharmacological properties. This strategy relies on a hydrophobic media to aid conformation pre-organization and facilitate interaction of reactive residues. The catalysts employed are sensitive to polar functional groups which are often masked with protecting groups during cyclization.
The flexibility and versatility of our method may provide a powerful complement to these existing stapling strategies. The geometry, length, flexibility, and polarity of the staple can be optimized by systematic modification of reacting residues and template structure. By harnessing the inherent reactivity of native peptides, we may also be able to utilize biotic peptides. We have demonstrated the efficacy of our method to generate $i, i+7$ cyclized peptides relevant to the p53-MDM2 interaction (e.g. Ac-QSQQTFOrnNLWRLLHQN, Figure 11). The functional group complexity of these longer peptide sequences does not reduce the cyclization efficiency (Figure 11B). Additional examples (Figure 11C) show how the length and flexibility of the staple may be tuned by modification of the reacting amino acid residues. While these data demonstrate the utility of Pd-catalyzed allylations to prepare long-chain macrocyclic peptides, the investigation of the pharmacological and conformational properties of these composite peptide macrocycles is ongoing.
3.2.7. Solid-phase synthesis of template constrained peptide macrocycles.

We next examined the potential of 1 to prepare macrocyclic peptides on solid support. Our strategy employed differentially histidine monomers which could be selectively deprotected following ligation of 1. This strategy would selectively unveil reacting partners and thus overcome the intrinsic chemoselectivities described above. We chose Fmoc-His(Mmt)-OH which may be deprotected with weakly acidic solutions - AcOH:TFE:CH₂Cl₂ (1:1:8 v/v). Importantly, these conditions do not decompose the cinnamyl carbonate of 1 or remove other standard side-chain protecting groups commonly employed in Fmoc-SPPS.

Tetrapeptide Orn-Gln-His-Phe was chosen to evaluate the efficacy of this approach. This would expand the scope as the primary amine side-chain of ornithine is not compatible with the solution phase histidine alkylations described above. Following acylation with 1, the Mmt protecting group was removed by treatment with AcOH:TFE:CH₂Cl₂ for two hours (Figure 12A). The optimal deprotection time was determined prior to installment of 1 by LC/MS analysis of test cleavages for the presence of the 4-methoxytritylcation. Following deprotection, treatment with [Pd(C₃H₅Cl)₂/xantphos and subsequent cleavage from solid-support provided the desired histidine-alkylated macrocycle in good purity (Figure 12B).
To examine the potential of this strategy to prepare stabilized helical motifs we prepared decapeptide OrnAVQRHEHAF. This sequence contains participating residues at $i,i+7$ relative positions (Orn1/His8) which would potentially be located on the same face of an alpha-helical conformation and represents a common peptide 'stapling' strategy. Following the three step deprotection-cyclization-cleavage protocol the desired cyclic decapeptide was isolated as a white solid following ether precipitation.

With the success of this model study our attention turned to biologically relevant $\alpha$-helical motifs. Extensive work by Walensky and coworkers has demonstrated the utility of stapled peptides to interrogate biological process related to the Bcl-2 family proteins. To allow ready comparison to these existing techniques we investigated the utility of our approach to prepare cyclic peptides encompassing the BH3 domain of Mcl-1. A set of six sequence were chosen based on existing binding data. To evaluate the effect of staple length a mixture of $i,i+3$ and $i,i+7$ staple positions were chosen. Sequences were prepared in parallel by standard Fmoc-SPPS techniques as their N-terminal acetate utilizing highly acid labile Lys(Mtt) side-chain

Figure 12. A. Solid-phase macrocyclization of Orn-Gln-His-Phe-NH$_2$(Rink). Conditions: a) AcOH, TFE, DCM (1:1:8); b) [Pd(C$_3$H$_5$)Cl]$_2$ (8 mol%), xantphos (20 mol%), DMF (degassed), 2h; c) TFA:H$_2$O:TIS (95:2.5:2.5), 1h. B. Crude HPLC analyses of 41 after cleavage. (C18, UV254 nm).

TIS = triisopropylsilane, TFE = trifluoroethanol, Mmt = p-methoxytrityl
protecting strategy to allow selective amine deprotection and ligation with 1. The acid sensitivity of the Mtt group was considerably reduced when incorporated into the peptide sequence and attached to solid support. As such, iterative treatment with TFA:TIS:DCM (3:2:95 v/v) was required for complete side-chain protecting group removal of participating Lys and His residues.

Figure 13. A. Solid-phase macrocyclization of Orn(γ-1)AVQRHEHAF-NH₂(Rink). Conditions: a) AcOH, TFE, DCM (1:1:8); b) [Pd(C₃H₅H₅)Cl]₂ (8 mol%), xantphos (20 mol%), DMF (degassed), 2h; c) TFA:H₂O:TIS (95:2.5:2.5), 1h. B. Crude HPLC analyses for the conversion of # to #. (C18, UV254 nm). TIS = triisopropylsilane, TFE = trifluoroethanol, Mmt = p-methoxytrityl.

Unfortunately, analysis of the completed peptides prior to ligation with 1, revealed the desired peptides were formed in low purity. Adjusting coupling times, reagents, pre-activation of amino acids resulted in only a moderately improved purity. The source of side products was unclear. In spite of the poor peptide purity, each sequence was coupled with 1 and cyclized as described above. In each case the desired macrocycles were observed by LC/MS, but with substantial impurities, indicative of the low purity observed from the starting sequence. The macrocycles were isolated by iterative preparative HPLC. Characterization was limited to mass spectral analysis as only low-milligram quantities of each were isolated.
indicate promise for Pd-catalyzed allylations to prepare long-chain macrocyclic peptides on solid-support, refined protocols for parallel peptide synthesis are necessary to make this a viable method. An alternative strategy to deblock participating residues, such as nucleophilic or basic cleavage, would be beneficial.

3.3. Conclusions

We have described methods to convert unmodified, unprotected linear peptides directly to stable macrocycles using 1 as a scaffold. Non-natural amino acids are not required. The catalyzed ring forming reaction is uniquely versatile and operates independent of product ring size and composition. Side chain functional groups present in tyrosine, histidine, glutamic acid and aspartic acid participate in the cyclization, as do a free carboxy or amino terminus under appropriate conditions. Alcohols, guanidines, carboxamides and thioethers neither participate nor interfere with the catalysis. The chemistry is well suited to probe consensus peptide binding sites, to generate peptide-based positive controls for assay development, to stabilize and protect elements of secondary structure (i.e. turns, helices) and to create prototype leads for

Figure 14. Solid-phase synthesis of stabilized alpha-helical peptide related to the BH3 domain of Mcl-1. Staple positions denoted with red characters. Coloration of helical represents stapled positions.
medicinal chemistry programs targeting protein/protein interactions. Simple procedures, mild reaction conditions, high yields and tunable chemoselectivity provide for myriad possibilities. The chemistry compares favorably to other methods for peptide cyclization. The ready availability of peptides commercially will hopefully facilitate additional research by others.
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## D. Spectroscopic Data

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General:

Unless stated otherwise, reactions were performed under an argon atmosphere in flame-dried glassware. Tetrahydrofuran (THF) was deoxygenated and dried by passing through an activated alumina solvent drying system. Anhydrous N,N-dimethylformamide (EMD DriSolv®) was used without further purification.

Purification of acidolysis products employed an Agilent 1100/1200 HPLC system equipped with G1361A preparative pumps, a G1314A autosampler, a G1314A VWD, and a G1364B automated fraction collector. Analytical HPLC was performed using the same system, but with a G1312A binary pump. Mass spectra were recorded using an Agilent 6130 LC/MS system equipped with an ESI source.

NMR methods:

NMR spectra were recorded on Bruker Avance (500 or 600 MHz) spectrometers. Data for $^1$H NMR spectra are reported as: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration), and are referenced to a residual DMSO-d6 (2.50ppm). $^{13}$C resonances are reported in terms of chemical shift (δ ppm) as referenced to DMSO-d6 (39.52 ppm). For mass-limited samples, solvent magnetic susceptibility matched Shigemi tubes were used with a sample volume of ~300 µL. Optimization of on-axis shims was accomplished using the TopShim automated tool within Bruker Topspin™ 2.1. Optimization of off-axis shims was performed manually, or with TopShim3D in the case of samples containing H$_2$O. $^1$H 90° transmitter pulse lengths were calibrated by back calculation from the 360° null. The pulse width or power level for soft pulses and shaped pulses were calculated using the Shape Tool within TopSpin™ 2.1.

COSY spectra were recorded using a phase sensitive, gradient enhanced double-quantum-filtered experiment, or magnitude mode gradient enhanced experiment with presaturation using the States-TPPI method. Data were typically recorded as a matrix of 2048 x 512 complex points and 2 transients per increment. Data were apodized with a π/3-shifted sine-bell in the F1 dimension truncated at 10%, and with an untruncated π/3-shifted sine-bell in the F2 dimension. Zero filling was applied in F2 to give a symmetrical matrix of 4K x 4K real points following mirror image linear prediction in F1 (64 coefficients) to 256 points.

TOCSY spectra were recorded using a phase sensitive experiment implementing preservation of equivalent pathways. A 60ms DIPSI-2 or MLEV pulse train was used for homonuclear Hartman-Hahn transfer. Data were typically recorded as a matrix of 2048 x 256 complex points and 2 or 8 transients per increment. Data were apodized with a π/3-shifted squared sine-bell in the F1 dimension truncated at

10%, and with an untruncated \(\pi/2\)-shifted squared sine-bell in the F2 dimension. Zero filling was applied in F2 to give a symmetrical matrix of 4K x 4K real points following mirror image linear prediction in F1 (64 coefficients) to 128 points.

NOESY spectra were recorded using a phase sensitive experiment with selection gradients during the mixing time. A 300ms mixing time was used for qualitative structural assignment. Data were typically recorded as a matrix of 4096 x 256 complex points and 8 transients per increment. Data were apodized with a \(\pi/3\)-shifted squared sine-bell in the F1 dimension truncated at 10%, and with an untruncated \(\pi/2\)-shifted squared sine-bell in the F2 dimension. Zero filling was applied in F2 to give a symmetrical matrix of 4K x 4K real points following forward linear prediction in F2 (32 coefficients) to 64 points, and mirror image linear prediction in F1 (64 coefficients) to 128 points.

Carbon chemical shifts were measured from 2D plots of either HSQC spectra for protonated carbons or HMBC spectra for non-protonated carbons. \(^1\)H-\(^{13}\)C HSQC spectra were recorded using a sensitivity improved phase sensitive experiment using an adiabatic shape pulse for \(^{13}\)C inversion, and \(^{13}\)C decoupling during acquisition. Experimental parameters were optimized for \(^1\)J\(_{\text{CH}}\) = 145Hz. \(^1\)H-\(^{13}\)C HMBC spectra were recorded using a gradient selected experiment with a J-filter element optimized for \(^1\)J\(_{\text{CH}}\) = 125-165Hz. Experimental parameters were optimized for long range \(^6\)J\(_{\text{CH}}\) = 8Hz.

**Solution conformation of compound 39:**

The solution conformation of 39 was determined from NMR spectra acquired in 9:1 DMSO-d\(_6\):H\(_2\)O and in 9:1 DMSO-d\(_6\):D\(_2\)O. All spectra were recorded on a Bruker AV-600 spectrometer equipped with an inverse triple resonance probe. Except for variable temperature experiments used for the determination of backbone NH temperature coefficients, all spectra were recorded at 283K. Water suppression was achieved with presaturation for COSY experiments, and with excitation sculpting for 1D-\(^1\)H, TOCSY and NOESY experiments. Sequence specific \(^1\)H assignments were determined by standard methods for unlabeled polypeptides employing TOCSY and NOESY data. Temperature dependence of backbone H\(^N\) chemical shifts was determined from 1D-\(^1\)H experiments and confirmed by COSY experiments.

Distance restraints were obtained from a \(^1\)H-\(^1\)H NOESY experiment using a 150ms mixing time and 2s interscan delay. Data were calibrated to the fixed reference distance Trp H\(^{1\text{a}}\)-H\(^{1\text{c}}\) (H18-H20, page 4) of 2.82Å. Volume integrals were grouped into bins, and classified as strong (\(<2.5\)Å), medium (\(<3.5\) Å) or weak (\(<4.5\) Å), based on the relationship of \(r^{-6}\) assuming linear buildup and the isolated spin pair approximation. Backbone phi angle restraints were derived from \(^3\)J\(_{\text{HNHa}}\) coupling constants measured from 1D-\(^1\)H and DQF-COSY experiments conducted in 9:1 DMSO-d\(_6\):H\(_2\)O, and were restrained to \(\pm 40^\circ\) of the

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predicted angle(s) derived the Karplus equation.\(^9\) Side chain chi-1 torsion restraints were derived from analysis of \(^3\)J\(_{\text{HαHβ}}\) coupling constants measured from 1D-\(^1\)H and E.COSY experiments conducted in 9:1 DMSO-d\(_6\):D\(_2\)O. Stereospecific assignment of β-methylenes was made by analysis of H\(^N\)-H\(^β\) NOEs, where possible, and chi-1 angles were restrained to ±60º of the predicted angle(s).

Structure calculations were carried out using Macromodel v9.8 (Schrödinger, Inc., San Diego, CA) using the OPLS-2005 force field with implicit GB/SA aqueous solvation and a constant dielectric (ε = 1.0). Distance and dihedral restraints were introduced as pseudoenergy terms comprising a flat bottomed harmonic potential of 100kJ/Å\(^2\), and 1000kJ/mol, respectively. An initial model was generated by a 10,000 step mixed Monte-Carlo long range, low-mode conformational search. Ambiguous NOEs were manually refined based on this initial model. The final structure calculation was carried out in the same manner. Redundant conformers were filtered within a heavy atom RMSD cutoff of 1.0Å, and the top 10 structures selected for the ensemble.

**Tabulated NOEs and coupling constants for macrocycle 39 in DMSO-d\(_6\)::H\(_2\)O (9:1):**

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### Tabulated NOEs for macrocycle 39

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**Total NOE restraints**
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- Intraresidue (42)
- Sequential $(i - j = 1)$ (31)
- Non-sequential, long-range $(i - j > 1)$ (7)

**RMSD (Å) pairwise averaged over ensemble**
- Heavy atoms 0.76
- Core macrocycle 0.36
- All atoms 0.95

**Constraint violations**
- No. of NOEs. > 0.5Å 4
- Sum of violations > 0.5Å (Å) 2.22
- Max. NOE violation (Å) 0.66
Resonance assignment for WLQMTGFY

9:1 DMSO-d$_6$:H$_2$O (600 MHz)
Resonance assignment for AFSVPGVWISYV

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9:1 DMSO-$d_6$:H$_2$O (600 MHz)
**Proteolytic degradation assay:**

Stock solutions of α-chymotrypsin (bovine type II, 61.75 U/mg) were freshly prepared in 1mM HCl, and diluted into assay buffer (56 mM Tris pH 7.8, 560µM CaCl$_2$, 0.1% Tween-80) just prior to addition of the substrate. Reactions were conducted in silanized glass vials. The reaction was initiated by addition of DMSO stock solution (50 µM) of the macrocycle 39 or linear precursor S33 to give a final substrate concentration of 5 µM, 50µg/mL α-chymotrypsin, and 10% DMSO. Control reactions contained BSA instead of α-chymotrypsin. Aliquots were removed in triplicate at 1, 2, 5, 10, 15 and 30 min (acyclic) or 1, 15, 30, 60, 120, and 180 min (cyclic), and diluted 1:1 with N,N-DMF containing 1% TFA, which resulted in a pH < 2. Time course data were obtained by HPLC-MS or HPLC-UV analysis and quantification against external calibration curves. Compound 38 was assayed in the same manner, except that Tween-80 was omitted from the reaction buffer and the initial substrate and enzyme concentrations were 50 µM and 5 µg/mL, respectively. No loss was observed in control reactions. Kinetic constants were determined by least squares fitting to the first order rate law $[S] = c + A(1 - e^{-kt})$ using the Solver tool in Microsoft Excel. Half lives were calculated as 0.693/k. α-Chymotrypsin cleavage sites were determined by purification of products from short reaction times, and analysis by HPLC-MS (Agilent 6130) for linear precursors S32 and S33 and by infusion ESI-MS/MS (Bruker Solarix) for macrocycles 38 and 39.

**Figure S1.** Temperature dependence of backbone H$^N$ chemical shifts for S32, S33, 38, and 39.
Analytical HPLC conditions for 38:
*Column:* Agilent Eclipse XBD C18, 4.6x150mm, 5µm
*Solvent A:* H$_2$O + 0.1%v TFA
*Solvent B:* ACN + 0.1%v TFA
*Injection Vol.:* 40µL
*Flow rate:* 1.00 ml/min

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Analytical HPLC Conditions for 39:
*Column:* Agilent SB-Aq, 4.6x50mm, 1.8µm
*Solvent A:* H$_2$O + 0.1%v TFA
*Solvent B:* ACN + 0.1%v TFA
*Injection Vol.:* 40µL
*Flow rate:* 1.00 ml/min

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ESI-MS/MS data for proteolysis of 39

Preparative HPLC Conditions for 39:
*Column:* Waters Sunfire, 10x250mm, 5µm
*Solvent A:* H$_2$O + 0.1%v TFA
*Solvent B:* ACN + 0.1%v TFA
*Flow rate:* 7.0 ml/min

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ESI-MS/MS data for proteolysis of 38

Preparative HPLC Conditions for 38:
Column: Waters Sunfire, 10x250mm, 5µm
Solvent A: H₂O + 0.1%v TFA
Solvent B: ACN + 0.1%v TFA
Flow rate: 7.0 ml/min

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Peptide Synthesis:
C-terminal carboxamide peptides were synthesized manually using standard Fmoc solid phase synthesis protocols on Rink Amide MBHA resin (200-400 mesh, 0.70 mmol/g, 1% DVB) on 0.25-0.50 mmol scale using a fritted glass reaction vessel. Fmoc-deprotection was achieved with 20% piperidine in DMF (2 x 30 min). The reaction vessel was washed with DMF (3x) and CH₂Cl₂ (2x). The vessel was then charged with the appropriate Fmoc-amino acid (4 equiv) and TBTU (4 equiv) followed by DMF (10-20 ml) and iPr₂NEt (10 eq). The resin was agitated for 2 hours, drained, and washed with DMF (3X). After all coupling were completed the resin was cleaved with TFA/thioanisole/water/TIPS (90:2.5:5:2.5) for 2 hours. The cleaved resin was removed by filtration and the filtrate was concentrated under vacuum. The peptide was precipitated with ether and isolated by centrifugation. The peptide pellet was repeated washed with Et₂O to ensure complete removal of cleavage reagents. Fmoc-4-(Boc-amino)-L-phenylalanine was used to prepare 4-aminophenylalanine containing peptides.

C-terminal carboxylate peptides were prepared on Wang Resin (0.84 mmol/g). The first amino acid (2.5 equiv) was pre-activated with DIC (2.5 equiv) in DMF (5-10 ml) and then added the pre-swelled resin (1 equiv) and DMAP (0.1 equiv) in DMF (5-10 ml). The resin suspension was agitated for 3 hours. The subsequent Fmoc deprotections, couplings, and resin cleavage were performed as described above.

H-Gly-Trp-Thi-5-Hydroxytryptamine was prepared by attachment of Fmoc-5-hydroxytryptamine to 2-Chlorotritylchloride resin (100-200 mesh, 0.84 mmol/g) via the phenolic oxygen as follows: A solution of Fmoc-5-hydroxytryptamine (398 mg, 1.00 mmol) in dichloromethane (10 ml) was added to a flask containing 2-Chlorotritylchloride resin (840 mg, 1.00 mmol) followed by iPr₂NEt (174 ul, 1.00 mmol). The mixture was agitated for 10 minutes then an addition aliquot of iPr₂NEt (261 ul, 1.50 mmol) was added and the mixture was agitated for an addition 2 hours. Methanol (500 uL) was added and the resin was mixed for an addition 15 minutes, then filtered through a sintered glass funnel. The resin was washed with CH₂Cl₂ (3x), DMF (3x), CH₃OH (3x), and dried under high vacuum. The substitution was estimated by mass. Chain elongation was performed as described above. Cleavage from the resin was achieved with 1:1:8 AcOH:TFE:CH₂Cl₂ for 2 hours.
Synthesis of 1:

**methyl 3-(3-bromophenyl)propanoate (S2).** To a solution of 3-bromophenylpropanoic acid S1 (11.52 g, 50.29 mmol) in anhydrous methanol (200 ml) was added dropwise thionyl chloride (7.18 g, 60.35 mmol) over 30 minutes and allowed to stir for 18h at room temperature. Rotary evaporation gave crude ester S2 as a colorless oil. Purification by column chromatography (SiO2, 15% EtOAc/hexanes) afforded S2 (11.80 g, 97%). ¹H NMR (CDCl₃, 500 MHz): δ 7.29-7.35 (m, 2H), 7.08-7.15 (m, 2H), 3.67 (s, 3H), 2.90 (t, J = 7.7 Hz, 2H), 2.62 (t, J = 7.7 Hz, 2H). ¹³C NMR (CDCl₃, 125 MHz): δ 172.9, 142.9, 131.4, 130.1, 129.4, 127.0, 122.5, 51.7, 35.3, 30.5. MS (ESI) Calculated for C₁₁H₁₁BrO₂ [M+H]⁺: 243.0, found 242.6.

**(E)-methyl 3-(3-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)phenyl)propanoate (S4).** To a solution of S2 (11.80 g, 48.54 mmol) in 4:1 THF/H₂O (160 ml) was added boronic ester S3 (17.38 g, 58.25 mmol) followed by K₂CO₃ (20.13 g, 145.62 mmol). The resulting suspension was degassed by bubbling Argon through the stirred suspension with a needle for 30 minutes. Following addition of Pd(PPh₃)₄ (1.68 g, 1.45 mmol) the reaction was heated to 75 °C in an oil bath for 48h or until complete consumption of S4 determined by HPLC/UV at 220 nm. The reaction was cooled, diluted with EtOAc (250 ml) and washed sequentially water, and brine. The organic layer was dried over Na₂SO₄, filtered and evaporated to give crude S3 as an amber viscous oil which was used without further purification. ¹H NMR (CDCl₃, 500 MHz): δ 7.19-7.25 (m, 3H), 7.04-7.08 (m, 1H), 6.56 (dt, J = 15.9, 1.7 Hz, 1H), 6.27 (dt, J = 15.9, 5.0 Hz, 1H), 4.34 (dd, J = 5.0, 1.7 Hz, 2H), 3.67 (s, 3H), 2.94 (t, J = 7.9 Hz, 2H), 2.63 (t, J = 7.9 Hz, 2H), 0.94 (s, 9H), 0.11 (s, 6H). ¹³C NMR (CDCl₃, 125 MHz): δ 173.4, 140.7, 137.3, 129.32, 129.27, 128.7, 127.3, 126.4, 124.4, 63.9, 51.7, 35.7, 30.9, 26.0, 18.5, -5.1. MS (ESI) Calculated for C₁₉H₂₁O₃Si [M+Na]⁺: 357.2, found 357.4.

**(E)-methyl 3-(3-(3-hydroxyprop-1-en-1-yl)phenyl)propanoate (S5).** To a solution of S4 (16.06 g, 48.0 mmol) in THF (160 ml) at room temperature was added TBAF (1.0M/THF, 64.9 ml, 64.9 mmol). The
resulting orange solution was allowed to stir for 2 hours. The reaction mixture was transferred to a separatory funnel, diluted with EtOAc (250 ml) and washed sequentially with sat. NH₄Cl and brine. The organic layer was dried over Na₂SO₄, filtered, and evaporated in vacuo to give crude S₅ as a viscous amber oil. Purification by column chromatography (SiO₂, gradient 30-65% EtOAc/hexanes) provides pure cinnamyl alcohol S₅ as a colorless oil (8.95 g, 85%). ¹H NMR (CDCl₃, 400 MHz): δ 7.16-7.25 (m, 3H), 7.02-7.1 (m, 1H), 6.57 (dt, J = 16.0, 1.3 Hz, 1H), 6.33 (dt, 16.0, 5.7 Hz, 1H), 4.29 (dd, J = 3.7, 3.7 Hz, 2H), 3.65 (s, 3H), 2.92 (t, J = 7.9 Hz, 2H), 2.61 (t, J = 7.9 Hz, 2H), 2.29 (br. s, 1H).

(E)-methyl 3-(3-(3-((tert-butoxycarbonyl)oxy)prop-1-en-1-yl)phenyl)propanoate (S₆). To a solution of S₅ (7.5 g, 34.1 mmol) in CH₂Cl₂ (175 ml) at room temperature was added NaOH (15 wt% aqueous, 35 ml) followed by tetrabutylammonium bisulfate (347 mg, 1.02 mmol). Ditertbutyldicarbonate (11.15 g, 51.1 mmol) was subsequently added in one portion and the mixture was allowed to stir overnight at room temperature. The reaction mixture was diluted with CH₂Cl₂ (200 ml) and washed with water and brine. The colorless crude oil obtained (S₆) was used without further purification. ¹H NMR (CDCl₃, 500 MHz): δ 7.20-7.25 (m, 3H), 7.06-7.12 (m, 1H), 6.63 (br. d, J = 15.9 Hz, 1H), 6.27 (dt, J = 15.9, 6.4 Hz, 1H), 4.70 (dd, J = 6.4, 1.2 Hz, 2H), 3.66 (s, 3H), 2.93 (t, J = 7.9 Hz, 2H), 2.62 (t, J = 7.9 Hz, 2H), 1.49 (s, 9H).

(E)-3-(3-(3-((tert-butoxycarbonyl)oxy)prop-1-en-1-yl)phenyl)propanoic acid (S₇). Crude methyl ester S₆ (10.92 g, 34.1 mmol) was dissolved in THF (170 ml) and aqueous LiOH (1.0 M, 52.0 ml) was added. The reaction was stirred for 4 hours at room temperature. The reaction was then diluted with EtOAc (300 ml) and 1.0 M HCl was added until the aqueous layer has a pH < 2. The organic layer was separated and washed with water and brine, dried over Na₂SO₄, filtered and concentrated to give S₇ (8.4 g, 80% over 2 steps) as an oil which was >95% pure by HPLC/UV. ¹H NMR (CDCl₃, 500 MHz): δ 7.21-7.27 (m, 3H), 7.08-7.13 (m, 1H), 6.64 (d, J = 15.9 Hz, 1H), 6.27 (dt, J = 15.9, 6.4 Hz, 1H), 4.70 (dd, J = 6.4, 1.2 Hz, 2H), 3.64 (s, 3H), 2.95 (t, J = 7.9 Hz, 2H), 2.62 (t, J = 7.9 Hz, 2H), 1.51 (s, 9H). ¹³C NMR (CDCl₃, 125 MHz): δ 178.0, 153.4, 140.5, 136.5, 134.3, 128.9, 128.1, 126.7, 124.8, 123.1, 82.3, 67.4, 35.3, 30.5, 27.8. MS (ESI-Neg) Calculated for C₁₇H₂₂O₅ [M-H]⁻: 305.1, found 305.2.

(E)-2,5-dioxopyrrolidin-1-yl 3-(3-(3-((tert-butoxycarbonyl)oxy)prop-1-en-1-yl)phenyl)propanoate (1). To a solution of S₇ (5.9 g, 19.3 mmol) in CH₂Cl₂ (60 ml, 0.35 M) at room temperature was added N-hydroxsuccinimide (2.66g, 23.11 mmol) followed by EDC-HCl (4.06 g, 21.18 mmol). The reaction was stirred for 3 hours then transferred to a separatory funnel and washed sequentially with 1N HCl, H₂O and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated to give an amber oil. Purification by column chromatography (SiO₂, 35% EtOAc/hexane) afforded succinimidyl ester 1 as a
white solid (6.09 g, 15.1 mmol, 78 %). Analytically pure crystals may be obtained by slow evaporation from THF/hexanes (2:1). \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta 7.24-7.28\) (m, 3H), 7.11-7.15 (m, 1H), 6.65 (br. d, \(J = 15.9\) Hz, 1H), 6.3 (dt, \(J = 15.9, 6.4\) Hz, 1H), 4.72 (dd, \(J = 6.4, 1.3\) Hz, 2H), 3.05 (t, \(J = 7.8\) Hz, 2H), 2.92 (t, \(J = 7.8\) Hz, 2H), 2.84 (br. s, 4H), 1.5 (s, 9H). \(^1^3\)C NMR (CDCl\(_3\), 125 MHz): \(\delta 169.0, 167.8, 153.4, 139.4, 136.7, 134.1, 129.0, 128.0, 126.7, 125.1, 123.3, 82.2, 67.4, 32.6, 30.4, 27.8, 25.6\).

IR (neat) \(\nu = 2947, 1820, 1781, 1732, 1370, 1269, 1252, 1211, 1160, 1068, 972, 930, 793\) cm\(^{-1}\). MS (ESI) Calculated for C\(_{21}\)H\(_{25}\)NO\(_7\) [M+Na]\(^+\): 426.2, found 426.2.

\((E)-2,5\text{-dioxopyrrolidin-1-yl 3-(3-(3-acetoxyprop-1-en-1-yl)phenyl)propanoate (S8).}\) A solution of 1 (558 mg, 1.38 mmol, 1 equiv.) and AcOH (1.97 mL, 34.5 mmol, 25 equiv.) in THF (20 ml) was sparged with argon for 15 minutes. The septa was removed briefly to allow the addition of Pd(PPh\(_3\))\(_4\) (40 mg, 0.035 mmol, 2.5 mol%). The reaction was stirred for 4 hours then diluted with EtOAc and transferred to a separatory funnel. The organic layer was washed with saturated aq. NaHCO\(_3\), H\(_2\)O, and brine, dried over Na\(_2\)SO\(_4\) and evaporated to give a yellow solid. Purification by column chromatography (SiO\(_2\), gradient 20-60% EtOAc/Hexane) afforded the title compound (443 mg, 1.28 mmol, 93 %) as a off-white solid. NMR (CDCl\(_3\), 500 MHz): \(\delta 7.22-7.25\) (m, 3H), 7.08-7.12 (m, 1H), 6.61 (dt, \(J = 16.0, 1.1\) Hz, 1H), 6.27 (dt, \(J = 16.0, 6.4\) Hz, 1H), 4.7 (dd, \(J = 6.4, 1.3\) Hz, 2H), 3.02 (t, \(J = 7.8\) Hz, 2H), 2.89 (t, \(J = 7.7\) Hz, 2H), 2.79 (br. s, 4H), 2.08 (s, 3H). \(^1^3\)C NMR (CDCl\(_3\), 125 MHz): \(\delta 170.8, 169.2, 167.9, 139.5, 136.6, 133.8, 129.0, 128.0, 126.6, 125.0, 123.6, 65.0, 32.5, 30.3, 25.6, 21.0\). MS (ESI) Calculated for C\(_{18}\)H\(_{19}\)NO\(_6\) [M+Na]\(^+\): 368.1, found 368.1

**Coupling of 1 to acyclic peptides:**

**General Procedure A.** An oven-dried, screw-capped scintillation vial was charged with appropriate peptide (0.2 mmol) and N-hydroxysuccinimidyl ester 1 (0.20 mmol) followed by addition of anhydrous DMF (2 ml, 0.10 M) and iPr\(_2\)NEt (0.8 mmol, 4 equiv.). The reaction was allowed to stir at room temperature until complete conversion as monitored by LC/MS. The solvent is removed under reduced pressure and purified as described below. Compounds purified by preparative HPLC were treated with silica bound tetraalkylaammonium carbonate (Si-CO\(_3\), Silicycle, 0.59 mmol/g, 2 equiv.) for 30 minutes in DMF, and re-concentrated to scavenge residual TFA prior to cyclization.
Palladium-catalyzed macrocyclization:

**General Procedure B.** An oven-dried vial was charged with acyclic peptide (0.05 mmol) and sealed with a septa. The vial was flushed with Argon followed by addition of argon-sparged anhydrous DMF (10 ml, 5 mM). After complete dissolution of the peptide, Pd(PPh$_3$)$_4$ (0.0025 mmol, 5 mol %) in 1:1 THF:DMF (0.5 ml) was added and the reaction was allowed to stir at room temperature for two hours or until complete conversion of starting material as monitored by LC/MS. The solvent is removed under reduced pressure. The resulting residue is reconstituted in DMSO and purified by preparative HPLC as indicated below.

**General Procedure C.** A solution of catalyst was prepared as follows: An oven-dried, serum-topped vial was placed in a glove bag and charged with [PdCl(C$_3$H$_5$)$_2$]$_2$ (14 mg, 0.038 mmol) and xantphos (55 mg, 0.095 mmol). The vial is sealed, removed from the glove bag, and degassed THF (7.0 ml) was added, followed by degassed DMF (7.0 ml). The resulting yellow solution was stirred under argon for 30 minutes. To a solution of acyclic peptide (0.05 mmol) in degassed DMF (10 ml, 5 mM) was added catalyst solution (735 uL, 0.04 mol% [PdCl(C$_3$H$_5$)$_2$]$_2$, 0.10 mol% xantphos). The reaction was allowed to stir at room temperature for two hours or until complete conversion of starting material as monitored by LC/MS. The solvent is removed under reduced pressure. The resulting residue is reconstituted in DMSO and purified by preparative HPLC as indicated below.

**General Procedure D.** As described in general procedure B with the addition of Cs$_2$CO$_3$. An oven-dried vial was charged with acyclic peptide (0.05 mmol) and Cs$_2$CO$_3$ (0.10 mmol, 2 equiv) and sealed with a septa. The vial was flushed with Argon followed by addition of argon-sparged anhydrous DMF or DMSO(10 ml, 5 mM). After complete dissolution of the peptide, Pd(PPh$_3$)$_4$ (0.0025 mmol, 5 mol %) in 1:1 THF:DMF (0.5 ml) was added and the reaction was allowed to stir at room temperature for two hours or until complete conversion of starting material as monitored by LC/MS. The solvent is removed under reduced pressure. The resulting residue is reconstituted in DMSO and purified by preparative HPLC as indicated below.

**Solid-supported macrocyclizations.** Peptide synthesis was performed as described above on Tentagel Rink amide resin (0.23 mmol/g) on 0.05 mmol scale. Prior to final Fmoc-deblocking the His(Mmt) side chain was removed by treatment with 1:1:8 AcOH:TFE:CH$_2$Cl$_2$ (8 mL). After two hours the vessel was drained and washed with CH$_2$Cl$_2$ (2x), DMF (2x), CH$_2$Cl$_2$ (2x). Following Fmoc- deprotection the N-terminus was acylation with 1 (3 equiv.) and iPr$_2$NEt (8 equiv.) The resin was washed, shrunk with methanol and dried under high vacuum.

The dried resin was transferred to a serum capped vial and sparged with argon. Degassed DMF (10 ml) was added and the resin allowed to swell for 10 minutes. [Pd(C$_3$H$_5$)$_2$Cl]$_2$/xantphos (8 mol%/20 mol%) catalyst solution (see general procedure C) was added and the resin gently stirred for two hours. The resin was washed with DMF (2x), CH$_2$Cl$_2$ (2x), shrunk with methanol and dried under high vacuum. The
macrocycle was cleaved by treatment with TFA:TIS:H$_2$O (95:2.5:2.5) for 1 hour. Cleaved macrocycles were analyzed by HPLC-MS (C18, MeCN/H$_2$O, 0.1%TFA).

Summary of acylation of macrocyclization efficiency.

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<th>Cyclization Procedure</th>
<th>Yield % (cyclization)</th>
<th>Peptide Sequence</th>
<th>Yield % (acylation)</th>
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$^a$DMSO Solvent.

Data for acyclic peptides:

**Acyclic-Ala-Trp-Thr-Tyr (2):**

Following general procedure A, the corresponding compound was prepared from H-AWTY-NH$_2$ (TFA, 163 mg, 0.250 mmol), diisopropylethylamine (174 μL, 0.999 mmol) and reagent 1 (101 mg, 0.250 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 40-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (149 mg, 0.180 mmol, 72%). $^1$H NMR (DMSO-d$_6$, 600 MHz): δ 10.76 (s, 1H), 9.13 (br s, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.99 (d, J = 7.3 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.22-7.31 (m, 4H), 7.19 (dd, J = 7.6, 7.6 Hz, 1H), 7.10 (app s, 2H), 7.60 (d, J = 7.4 Hz, 1H), 6.96-7.02 (m, 3H), 6.89 (dd, 7.4, 7.4 Hz, 1H), 6.57-6.63 (m, 3H), 6.30 (dt, 15.9, 6.3 Hz, 1H), 4.63 (d, J = 5.8 Hz, 2H), 4.52 (ddd, J = 4.3, 4.3 Hz, 1H), 4.33 (ddd, J = 4.3, 4.3 Hz, 1H), 4.24 (dq, J = 7.1, 7.1 Hz, 1H), 4.16 (dd, J = 7.9, 4.1 Hz, 1H), 3.89-3.96 (m, 1H), 3.12 (dd, J = 15.0, 4.2 Hz, 1H), 2.95 (dd, J = 14.8, 9.0 Hz, 1H), 2.90 (dd, J = 14.0, 4.9 Hz, 1H), 2.65-2.78 (m, 3H), 2.28-2.41 (m, 2H), 1.39 (s, 9H), 1.08 (d, J = 6.8 Hz, 3H), 0.90 (d, J =
$^{13}$C NMR (DMSO- $d_6$, 150 MHz): $\delta$ 173.2, 172.8, 171.7, 171.6, 169.6, 156.1, 153.1, 142.1, 136.3, 136.2, 133.8, 128.9, 128.4, 128.1, 127.7, 126.7, 124.6, 123.9, 123.6, 121.1, 118.7, 118.5, 115.2, 111.5, 110.3, 81.8, 67.2, 66.9, 58.3, 54.6, 48.4, 36.9, 36.9, 31.2, 27.7, 19.3, 18.4. MS (ESI) Calculated for $C_{44}H_{54}N_6O_{10}\left[M-OCO\text{Bu}^t\right]^+$: 709.3, found 709.0.

**Acyclic-Ala-Trp-Thr-Tyr (3):** Following general procedure A, the corresponding compound was prepared from H-AWTY-NH$_2$ (•TFA, 195 mg, 0.299 mmol), diisopropylethylamine (208 μL, 1.19 mmol) and reagent S8 (103 mg, 0.299 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 40-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (177 mg, 0.230 mmol, 77%). $^1$H NMR (DMSO- $d_6$, 500 MHz): $\delta$ 10.77 (d, $J = 1.9$ Hz, 1H), 9.13 (br. s, $J = 7.5$ Hz, 1H), 7.99 (d, $J = 7.3$ Hz, 1H), 7.75 (d, $J = 8.1$ Hz, 1H), 7.67 (d, $J = 8.1$ Hz, 1H), 7.54 (d, $J = 7.9$ Hz, 1H), 7.18-7.32 (m, 5H), 7.09-7.13 (m, 2H), 7.07 (br. d, $J = 7.3$ Hz, 1H), 6.98-7.04 (m, 3H), 6.9 (dd, $J = 7.4$ Hz, 1H), 6.58-6.64 (m, 3H), 6.31 (dy, $J = 15.9$, 6.1 Hz, 1H), 4.65 (br. d, $J = 6.1$ Hz, 2H), 4.53 (ddd, $J = 8.3, 8.3, 6.8$ Hz, 1H), 4.25 (dq, $J = 7.2, 7.2$ Hz, 1H), 4.18 (dd, $J = 8.2, 4.2$ Hz, 1H), 3.90-3.97 (m, 1H), 3.13 (dd, $J = 15.1, 4.4$ Hz, 1H), 2.97 (dd, $J = 15.2, 8.7$ Hz, 1H), 2.91 (dd, $J = 14.1, 5.1$ Hz, 1H), 2.66-2.79 (m, 3H), 2.28-2.43 (m, 2H), 2.03 (s, 3H), 1.1 (d, $J = 7.1$ Hz, 3H), 0.92 (d, $J = 6.6$ Hz, 3H). $^{13}$C NMR (DMSO- $d_6$, 125 MHz): $\delta$ 173.4, 172.9, 171.9, 171.7, 170.6, 169.8, 156.2, 142.2, 136.5, 136.4, 133.6, 130.5, 129.1, 128.4, 128.3, 127.8, 126.8, 124.7, 124.1, 124.0, 121.3, 118.9, 118.7, 115.4, 111.7, 110.4, 67.0, 64.8, 58.4, 54.7, 53.9, 48.6, 37.1, 37.0, 31.4, 27.5, 21.2, 19.5, 18.6. MS (ESI) Calculated for $C_{41}H_{48}N_6O_9$ [M+H]$^+$: 769.3, found 769.2.

**Acyclic-Ser-Met-Tyr (S9):** Following general procedure A, the corresponding compound was prepared from H-SMY-NH$_2$ (•TFA, 20 mg, 0.039 mmol), diisopropylethylamine (27 μL, 0.156 mmol) and reagent 1 (16 mg, 0.039 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 40-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (19 mg, 0.028 mmol, 71%). $^1$H NMR (DMSO- $d_6$, 400 MHz): $\delta$ 9.14 (br s, 1H), 8.28 (d, $J = 6.8$ Hz, 1H), 8.04 (d, $J = 7.9$ Hz, 1H), 7.77 (d, $J = 8.4$ Hz, 1H), 7.18-7.29 (m, 3H), 7.12 (br s, 1H), 7.08 (d, $J = 7.08$ Hz, 1H), 7.06 (br s, 1H), 6.95 (d, $J = 8.4$ Hz, 2H), 6.57-6.63 (m, 3H), 6.31 (dt, $J = 16, 6.3$ Hz, 1H), 4.64 (dd, 6.3, 1.0 Hz, 2H), 4.34 (ddd, $J = 7.0, 7.0, 6.8$ Hz, 1H), 4.23 (ddd, $J = 9.8, 8.7, 4.6$ Hz, 1H), 4.89 (ddd, $J = 8.6, 7.1, 4.7$ Hz, 1H), 3.57 (dd, $J = 10.3, 6.1$ Hz, 1H), 3.47 (dd, $J = 10.3, 6.9$ Hz, 3H).
Hz, 1H), 2.91 (dd, J = 14.0, 4.5 Hz, 1H), 4.77 (t, J = 8 Hz, 2H), 2.54-5.62 (m, 1H), 2.41-2.48 (m, 4H), 2.30-2.37 (m, 1H), 2.23-2.29 (m, 1H), 1.95 (s, 3H), 1.39 (s, 9H). $^{13}$C NMR (DMSO-d$_6$, 150 MHz): δ 173.4, 172.0, 171.5, 170.9, 156.1, 153.1, 142.1, 136.2, 133.8, 130.2, 128.9, 128.4, 128.2, 126.7, 124.6, 123.6, 115.2, 81.8, 67.2, 62.1, 55.0, 54.6, 53.0, 40.8, 36.9, 36.8, 31.3, 31.2, 29.6, 27.7, 14.8. MS (ESI) Calculated for C$_{34}$H$_{46}$N$_4$O$_9$S [M-OCO$_2$tBu]$^+$: 569.2, found 568.9.

**Acyclic-Ile-Trp-Tyr (S10):**

Acyclic-Ala-Val-Tyr (S11):

Acyclic-Ile-Trp-Tyr (S10): Following general procedure A, the corresponding compound was prepared from H-IWY-NH$_2$ (•TFA, 203 mg, 0.342 mmol), diisopropylethylamine (238 μL, 1.37 mmol) and reagent 1 (138 mg, 0.342 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 40-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (171 mg, 0.222 mmol, 65%). $^1$H NMR (DMSO-d$_6$, 500 MHz): δ 10.78 (d, J = 1.4 Hz, 1H), 9.12 (s, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 8 Hz, 1H), 7.26-7.30 (m, 2H), 7.17-7.25 (m, 3H), 7.06-7.10 (m, 2H), 7.00-7.05 (m, 1H), 6.92-6.97 (m, 3H), 6.57-6.64 (m, 3H), 6.31 (dt, J = 15.9, 6.3 Hz, 1H), 4.65 (d, J = 6.1 Hz, 2H), 4.48 (ddd, J = 8.3, 8.3, 4.9 Hz, 1H), 4.62 (ddd, J = 7.8, 7.8, 5.9 Hz, 1H), 4.11 (ddd, J = 8.2, 8.2 Hz, 1H), 3.02 (ddd, J = 14.9, 4.5 Hz, 1H), 2.89 (ddd, J = 14.9, 8.9 Hz, 1H), 2.67-2.84 (m, 4H), 2.36 (ddd, J = 14.9, 8.6, 5.9 Hz, 1H), 1.52-1.62 (m, 1H), 1.41 (s, 9H), 1.32-1.39 (m, 1H), 1.15-1.26 (m, 1H), 0.83-0.95 (m, 1H), 0.69 (t, J = 7.3 Hz, 3H), 0.64 (d, J = 6.9 Hz, 3H). $^{13}$C NMR (DMSO-d$_6$, 150 MHz): δ 172.9, 171.7, 171.5, 171.2, 161.8, 156.1, 153.1, 142.0, 136.3, 136.1, 133.8, 130.4, 128.9, 128.4, 128.0, 127.6, 126.7, 124.5, 123.7, 123.5, 121.1, 118.6, 118.5, 115.2, 111.5, 110.3, 81.8, 67.2, 57.2, 54.3, 53.8, 40.8, 37.1, 36.8, 36.6, 31.3, 27.7, 24.5, 24.3, 15.5, 11.2. MS (ESI) Calculated for C$_{43}$H$_{53}$N$_5$O$_8$ [M-OCO$_2$tBu]$^+$: 650.3, found 649.9.

**Acyclic-Ala-Val-Tyr (S11):**

Acyclic-Ala-Val-Tyr (S11):

Following general procedure A, the corresponding compound was prepared from H-AVY-NH$_2$ (•TFA, 18 mg, 0.039 mmol), diisopropylethylamine (238 μL, 1.37 mmol) and reagent 1 (138 mg, 0.039 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 40-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (17 mg, 0.026 mmol, 17%). $^1$H NMR (DMSO-d$_6$, 400 MHz): δ 9.11 (br s, 1H), 8.04 (d, J = 7.3 Hz, 1H), 7.92 (s, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.70 (d, J = 8.9 Hz, 2H), 7.26 (br s, 1H), 7.22-7.26 (m, 2H), 7.20 (app t, J = 7.5 Hz, 1H), 7.08 (d, J = 7.4 Hz, 1H), 7.00 (br s, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.56-6.63 (m, 2H), 6.31 (dt, J = 15.8, 6.3 Hz, 1H), 4.64 (d, J = 6.06 Hz, 2H), 4.26-4.36 (m, 2H), 4.03 (dd, J = 8.4, 6.7 Hz, 1H), 2.83 (dd, J = 13.9, 5.2 Hz, 1H), 2.76 (t, J = 7.7 Hz, 2H), 2.66 (dd, J = 14.0, 8.9 Hz, 2H).
(Hz), 2.34-2.44 (m, 1H), 1.88 (ddddd, J = 13.3, 6.6, 6.6, 6.6 Hz, 1H), 1.39 (s, 9H), 1.10 (d, J = 7.2 Hz, 3H), 0.71 (d, J = 6.4 Hz, 6H). $^{13}$C NMR (DMSO-d$_6$, 150 MHz): δ 173.2, 172.7, 171.6, 170.7, 156.1, 153.1, 142.0, 136.2, 133.8, 130.3, 128.9, 128.4, 128.1, 126.7, 124.6, 123.6, 115.1, 81.8, 67.2, 58.2, 54.1, 48.4, 40.5, 36.9, 31.2, 30.7, 27.7, 19.4, 18.3, 18.2. MS (ESI) Calculated for C$_{34}$H$_{46}$N$_4$O$_8$ [M-OCO$_2$ tBu]$^+$: 521.3, found 521.0.

**Acyclic-Val-Met-Phe-Tyr (S12):**

Following general procedure A, the corresponding compound was prepared from H-VMFY-NH$_2$ (•TFA, 149 mg, 0.222 mmol), diisopropylethylamine (155 µL, 0.887 mmol) and reagent 1 (89 mg, 0.222 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 40-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (111 mg, 0.131 mmol, 59%). $^1$H NMR (DMSO-d$_6$, 600 MHz): δ 9.13 (s, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.83-7.90 (m, 2H), 7.27 (s, 1H), 7.10-7.25 (m, 9H), 7.08 (d, J = 7.2 Hz, 1H), 7.03 (s, 1H), 6.97 (d, J = 8.1 Hz, 2H), 6.57-6.65 (m, 2H), 6.30 (dt, J = 16.0, 6.0 Hz, 1H), 4.63 (d, J = 6.1 Hz, 2H), 4.45 (dd, J = 8.2, 8.2, 4.8 Hz, 1H), 4.22-4.35 (m, 2H), 4.07 (dd, J = 7.5, 7.5 Hz, 1H), 2.9 (dd, J = 14.0, 4.2 Hz, 2H), 2.64-2.88 (m, 6H), 2.48-2.56 (m, 1H), 2.26-2.44 (m, 3H), 1.95 (d, J = 3H), 1.74-1.90 (m, 2H), 1.64-1.73 (m, 1H), 0.69 (d, J = 6.6 Hz, 6H). $^{13}$C NMR (DMSO-d$_6$, 150 MHz): δ 173.0, 172.0, 171.5, 171.1, 170.7, 156.1, 153.1, 142.0, 137.9, 136.2, 133.8, 130.4, 129.4, 128.9, 128.4, 128.3, 128.0, 126.7, 126.5, 124.6, 123.6, 115.2, 81.8, 67.2, 58.2, 54.4, 54.1, 52.2, 37.7, 37.2, 36.8, 32.0, 31.3, 30.5. MS (ESI) Calculated for C$_{45}$H$_{59}$N$_5$O$_9$S [M+Na]$^+$: 868.4, found 868.9.

**Acyclic-Trp-Ile-Gln-Tyr (S13):**

Following general procedure A, the corresponding compound was prepared from H-WIQY-NH$_2$ (•TFA, 77 mg, 0.107 mmol), diisopropylethylamine (74 µL, 0.427 mmol) and reagent 1 (43 mg, 0.107 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 40-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (67 mg, 0.075 mmol, 70%). $^1$H NMR (DMSO-d$_6$, 400 MHz): δ 10.73 (s, 1H), 9.12 (br s, 1H), 8.02-8.06 (m, 2H), 7.90 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.30 (br s, 1H), 7.18-7.25 (m, 3H), 7.14 (dd, J = 7.7, 7.7 Hz, 1H), 6.99-7.06 (m, 3H), 6.91-6.99 (m, 4H), 6.478 (br s, 1H), 6.58 (d, J = 7.9 Hz, 2H), 6.56 (d, J = 15.3 Hz, 1H), 6.29 (dt, J = 16.0, 6.2 Hz, 1H), 4.62 (d, J = 6.2 Hz, 2H), 4.58 (dd, J = 9.3, 9.3, 4.7 Hz, 1H), 4.30 (ddd, J = 7.6, 7.6, 7.6 Hz, 1H), 4.20 (ddd, J = 7.7, 7.7,
7.7 Hz, 1H), 4.14 (dd, J = 7.7, 7.7 Hz, 1H), 3.07 (dd, J = 14.7, 4.1 Hz, 1H), 2.87 (dd, J = 14.6, 9.5 Hz, 1H), 2.82 (dd, J = 14.0, 5.3 Hz, 1H), 2.60-2.66 (m, 2H), 2.32 (dd, J = 7.7, 7.7 Hz, 1H), 2.03-2.08 (m, 1H), 1.81 (dddd, J = 13.8, 6.4, 6.4, 6.4 Hz, 1H), 1.64-1.74 (m, 2H), 1.39 (s, 9H), 0.97-1.07 (m, 1H), 0.76 (t, J = 7.3 Hz, 3H), 0.75 (d, J = 6.8 Hz, 3H). 13C NMR (DMSO-d6, 150 MHz): δ 174.3, 173.1, 172.0, 171.7, 171.2, 171.0, 156.1, 153.1, 142.0, 136.3, 136.1, 133.8, 130.3, 128.9, 128.2, 128.0, 127.7, 126.7, 124.5, 123.9, 123.6, 121.1, 118.9, 118.5, 115.2, 110.5, 81.8, 67.2, 57.4, 54.4, 53.6, 52.7, 40.4, 37.2. MS (ESI) Calculated for C48H61N7O10 [M-OCO2tBu]+: 778.4, found 777.9.

**Acyclic-Ile-Ala-Arg-Tyr (S14):**

Following general procedure A, the corresponding compound was prepared from H-LARY-NH₂ (+TFA, 88 mg, 0.102 mmol), diisopropylethylamine (71 μL, 0.408 mmol) and reagent 1 (41 mg, 0.102 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 20-100% CH3CN/H2O with 0.1% TFA. The fractions collected were combined and lyophilized (54 mg, 0.067 mmol, 67%). 1H NMR (DMSO-d6, 600 MHz): δ 8.06 (d, J = 6.8 Hz, 1H), 7.94-7.99 (m, 2H), 7.88 (d, J = 7.7 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.55 (dd, J = 5.5, 5.5 Hz, 1H), 7.31 (s, 1H), 7.22-7.27 (m, 2H), 7.19 (dd, J = 7.7, 7.7 Hz, 1H), 7.07 (d, J = 7.4 Hz, 1H), 7.04 (s, 1H), 6.95 (d, J = 8.5 Hz, 2H), 6.56-6.62 (m, 3H), 6.30 (dt, J = 16.2, 6.5 Hz, 1H), 4.63 (d, J = 6.2 Hz, 2H), 4.29 (ddd, J = 8.1, 8.1, 5.4 Hz, 1H), 4.24 (dq, J = 7.8, 7.8 Hz, 1H), 4.12-4.20 (m, 2H), 2.99-3.05 (m, 2H), 2.80-2.87 (m, 2H), 2.72-2.79 (m, 2H), 2.65-2.69 (m, 1H), 2.55 (d, J = 4.7 Hz, 1H), 2.43-2.49 (m, 2H), 2.35-2.42 (m, 1H), 1.59 (dddd, J = 14.3, 6.7, 6.7, 6.7 Hz, 1H), 1.43-1.51 (m, 1H), 1.39 (s, 9H), 1.31-1.37 (m, 2H), 1.15 (d, J = 7.3 Hz, 3H), 0.78 (d, J = 6.4 Hz, 3H), 0.72 (d, J = 6.6 Hz, 3H). 13C NMR (DMSO-d6, 150 MHz): δ 173.1, 172.6, 172.6, 171.9, 171.1, 161.9, 159.0 (TFA, q, J = 34.5 Hz), 157.1, 156.1, 153.1, 141.9, 136.2, 133.8, 130.4, 128.9, 128.4, 128.0, 126.7, 124.5, 123.6, 116.6 (TFA, q, J = 295 Hz) 115.2, 81.8, 67.2, 54.3, 52.6, 51.2, 48.7, 40.9, 40.7, 37.1, 36.8, 31.2, 29.3, 27.7, 25.1, 24.3, 23.4, 21.7, 18.0. MS (ESI) Calculated for C41H60N8O9 [M+H]+: 809.4, found 809.0.

**Acyclic-Ile-Met-Ser-Tyr-Trp (S15):**

Following general procedure A, the corresponding compound was prepared from H-IMSYW-NH₂ (+TFA, 211 mg, 0.292 mmol), diisopropylethylamine (204 μL, 1.17 mmol) and reagent 1 (118 mg, 0.292 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 40-100% CH3CN/H2O with 0.1% TFA. The fractions
collected were combined and lyophilized (202 mg, 0.225 mmol, 77%). \( ^{1}H \) NMR (DMSO-d\(_{6} \), 400 MHz): \( \delta \) 10.78 (s, 1H), 8.02-8.10 (m, 2H), 7.95 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 6.8 Hz, 1H), 7.78 (d, J = 7.3 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.7 (br s, 1H), 7.21-7.25 (m, 1H), 7.19 (dd, J = 7.6, 7.6 Hz, 1H), 7.14 (br s, 1H), 7.06-7.11 (m, 3H), 7.02 (dd, J = 7.4, 7.4 Hz, 1H), 6.95 (dd, J = 7.4, 7.4 Hz, 1H), 6.88 (d, J = 8.3 Hz, 2H), 6.60 (d, J = 15.9 Hz, 1H), 6.54 (d, J = 8.3 Hz, 2H), 6.30 (dt, J = 16.2, 6.4 Hz, 1H), 4.63 (d, J = 5.5 Hz, 2H), 4.63 (ddd, J = 8.3, 8.3, 5.6 Hz, 1H), 4.23-4.35 (m, 3H), 7.09 (dd, J = 8.2, 8.2 Hz), 3.55 (dd, J = 10.5, 5.9 Hz, 1H), 3.45 (dd, J = 10.4, 6.6 Hz, 1H), 3.12 (dd, J = 14.4, 5.0 Hz, 1H), 2.88 (dd, J = 15.1, 8.9 Hz), 2.71-2.82 (m, 3H), 2.60 (dd, J = 14.3, 9.1 Hz, 1H), 2.30-2.43 (m, 4H), 1.82-1.90 (1H), 1.70-1.79 (m, 1H), 1.57-1.65 (m, 1H), 1.39 (s, 9H), 1.23-1.32 (m, 1H), 0.90-1.0 (m, 1H), 0.67-0.74 (m, 6H).

\( ^{13}C \) NMR (DMSO-d\(_{6} \), 150 MHz): \( \delta \) 173.6, 171.8, 171.7, 171.3, 170.9, 170.5, 156.1, 153.1, 141.9, 136.4, 136.1, 133.8, 130.3, 128.9, 128.4, 127.9, 127.6, 126.7, 124.5, 123.8, 123.6, 121.2, 118.7, 118.6, 115.2, 111.6, 110.5, 81.8, 67.2, 62.0, 57.2, 55.2, 55.1. MS (ESI) Calculated for C\(_{51}H_{67}N_{7}O_{11}S \) [M\(-OCO\_tBu\)]\(^{+}\): 868.4, found 867.9.

\textbf{Acyclic-Ala-Phe-Thr-Ile-Tyr (S16):}

Following general procedure A, the corresponding compound was prepared from H-AFTIY-NH\(_{2}\) (+TFA, 31 mg, 0.043 mmol), diisopropylethylamine (30 \( \mu \)L, 0.171 mmol) and reagent 1 (17 mg, 0.043 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 40-100\% CH\(_{3}\)CN/H\(_{2}\)O with 0.1\% TFA. The fractions collected were combined and lyophilized (26 mg, 0.029 mmol, 67\%). \( ^{1}H \) NMR (DMSO-d\(_{6} \), 400 MHz): \( \delta \) 8.00 (d, J = 8.28 Hz, 1H), 7.99 (d, J = 7.92 Hz, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.69-7.26 (m, 7H), 7.11-7.15 (m, 1H), 7.10 (br s, 1H), 7.07 (d, J = 7.9 Hz, 1H), 7.03 (br s, 1H), 6.95 (d, J = 8.9 Hz, 2H), 6.56-6.62 (m, 3H), 6.30 (dt, J = 15.8, 6.2 Hz, 1H), 4.63 (dd, J = 6.0, 0.9 Hz, 2H), 4.53 (ddd, J = 8.8, 8.8, 4.3 Hz, 1H), 4.25-4.35 (m, 2H), 4.21 (dq, J = 7.2, 7.2 Hz), 4.10 (dd, J = 7.7, 6.4 Hz, 1H), 3.95-4.02 (m, 1H), 3.03 (dd, J = 14.2, 4.1 Hz, 1H), 2.85-2.90 (m, 1H), 2.80 (dd, J = 14.1, 9.9 Hz, 1H), 2.70-2.76 (m, 2H), 2.61 (dd, J = 13.9, 9.5 Hz, 1H), 2.29-2.42 (m, 2H), 1.62-1.71 (m, 1H), 1.39 (s, 9H), 1.11-1.21 (m, 1H), 1.06 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H), 0.67-0.74 (m, 6H). \( ^{13}C \) NMR (DMSO-d\(_{6} \), 150 MHz): \( \delta \) 173.2, 172.6, 171.6, 171.3, 170.7, 170.3, 156.1, 153.1, 142.0, 138.1, 136.2, 133.8, 130.2, 129.6, 129.0, 128.4, 128.3, 128.2, 126.7, 126.5, 124.6, 123.6, 115.2, 81.8, 67.2, 67.0, 58.0, 57.7, 54.5, 54.1, 48.4, 40.8, 37.3, 36.9, 36.88, 36.80, 36.1, 31.2, 27.7, 24.1, 19.5, 18.4, 15.6, 11.6. MS (ESI) Calculated for C\(_{48}H_{60}N_{6}O_{11} \) [M+H]\(^{+}\): 901.5, found 901.0.
Acyclic-Gly-Ser-Phe-Asn-Tyr (S17):

Following general procedure A, the corresponding compound was prepared from H-GSFNY-NH₂ (•TFA, 120 mg, 0.172 mmol), diisopropylethylamine (119 μL, 0.686 mmol) and reagent 1 (69 mg, 0.172 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 40-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (120 mg, 0.137 mmol, 80%). ¹H NMR (DMSO-d₆, 600 MHz): δ 8.14 (d, J = 6.6 Hz, 1H), 8.08-8.12 (m, 1H), 8.02 (d, J = 7.1 Hz, 1H), 7.89-7.94 (m, 2H), 7.87 (d, J = 7.2 Hz, 1H), 7.40 (app. s, 1H) 7.34 (app s, 1H) 7.06-7.30 (m, 10H), 7.93-7.99 (m, 3H), 7.56-7.63 (m, 3H), 6.31 (dt, J = 15.7, 6.6 Hz, 1H), 4.64 (d, J = 4.9 Hz, 2H), 4.41-4.50 (m, 2H), 4.18-4.26 (2H), 4.67-4.73 (m, 2H), 3.43-3.50 (m, 2H), 2.97 (d, J = 12.7 Hz, 1H), 2.92 (d, J = 13.2 Hz, 1H), 2.72-2.80 (m, 3H), 2.39-2.57 (m, 3H), 2.35 (dd, J = 15.1, 5.1 Hz, 1H), 1.39 (s, 9H). ¹³C NMR (DMSO-d₆, 100 MHz): δ 173.2, 172.2, 172.0, 171.2, 170.7, 170.3, 169.5, 153.1, 142.1, 138.0, 136.2, 133.8, 130.3, 129.5, 129.0, 128.3, 126.8, 124.5, 123.6, 115.2, 81.8, 67.2, 61.9, 55.4, 54.8, 54.4, 50.2, 42.4, 37.3. MS (ESI) Calculated for C₄₄H₅₅N₇O₁₂ [M+H]⁺: 874.4, found 874.0

Acyclic-Ser-Phe-Phe(4-NH₂) (S18):

Following general procedure A, the corresponding compound was prepared from H-SFF(4-NH₂)-NH₂ (•2TFA, 170 mg, 0.265 mmol), diisopropylethylamine (185 μL, 1.06 mmol) and reagent 1 (107 mg, 0.265 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 30-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (115 mg, 0.164 mmol, 62%). ¹H NMR (DMSO-d₆, 500 MHz): δ 8.08 (d, J = 7.7 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 7.7 Hz, 1H), 7.22-7.28 (m, 3H), 7.16-7.28 (m, 4H), 7.12-7.15 (m, 4H), 7.1 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 7.6 Hz, 1H), 6.6 (d, J = 15.8 Hz, 1H), 6.31 (dt, J = 16.1, 6.2 Hz, 1H), 6.64 (dd, J = 6.1, 1.0 Hz, 2H), 4.32-4.38 (m, 2H), 4.28 (ddd, J = 6.8, 6.8, 6.8 Hz, 1H), 3.41-3.50 (m, 2H), 3 (dd, J = 13.7, 4.8 Hz, 1H), 2.92 (dd, J = 14.1, 4.5 Hz, 1H), 2.68-7.78 (m, 4H), 2.34-2.45 (m, 2H), 1.39 (s, 9H). ¹³C NMR (DMSO-d₆, 100 MHz): δ 173.0, 172.6, 172.1, 171.5, 170.4, 157.2, 153.3, 142.1, 136.5, 136.3, 133.9, 130.7, 129.1, 128.4, 127.8, 126.9, 124.7, 124.1, 123.8, 121.3, 119.0, 118.6, 118.3, 115.9, 111.7, 110.6, 82.0, 67.4, 67.0, 58.5, 54.5, 54.0, 52.7, 40.9, 40.6. MS (ESI) Calculated for C₃₈H₄₇N₅O₆ [M+H]⁺: 702.3, found 702.3.
**Acyclic-Asn-Trp-Thr-Phe(4-NH<sub>2</sub>) (S19):**

Following general procedure A, the corresponding compound was prepared from H-NWTF(4-NH<sub>2</sub>)-NH<sub>2</sub> (<sup>•</sup>TFA, 162 mg, 0.200 mmol), diisopropylethylamine (140 µL, 0.801 mmol) and reagent 1 (81 mg, 0.200 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 30-100% CH<sub>3</sub>CN/H<sub>2</sub>O with 0.1% TFA. The fractions collected were combined and lyophilized (106 mg, 0.122 mmol, 61%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500 MHz): δ 10.8 (d, J = 1.9 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.9 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.4 (br. s, J = Hz, 1H), 7.33 (br. s, J = Hz, 1H), 7.24-7.31 (m, 5H), 7.21 (dd, J = 7.8, 7.8 Hz, 1H), 7.11-7.19 (m, 4H), 7.08 (br. d, J = 7.3 Hz, 1H), 7.01 (dd, J = 7.1, 7.1 Hz, 1H), 6.97 (br. s, J = Hz, 1H), 6.91 (dd, J = 7.4, 7.4 Hz, 1H), 6.62 (d, J = 16 Hz, 1H), 6.32 (dt, J = 15.9, .62 Hz, 1H), 4.65 (dd, J = 6.3, 1.1 Hz, 2H), 4.56 (dq, J = 7.3, 7.3 Hz, 1H), 4.5 (ddd, J = 5.1, 5.1, 4.5 Hz, 1H), 4.41 (ddd, J = 8.5, 8.5, 5.2 Hz, 1H), 4.12 (dd, J = 8.0, 4.50 Hz, 1H), 3.92 (dddd, J = 12.5, 6.2, 6.2, 6.2 Hz, 1H), 3.15 (dd, J = 14.7, 4.0 Hz, 1H), 3.07 (dd, J = 13.9, 4.9 Hz, 1H), 2.98 (dd, J = 15.0, 8.7 Hz, 1H), 2.82 (dd, J = 13.8, 8.7 Hz, 1H), 2.66-2.76 (m, 2H), 2.44-2.54 (m, 1H), 2.27-2.39 (m, 3H), 1.41 (s, 9H). <sup>1</sup>C NMR (DMSO-d<sub>6</sub>, 100 MHz): δ 173.1, 172.3, 172.0, 171.9, 171.7, 170.0, 153.3, 142.2, 137.5, 136.5, 136.3, 133.9, 131.8, 130.9, 129.1, 128.5, 126.9, 124.7, 124.1, 123.8, 122.5, 121.3, 118.8, 118.7, 111.7, 110.3, 82.0, 67.4, 67.1, 59.1, 54.4, 54.1, 50.1, 37.5, 37.2, 31.4, 27.85, 27.78, 27.5, 19.7. MS (ESI) Calculated for C<sub>45</sub>H<sub>56</sub>N<sub>8</sub>O<sub>10</sub> [M+H]<sup>+</sup>: 869.4, found 869.3.

**Acyclic-Ala-Leu-Glu-Tyr (15):**

Following general procedure A, the corresponding compound was prepared from H-ALEY-NH<sub>2</sub> (<sup>•</sup>TFA, 183 mg, 0.301 mmol), diisopropylethylamine (210 µL, 1.205 mmol) and reagent 1 (122 mg, 0.301 mmol). The product was isolated by flash chromatography (SiO<sub>2</sub>, gradient 0-10% CH<sub>3</sub>OH/CHCl<sub>3</sub>). The fractions collected were combined and concentrated under reduced pressure (160 mg, 0.205 mmol, 68%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz): δ 8.04 (d, J = 6.8 Hz, 1H), 7.96 (d, J = 7.2 Hz, 1H), 7.82 (d, J = 7.1 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.17-7.30 (m, 4H), 7.08 (d, J = 7.0 Hz, 1H), 7.02 (s, 1H), 6.96 (d, J = 7.7 Hz, 2H), 6.56-6.64 (m, 3H), 6.31 (dt, J = 15.8, 6.2 Hz, 1H), 4.64 (d, J = 5.3 Hz, 2H), 4.12-431 (m, 4H), 2.72-2.83 (m, 3H), 2.62-2.68 (m, 1H), 2.49-2.54 (m, 1H), 2.44-2.48 (m, 2H), 2.36-2.43 (m, 2H), 2.11-2.20 (m, 2H), 1.78-1.88 (m, 1H), 1.64-1.74 (m, 1H), 1.51-1.59 (m, 1H), 1.35-1.46 (m, 10H), 1.12 (d, J = 7.1 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H), 0.79 (d, J = 6.2 Hz, 3H). <sup>1</sup>C NMR (DMSO-d<sub>6</sub>, 150 MHz): δ 174.3, 173.0, 172.8, 172.3, 171.7, 170.9, 156.1, 153.1, 142.1, 136.2, 133.8, 130.3, 128.9, 128.4, 128.0, 126.7, 124.5, 123.6, 115.2, 81.8,
Acyclic-Phe-Leu-Hyp (S21):

Following general procedure A, the corresponding compound was prepared from H-FLHyp-OH (•TFA, 215 mg, 0.425 mmol), diisopropylethylamine (296 µL, 1.70 mmol) and reagent 1 (172 mg, 0.425 mmol). The product was isolated by flash chromatography (SiO₂, gradient 0-10% CH₃OH/CHCl₃). The fractions collected were combined and concentrated under reduced pressure (165 mg, 0.242 mmol, 57%). ¹H NMR (DMSO-d₆, 500 MHz): δ 8.10 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.12-7.26 (m, 8H), 7.00 (d, J = 7.4 Hz, 1H), 6.60 (d, J = 15.9 Hz, 1H), 6.31 (dt, J = 15.9, 6.3 Hz, 1H), 4.65 (dd, J = 6.1, 1.1 Hz, 2H), 4.50-4.55 (m, 2H), 4.31-4.37 (m, 1H), 3.59 (dd, J = 10.2, 4.6 Hz, 1H), 3.50-3.56 (m, 1H), 2.96 (dd, J = 13.9, 4.0 Hz, 1H), 2.60-2.72 (m, 3H), 2.29-2.35 (m, 2H), 2.07 (ddd, J = 11.9, 8.0, 2.5 Hz, 1H), 1.89 (ddd, J = 12.8, 8.0, 4.8 Hz, 1H), 1.62 (ddd, J = 13.4, 13.4, 6.9, 6.9 Hz, 1H), 1.41 (s, 9H), 0.86-0.89 (m, 6H). ¹³C NMR (DMSO-d₆, 125 MHz): δ 171.7, 171.5, 170.8, 153.3, 142.2, 138.4, 136.3, 133.9, 129.6, 129.1, 128.4, 126.9, 126.6, 124.6, 123.7, 82.0, 69.4, 67.4, 58.2, 55.1, 54.0, 49.0, 40.7, 38.1, 37.6, 37.2, 31.4, 27.8, 24.4, 23.6, 22.1. MS (ESI) Calculated for C₃₇H₄₈N₅O₅ [M-OCO₂tBu]⁺: 562.3, found 562.4.

Acyclic-Gly-Val-Trp (S22):

Following general procedure A, the corresponding compound was prepared from H-GVW-OH (•TFA, 57 mg, 0.120 mmol), diisopropylethylamine (84 µL, 0.481 mmol) and reagent 1 (48 mg, 0.120 mmol). The product was isolated by flash chromatography (SiO₂, gradient 0-10% CH₃OH/CHCl₃). The fractions collected were combined and concentrated under reduced pressure (48 mg, 0.073 mmol, 61%). ¹H NMR (DMSO-d₆, 500 MHz): δ 10.80 (s, 1H), 8.23 (d, J = 7.7 Hz, 1H), 8.09 (d, J = 6.0 Hz, 1H), 7.72 (d, J = 9.2 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.28-7.32 (m, 2H), 7.20-7.27 (m, 2H), 7.09-7.15 (m, 2H), 7.03 (dd, J = 7.6, 7.6 Hz, 1H), 6.95 (dd, J = 7.1, 7.1 Hz, 1H), 6.62 (d, J = 16.0 Hz, 1H), 6.32 (dt, 16.0, 6.3 Hz, 1H), 4.65 (dd, J = 6.1, 1.2 Hz, 2H), 4.43 (ddd, J = 7.9, 7.9, 5.5 Hz, 1H), 4.24 (dd, J = 9.0, 6.6 Hz, 1H), 3.66-3.76 (m, 2H), 3.15 (dd, J = 14.7, 5.3 Hz, 1H), 3.01 (dd, J = 14.7, 8.3 Hz, 1H), 2.71-2.82 (m, 2H), 2.40-2.46 (m, 2H), 1.94 (ddd, J = 13.4, 6.8, 6.8, 6.8 Hz, 1H), 1.41 (s, 9H), 0.82 (d, J = 6.7 Hz, 3H), 0.77 (d, J = 6.9 Hz, 3H). ¹³C NMR (DMSO-d₆, 125 MHz): δ 173.7, 172.2, 171.3, 169.2, 153.3, 142.2, 136.5, 136.3, 133.4, 129.1, 128.5, 127.7, 126.9, 124.7, 124.1, 123.8, 121.3, 118.8, 118.6, 111.8, 110.3, 82.0, 67.4, 57.5, 53.5, 42.4, 37.1, 31.4, 27.8, 27.5, 19.6, 18.3. MS (ESI) Calculated for C₃₅H₄₄N₄O₅ [M-OCO₂tBu]⁺: 531.3, found 531.3.
Acyclic-Ala-Val-Pro-His-OH (S23):

Following general procedure A, the corresponding compound was prepared from H-A(D-)V(D-)PH-OH (~2TFA, 155 mg, 0.289 mmol), diisopropylethylamine (201 μL, 1.16 mmol) and reagent 1 (117 mg, 0.289 mmol). The product was isolated by flash chromatography (SiO₂, gradient 0-10% CH₃OH/CHCl₃). The fractions collected were combined and concentrated under reduced pressure (152 mg, 0.214 mmol, 74%). ¹H NMR (DMSO-d₆, 500 MHz): δ ~3:1 mixture of rotamers; major: δ 8.97 (d, J = 1.2 Hz, 1H), 8.29 (d, J = 8.2 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 8 (d, J = 7.8 Hz, 1H), 7.36 (s, 1H), 7.29 (s, 1H), 7.17-7.26 (m, 2H), 7.09 (d, J = 7.8 Hz, 1H), 6.62 (d, J = 16 Hz, 1H), 6.32 (dt, J = 15.9, 6.2 Hz, 1H), 4.65 (d, J = 6.1 Hz, 2H), 4.52 (ddd, J = 9.6, 8.7, 4.6 Hz, 1H), 4.37 (dddd, J = 6.2, 6.2, 6.2 Hz, 1H), 4.24-4.32 (m, 1H), 3.58-3.70 (m, 1H), 3.45-3.57 (m, 1H), 3.14 (dd, J = 15.0, 4.1 Hz, 1H), 2.95 (dd, J = 15.1, 9.9 Hz, 1H), 2.32-2.47 (m, 2H), 1.87-1.99 (m, 2H), 1.69-1.80 (m, 2H), 1.50-1.58 (m, 1H), 1.4 (s, 9H), 1.13 (d, J = 7 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H). ¹³C NMR (DMSO-d₆, 100 MHz): δ 172.7, 172.3, 171.8, 171.4, 171.2, 153.3, 142.2, 136.3, 134.2, 133.9, 129.9, 129.1, 128.5, 126.8, 124.7, 123.7, 118.5, 117.5, 116.1, 82.0, 67.4, 59.8, 55.9, 55.5, 51.3, 48.3, 37.0, 31.4, 30.6, 29.8, 27.8, 27.0, 24.7, 19.6, 19.5, 18.6. MS (ESI) Calculated for C₃₆H₅₀N₆O₉ [M+H]⁺: 711.4, found 711.4.

Acyclic-Ala-Val-Pro-His-NH₂ (S24):

Following general procedure A, the corresponding compound was prepared from H-A(D-)V(D-P)H-NH₂ (~2TFA, 175 mg, 0.327 mmol), diisopropylethylamine (228 μL, 1.307 mmol) and reagent 1 (132 mg, 0.327 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 20-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (181 mg, 0.255 mmol, 78%). ¹H NMR (DMSO-d₆, 500 MHz): δ 8.94 (d, J = 1.2 Hz, 1H), 8.53 (d, J = 8.7 Hz, 1H), 8.06 (d, J = 8 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.37 (s, 1H), 7.21-7.33 (m, 5H), 7.11 (d, J = 7.3 Hz, 1H), 6.64 (d, J = 15.9 Hz, 1H), 6.33 (dt, J = 15.9, 6.3 Hz, 1H), 4.67 (dd, J = 6.3, 1.1 Hz, 2H), 4.49 (ddd, J = 9.4, 9.4, 4.3 Hz, 1H), 4.33 (dq, J = 7.2, 7.2 Hz, 1H), 4.24 (dd, J = 8.3, 8.3 Hz, 1H), 4.2 (dd, J = 7.1, 7.1 Hz, 1H), 3.75-3.82 (m, 1H), 3.52 (ddd, J = 9.5, 7.4, 7.2 Hz, 1H), 3.22 (dd, J = 15.2, 4.3 Hz, 1H), 2.88 (dd, J = 15.2, 10.1 Hz, 1H), 2.79 (t, J = 7.7 Hz, 2H), 2.36-2.47 (m, 2H), 1.86-2.01 (m, 3H), 1.72-1.83 (m, 1H), 1.59 (ddd, J = 13.8, 13.8, 7.0 Hz, 1H), 1.42 (s, 9H), 1.12 (d, J = 6.7 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H). ¹³C NMR (DMSO-d₆, 100 MHz): δ 172.3, 172.1, 171.8, 171.2, 170.3, 152.8, 141.6, 135.8, 133.6, 133.4, 129.9, 128.6, 128.0, 126.3, 124.2, 123.2, 116.7, 81.5, 66.9, 59.8, 55.8, 51.3, 48.5, 47.7, 36.5, 30.8, 30.1, 28.9, 27.3, 26.3, 24.7, 18.8. MS (ESI) Calculated for C₃₆H₅₁N₇O₈ [M+H]⁺: 710.4, found 710.4.
Acyclic-Ala-Arg-His-Phe-NH\(_2\) (S25):

Following general procedure A, the corresponding compound was prepared from H-ARHF-NH\(_2\) (+4TFA, 54 mg, 0.055 mmol), diisopropylethylamine (38 μL, 0.219 mmol) and reagent 1 (22 mg, 0.055 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 10-100% CH\(_3\)CN/H\(_2\)O with 0.1% TFA. The fractions collected were combined and lyophilized (28 mg, 0.035 mmol, 63%). \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): δ 8.94 (d, J = 1.2 Hz, 1H), 8.03-8.11 (m, 4H), 7.63 (dd, J = 5.6 Hz, 1H), 7.59 (br. s, 1H), 7.20-7.29 (m, 9H), 7.15-7.19 (m, 1H), 7.09 (br. d, J = 7.4 Hz, 1H), 6.62 (br. d, J = 15.9 Hz, 1H), 6.32 (dt, J = 16.0, 6.3 Hz, 1H), 4.65 (dd, J = 6.1, 1.1 Hz, 2H), 4.53 (ddd, J = 7.8, 7.8, 5.9 Hz, 1H), 4.41 (ddd, J = 8.6, 8.2, 4.9 Hz, 1H), 4.23 (dq, J = 7.0, 7.0, Hz, 1H), 4.17 (ddd, J = 7.8, 7.8, 5.6 Hz, 1H), 2.98-3.07 (m, 4H), 2.97 (dd, J = 15.7, 8.0 Hz, 1H), 2.74-2.85 (m, 3H), 2.35-2.46 (m, 2H), 1.57-1.60 (m, 1H), 1.43-1.53 (m, 2H), 1.41 (s, 9H), 1.12 (d, J = 7.2 Hz, 3H). \(^1\)C NMR (DMSO-d\(_6\), 100 MHz): δ 173.4, 173.2, 172.0, 171.8, 169.9, 157.3, 153.3, 142.2, 138.0, 136.3, 134.2, 133.9, 129.6, 129.5, 129.1, 128.6, 128.5, 126.9, 126.8, 124.7, 123.8, 118.2, 117.4, 115.9, 82.0, 67.4, 54.4, 52.7, 51.9, 48.8, 40.9, 37.9, 37.0, 31.3, 29.1, 27.8, 27.5, 25.5, 18.4. MS (ESI) Calculated for C\(_{41}\)H\(_{56}\)N\(_10\)O\(_8\) [M+H]\(^+\): 816.4, found 817.2.

Acyclic-Ala-Ile-His-Phe-NH\(_2\) (S26):

Following general procedure A, the corresponding compound was prepared from H-AIHF-NH\(_2\) (+2TFA, 44 mg, 0.062 mmol), diisopropylethylamine (43 μL, 0.247 mmol) and reagent 1 (25 mg, 0.062 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 20-100% CH\(_3\)CN/H\(_2\)O with 0.1% TFA. The fractions collected were combined and lyophilized (34 mg, 0.044 mmol, 72%). \(^1\)H NMR (DMSO-d\(_6\), 500 MHz): δ 8.94 (d, J = 1.6 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 8.04 (d, J = 7.4 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.51 (br. s, 1H), 7.27-7.29 (m, 2H), 7.18-7.26 (m, 6H), 7.14-7.18 (m, 2H), 7.1 (br. d, J = 7.4 Hz, 1H), 6.62 (d, J = 16 Hz, 1H), 6.32 (dt, J = 16.0, 6.2 Hz, 1H), 4.65 (dd, J = 6.3, 1.2 Hz, 2H), 4.58 (ddd, J = 7.9, 7.9, 6.1 Hz, 1H), 4.41 (ddd, J = 8.3, 8.3, 5.1 Hz, 1H), 4.29 (dq, J = 7.0, 7.0 Hz, 1H), 4.07 (t, J = 7.6 Hz, 1H), 2.95-3.00 (m, 2H), 2.91 (dd, J = 15.4, 801 Hz, 1H), 2.75-2.85 (m, 3H), 2.36-2.45 (m, 2H), 1.59-1.66 (m, 1H), 1.41 (s, 9H), 1.27-1.34 (m, 1H), 1.1 (d, J = 7 Hz, 3H), 0.94-1.04 (m, 1H), 0.74 (t, J = 7.4 Hz, 3H), 0.69 (d, J = 6.7 Hz, 3H). \(^1\)C NMR (DMSO-d\(_6\), 100 MHz): δ 173.2, 172.9, 171.8, 171.4, 170.0, 153.3, 142.2, 138.0, 136.3, 134.2, 133.9, 129.6, 129.5, 129.1, 128.5, 128.5, 126.9, 126.8, 124.7, 123.8, 117.3, 82.0, 67.4, 57.4, 54.3, 51.8, 48.5, 37.9, 37.1, 36.9, 31.4, 27.8, 27.5, 24.7, 18.3, 15.7, 11.5. MS (ESI) Calculated for C\(_{41}\)H\(_{56}\)N\(_7\)O\(_8\) [M+H]\(^+\): 774.4, found 774.2.
Acyclic-β-Ala-Pro[4-(2-methoxy-4-methylphenoxy)]-His (S27):

Following general procedure A, the corresponding compound was prepared from H-β-(AP(4-OAr)H-NH₂ (•2TFA, 112 mg, 0.163 mmol), diisopropylethylamine (114 μL, 0.653 mmol) and reagent 1 (66 mg, 0.163 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 30-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (95 mg, 0.127 mmol, 78%). ¹H NMR (DMSO-d₆, 500 MHz): 5:1 mixture of rotamers. Major: δ 8.86 (d, J = 0.9 Hz, 1H), 8.14 (d, J = 8.7 Hz, 1H), 7.91 (d, J = 5.7 Hz, 1H), 7.33 (br. s, 1H), 7.25-7.31 (m, 2H), 7.17-7.24 (m, 3H), 7.06-7.10 (m, 2H), 6.75-6.82 (m, 2H), 6.64 (br. d, J = 8.3 Hz, 1H), 6.59 (d, J = 16 Hz, 1H), 6.3 (dt, J = 15.9, 6.3 Hz, 1H), 4.76-4.80 (m, 1H), 4.64 (d, J = 6.4 Hz, 2H), 4.51 (ddd, J = 9.2, 9.2, 4.6 Hz, 1H), 4.29 (dd, J = 9.9, 3.9 Hz, 1H), 3.71-3.73 (m, 1H), 3.7 (s, 3H), 3.19-3.29 (m, 3H), 2.93 (dd, J = 13.0, 3.1 Hz, 1H), 1.4 (s, 9H). ¹³C NMR (DMSO-d₆, 100 MHz): δ 172.4, 172.0, 171.9, 171.8, 171.6, 171.6, 156.3, 153.3, 142.1, 136.3, 134.1, 133.9, 132.9, 130.5, 129.0, 128.6, 126.9, 124.7, 123.7, 121.3, 118.8, 116.9, 113.8, 82.0, 78.2, 67.4, 59.7, 55.9, 52.3, 51.7, 37.3, 35.1, 34.7, 31.4, 27.8, 26.5, 21.2. MS (ESI) Calculated for C₃₉H₅₀N₆O₉ [M+H]⁺: 747.4, found 747.3.

Acyclic-Val-Gln-Tyr-His-NH₂ (18):

Following general procedure A, the corresponding compound was prepared from H-VQYH-NH₂ (•2TFA, 170 mg, 0.220 mmol), diisopropylethylamine (153 μL, 0.88 mmol) and reagent 1 (89 mg, 0.220 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 20-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (103 mg, 0.123 mmol, 56%). ¹H NMR (DMSO-d₆, 500 MHz): δ 8.94 (d, J = 1.4 Hz, 1H), 8.19 (d, J = 8.3 Hz, 1H), 8.11 (d, J = 7.3 Hz, 1H), 7.91 (d, J = 7.8 Hz, 2H), 7.32 (br. s, J = Hz, 1H), 7.18-7.30 (m, 5H), 7.14 (br. s, J = Hz, 1H), 7.1 (br. d, J = 7.3 Hz, 1H), 6.96 (d, J = 8.4 Hz, 2H), 6.83 (br. s, J = Hz, 1H), 6.57-6.63 (m, 3H), 6.31 (dt, J = 16.0, 6.2 Hz, 1H), 4.65 (dd, J = 6.4, 1.2 Hz, 2H), 4.46 (ddd, J = 8.2, 8.2, 5.5 Hz, 1H), 4.32 (ddd, J = 8.1, 8.1, 5.0 Hz, 1H), 4.16 (ddd, J = 8.0, 8.0, 5.7 Hz, 1H), 4.04-4.09 (m, 1H), 3.1 (dd, J = 15.3, 5.2 Hz, 1H), 2.89 (dd, J = 15.4, 8.6 Hz, 1H), 2.74-2.86 (m, 3H), 2.68 (dd, J = 14.1, 9.1 Hz, 1H), 2.50-2.58 (m, 1H), 2.39-2.46 (m, 1H), 2.00-2.12 (m, 2H), 1.75-1.90 (m, 2H), 1.61-1.70 (m, 1H), 1.4 (s, 9H), 0.73 (d, J = 6.7 Hz, 6H). ¹³C NMR (DMSO-d₆, 100 MHz): δ 174.6, 172.4, 172.0, 171.9, 171.8, 171.8, 156.3, 153.3, 142.1, 136.3, 134.1, 133.9, 130.4, 129.9, 129.1, 128.5, 127.9, 126.8, 124.7, 123.7, 117.3,
Acyclic-Gly-Thr-His-Tyr-NH₂ (S29):

Following general procedure A, the corresponding compound was prepared from H-GTHY-NH₂ (+2TFA, 37 mg, 0.053 mmol), diisopropylethylamine (37 μL, 0.210 mmol) and reagent 1 (21 mg, 0.053 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 20-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (27 mg, 0.036 mmol, 68%). ¹H NMR (DMSO-d₆, 500 MHz): δ 8.92 (d, J = 1.4 Hz, H), 8.2 (t, J = 5.9 Hz, H), 8.15 (d, J = 8 Hz, H), 7.95 (d, J = 7.8 Hz, H), 7.8 (d, J = 8 Hz, H), 7.44 (br. s, H), 7.24-7.30 (m, H), 7.22 (t, J = 7.5 Hz, H), 7.15 (br. s, H), 7.1 (br. d, J = 7.3 Hz, H), 7.01 (d, J = 8.5 Hz, H), 6.59-6.65 (m, H), 6.32 (dt, J = 16.1, 6.3 Hz, H), 4.65 (dd, J = 6.3m 1.1 Hz, H), 4.54 (ddd, J = 8.0, 8.0, 5.4 Hz, H), 4.3 (ddd, J = 8.3, 8.3, 5.2 Hz, H), 4.19 (dd, J = 8.0, 4.5 Hz, H), 3.94 (dd, J = 6.5, 6.5, 4.7 Hz, H), 3.71-3.81 (m, H), 3.06 (dd, J = 15.3, 5.1 Hz, H), 2.93 (dd, J = 15.3, 8.3 Hz, H), 2.87 (dd, J = 13.7, 4.9 Hz, H), 2.76-2.81 (m, H), 2.69 (dd, J = 14.0, 8.9 Hz, H), 2.40-2.47 (m, H), 1.41 (s, H), 0.99 (d, J = 6.4 Hz, H). ¹³C NMR (DMSO-d₆, 100 MHz): δ 173.6, 172.5, 170.5, 170.0, 169.9, 156.3, 153.3, 142.2, 136.4, 134.2, 133.9, 130.5, 129.6, 129.1, 128.5, 128.1, 126.9, 124.7, 117.5, 115.4, 82.0, 67.4, 66.9, 58.6, 55.0, 52.1, 42.6, 37.1, 31.8, 31.3, 27.8, 27.2, 20.0. MS (ESI) Calculated for C₃₈H₄₉N₇O₁₀ [M+H]⁺: 764.4, found 764.1.

Acyclic-Val-Orn-Met-Tyr (S30):

Following general procedure A, the corresponding compound was prepared from Fmoc-VOMY -NH₂ (+1TFA, 94 mg, 0.110 mmol), diisopropylethylamine (76 μL, 0.440 mmol) and reagent 1 (22 mg, 0.110 mmol). The reaction mixture was evaporated under reduced pressure. The resulting residue was treated with 20% piperidine/DMF (8 ml) for two hours and evaporated. The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 30-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (56 mg, 0.069 mmol, 62%). ¹H NMR (DMSO-d₆, 500 MHz): δ 8.49 (d, J = 7.7 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.03-8.09 (m, 3H), 7.84 (dd, J = 5.7, 5.7 Hz,
1H), 7.77 (d, J = 8.1 Hz, 1H), 7.4 (br. s, J = Hz, 1H), 7.19-7.29 (m, 3H), 7.09 (br. d, J = 7.4 Hz, 1H), 7.05 (br. s, J = Hz, 1H), 6.98 (d, J = 8.6 Hz, 2H), 6.58-6.64 (m, 3H), 6.31 (dt, J = 15.9, 6.3 Hz, 1H), 4.65 (dd, J = 6.3, 1.2 Hz, 2H), 4.25-4.37 (m, 3H), 3.56-3.62 (m, 1H), 2.96-3.09 (m, 2H), 2.84 (dd, J = 13.9, 5.2 Hz, 1H), 2.75-2.80 (m, 2H), 2.68 (dd, J = 14.1, 8.6 Hz, 1H), 2.30-2.42 (m, 4H), 1.96-2.06 (m, 4H), 1.80-1.89 (m, 1H), 1.67-1.76 (m, 1H), 1.55-1.64 (m, 1H), 1.31-1.51 (m, 12H), 0.9 (d, J = 2.4 Hz, 3H), 0.89 (d, J = 2.7 Hz, 3H).

13C NMR (DMSO-d6, 100 MHz): δ 173.3, 171.8, 171.5, 170.9, 168.2, 156.3, 153.3, 142.3, 136.3, 133.9, 130.6, 129.1, 128.5, 128.1, 126.9, 124.7, 123.8, 115.3, 82.0, 67.4, 57.6, 54.4, 52.8, 52.5, 38.5, 37.5, 37.3, 32.6, 31.5, 30.4, 29.8, 27.8, 18.7, 18.1, 15.0. MS (ESI) Calculated for C41H60N6O9S [M+H]+: 813.4, found 813.2.

**Acyclic-Orn-Thr-Tyr (S35):**

Following general procedure A, the corresponding compound was prepared from Orn(Fmoc)-Thr-Tyr-NH2 (+1TFA, 109 mg, 0.15 mmol), diisopropylethylamine (52 μL, 0.30 mmol) and reagent 1 (60 mg, 0.15 mmol). The reaction mixture was evaporated under reduced pressure. The resulting residue was treated with DBU (1 equiv.) and Si-Thiol (Silicycle, 1.22 g/mmol) in DMF (1 ml) for one hour. The product was filtered and purified by preparative HPLC (Waters Xbridge C18 19x250 mm) using a gradient of 30-100% CH3CN/H2O with 0.1% TFA. The fractions collected were combined and evaporated (116 mg, 0.145 mmol, 97%). 1H NMR (DMSO-d6, 500 MHz): δ 9.20 (br s, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.65-7.70 (m, 3H), 7.42 (br s, 1H), 7.30 (br s, 1H), 7.27 (br d, J = 7.6 Hz, 1H), 7.24 (dd, J = 7.6, 7.3 Hz, 1H), 7.16 (br s, 1H), 7.11 (br d, J = 7.3 Hz, 1H), 7.01 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 15.9 Hz, 1H), 6.63 (d, J = 8.4 Hz, 2H), 6.34 (dt, J = 15.9, 6.2 Hz, 1H), 4.67 (d, J = 6.1 Hz, 2H), 4.38-4.43 (m, 1H), 4.36 (ddd, J = 8.1, 8.0, 5.0 Hz, 1H), 4.18 (dd, J = 8.2, 4.2 Hz, 1H), 3.96-4.02 (m, 1H), 2.91 (dd, J = 14.0, 5.0 Hz, 1H), 2.80 (dd, J = 9.0, 6.8 Hz, 2H), 2.66-2.78 (m, 3H), 2.45 (dd, J = 8.3, 6.8 Hz, 2H), 1.63-1.72 (m, 1H), 1.46-1.54 (m, 3H), 1.43 (s, 9H), 0.97 (d, J = 6.3 Hz, 3H). 13C NMR (DMSO-d6, 100 MHz): δ 173.1, 171.6, 169.4, 155.8, 152.8, 141.7, 135.9, 133.4, 130.1, 128.7, 128.0, 127.7, 126.4, 124.3, 123.4, 114.9, 81.6, 66.9, 66.4, 58.1, 54.1, 51.6, 38.5, 36.7, 31.0, 28.8, 27.4, 23.5, 19.4. MS (ESI) Calculated for C35H45N6O9S [M+H]+: 684.4, found 684.2.
**Acyclic-Gly-Thi-Trp-5HT (S31):**

Following general procedure A, the corresponding compound was prepared from H-GThiW-5HT-NH₂ (+TFA, 52 mg, 0.091 mmol), diisopropylethylamine (63 μL, 0.363 mmol) and reagent 1 (37 mg, 0.091 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 40-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (45 mg, 0.052 mmol, 57%). ¹H NMR (DMSO-d₆, 600 MHz): δ 10.75 (s, 1H), 10.42 (s, 1H), 8.08-8.14 (m, 2H), 7.85 (t, J = 5.6 Hz, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.22-7.27 (m, 3H), 7.20 (t, J = 7.5 Hz, 1H), 7.06-7.11 (m, 3H), 7.02 (dd, J = 7.4, 7.4 Hz, 1H), 6.96-6.98 (m, 1H), 6.94 (dd, J = 7.4, 7.4 Hz, 1H), 6.85 (dd, J = 4.7, 4.0 Hz, 1H), 6.80-6.83 (m, 2H), 6.59 (d, J = 16.2 Hz, 1H), 6.57 (dd, J = 8.6, 2.2 Hz, 1H), 6.29 (dt, J = 16.0, 6.3 Hz, 1H), 4.63 (d, J = 6.4 Hz, 2H), 4.44-4.52 (m, 2H), 3.74 (dd, J = 16.5, 5.7 Hz, 1H), 3.62 (dd, J = 16.3, 5.6 Hz, 1H), 3.21-3.27 (m, 2H), 3.18 (dd, J = 15.1, 4.3 Hz, 1H), 3.11 (dd, J = 14.5, 5.4 Hz, 1H), 2.96-3.01 (m, 2H), 2.78 (t, J = 7.7 Hz, 1H), 2.62 (t, J = 7.7 Hz, 1H), 2.40-2.45 (m, 2H), 1.40 (s, 9H). ¹³C NMR (DMSO-d₆, 150 MHz): δ 172.3, 171.2, 170.4, 169.5, 153.1, 150.5, 142.1, 139.7, 136.4, 136.2, 133.7, 131.1, 129.0, 128.3, 128.1, 127.7, 127.0, 126.8, 126.6, 124.8, 124.5, 123.9, 123.7, 123.4, 121.2, 118.8, 118.6, 112.0, 111.60, 111.57, 111.0, 110.3, 102.5, 81.8, 67.2, 54.2, 54.1, 42.4, 37.0, 31.9. MS (ESI) Calculated for C₄₇H₆₂N₆O₈S [M+H]⁺: 861.4, found 861.3.

**Acyclic-Ala-Phe-Ser-Val-Pro-Gly-Val-Trp-Ile-Ser-Tyr-Val (S32):**

Following general procedure A, the corresponding compound was prepared from H-AFSVPGWISYV-NH₂ (+TFA, 75 mg, 0.052 mmol), diisopropylethylamine (36 μL, 0.209 mmol) and reagent 1 (21 mg, 0.052 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 30-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (61 mg, 0.038 mmol, 72%). ¹H NMR (DMSO-d₆, 600 MHz): δ 10.68 (s, 1H), 8.18 (d, J = 8 Hz, 1H), 8.09 (dd, J = 5.6 Hz, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.91-7.98 (m, 3H), 7.89 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.7 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.71 (d, J = 9.1 Hz, 1H), 7.56 (d, J = 8.9 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.16-7.28 (m, 9H), 7.10-7.15 (m, 1H), 7.04-7.09 (m, 3H), 7 (t, J = 7.4 Hz, 1H), 6.96 (d, J = 8.3 Hz, 2H), 6.92 (t, J = 7.5 Hz, 1H), 6.6 (d, J = 16 Hz, 1H), 6.56 (d, J = 8.1 Hz, 2H), 6.3 (dt, J = 16.0, 6.3 Hz, 1H), 4.63 (d, J = 6.1 Hz, 2H), 4.55 (ddd, J = 8.4, 8.4, 8.4 Hz, 1H), 4.44-4.52 (m, 2H), 3.74 (dd, J = 16.5, 5.7 Hz, 1H), 3.62 (dd, J = 16.3, 5.6 Hz, 1H), 3.21-3.27 (m, 2H), 3.18 (dd, J = 15.1, 4.3 Hz, 1H), 3.11 (dd, J = 14.5, 5.4 Hz, 1H), 2.96-3.01 (m, 2H), 2.78 (t, J = 7.7 Hz, 1H), 2.62 (t, J = 7.7 Hz, 1H), 2.40-2.45 (m, 2H), 1.40 (s, 9H).
4.63 (ddd, J = 8.7, 8.7, 4.2 Hz, 1H), 6.06 (ddd, J = 8.0, 8.0, 5.0 Hz, 1H), 4.12-4.36 (m, 4H), 4.14-4.23 (m, 3H), 4.06 (dd, J = 8.8, 6.7 Hz, 1H), 3.71 (dd, J = 16.5, 5.8 Hz, 1H), 3.61-3.66 (m, 1H), 3.44-3.50 (m, 5H), 3.06 (dd, J = 14.3, 3.9 Hz, 1H), 3.01 (dd, J = 13.9, 3.7 Hz, 1H), 2.84-2.93 (m, 2H), 2.67-2.79 (m, 4H), 1.84-2.03 (m, 5H), 1.73-1.81 (m, 2H), 1.61-1.69 (m, 1H), 1.39 (s, 9H), 1.32-1.38 (m, 1H), 1.04 (dd, J = 7 Hz, 3H), 0.96-1.03 (m, 1H), 0.87 (d, J = 6.4 Hz, 3H), 0.70-0.83 (m, 21H).

13C NMR (DMSO-d6, 150 MHz): δ 173.1, 172.4, 172.3, 171.64, 171.56, 171.03, 171.00, 170.9, 170.2, 170.05, 170.01, 168.8, 156.1, 153.1, 142.0, 138.0, 136.3, 136.2, 133.8, 130.3, 129.6, 128.9, 128.34, 128.26, 127.9, 127.6, 126.7, 126.5, 124.6, 123.9, 123.7, 121.1, 118.7, 118.5, 115.2, 111.5, 110.3, 81.8, 67.2, 62.1, 62.0, 59.89, 57.90, 57.7, 57.1, 56.0, 55.3, 55.2, 54.7, 53.9, 53.7, 48.6, 47.4, 42.4, 37.6, 37.2, 36.9, 36.6, 31.1, 31.0, 30.7, 30.4, 29.5, 27.7, 24.7, 24.5, 19.6, 19.6, 19.5, 18.4, 18.2. MS (ESI) Calculated for C83H114N14O19 [M+2H]2+: 806.4, found 806.2.

**Acyclic-Trp-Leu-Gln-Met-Thr-Gly-Phe-Tyr (S33):**

Following general procedure A, the corresponding compound was prepared from H-WLQMTGFY-NH2 (+TFA, 83 mg, 0.072 mmol), diisopropylethylamine (50 μL, 0.287 mmol) and reagent 1 (29 mg, 0.072 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 40-100% CH3CN/H2O with 0.1% TFA. The fractions collected were combined and lyophilized (61 mg, 0.046 mmol, 64%). 1H NMR (DMSO-d6, 500 MHz): δ 10.74 (d, J = 1.6 Hz, 1H), 7.97-8.10 (m, 7H), 7.73 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.11-7.26 (m, 10H), 7.08 (d, J = 2.6 Hz, 1H), 6.97-7.05 (m, 5H), 6.95 (t, J = 7.9 Hz, 1H), 6.78 (br. s, J = Hz, 1H), 6.62 (d, J = 8.4 Hz, 2H), 6.58 (d, J = 16.1 Hz, 1H), 6.3 (dt, J = 16.1, 6.2 Hz, 1H), 4.64 (dd, J = 6.3, 1.1 Hz, 2H), 4.55 (ddd, J = 8.6, 8.6, 4.6 Hz, 1H), 4.46 (ddd, J = 8.7, 8.7, 4.7 Hz, 1H), 4.41 (ddd, J = 8.4, 8.4, 4.8 Hz, 1H), 4.27-4.33 (m, 2H), 4.23 (dq, J = 7.7, 7.7 Hz, 1H), 4.18 (dd, J = 8.0, 3.9 Hz, 1H), 3.91-3.97 (m, 1H), 3.68 (dd, J = 17.0, 5.4 Hz, 1H), 3.62 (dd, J = 16.7, 5.2 Hz, 1H), 3.08 (dd, J = 14.6, 4.2 Hz, 1H), 2.93 (dd, J = 13.7, 4.4 Hz, 1H), 2.83-2.91 (m, 2H), 2.60-2.72 (m, 4H), 2.50-2.46 (m, 4H), 2.06-2.13 (m, 2H), 1.98 (s, 3H), 1.81-1.96 (m, 2H), 1.70-1.81 (m, 2H), 1.49-1.61 (m, 1H), 1.36-1.46 (m, 1H), 0.85 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H). 13C NMR (DMSO-d6, 125 MHz): δ 174.3, 173.3, 172.4, 172.1, 171.8, 171.7, 171.6, 171.0, 170.7, 169.0, 156.2, 153.3, 142.2, 138.1, 136.5, 136.3, 133.9, 130.6, 129.7, 129.1, 128.5, 128.4, 128.3, 127.9, 126.9, 126.7, 124.6, 124.1, 123.7, 121.2, 119.0, 118.6, 115.3, 111.7, 110.6, 82.0, 67.4, 67.1, 58.7, 54.7, 54.5, 53.7, 52.6, 52.3, 51.5, 42.4, 41.3, 38.0, 37.3, 37.3, 32.2, 31.9, 31.4, 30.0, 28.2, 28.1, 27.8, 24.6, 23.5, 22.2, 20.0, 15.1. MS (ESI) Calculated for C68H88N14O15S [M+H]+: 1332.6, found 1332.2.
Acyclic-Thr-Ala-Trp-Ile-Pro-Tyr-His-Asn-Val (S34):

Following general procedure A, the corresponding compound was prepared from H-TAWIPYHV-\text{-}NH\textsubscript{2} (\textbullet\textsubscript{2}TFA, 196 mg, 0.148 mmol), diisopropylethylamine (103 \muL, 0.591 mmol) and reagent 1 (60 mg, 0.148 mmol). The product was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 30-100\% CH\textsubscript{3}CN/H\textsubscript{2}O with 0.1\% TFA. The fractions collected were combined and lyophilized (131 mg, 0.095 mmol, 64\%). \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 500 MHz): \delta 10.76 (s, 1H), 8.92 (s, 1H), 8.31 (d, J = 7.1 Hz, 1H), 8.18 (d, J = 7.7 Hz, 1H), 7.89-7.98 (m, 2H), 7.84 (d, J = 7.2 Hz, 1H), 7.77-7.81 (m, 2H), 7.47 (d, J = 7.9 Hz, 1H), 7.44 (s, 1H), 7.38 (s, 1H), 7.33 (s, 1H), 7.25-7.29 (m, 2H), 7.16-7.24 (m, 2H), 7.04-7.09 (m, 3H), 6.90-7.03 (m, 4H), 6.91 (d, J = 7.3 Hz, 1H), 6.56-6.62 (m, 3H), 6.29 (dt, J = 15.8, 6.2 Hz, 1H), 4.63 (dd, J = 6.2, 0.9 Hz, 2H), 4.49-4.61 (m, 3H), 4.18-4.32 (m, 5H), 3.90 (ddd, J = 10.0, 10.0, 5.7 Hz, 1H), 3.50-3.56 (m, 1H), 3.41-3.47 (m, 1H), 3.00-3.10 (m, 2H), 2.86-2.97 (m, 2H), 2.75-2.82 (m, 2H), 2.41-2.57 (m, 5H), 2 (dq, J = 13.5, 6.8 Hz, 1H), 1.82-1.91 (m, 1H), 1.59-1.75 (m, 4H), 1.41-1.48 (m, 1H), 1.39 (s, 9H), 0.92 (d, J = 6.2 Hz, 3H), 0.71-0.81 (m, 12H). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 125 MHz): \delta 173.0, 172.2, 172.0, 171.9, 171.5, 171.3, 171.2, 170.3, 170.2, 169.8, 161.8, 156.1, 153.1, 142.0, 136.3, 136.1, 134.0, 133.8, 130.3, 129.3, 128.9, 128.4, 128.0, 127.7, 126.7, 124.5, 123.9, 123.6, 121.1, 118.7, 118.5, 117.3, 116.7, 115.2, 114.8, 112.9, 111.5, 110.0, 81.8, 67.2, 66.9, 59.6, 58.3, 57.9, 54.9, 53.5, 51.6, 50.3, 48.6, 37.1, 36.9, 36.4, 31.3, 30.4, 29.2, 27.7, 24.5, 24.4, 24.3, 19.8, 19.6, 18.4, 17.8, 15.3, 11.1. MS (ESI) Calculated for C\textsubscript{70}H\textsubscript{94}N\textsubscript{14}O\textsubscript{16} [M+H]\textsuperscript{+}: 1387.7, found 1387.4.

Data for macrocyclic compounds:

Cyclic-Ala-Trp-Thr-Tyr (4):

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100\% CH\textsubscript{3}CN/H\textsubscript{2}O with 0.1\% TFA. The fractions collected were combined and lyophilized (8 mg, 0.011 mmol, 78\%). \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 500 MHz): \delta 10.81 (d, J = 1.8 Hz, 1H), 8.1 (d, J = 7.5 Hz, 1H), 8.01 (d, J = 7.4 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.25-7.36 (m, 3H), 7.06-7.22 (m, 5H), 6.89-7.05 (m, 3H), 6.79 (d, J = 8.7 Hz, 2H), 6.61 (d, J = 8.3 Hz, 2H), 6.53 (d, J = 15.9 Hz, 1H), 2.28 (dt, J = 16.0, 5.7 Hz, 1H), 4.15 (d, J = 5.4 Hz, 2H), 4.31-4.42 (m, 3H), 4.07-4.14 (m, 1H), 3.91-3.99 (m, 1H), 2.86-3.16 (m, 4H), 2.65-2.80 (m, 3H), 2.23-3.38 (m, 1H), 1.82-1.92 (m, 1H), 1.59-1.75 (m, 4H), 1.41-1.48 (m, 1H), 1.39 (s, 9H), 0.92 (d, J = 6.2 Hz, 3H), 0.71-0.81 (m, 12H). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 125 MHz): \delta 173.0, 172.2, 172.0, 171.9, 171.5, 171.3, 171.2, 170.3, 170.2, 169.8, 161.8, 156.1, 153.1, 142.0, 136.3, 136.1, 134.0, 133.8, 130.3, 129.3, 128.9, 128.4, 128.0, 127.7, 126.7, 124.5, 123.9, 123.6, 121.1, 118.7, 118.5, 117.3, 116.7, 115.2, 114.8, 112.9, 111.5, 110.0, 81.8, 67.2, 66.9, 59.6, 58.3, 57.9, 54.9, 53.5, 51.6, 50.3, 48.6, 37.1, 36.9, 36.4, 31.3, 30.4, 29.2, 27.7, 24.5, 24.4, 24.3, 19.8, 19.6, 18.4, 17.8, 15.3, 11.1. MS (ESI) Calculated for C\textsubscript{70}H\textsubscript{94}N\textsubscript{14}O\textsubscript{16} [M+H]\textsuperscript{+}: 1387.7, found 1387.4.
Cyclic-Ser-Met-Tyr (5):
Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH<sub>3</sub>CN/H<sub>2</sub>O with 0.1% TFA. The fractions collected were combined and lyophilized (15 mg, 0.026 mmol, 80%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 600 MHz): δ 7.96 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.37 (s, 1H), 7.24 (s, 1H), 7.13-7.21 (m, 2H), 7.04-7.11 (m, 3H), 7.00 (d, J = 8.1 Hz, 1H), 6.81 (d, J = 8.46 Hz, 2H), 6.60 (d, J = 15.9, 1H), 6.36 (dt, J = 16.1, 5.7 Hz, 1H), 4.77 (d, J = 5.5 Hz, 2H), 4.21-4.31 (m, 2H), 4.14 (ddd, J = 6.9, 6.9, 6.9 Hz, 1H), 3.12 (dd, J = 10.6, 5.3 Hz, 1H), 3.06 (d, J = 10.9, 6.9 Hz, 1H), 2.89 (app d, J = 14.2 Hz, 1H), 2.68-2.84 (m, 3H), 2.55-2.64 (m, 1H), 2.27-2.39 (m, 3H), 1.96 (s, 1H), 1.74-1.82 (m, 1H), 1.58-1.66 (m, 1H). <sup>1</sup>C NMR (DMSO-d<sub>6</sub>, 150 MHz): δ 173.3, 171.8, 171.2, 170.2, 156.8, 141.4, 136.2, 132.8, 130.3, 130.0, 128.8, 128.6, 126.0, 125.6, 124.5, 115.0, 68.0, 62.2, 54.7, 54.1, 52.1, 36.4, 35.3, 31.9, 30.7, 29.7, 14.9. MS (ESI) Calculated for C<sub>29</sub>H<sub>36</sub>N<sub>4</sub>O<sub>6</sub>S [M+H]<sup>+</sup>: 569.2, found 569.2.

Cyclic-Ile-Trp-Tyr (6):
Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH<sub>3</sub>CN/H<sub>2</sub>O with 0.1% TFA. The fractions collected were combined and lyophilized (12 mg, 0.019 mmol, 72%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500 MHz): 10.8 (d, J = 1.8 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.52 (br. s, J = Hz, 1H), 7.36 (d, J = 8.5 Hz, 1H), 7.31 (br. d, J = 7.9 Hz, 1H), 7.19 (br. s, J = Hz, 1H), 7.09-7.06 (m, 3H), 6.92-7.07 (m, 6H), 6.8 (d, J = 8.7 Hz, 2H), 6.68 (d, J = 16 Hz, 1H), 6.51 (dt, J = 15.8, 6.4 Hz, 1H), 4.66-4.77 (m, 2H), 4.54 (ddd, J = 8.3, 8.3, 5.6 Hz, 1H), 4.24 (ddd, J = 8.2, 8.2, 4.8 Hz, 1H), 3.84 (app. dd, J = 8.0, 6.9 Hz, 1H), 2.95 (ddd, J = 15.0, 5.4 Hz, 1H), 2.68-2.90 (m, 6H), 2.27-2.35 (m, 1H), 1.11-1.19 (m, 1H), 0.57-0.71 (m, 2H), 0.26-0.31 (m, 3H), 0.08 (d, J = 6.7 Hz, 3H). <sup>1</sup>C NMR (DMSO-d<sub>6</sub>, 125 MHz): δ 173.9, 171.6, 171.4, 170.9, 157.2, 140.9, 136.7, 136.5, 134.3, 130.6, 129.9, 129.1, 128.7, 127.7, 125.8, 125.6, 125.3, 124.2, 121.3, 119.0, 118.6, 114.7, 111.8, 110.4, 68.5, 56.8, 54.6, 53.0, 38.2, 36.7, 34.9, 30.9, 27.1, 23.8, 15.1, 11.3. MS (ESI) Calculated for C<sub>38</sub>H<sub>38</sub>N<sub>6</sub>O<sub>5</sub>S [M+H]<sup>+</sup>: 650.3, found 650.0.
**Cyclic-Ala-Val-Tyr (7):**

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (10 mg, 0.020 mmol, 78%). $^1$H NMR (DMSO-d$_6$, 600 MHz): $\delta$ 7.82 (d, J = 8.9 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 7.1 Hz, 1H), 7.22 (s, 1H), 7.15-7.20 (m, 3H), 7.08 (s, 1H), 7.00-7.05 (m, 3H), 6.78 (d, J = 8.5 Hz, 2H), 6.64 (d, J = 16.0 Hz, 1H), 6.31 (dt, J = 15.8, 6.0 Hz, 1H), 4.74 (d, J = 5.8 Hz, 2H), 5.82 (ddd, J = 9.8, 9.8, 2.9 Hz, 1H), 4.74 (dq, J = 7.0, 7.0 Hz, 1H), 3.93 (dd, J = 8.6, 8.6 Hz, 1H), 2.81-2.89 (m, 2H), 2.71-2.79 (m, 2H), 2.53-2.60 (m, 1H), 2.21-2.27 (m, 1H), 1.81 (ddddd, J = 13.5, 6.5, 6.5, 6.5 Hz, 1H), 1.38 (d, J = 6.8 Hz, 3H), 0.63 (d, J = 6.6 Hz, 6H). $^{13}$C NMR (DMSO-d$_6$, 150 MHz): $\delta$ 173.5, 172.2, 171.3, 170.9, 157.0, 141.4, 136.0, 133.2, 130.0, 129.7, 128.8, 128.8, 125.9, 125.5, 125.0, 114.9, 68.2, 58.4, 53.3, 47.9, 36.4, 35.8, 31.1, 29.9, 19.5, 19.4, 18.4. MS (ESI) Calculated for C$_{29}$H$_{36}$N$_{4}$O$_{5}$ [M+H]$^+$: 521.3, found 521.2.

**Cyclic-Trp-Ile-Gln-Tyr (8):**

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (11 mg, 0.014 mmol, 81%). $^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 10.76 (d, J = 1.9 Hz, 1H), 8.22 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.37 (br. s, 1H), 7.27-7.34 (m, 2H), 7.76-7.25 (m, 3H), 7.08-7.15 (m, 3H), 6.99-7.08 (m, 4H), 6.95 (t, J = 7.4 Hz, 1H), 6.81 (d, J = 8.7 Hz, 2H), 6.73 (br. s, 1H), 6.61 (d, J = 16 Hz, 1H), 6.35 (dt, J = 15.9, 5.6 Hz, 1H), 4.69-4.79 (m, 2H), 4.38 (ddd, J = 9.6, 7.8, 4.4 Hz, 1H), 4.32 (ddd, J = 10.8, 7.7, 3.1 Hz, 1H), 4.2 (dd, J = 8.0, 5.7 Hz, 1H), 4.12 (ddd, J = 7.9, 7.9, 5.1 Hz, 1H), 3.14 (dd, J = 15.0, 4.3 Hz, 1H), 2.85-2.96 (m, 2H), 2.74-2.83 (m, 1H), 2.63-2.74 (m, 2H), 2.30-2.41 (m, 2H), 1.99-2.15 (m, 1H), 1.78-1.93 (m, 1H), 1.57-1.73 (m, 2H), 1.17-1.31 (m, 1H), 0.89-1.01 (m, 1H), 0.64-0.74 (m, 6H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 174.3, 174.0, 172.5, 171.83, 171.81, 170.8, 157.0, 142.2, 136.6, 136.5, 132.7, 130.4, 130.2, 129.0, 128.1, 127.7, 126.6, 125.6, 124.7, 123.7, 121.4, 118.8, 118.7, 115.0, 111.8, 110.9, 68.1, 56.6, 54.8, 54.6, 52.6, 37.8, 36.9, 36.7, 32.0, 30.9, 28.0, 27.5, 24.5, 15.6, 11.8. MS (ESI) Calculated for C$_{43}$H$_{58}$N$_{7}$O$_{7}$ [M+H]$^+$: 778.4, found 778.0.
**Cyclic-Val-Met-Phe-Tyr (9):**

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (9 mg, 0.012 mmol, 73%). $^1$H NMR (DMSO-d$_6$, 600 MHz): δ 8.24 (d, J = 8.6 Hz, 1H), 8.04 (d, J = 7.0 Hz, 1H), 7.82 (d, J = 8.9 Hz, 1H), 7.39-7.43 (m, 2H), 7.09-7.22 (m, 11H), 7.01 (d, J = 6.7 Hz, 1H), 6.82 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 15.7 Hz, 1H), 6.53 (dd, J = 16.0, 6.6, 4.9 Hz, 1H), 4.74-4.85 (m, 2H), 4.32-4.41 (m, 2H), 4.09-4.16 (m, 2H), 3.13 (dd, J = 13.8, 4.8 Hz, 1H), 2.94 (dd, J = 14.0, 2.5 Hz, 1H), 2.77-2.85 (m, 4H), 2.65 (dd, J = 13.9, 11.6 Hz, 1H), 2.26-2.40 (m, 3H), 1.97 (s, 3H), 1.66-2.04 (m, 3H), 0.254 (d, J = 6.9 Hz, 3H), 0.17 (d, J = 6.7 Hz, 3H). $^{13}$C NMR (DMSO-d$_6$, 100 MHz): δ 173.5, 171.5, 171.4, 170.8, 170.1, 156.7, 140.8, 137.0, 136.2, 132.3, 130.0, 129.8, 129.5, 128.5, 128.2, 127.8, 126.2, 125.7, 124.9, 124.6, 67.8, 56.7, 54.6, 53.0, 52.4, 48.6, 36.9, 36.8, 34.8, 31.1, 30.4, 29.3, 18.7, 16.2, 14.4. MS (ESI) Calculated for C$_{40}$H$_{49}$N$_5$O$_6$S [M+H]$^+$: 728.3, found 728.2.

**Cyclic-Gly-Thi-Trp-SHT (10):**

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (16 mg, 0.021 mmol, 69%). $^1$H NMR (DMSO-d$_6$, 500 MHz): δ 10.79 (s, 1H), 10.60 (s, 1H), 8.57 (d, J = 7.6 Hz, 1H), 8.47 (t, J = 5.5 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.81 (t, J = 5.9 Hz, 1H), 7.53-7.56 (m, 2H), 7.48 (d, J = 7.9 Hz, 1H), 7.46 (d, J = 7.9 Hz, 1H), 7.32-7.37 (m, 2H), 7.30 (d, J = 7.7 Hz, 1H), 7.23-7.27 (m, 2H), 7.22 (d, J = 7.7 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H), 7.15-7.18 (m, 2H), 7.10 (d, J = 1.9 Hz, 1H), 7.03 (d, J = 1.9 Hz, 1H), 7.03 (d, J = 7.9 Hz, 2H), 6.96 (dd, J = 7.4, 7.4 Hz, 1H), 6.84 (dd, J = 5.0, 3.3 Hz, 1H), 6.78-6.80 (m, 1H), 6.76 (d, J = 16.1 Hz, 1H), 6.71 (dd, J = 8.7, 2.3 Hz, 1H), 6.38 (dt, J = 16.0, 6.1 Hz, 1H), 4.52 (ddd, J = 9.2, 9.2, 4.6 Hz, 1H), 4.28 (ddd, J = 10.5, 7.6, 3.7 Hz, 1H), 3.82 (dd, J = 15.8, 5.4 Hz, 1H), 3.49 (dd, J = 15.7, 5.8 Hz, 1H), 3.42-3.46 (m, 1H), 3.30 (dd, J = 14.6, 4.7 Hz, 1H), 3.08-3.16 (m, 2H), 2.99-3.07 (m, 1H), 2.87-2.95 (m, 2H), 2.75 (ddd, J = 14.5, 10.6, 5.2 Hz, 1H), 2.65-2.71 (m, 1H), 2.62 (ddd, J = 15.3, 10.5, 5.8 Hz, 1H), 2.28 (ddd, J = 15.4, 8.4, 6.6 Hz, 1H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): δ 173.4, 171.4, 170.5, 151.4, 142.5, 140.1, 137.0, 136.5, 133.8, 132.0, 129.0, 128.3, 127.84, 127.80, 127.3, 127.1, 126.7, 126.1, 125.0, 123.9, 123.8, 121.4, 121.3, 118.83, 118.77, 112.8, 112.5, 111.84, 111.77, 110.9, 103.7, 68.9, 55.9, 54.3, 43.4, 36.9, 31.3, 30.5, 27.8. MS (ESI) Calculated for C$_{42}$H$_{42}$N$_6$O$_6$S [M+H]$^+$: 743.3, found 743.2.
Cyclic- Ile-Ala-Arg-Tyr (11):

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (13 mg, 0.019 mmol, 84%).

$^1$H NMR (DMSO-d₆, 600 MHz): δ 8.01 (d, J = 7.4 Hz, 1H), 7.83 (d, J = 7.0 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 7.1 Hz, 1H), 7.44 (dd, J = 5.8, 5.8 Hz, 1H), 7.31 (br s, 1H), 7.21-7.25 (m, 1H), 7.19 (dd, J = 7.5, 7.5 Hz, 1H), 7.07-7.12 (m, 4H), 7.05 (d, J = 7.6 Hz, 1H), 6.81 (d, J = 8.5 Hz, 2H), 6.60 (d, J = 16.3 Hz, 1H), 6.34 (dt, J = 16.1, 5.4 Hz, 1H), 4.71 (d, J = 5.3 Hz, 2H), 4.35 (ddd, J = 11.2, 8.3, 3.0 Hz, 1H), 4.05-4.15 (m, 3H), 2.96-3.03 (m, 3H), 2.85 (ddd, J = 13.8, 7.1, 7.1 Hz, 1H), 2.72 (ddd, J = 13.8, 6.8, 6.8 Hz, 1H), 2.64 (dd, J = 13.9, 11.4 Hz, 1H), 2.41-2.45 (m, 2H), 1.54-1.62 (m, 1H), 1.28-1.46 (m, 6H), 1.00 (d, J = 7.2 Hz, 3H), 0.76 (d, J = 6.1 Hz, 3H), 0.72 (d, J = 6.2 Hz, 3H).

$^{13}$C NMR (DMSO-d₆, 125 MHz): δ 173.7, 172.7, 172.6, 172.5, 171.6, 158.9, 158.6, 141.9, 136.6, 132.6, 132.5, 130.4, 130.1, 128.9, 128.4, 126.9, 125.7, 124.3, 117.8, 115.4, 115.0, 68.2, 54.3, 52.6, 51.8, 48.8, 40.9, 36.8, 36.5, 30.9, 29.3, 25.3, 24.5, 23.4, 21.8, 18.5. MS (ESI) Calculated for C₃₆H₅₀N₈O₆ [M+H]⁺: 691.4, found 691.3.

Cyclic-Ile-Met-Ser-Tyr-Trp (12):

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (18 mg, 0.027 mmol, 73%).

$^1$H NMR (DMSO-d₆, 500 MHz): δ 10.79 (s, 1H), 8.11 (d, J = 7.5 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.17-7.24 (m, 4H), 7.11-7.16 (m, 4H), 7.01-7.08 (m, 2H), 6.97 (dd, J = 7.3, 7.3 Hz), 6.83 (d, J = 8.6 Hz, 2H), 6.56 (d, J = 15.9 Hz, 1H), 6.39 (dt, J = 16.1, 5.5 Hz, 1H), 4.76 (d, J = 5.2 Hz, 2H), 4.43 (ddd, J = 8.5, 8.5, 5.2 Hz, 1H), 4.22-4.33 (m, 3H), 4.10 (dd, J = 8.4, 6.0 Hz, 1H), 3.55 (dd, J = 10.4, 6.0 Hz, 1H), 3.49 (dd, J = 10.5, 6.7 Hz, 1H), 3.16 (dd, J = 14.7, 4.9 Hz, 1H), 2.82-2.96 (m, 3H), 2.70-2.77 (m, 1H), 2.50-2.60 (m, 2H), 2.40-2.46 (m, 1H), 2.27-2.39 (m, 1H), 1.92 (s, 3H), 1.71-1.89 (m, 2H), 1.60-1.69 (m, 1H), 1.12-1.20 (m, 1H), 0.85-0.95 (m, 1H), 0.56-0.62 (m, 6H).

$^{13}$C NMR (DMSO-d₆, 125 MHz): δ 173.8, 172.3, 171.49, 171.48, 171.3, 171.1, 157.1, 141.8, 136.7, 136.5, 132.7, 130.6, 130.2, 128.9, 128.6, 127.8, 126.2, 125.6, 124.7, 123.9, 121.3, 118.9, 118.8, 114.9, 111.7, 110.7, 68.1, 61.9, 57.7, 55.7, 55.2, 54.0, 52.2, 36.9, 36.4, 36.3, 32.0, 31.0, 29.6, 28.1, 24.5, 15.9, 14.9, 11.4. MS (ESI) Calculated for C₄₆H₅₇N₈O₆S [M+H]⁺: 868.4, found 868.0.
Cyclic- Ala-Phe-Thr-Ile-Tyr (13):

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (14 mg, 0.018 mmol, 85%). $^1$H NMR (DMSO-d$_6$, 600 MHz): $\delta$ 8.10 (d, J = 7.3 Hz, 1H), 8.08 (d, J = 8.9 Hz, 1H), 7.55-7.62 (m, 4H), 7.49-7.54 (m, 3H), 7.30 (s, 1H), 7.23 (s, 1H), 7.15-7.20 (m, 6H), 7.09-7.14 (m, 3H), 7.01-7.05 (m, 2H), 6.79 (d, J = 8.5 Hz, 2H), 6.63 (d, J = 16.3 Hz, 1H), 6.40 (dt, J = 15.9, 5.7 Hz, 1H), 4.61-4.69 (m, 2H), 4.46 (ddd, J = 9.0, 9.0, 4.6 Hz, 1H), 4.34-4.39 (m, 1H), 4.20 (dd, J = 8.04, 4.6 Hz, 1H), 4.12-4.17 (m, 2H), 3.85 (dq, J = 5.7, 5.7 Hz, 1H), 3.04 (J = 14.0, 4.4 Hz, 1H), 2.85-2.90 (m, 1H), 2.69-2.84 (m, 4H), 2.29-2.36 (m, 1H), 1.62-1.70 (m, 1H), 1.28-1.36 (m, 1H), 1.04 (d, J = 7.0 Hz, 3H), 0.93-1.01 (m, 1H), 0.82 (d, J = 6.1 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H), 0.73 (t, J = 7.5 Hz, 3H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 173.4, 172.8, 171.8, 171.1, 171.0, 169.5, 157.1, 141.8, 138.1, 136.4, 133.4, 132.7, 132.45, 132.37, 131.84, 131.77, 130.5, 130.1, 129.5, 129.1, 129.0, 128.7, 128.4, 128.3, 126.5, 125.7, 125.4, 124.6, 114.6, 68.2, 67.0, 58.1, 57.1, 54.2, 54.0, 48.7, 37.2, 37.0, 36.6, 35.7, 35.0, 24.3, 18.9, 18.5. MS (ESI) Calculated for C$_{43}$H$_{54}$N$_6$O$_8$ [M+H]$^+$: 783.4, found 783.3.

Cyclic-Gly-Ser-Phe-Asn-Tyr (14):

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (12 mg, 0.016 mmol, 74%). $^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 8.17 (t, J = 5.7 Hz, 1H), 8.15 (d, J = 8.7 Hz, 1H), 8.06 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.45 (br s, 1H), 7.28 (br s, 1H), 7.24 (d, J = 7.6 Hz, 1H), 7.17-7.22 (m, 2H), 7.12-7.17 (m, 3H), 7.05-7.11 (m, 3H), 7.04-7.10 (m, 5H), 6.95-7.01 (m, 1H), 6.80 (d, J = 8.9 Hz, 2H), 6.12 (d, J = 16.3 Hz, 1H), 6.33 (dt, J = 16.2, 5.8 Hz, 1H), 4.61 (d, J = 13.8, 6.2 Hz, 1H), 4.46-4.56 (m, 2H), 3.64 (ddd, J = 8.6, 8.6, 4.4 Hz), 4.30 (ddd, J = 7.6, 6.0, 6.0 Hz, 1H), 4.22 (ddd, J = 11.0, 8.2, 3.0 Hz, 1H), 3.77 (dd, J = 16.7, 6.0 Hz, 1H), 3.64 (d, J = 16.6, 5.3 Hz, 1H), 3.42-3.50 (m, 2H), 3.07 (dd, J = 14.0, 3.0 Hz, 1H), 2.74-2.94 (m, 3H), 2.70 (dd, J = 14.0, 11.1 Hz, 1H), 2.49-2.61 (m, 3H), 2.38-2.46 (m, 1H), 2.35 (dd, J = 15.6, 6.0 Hz, 1H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 173.8, 172.43, 172.41, 171.0, 170.5, 170.1, 169.5, 157.2, 142.2, 137.8, 136.7, 132.9, 130.7, 130.5, 129.8, 128.8, 128.5, 128.4, 126.8, 126.6, 125.3, 124.2, 114.8, 68.5, 61.7, 55.2, 55.0, 54.1, 50.0, 42.6, 38.3, 37.5, 36.3, 36.1. MS (ESI) Calculated for C$_{39}$H$_{48}$N$_7$O$_9$ [M+H]$^+$: 756.3, found 756.2.
**Cyclic-Ala-Leu-Glu-Tyr (16):**

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (17 mg, 0.026 mmol, 67%). ¹H NMR (DMSO-d₆, 600 MHz): δ 8.03 (d, J = 5.8 Hz, 1H), 7.99 (d, J = 7.2 Hz, 1H), 7.93 (d, J = 9.1 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.35-7.42 (m, 2H), 7.12-7.19 (m, 2H), 6.98-7.06 (m, 2H), 6.96 (d, J = 8.1 Hz, 2H), 6.59 (d, J = 8.2 Hz, 2H), 6.54 (d, J = 16.6 Hz, 1H), 6.33 (dt, J = 15.9, 4.6 Hz, 1H), 4.80-4.87 (m, 1H), 4.54-4.61 (m, 1H), 4.13-4.35 (m, 4H), 2.78-2.92 (m, 2H), 2.61-2.71 (m, 1H), 2.22-2.40 (m, 3H), 1.64-1.74 (m, 1H), 1.62-1.61 (m, 1H), 1.32-1.46 (m, 2H), 0.99 (d, J = 6.2 Hz, 3H), 0.85 (d, J = 6.2 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H). ¹³C NMR (DMSO-d₆, 150 MHz): δ 173.1, 172.6, 172.4, 172.3, 171.6, 170.7, 156.1, 141.7, 136.4, 131.6, 130.4, 128.7, 128.4, 128.0, 125.5, 124.4, 123.9, 115.2, 63.4, 54.2, 51.6, 51.5, 48.4, 37.2, 34.1, 30.0, 29.9, 27.9, 24.5, 23.2, 22.1, 19.2. MS (ESI) Calculated for C₃₅H₄₅N₅O₈ [M+H]^+: 664.3, found 664.3.

**Cyclic-Ala-Leu-Glu-Tyr (17):**

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Xbridge RP18 20x250 mm) using a gradient of 35-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (11 mg, 0.160 mmol, 76%). ¹H NMR (DMSO-d₆, 600 MHz): δ 12.04 (s, 1H), 8.1 (d, J = 6.9 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 8 Hz, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.31 (br. s, J = Hz, 1H), 7.17-7.22 (m, 3H), 7.02-7.13 (m, 4H), 6.83 (d, J = 8.6 Hz, 2H), 6.65 (d, J = 16 Hz, 1H), 6.37 (dt, J = 16.0, 5.6 Hz, 1H), 4.76 (d, J = 5.1 Hz, 2H), 4.32 (ddd, J = 10.9, 8.1, 3.1 Hz, 1H), 4.18 (dt, J = 7.6, 7.6 Hz, 1H), 4.02-4.13 (m, 2H), 2.96 (ddd, J = 14.2, 2.8 Hz, 1H), 2.76-2.82 (m, 2H), 2.67 (ddd, J = 14.3, 10.9 Hz, 1H), 2.36-2.42 (m, 1H), 2.11-2.23 (m, 2H), 1.79-1.89 (m, 1H), 1.66-1.76 (m, 1H), 1.57 (ddddd, J = 13.3, 13.3, 6.7, 6.7 Hz, 1H), 1.40-1.48 (m, 2H), 1.03 (d, J = 7.2 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H). ¹³C NMR (DMSO-d₆, 150 MHz): δ 173.9, 172.6, 172.2, 171.85, 171.8, 170.9, 156.6, 141.4, 136.0, 132.4, 132.3, 130.2, 128.3, 127.9, 126.0, 125.4, 124.3, 114.5, 67.7, 54.0, 51.6, 51.1, 48.9, 40.1, 36.3, 35.6, 30.2, 29.6, 26.7, 23.5, 22.9, 21.2, 17.3. MS (ESI) Calculated for C₃₅H₄₅N₅O₈ [M+H]^+: 664.3, found 664.3.
Cyclic-Val-Gln-Tyr-His (19): Following general procedure C, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (14mg, 0.020 mmol, 75%). $^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 9.16 (br. s, J = Hz, 1H), 9.02 (s, 1H), 8.31 (br. s, J = Hz, 1H), 8.1 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 6.9 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 7.26-7.36 (m, 4H), 7.21 (d, J = 7.5 Hz, 1H), 7.15 (br. d, J = 7.8 Hz, 1H), 7.11 (br. d, J = 7.5 Hz, 1H), 7.01 (br. s, J = Hz, 1H), 6.97 (d, J = 8.6 Hz, 2H), 6.81 (br. s, J = Hz, 1H), 6.75 (d, J = 15.6 Hz, 1H), 6.59 (d, J = 8.4 Hz, 2H), 6.38 (dt, J = 15.4, 7.0 Hz, 1H), 4.92 (dd, J = 14.9, 5.9 Hz, 1H), 4.88 (dd, J = 14.9, 7.3 Hz, 1H), 4.47 (dd, J = 10.6, 8.5, 3.4 Hz, 1H), 4.28 (dd, J = 8.9, 7.9, 5.0 Hz, 1H), 3.99 (dd, J = 7.8, 5.7, 5.7 Hz, 1H), 3.82-3.88 (m, 1H), 3.16 (dd, J = 15.2, 3.1 Hz, 1H), 2.86-2.94 (m, 2H), 2.79-2.85 (m, 2H), 2.74 (dd, J = 14.3, 9.4 Hz, 1H), 2.54-2.63 (m, 1H), 2.45-2.5 (m, 1H), 1.98-2.13 (m, 2H), 1.92 (dd, J = 13.6, 12.5, 6.8 Hz, 1H), 1.77 (dd, J = 13.8, 13.8, 7.0 Hz, 1H), 1.65 (dd, J = 14.6, 14.6, 7.6 Hz, 1H), 0.67 (dd, J = 6.7, 2.0 Hz, 6H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 174.0, 173.1, 173.0, 172.2, 172.1, 171.1, 155.7, 141.4, 135.7, 135.5, 134.8, 134.3, 130.7, 130.1, 129.0, 128.4, 125.6, 125.5, 122.2, 118.2, 114.9, 59.0, 54.7, 53.9, 51.1, 50.1, 35.9, 35.6, 31.1, 30.6, 29.0, 26.6, 26.4, 18.2. MS (ESI) Calculated for C$_{37}$H$_{46}$N$_8$O$_7$ [M+H]$^+$: 715.4, found 715.0

Cyclic-Val-Gln-Tyr-His (20): Following general procedure C, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (12 mg, 0.017 mmol, 68%). $^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 8.95 (d, J = 1.1 Hz, 1H), 8.28 (d, J = 8.3 Hz, 1H), 7.92 (d, J = 6.9 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.50-7.55 (m, 2H), 7.34-7.38 (m, 2H), 7.28 (br. s, J = Hz, 2H), 7.14-7.17 (m, 2H), 7.13 (d, J = 8.7 Hz, 2H), 7.00-7.04 (m, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.81 (br. s, J = Hz, 1H), 6.67 (d, J = 16 Hz, 1H), 6.55 (ddd, J = 15.9, 6.6, 5.6 Hz, 1H), 4.78 (dd, J = 14.5, 4.9 Hz, 1H), 4.7 (dd, J = 14.5, 6.9 Hz, 1H), 4.52 (ddd, J = 8.2, 8.2, 5.5 Hz, 1H), 4.26 (ddd, J = 10.0, 7.0, 2.4 Hz, 1H), 4.15 (ddd, J = 7.5, 7.5, 7.5 Hz, 1H), 3.94 (dd, J = 8.6, 6.7 Hz, 1H), 3.11 (dd, J = 15.5, 5.4 Hz, 1H), 2.92 (dd, J = 15.3, 8.2 Hz, 1H), 2.80-2.88 (m, 3H), 2.65 (dd, J = 14.1, 11.7 Hz, 1H), 2.33-2.42 (m, 1H), 1.96-2.09 (m, 2H), 1.71-1.80 (m, 1H), 1.55-1.64 (m, 1H), 1.42 (ddd, J = 13.4, 13.4, 6.7 Hz, 1H), 0.21 (d, J = 7.1 Hz, 3H), 0.19 (d, J = 7.8 Hz, 3H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 174.5, 172.2, 171.9, 171.5, 171.0, 157.2, 141.0, 136.7, 134.14, 134.07, 130.6, 129.9, 129.6, 129.2, 128.7, 125.7, 125.4, 125.2, 117.3, 114.9, 68.4, 57.2, 55.5, 52.0, 51.8, 36.3, 34.4, 32.2, 31.8, 30.6, 27.4, 26.9, 19.1, 18.2. MS (ESI) Calculated for C$_{37}$H$_{46}$N$_8$O$_7$ [M+H]$^+$: 715.4, found 715.4
**Cyclic-Gly-Val-Trp (21):**

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (21 mg, 0.039 mmol, 74%). $^1$H NMR (DMSO-d$_6$, 500 MHz): δ 10.82 (s, 1H), 8.31 (d, J = 7.2 Hz, 1H), 8.18 (dd, J = 6.8, 4.3 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.27-7.31 (m, 2H), 8.10-7.18 (m, 3H), 7.00-7.05 (m, 2H), 6.95 (dd, J = 7.8, 7.8 Hz, 1H), 6.58 (d, J = 15.9 Hz, 1H), 6.11 (dt, J = 16.0, 5.3 Hz, 1H), 4.79 (ddd, J = 13.9, 5.0, 1.3 Hz, 1H), 4.40-4.48 (m, 2H), 4.02-4.14 (m, 3H), 3.57 (dd, J = 17.3, 3.9 Hz, 1H), 3.20 (dd, J = 14.8, 5.9 Hz, 1H), 3.10 (dd, J = 14.9, 9.1 Hz, 1H), 2.91-2.97 (m, 1H), 2.82 (ddd, J = 14.7, 8.9, 1.9 Hz, 1H), 2.59 (ddd, J = 15.2, 9.8, 2.1 Hz, 1H), 2.32 (ddd, J = 15.2, 8.9, 2.5 Hz, 1H), 1.90-1.98 (m, 1H), 0.69 (d, J = 6.8 Hz, 3H), 0.60 (d, J = 7.0 Hz, 3H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): δ 172.3, 171.6, 171.0, 169.4, 141.9, 136.5, 136.4, 131.4, 128.3, 128.2, 127.3, 125.4, 123.9, 123.5, 123.2, 120.9, 118.4, 117.9, 111.3, 110.0, 64.4, 57.1, 53.4, 42.2, 35.4, 30.6, 29.6, 26.3, 19.3, 17.0. MS (ESI) Calculated for C$_{30}$H$_{34}$N$_4$O$_5$ [M+H]$^+$: 531.3, found 531.3.

**Cyclic-Phe-Leu-Hyp (22):**

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (16 mg, 0.029 mmol, 71%). $^1$H NMR (DMSO-d$_6$, 500 MHz, mix of diastereomers): δ 8.35 (d, J = 7.6 Hz, 1H), 8.28 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.32-7.37 (m, 3H), 7.12-7.29 (m, 1H), 6.98-7.10 (m, 4H), 6.83 (ddd, J = 16.0, 9.0, 4.1 Hz, 1H), 6.65 (d, J = 16.2 Hz, 1H), 6.59 (d, J = 16.2 Hz, 1H), 6.12 (ddd, J = 16.2, 6.0, 4.0 Hz, 1H), 5.28 (ddd, J = 12.5, 3.9, 1.7 Hz, 1H), 5.02 (ddd, J = 14.1, 3.8, 1.7 Hz, 1H), 4.32-4.57 (m, 1OH), 3.94-3.60 (m, 4H), 3.13 (dd, J = 14.2, 4.5 Hz, 2H), 2.94-3.07 (m, 3H), 2.64-2.73 (m, 3H), 2.50-2.58 (m, 2H), 2.38-2.46 (m, 2H), 2.24-2.34 (m, 2H), 2.07-2.21 (m, 2H), 1.88 (ddd, J = 13.7, 10.2, 4.1 Hz, 1H), 1.62-1.72 (m, 1H), 1.53 (ddd, J = 14.3, 12.4, 3.4 Hz, 1H), 1.32-1.43 (m, 1H), 1.18-1.29 (m, 3H), 1.06 (ddd, J = 14.2, 10.9, 3.4 Hz, 1H), 0.85 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H), 0.74 (d, J = 6.4 Hz, 3H), 0.53 (d, J = 6.6 Hz, 3H). MS (ESI) Calculated for C$_{32}$H$_{39}$N$_3$O$_6$ [M+H]$^+$: 562.3, found 562.3.
**Cyclic-Ala-Val-Pro-His-OH (23):**

Following general procedure C, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (16 mg, 0.029 mmol, 69%). **¹H NMR (DMSO-d₆, 500 MHz):** δ 9.05 (s, 1H), 8.12 (d, J = 7.9 Hz, 1H), 8.04 (d, J = 7.7 Hz, 1H), 7.48 (s, 1H), 7.43 (d, J = 8.9 Hz, 1H), 7.16-7.27 (m, 1H), 7.09-7.14 (m, 1H), 6.66 (d, J = 15.9 Hz, 1H), 6.34 (dt, J = 16.0, 6.6 Hz, 1H), 4.84-4.98 (m, 2H), 4.22-4.30 (m, 2H), 4.18 (dd, J = 8.5, 3.6 Hz, 1H), 4.09 (t, J = 8.9 Hz, 1H), 3.55-3.63 (m, 1H), 3.48-3.46 (m, 1H), 3.05-3.18 (m, 2H), 2.79-2.81 (m, 1H), 2.61 (ddd, J = 15.0, 10.2, 4.1 Hz, 1H), 2.33-2.41 (m, 1H), 1.60-1.86 (m, 3H), 1.13 (d, J = 7.1 Hz, 3H), 0.79 (d, J = 6.6 Hz, 3H), 0.57 (d, J = 6.7 Hz, 3H). **¹³C NMR (DMSO-d₆, 125 MHz):** δ 172.5, 172.13, 172.07, 171.5, 170.5, 141.9, 135.9, 135.4, 135.0, 130.9, 129.0, 129.1, 127.1, 122.6, 120.4, 60.0, 56.0, 51.4, 50.9, 48.6, 47.4, 35.3, 30.6, 29.9, 29.5, 26.0, 24.6, 19.5, 18.6, 18.5. MS (ESI) Calculated for C₃₁H₄₀N₆O₆ [M+H]⁺: 593.3, found 593.1

**Cyclic-Ala-Val-Pro-His-NH₂ (24):**

Following general procedure C, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (74 mg, 0.13 mmol, 77%). **¹H NMR (DMSO-d₆, 500 MHz):** δ 9.08 (d, J = 1.4 Hz, 1H), 8.17 (d, J = 8.3 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.9 Hz, 1H), 7.40 (br. s, 1H), 7.34 (br. s, 1H), 7.21-7.29 (m, 2H), 7.11-7.20 (m, 3H), 6.56 (d, J = 16.0 Hz, 1H), 6.35 (dt, J = 16.0, 6.2 Hz, 1H), 4.89-5.00 (m, 2H), 4.25-4.36 (m, 2H), 4.11-4.19 (m, 2H), 3.53-3.61 (m, 1H), 3.29-3.37 (m, 1H), 3.03-3.13 (m, 2H), 2.79-2.89 (m, 1H), 2.65-2.73 (m, 1H), 2.48-2.55 (m, 1H), 2.40 (ddd, J = 15.0, 6.5, 6.5 Hz, 1H), 1.79-1.88 (m, 1H), 1.63-1.77 (m, 2H), 1.52-1.62 (m, 1H), 1.12 (d, J = 7.0 Hz, 3H), 0.75 (d, J = 6.7 Hz, 3H), 0.71 (d, J = 6.6 Hz, 1H). **¹³C NMR (DMSO-d₆, 125 MHz):** δ 172.6, 172.2, 172.1, 172.0, 171.6, 170.5, 141.9, 135.9, 135.4, 135.0, 130.9, 128.5, 127.8, 124.1, 123.3, 120.4, 60.4, 56.1, 51.9, 50.6, 49.1, 48.2, 47.5, 35.7, 30.8, 29.9, 29.3, 26.4, 24.9, 19.6, 18.6, 18.0. MS (ESI) Calculated for C₃₁H₄₁N₆O₅ [M+H]⁺: 592.3, found 592.3

**Cyclic-Gly-Thr-His-Tyr-NH₂ (25):**

Following general procedure C, the corresponding compound was isolated by preparative HPLC (Waters Xbridge RP 18 20x250 mm) using a gradient of 25-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (24 mg, 0.038 mmol, 73%). **¹H NMR (DMSO-d₆, 500 MHz):** δ 8.99 (br. s, 1H), 8.14 (t, J = 5.9 Hz, 2H), 8.05 (d, J = 8.3 Hz, 1H), 7.96 (d, J = 7.7 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.48 (s, 1H), 7.43 (d, J = 8.9 Hz, 1H), 7.16-7.27 (m, 1H), 7.09-7.14 (m, 1H), 6.66 (d, J = 15.9 Hz, 1H), 6.34 (dt, J = 16.0, 6.6 Hz, 1H), 4.84-4.98 (m, 2H), 4.22-4.30 (m, 2H), 4.18 (dd, J = 8.5, 3.6 Hz, 1H), 4.09 (t, J = 8.9 Hz, 1H), 3.55-3.63 (m, 1H), 3.48-3.46 (m, 1H), 3.05-3.18 (m, 2H), 2.79-2.81 (m, 1H), 2.61 (ddd, J = 15.0, 10.2, 4.1 Hz, 1H), 2.33-2.41 (m, 1H), 1.60-1.86 (m, 3H), 1.13 (d, J = 7.1 Hz, 3H), 0.79 (d, J = 6.6 Hz, 3H), 0.57 (d, J = 6.7 Hz, 3H). **¹³C NMR (DMSO-d₆, 125 MHz):** δ 172.5, 172.13, 172.07, 171.5, 170.5, 141.9, 135.9, 135.4, 135.0, 130.9, 129.0, 129.1, 127.1, 122.6, 120.4, 60.0, 56.0, 51.4, 50.9, 48.6, 47.4, 35.3, 30.6, 29.9, 29.5, 26.0, 24.6, 19.5, 18.6, 18.5. MS (ESI) Calculated for C₃₁H₄₁N₆O₅ [M+H]⁺: 592.3, found 592.3
Hz, 1H), 7.54 (br. s, 1H), 7.4 (br. s, 1H), 7.36 (br. s, 1H), 7.19-7.22 (m, 2H), 7.16 (br. d, J = 7.6 Hz, 1H),
7.08 (br. d, J = 7.6 Hz, 1H), 6.74 (d, J = 15.7 Hz, 1H), 6.61 (d, J = 8.1 Hz, 2H), 6.49 (dt, J = 15.6, 7.1 Hz, 1H),
4.92 (dd, J = 14.8, 6.4 Hz, 1H), 4.8 (dd, J = 14.8, 7.3 Hz, 1H), 4.53 (ddd, J = 8.5, 8.5, 3.8 Hz, 1H),
4.28 (ddd, J = 8.7, 8.7, 4.7 Hz, 1H), 4.63 (dd, J = 7.6, 4.0 Hz, 1H), 3.92 (dq, J = 6.2, 6.2 Hz, 1H),
3.8 (d, J = 15.6, 5.6 Hz, 1H), 3.75 (dd, J = 16.6, 6.2 Hz, 1H), 3.05 (dd, J = 15.5, 3.6 Hz, 1H),
2.81-2.94 (m, 4H), 2.67 (dd, J = 13.8, 9.3 Hz, 1H), 2.34-2.41 (m, 1H), 1.04 (d, J = 6.4 Hz, 3H).

**Cyclic-β-Ala-Pro[4-(2-methoxy-4-methylphenoxy)]-His (26):**

Following general procedure C, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (57 mg, 0.091 mmol, 81%).

**1H NMR (DMSO-d₆, 500 MHz):** δ 8.85 (d, J = 1.2 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.65 (t, J = 5.7 Hz, 1H), 7.21-7.31 (m, 5H), 7.15-7.20 (m, 2H), 6.83 (d, J = 8 Hz, 1H), 6.78 (d, J = Hz, 1H), 6.66-6.74 (m, 2H), 6.38 (dt, J = 15.7, 7.0 Hz, 1H), 4.89 (dd, J = 14.8, 6.4 Hz, 1H), 4.70-4.75 (m, 1H), 4.59 (dd, J = 14.7, 7.3 Hz, 1H), 4.35-4.42 (m, 2H), 3.71 (s, 3H),
3.67-3.70 (m, 1H), 3.34 (br. d, J = 11.3 Hz, 1H), 3.17 (m, 1H), 3.07 (d, J = 6.4 Hz, 2H), 2.92-3.00 (m, 1H),
2.84-2.90 (m, 1H), 2.78-2.83 (m, 1H), 2.27-2.41 (m, 3H), 2.25 (s, 3H), 1.85-2.00 (m, 2H).

**13C NMR (DMSO-d₆, 125 MHz):** δ 171.5, 171.2, 171.0, 170.5, 170.1, 169.9, 156.3, 142.3, 136.8, 136.0, 134.7, 130.6, 130.2, 129.5, 128.8, 128.2, 125.6, 125.4, 122.3, 120.2, 115.4, 67.2, 58.6, 55.1, 51.5, 51.0, 42.0, 37.1, 35.4, 29.9, 26.9, 20.2. MS (ESI) Calculated for C₃₅H₃₉N₇O₇ [M+H]+: 646.3, found 646.1.

**Cyclic-Ala-Ile-His-Phe-NH₂ (27):**

Following general procedure C, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (25 mg, 0.032 mmol, 71%).

**1H NMR (DMSO-d₆, 500 MHz):** δ 9.04 (d, J = 1.5 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 8 (d, J = 5.7 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 7.3 Hz, 1H),
7.59 (br. s, 1H), 7.55 (br. s, 1H), 7.44 (br. s, 1H), 7.14-7.25 (m, 7H), 7.1 (d, J = 7.7 Hz, 1H), 7.06 (d, J = 7.7 Hz, 1H),
6.71-6.82 (m, 2H), 4.85-4.96 (m, 2H), 4.61 (ddd, J = 8.3, 9.3, 3.8 Hz, 1H), 4.44 (ddd, J = 8.1, 8.1, 5.0 Hz, 1H),
4.14 (dq, J = 6.7, 6.7 Hz, 1H), 3.86 (t, J = 7.6 Hz, 1H), 2.87-3.04 (m, 4H), 2.81 (ddd, J = 13.8, 8.3 Hz, 1H),
2.70-2.77 (m, 1H), 2.40-2.46 (m, 2H), 1.52-1.62 (m, 1H), 1.36-1.46 (m, 1H), 1 (d, J = 7 Hz, 1H), 1.04 (d, J = 6.4 Hz, 3H).
Hz, 3H), 0.74 (t, J = 6.8 Hz, 3H), 0.75 (d, J = 6.8 Hz, 3H). 13C NMR (DMSO-d6, 125 MHz): δ 173.2, 173.1, 172.0, 171.8, 170.2, 142.1, 137.8, 136.2, 136.1, 134.8, 130.5, 129.7, 129.5, 128.7, 128.5, 126.8, 126.1, 124.6, 123.1, 119.8, 57.9, 54.2, 51.2, 51.1, 48.8, 38.2, 36.1, 34.5, 29.9, 27.3, 25.1, 18.4, 15.8, 11.4. MS (ESI) Calculated for C_{36}H_{45}N_{7}O_{5} [M+H]^+: 656.3, found 656.2

**Cyclic-Ala-Arg-His-Phe-NH_{2} (28):**

Following general procedure C, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH_{3}CN/H_{2}O with 0.1% TFA. The fractions collected were combined and lyophilized (36 mg, 0.044 mmol, 76%). 1H NMR (DMSO-d6, 500 MHz): δ 9.03 (s, 1H), 8.11-8.14 (m, 2H), 7.97 (d, J = 6.2 Hz, 1H), 7.96 (d, J = 7.7 Hz, 1H), 7.7 (br. s, 1H), 7.48 (br. s, 1H), 7.38-7.41 (m, 2H), 7.28 (br. s, 1H), 7.14-7.25 (m, 7H), 7.1 (d, J = 7.4 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.8 (ddd, J = 15.7, 7.9, 5.6 Hz, 1H), 6.74 (d, J = 15.7 Hz, 1H), 4.91 (dd, J = 14.6, 5.2 Hz, 1H), 4.86 (dd, J = 14.8, 8.0 Hz, 1H), 4.57 (ddd, J = 8.7, 8.7, 3.5 Hz, 1H), 4.41 (ddd, J = 8.5, 8.5, 4.9 Hz, 1H), 4.05 (dq, J = 7.2, 7.2 Hz, 1H), 3.91-3.96 (m, 1H), 2.86-3.03 (m, 5H), 2.88 (dd, J = 15.6, 9.4 Hz, 1H), 2.79 (dd, J = 13.8, 8.9 Hz, 1H), 2.71 (dd, J = 15.0, 7.8 Hz, 1H), 2.34-2.41 (m, 2H), 1.40-1.52 (m, 4H), 1.09 (d, J = 7 Hz, 3H). 13C NMR (DMSO-d6, 125 MHz): δ 173.5, 173.4, 172.3, 172.1, 170.2, 157.1, 142.1, 137.9, 136.3, 136.3, 134.8, 130.4, 129.7, 129.4, 128.7, 128.6, 126.9, 126.1, 124.5, 123.0, 119.7, 117.6, 115.3, 54.3, 52.9, 51.1, 51.0, 49.0, 40.9, 38.1, 34.4, 29.7, 28.7, 27.5, 25.6, 18.1. MS (ESI) Calculated for C_{36}H_{46}N_{10}O_{5} [M+H]^+: 699.4, found 699.2

**Cyclic-Thr-Ala-Trp-Ile-Pro-Tyr-His-Asn-Val (29):**

Following general procedure C, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH_{3}CN/H_{2}O with 0.1% TFA. The fractions collected were combined and lyophilized (25 mg, 0.020 mmol, 69%). 1H NMR (DMSO-d6, 500 MHz): δ 10.8 (d, J = 1.7 Hz, 1H), 9.04 (s, 1H), 8.33 (d, J = 7.2 Hz, 1H), 8.18 (d, J = 7.3 Hz, 1H), 7.98 (d, J = 6 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.73-7.82 (m, 2H), 7.54 (d, J = 8.7 Hz, 1H), 7.40-7.48 (m, 3H), 7.28-7.32 (m, 2H), 7.12-7.21 (m, 6H), 7.08-7.11 (m, 2H), 7.00-7.05 (m, 3H), 6.94 (t, J = 7.3 Hz, 1H), 6.63 (d, J = 15.9 Hz, 1H), 6.44 (dt, J = 15.9, 6.5 Hz, 1H), 4.9 (d, J = 6.1 Hz, 2H), 4.53-4.61 (m, 2H), 4.25-4.40 (m, 4H), 4.06-4.16 (m, 3H), 3.99 (dq, J = 6.9, 6.9 Hz, 1H), 3.37-3.44 (m, 1H), 3.14 (ddd, J = 15.6, 15.6, 4.8 Hz, 1H), 2.89-3.03 (m, 2H), 2.63-2.66 (m, 3H), 2.50-2.60 (m, 2H), 2.28-2.31 (m, 1H), 2.02 (ddd, J = 13.3, 6.7, 6.7, 6.7 Hz, 1H), 1.84-1.92 (m, 1H), 1.58-1.75
(m, 3H), 1.37-1.47 (m, 1H), 1.04 (d, J = 7.2 Hz, 3H), 0.94-1.01 (m, 1H), 0.93 (d, J = 6 Hz, 3H), 0.8 (d, J = 7.3 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H), 0.7 (d, J = 7.3 Hz, 3H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): δ 173.1, 172.7, 172.4, 172.1, 171.7, 171.5, 171.3, 170.7, 170.2, 170.1, 142.2, 138.4, 136.5, 136.0, 135.1, 135.0, 130.1, 129.4, 128.9, 128.5, 127.7, 126.75, 126.70, 125.1, 123.9, 123.0, 121.3, 120.3, 118.8, 118.6, 117.7, 115.4, 111.8, 110.5, 67.1, 60.3, 58.5, 58.0, 55.5, 54.9, 54.6, 51.7, 50.7, 50.5, 49.8, 47.5, 37.5, 37.1, 36.8, 36.5, 31.8, 30.7, 29.4, 27.6, 27.4, 24.6, 24.5, 20.2, 19.8, 18.0, 17.9, 15.7, 11.3. MS (ESI) Calculated for C$_{65}$H$_{84}$N$_{14}$O$_{13}$ [M+H]$^+$: 1269.6, found 1269.4

**Cyclic-Asn-Trp-Thr-Phe(4-NH$_2$) (30):**

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Xbridge RP18 20x250 mm) using a gradient of 35-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (48 mg, 0.064 mmol, 77%). $^1$H NMR (DMSO-d$_6$, 500 MHz): δ 10.81 (d, J = 1.4 Hz, 1H), 8.31 (d, J = 6.1 Hz, 1H), 7.9 (d, J = 5.8 Hz, 1H), 7.55 (d, J = 15.9 Hz, 1H), 6.51 (d, J = 15.7, 6.5 Hz, 1H), 4.41 (ddd, J = 6.6, 6.6, 6.6 Hz, 1H), 4.33 (ddd, J = 5.9, 5.9, 5.9 Hz, 1H), 4.26 (ddd, J = 10.9, 7.9, 3.0 Hz, 1H), 3.89-3.88 (m, 2H), 3.03-3.11 (m, 3H), 2.63-2.80 (m, 3H), 2.26-2.45 (m, 4H), 0.7 (d, J = 6.1 Hz, 3H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): δ 173.8, 173.1, 172.6, 172.4, 172.0, 170.5, 142.1, 136.6, 136.3, 130.5, 129.1, 128.5, 127.8, 126.4, 125.0, 124.5, 121.4, 119.4, 118.8, 118.7, 119.5, 118.5, 117.1, 114.8, 112.5, 111.8, 109.7, 66.6, 59.9, 55.2, 54.8, 51.4, 36.8, 36.7, 36.4, 30.6, 27.1, 19.4. MS (ESI) Calculated for C$_{40}$H$_{46}$N$_{8}$O$_{7}$ [M+H]$^+$: 751.4, found 751.2

**Cyclic-Val-Orn-Met-Try (32):**

Following general procedure C, the corresponding compound was isolated by preparative HPLC (Waters Xbridge RP18 20x250 mm) using a gradient of 20-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (12 mg, 0.017 mmol, 64%). $^1$H NMR (DMSO-d$_6$, 500 MHz): δ 8.38 (d, J = 7.9 Hz, 1H), 8.11 (d, J = 6.1 Hz, 1H), 7.97-8.04 (m, 4H), 7.55 (s, 1H), 7.31 (s, 1H), 7.15-7.20 (m, 3H), 7.13 (br. d, J = 7.6 Hz, 1H), 7.06 (br. s, J = Hz, 1H), 7.01 (br. d, J = 7.4 Hz, 1H), 6.83 (br. d, J = 8.1 Hz, 2H), 6.67 (d, J = 15.9 Hz, 1H), 6.31 (dt, J = 15.9, 6.0 Hz, 1H), 4.73-4.81 (m, 2H), 4.29-4.38 (m, 1H), 4.21-4.27 (m, 1H), 3.52-3.58 (m, 1H), 2.95-3.02 (m, 1H), 2.84-2.94 (m, 2H), 2.71-2.72 (m, 2H), 2.62 (dd, J = 12.9, 12.2 Hz, 1H), 2.31-2.37 (m, 2H), 2.21-2.22 (n, J = Hz, 1H), 1.93-2.01 (n, J = Hz, 4H), 1.86-1.93 (n, J = Hz, 1H), 1.71 (ddd, J = 15.1, 15.1, 7.7 Hz, 1H), 1.42-1.50 (m, 1H), 1.31-1.40 (m, 2H), 1.20-1.28 (m, 1H), 0.88 (d, J = 7 Hz, 6H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): δ 173.6,
Cyclic-Val-Orn-Met-Try (33):
Following general procedure C, the corresponding compound was isolated by preparative HPLC (Waters Xbridge RP18 20x250 mm) using a gradient of 25-100% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (12 mg, 0.017 mmol, 77%). $^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 8.91 (br. s, J = 8 Hz, 2H), 8.48 (d, J = 7 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.74 (dd, J = 6.6, 5.3 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.35-7.39 (m, 2H), 7.27 (t, J = 7.9 Hz, 1H), 7.15 (br. d, J = 7.9 Hz, 1H), 7.02 (br. s, J = Hz, 1H), 6.93-6.97 (m, 3H), 6.59 (d, J = 8.6 Hz, 2H), 6.52 (br. d, J = 15.7 Hz, 1H), 6.05 (dt, J = 15.4, 7.7 Hz, 1H), 4.3 (ddd, J = 8.3, 8.3, 5.3 Hz, 1H), 4.25 (ddd, J = 8.8, 8.8, 4.6 Hz, 1H), 4.01-4.07 (m, 1H), 3.71-3.79 (m, 1H), 3.52 -3.64 (m, 2H), 3 (ddd, J = 14.7, 14.7, 7.7 Hz, 1H), 2.75-2.89 (m, 4H), 2.65 (dd, J = 13.8, 8.6 Hz, 1H), 2.40-2.47 (m, 1H), 2.35-2.39 (m, 1H), 2.25-2.34 (m, 2H), 2.04 (ddd, J = 13.8, 12.2, 6.9 Hz, 1H), 1.98 (s, 3H), 1.79-1.87 (m, 1H), 1.63-1.72 (m, 1H), 1.30-1.39 (m, 1H), 1.10-1.25 (m, 3H), 0.95 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 172.6, 171.1, 170.6, 170.4, 166.0, 155.9, 141.1, 138.5, 134.5, 130.2, 129.3, 129.0, 128.4, 127.6, 122.0, 117.3, 114.8, 62.0, 53.9, 53.5, 51.6, 48.6, 36.6, 36.0, 34.8, 32.0, 30.6, 30.0, 29.1, 28.4, 27.0, 18.2, 17.9. MS (ESI) Calculated for C$_{36}$H$_{50}$N$_6$O$_6$S $[M+H]^+$: 695.4, found 695.2

Cyclic-Orn-Thr-Try (35):
Following general procedure D, the corresponding compound was isolated by preparative HPLC (Waters Xbridge RP18 20x250 mm) using a gradient of 10-70% CH$_3$CN/H$_2$O with 0.1% TFA. The fractions collected were combined and lyophilized (22 mg, 0.033 mmol, 80%). $^1$H NMR (DMSO-d$_6$, 600 MHz): $\delta$ 7.90 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.53 (br s, 3H), 7.37 (s, 1H), 7.20-7.22 (m, 2H), 7.41 (br s, 1H), 7.19 (br s, 1H), 7.13 (d, J = 8.6 Hz, 2H), 7.04-7.08 (m, 1H), 6.85 (d, J = 8.6 Hz, 2H), 6.66 (d, J = 15.9 Hz, 1H), 6.46 (dt, J = 15.9, 5.8 Hz, 1H), 4.78 (d, J = 5.8 Hz, 2H), 4.34 (ddd, J = 10.6, 8.3, 2.8 Hz, 1H), 4.21 (ddd, J = 8.3, 8.1, 5.3 Hz, 1H), 4.14 (dd, J = 7.8, 5.2 Hz, 1H), 3.94 (tdd, J = 6.3, 5.9, 5.2 Hz, 1H), 2.88 (ddd, J = 14.7, 6.8, 4.5 Hz, 1H), 2.82 (ddd, J = 14.7, 10.1, 4.1 Hz, 1H), 3.00 (dd, J = 14.2, 2.8 Hz, 1H), 2.74 (dd, J = 14.2, 10.6 Hz, 1H), 2.69 (14.5, 10.1, 4.5 Hz, 1H), 2.48-2.55 (m, 2H), 2.37 (ddd, J = 14.5, 6.8, 4.1 Hz, 1H), 1.31-1.39 (m, 1H), 1.06-1.20 (m, 3H), 1.01 (d, J = 6.3 Hz, 3H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): $\delta$ 172.9, 171.1, 170.7, 169.3, 156.4, 140.9, 135.8, 132.8, 129.9, 129.6, 128.4, 128.2, 125.0, 124.9, 124.2, 114.4, 67.7, 65.6, 57.8, 53.8, 51.0, 37.8, 35.7, 34.4, 29.9, 29.4, 22.5, 19.1. MS (ESI) Calculated for C$_{30}$H$_{30}$N$_5$O$_6$S $[M+H]^+$: 566.3, found 566.2.
**Cyclic-Ser-Phe-Phe(4-NH₂) (37):**

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (13 mg, 0.023 mmol, 72%). ¹H NMR (DMSO-d₆, 500 MHz): δ 7.99 (d, J = 8.7 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.10-7.25 (m, 8H), 7.08 (br s, 1H), 6.96-7.02 (m, 2H), 6.66 (br s, 1H), 6.45 (d, J = 15.7 Hz, 1H), 6.16 (dt, J = 15.9, 5.8 Hz, 1H), 4.78 (dd, J = 8.2, 8.2, 4.9 Hz, 1H), 4.31 (ddd, J = 11.3, 8.6, 2.9 Hz, 1H), 4.09 (ddd, J = 6.2, 6.2, 6.2 Hz, 1H), 3.88 (d, J = 4.9 Hz, 2H), 3.1-3.2 (m, 2H), 3.00 (dd, J = 13.8, 4.8 Hz, 1H), 2.84 (dd, J = 14.5, 2.6 Hz, 1H), 2.67-2.78 (m, 3H), 2.48-2.57 (m, 1H), 2.27-2.35 (m, 1H). ¹³C NMR (DMSO-d₆, 125 MHz): δ 173.6, 172.1, 171.0, 170.2, 141.6, 138.0, 136.7, 130.1, 129.8, 128.7, 128.5, 128.4, 126.7, 126.2, 124.4, 62.3, 54.9, 54.4, 54.1, 37.5, 36.9, 35.8, 31.0. MS (ESI) Calculated for C₃₃H₆₇N₃O₅ [M+H]^+: 584.3, found 584.3.

**Cyclic-Ala-Phe-Ser-Val-Pro-Gly-Val-Trp-Ile-Ser-Tyr-Val (38):**

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH₃CN/H₂O with 0.1% TFA. The fractions collected were combined and lyophilized (10 mg, 0.007 mmol, 66%). ¹H NMR (DMSO-d₆, 600 MHz): δ 10.67 (s, 1H), 8.24 (dd, J = 5.87 Hz, 1H), 8.09 (dd, J = 7.7 Hz, 1H), 8.02-8.08 (m, 3H), 7.91 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.69-7.75 (m, 2H), 7.56-7.61 (m, 1H), 7.49-7.55 (m, 2H), 7.38 (d, J = 8.7 Hz, 1H), 7.31 (s, 1H), 7.23-7.28 (m, 3H), 7.13-7.22 (m, 5H), 7.10-7.13 (m, 3H), 7.05-7.09 (m, 3H), 6.99 (dd, J = 7.6, 7.6 Hz, 1H), 6.91 (dd, J = 7.5, 7.5 Hz, 1H), 6.78 (d, J = 8.3 Hz, 2H), 6.65 (d, J = 15.9 Hz, 1H), 6.42 (dt, J = 15.9, 5.8 Hz, 1H), 4.58 (d, J = 5.5 Hz, 2H), 4.53 (ddd, J = 8.5, 8.5, 5.4 Hz, 1H), 4.44-4.50 (m, 2H), 4.27-4.34 (m, 3H), 4.25 (dd, J = 7.6, 5.5 Hz, 1H), 4.14-4.20 (m, 2H), 4.05-4.13 (m, 3H), 3.75 (dd, J = 16.7, 6.1 Hz, 1H), 3.62-3.72 (m, 1H), 3.46-3.60 (m, 4H), 3.01-3.07 (m, 1H), 2.98 (dd, J = 13.7, 3.0 Hz, 1H), 2.87 (dd, J = 15.1, 9.6 Hz, 1H), 2.32-2.43 (m, 2H), 1.85-2.03 (m, 5H), 1.70-1.79 (m, 2H), 1.55-1.63 (m, 1H), 1.28-1.37 (m, 1H), 1.62 (d, J = 7 Hz, 3H), 0.94-1.0 (m, 1H), 0.85 (d, J = 6.6 Hz, 3H), 0.78-0.83 (m, 9H), 0.73 (d, J = 6.4 Hz, 3H), 0.63-0.72 (m, 6H), 0.67 (d, J = 6.8 Hz, 3H). ¹³C NMR (DMSO-d₆, 150 MHz, from HMBC/HSQC): δ 173.2, 172.45, 172.4, 172.3, 171.9, 171.4, 171.1, 171.07, 171.02, 170.5, 170, 169.9, 168.9, 157.1, 141.9, 137.9, 136.3, 133.2, 132.3, 131.6, 130.3, 129.1, 129, 127.9, 127.8, 126.1, 126, 124.8, 124.1, 123.5, 120.7, 118.2, 118, 114.2, 111.1, 110.3, 67.9, 61.6, 61.5, 59.6,
57.9, 57.6, 56.8, 55.6, 54.9, 53.8, 53.6, 53.3, 48.7, 47, 42.3, 37.2, 37.1, 37, 36.4, 36.1, 30.6, 30.2, 29.3, 27.3, 24.5, 24.2, 22.1, 19.3, 19.1, 17.8, 17.5, 15.2, 11.1. MS (ESI) Calculated for C\textsubscript{78}H\textsubscript{104}N\textsubscript{14}O\textsubscript{16} [M+H]\textsuperscript{+}: 1493.8, found 1493.7

*Cyclic-Trp-Leu-Gln-Met-Thr-Gly-Phe-Tyr (39):*

Following general procedure B, the corresponding compound was isolated by preparative HPLC (Waters Sunfire C18 30x150 mm) using a gradient of 35-100% CH\textsubscript{3}CN/H\textsubscript{2}O with 0.1% TFA. The fractions collected were combined and lyophilized (21 mg, 0.017 mmol, 71%). \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 500 MHz): δ 10.76 (d, J = 1.9 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H), 8.04-8.09 (m, 2H), 8.02 (d, J = 7.4 Hz, 1H), 7.96 (t, J = 5.4 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.3 (d, J = 7.9 Hz, 1H), 7.23-7.27 (m, 3H), 7.17-7.23 (m, 6H), 7.12-7.17 (m, 3H), 7.06-7.10 (m, 2H), 7.01-7.05 (m, 2H), 6.95 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 6.72 (br. s, J = Hz, 1H), 6.66 (d, J = 15.9 Hz, 1H), 6.43 (dt, J = 15.9, 5.8 Hz, 1H), 4.61 (d, J = 5.4 Hz, 2H), 4.52 (ddd, J = 8.9, 8.9, 4.6 Hz, 1H), 4.45 (ddd, J = 8.4, 8.4, 5.0 Hz, 1H), 4.4 (ddd, J = 8.1, 8.1, 5.0 Hz, 1H), 4.35 (ddd, J = 8.9, 8.9, 4.0 Hz, 1H), 4.13-4.25 (m, 3H), 3.93-3.99 (m, 1H), 3.69 (dd, J = 17.1, 5.7 Hz, 1H), 3.56 (dd, J = 16.8, 5.2 Hz, 1H), 3.1 (dd, J = 14.9, 4.8 Hz, 1H), 2.99 (dd, J = 13.8, 4.2 Hz, 1H), 2.87-2.96 (m, 2H), 2.64-2.78 (m, 4H), 2.31-2.45 (m, 4H), 1.85-1.98 (m, 5H), 1.69-1.83 (m, 2H), 1.00 (d, J = 6.4 Hz, 3H), 0.75-0.86 (m, 6H). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 125 MHz): δ 174.2, 173.4, 172.3, 172.3, 172.1, 171.53, 171.51, 171.3, 170.7, 168.8, 157.3, 142.1, 138.2, 136.6, 136.5, 132.7, 130.7, 130.4, 129.7, 129.1, 128.5, 128.2, 127.8, 126.8, 126.7, 125.4, 124.6, 123.9, 121.3, 118.8, 118.7, 114.7, 111.8, 110.6, 68.4, 67.1, 58.8, 54.6, 54.5, 54.2, 52.9, 52.4, 51.6, 42.3, 41.0, 38.0, 37.2, 37.1, 32.2, 31.9, 31.3, 29.9, 29.2, 27.6, 24.5, 23.6, 22.0, 20.0, 15.0. MS (ESI) Calculated for C\textsubscript{63}H\textsubscript{79}N\textsubscript{11}O\textsubscript{12}S [M+H]\textsuperscript{+}: 1214.6, found 1214.2.
Cyclic and Acyclic Ac-QSQQTFXNLWRLLXQN (p53-MDM2 peptides): Peptides were prepared as described above in a 24-well MiniBlock parallel reactor. Cyclization was achieved using standard procedure C. $^1$H/$^13$C NMR spectra for the side-chain acylated linear peptides are below. Full homo-/heteronuclear correlation data for entry 1 and 2 are included. Characterization of macrocycles corresponding to entries 3 and 4 is incomplete. Yields refer to material isolated by preparative HPLC.

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P1: 10.00 usec
PLW1: 13.5000000 MHz
SFQ1: 500.1330008 MHz

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SOLVENT         CDCl3
NS                    8
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SWH            8064.516 Hz
FIDRES    0.123055 Hz
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NUCLEUS              1H

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EXPNO                1
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SOLVENT           CDCl3
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PULPROG  zgpg30
TD       65536
SOLVENT  CDCl3
NS       32
DS       2
SNR      31250.000 Hz
FIDRES   0.476837 Hz
AQ        1.0485760 sec
RG       202.91
DM       16.000 usec
DE       18.00 usec
TE       298.0 K
D1       2.00000000 sec
D11      0.03000000 sec
TD0      1

======== CHANNEL f1 ========
SFO1     125.7722511 MHz
NUC1     13C
PLW1     23.00000000 W

======== CHANNEL f2 ========
SFO2     500.1330008 MHz
NUC2     1H
CPDPRG[2] waltz16
PCLM2    8.00 usec
PCLM3    13.50000000 W
PCLM4    1.35000001 W

F2 - Processing parameters
SI        131072
SF        125.7577892 MHz
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### F2 - Acquisition Parameters

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- **Time:** 15.37
- **Instrum:** av500
- **Probhd:** 5 mm DCH 13C-1
- **Pulprog:** zgpg30
- **TD:** 65536
- **Solvent:** CDCl3
- **NS:** 31
- **DS:** 3
- **SNR:** 31250.00 Hz
- **Fidres:** 0.476837 Hz
- **AQ:** 1.0485760 sec
- **RG:** 202.91
- **Dw:** 16.000 usec
- **De:** 18.00 usec
- **Te:** 298.0 K
- **D1:** 2.00000000 sec
- **D11:** 0.03000000 sec
- **Tdd:** 1

#### CHANNEL f1

- **Sfo1:** 125.7722511 MHz
- **Nuc1:** 13C
- **Plw1:** 23.00000000 W
- **Plw2:** 13.50000000 W
- **Plw12:** 0.21094000 W
- **Plw13:** 0.13500001 W

#### CHANNEL f2

- **Sfo2:** 500.1330008 MHz
- **Nuc2:** 1H
- **Cpdpg2:** waltz16
- **Pcw2:** 80.00 usec
- **Pw2:** 13.50000000 W
- **Pwl21:** 0.21094000 W
- **Pwl22:** 0.13500001 W

### F2 - Processing parameters

- **Si:** 131.072
- **SF:** 125.7577892 MHz
- **Wdn:** EM
- **Sdb:** 0
- **Lb:** 1.00 Hz
- **Gb:** 0
- **Pc:** 1.40
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#### CHANNEL f1

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#### F2 - Processing parameters

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| SF    | 125.7577892 MHz |
| WDN   | EM      |
| SSB   | 1.00 Hz |
| LB    | 0      |
| GR    | 0      |
| PC    | 1.00   |
**Acyclic-Ala-Trp-Thr-Tyr (2):**

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Acyclic-Ala-Trp-Thr-Tyr (3):
Acyclic-Ala-Trp-Thr-Tyr (3):
Acyclic-Ser-Met-Tyr (S9):

Current Data Parameters
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EXPN0  1
PROCNO  1

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Date_   20110831
Time    15.21
INSTRUM av600
PROBHD  5 mm BB5
PULPROG zg30
TD      65536
SOLVENT DMSO
NS      8
DS      0
SNR     12736.237 Hz
FIDRES  0.188846 Hz
AQ      2.6476543 sec
RG      114
DW      40.400 usec
DE      6.50 usec
TE      294.6 K
D1      2.00000000 sec
D10     1

======== CHANNEL f1 ========
NUC1    1H
P1      14.00 usec
PL1     -1.00 dB
PL1W    31.62277603 W
SP1     600.1336008 MHz

F2 - Processing parameters
SI      65536
SP      600.1300273 MHz
WOW     EM
SSB     0
LB      0.30 Hz
PC      1.00
Acyclic-Ser-Met-Tyr (S9):
Acyclic-Ile-Trp-Tyr (S10):
Acyclic-Ile-Trp-Tyr (S10):
Acyclic-Ala-Val-Tyr (S11):

Current Data Parameters
NAME: KL-III-286
EXPNO: 1
PROCNO: 1

F2 - Acquisition Parameters
Date: 20110829
Time: 13.37
INSTRUM: av600
PROBHD: 5 mm BB5
PULPROG: zg30
TD: 65536
SOLVENT: DMSO
NS: 8
DS: 0
SN: 12376.237 Hz
FIDRES: 0.188846 Hz
AQ: 2.6476543 sec
RG: 114
DE: 40.400 usec
TE: 294.3 K
TD0: 2.00000000 sec

F2 - Processing parameters
SI: 65536
SF: 600.1300273 MHz
WDW: EM
SSB: 0
LB: 0.30 Hz
PC: 1.00
Acyclic-Ala-Val-Tyr (S11):
Current Data Parameters
NAME  KL-III-286
EXPNO  1
PROCNO  1

F2 - Acquisition Parameters
Date  20110829
Time  13.37
INSTRUM  av600
PROBHD  5 mm BB5
PULPROG  zg30
TD  65536
SOLVENT  DMSO
NS  8
DS  0
SWH  12376.237 Hz
FIDRES  0.188846 Hz
AQ  2.6476543 sec
RG  114
DW  40.400 usec
DE  6.50 usec
TE  294.3 K
TD0  2.00000000 sec

F2 - Processing parameters
SI  65536
SP  600.1300273 MHz
WDW  EM
SSB  0
LB  0.30 Hz
PC  1.00
Acyclic-Ala-Val-Tyr (S11):
Acyclic-Val-Met-Phe-Tyr (S12):
Acyclic-Val-Met-Phe-Tyr (S12):
Acyclic-Leu-Ala-Arg-Tyr (S14):

- Current Data Parameters
  - NAME: KL-4-8
  - EXPNO: 1
  - PROCNO: 1

- F2 - Acquisition Parameters
  - Date: 20110926
  - Time: 17:17
  - INSTRUM: av600
  - PULP HD: zg30
  - TD: 65536
  - NS: 8
  - DS: 0
  - SWH: 12376.237 Hz
  - FIDRES: 0.188846 Hz
  - AQ: 2.6476543 sec
  - RG: 45.3
  - DW: 40.400 usec
  - DE: 6.50 usec
  - TE: 295.3 K
  - D1: 2.00000000 sec
  - TD0: 1

- F2 - Processing parameters
  - SI: 65536
  - SP: 600.1300273 MHz
  - WD: EM
  - SSB: 0
  - LB: 0.30 Hz
  - PC: 1.00
**Acyclic-Leu-Ala-Arg-Tyr (S14):**
Acyclic-Leu-Ala-Arg-Tyr (S14):

Current Data Parameters
NAME               KL-4-8
EXPNO               1
PROCNO               1

F2 - Acquisition Parameters
Date                20110926
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INSTRUM             av600
PROBHD               5 mm BB5
PULPROG             zg30
TD                    65536
SOLVENT             DMSO
NS                   8
DS                   0
SNM                12376.237 Hz
FIDRES             0.188846 Hz
AQ                    2.6476543 sec
RG                   45.3
DW                  40.400 usec
DE                   6.50 usec
TE                295.3 K
D1                2.00000000 sec
TD0                 1

======== CHANNEL f1 =======
NXXi                1H
P1                 14.00 usec
PL1               -1.00 dB
PL1W          31.62277603 W
SP01         600.1336008 MHz

F2 - Processing parameters
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SP        600.1300273 MHz
W6W               EM
SSB                 0
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Acyclic-Leu-Ala-Arg-Tyr (S14):
Acyclic-Ile-Met-Ser-Tyr-Trp (S15):

Current Data Parameters
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EXPNO    1
PROCNO   1

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INSTRUM   av600
PROBHD    5 mm BB5
PULPROG   zg30
TD        65536
SOLVENT   DMSO
NS        8
DS        0
SNH       12376.237 Hz
FIDRES    0.188846 Hz
AQ        2.6476543 sec
RG        128
DM        40.400 usec
DE        6.50 usec
TE        294.5 K
TD0       2.00000000 sec

F2 - Processing parameters
SI        65536
SF        600.1300273 MHz
WDW       EM
SSB       0
LB        0.30 Hz
GB        0
PC        1.00
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Acyclic-Ala-Phe-Thr-Ile-Tyr (S16):
Acyclic-Gly-Ser-Phe-Asn-Tyr (S17):
Acyclic-Gly-Ser-Phe-Asn-Tyr (S17):
Acyclic-Ser-Phe-Phe(4-NH$_2$) (S18):

![Chemical Structure Image]

Current Data Parameters
NAME KL-4-62_reprep
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 20120125
Time 19.30
INSTRUM av600
PROBHD 5 mm BB5
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 0
SNR 12376.237 Hz
FIDRES 0.188846 Hz
AQ 2.6476543 sec
RG 161.3
DW 40.400 usec
DE 6.50 usec
TE 295.2 K
D1 2.0000000 sec
TD0 1

F2 - Processing parameters
SI 65536
SF 600.1336008 MHz
WDW EM
SSB 0
LB 0.30 Hz
PC 1.00
Acyclic-Ser-Phe-Phe(4-NH$_2$) (S18):
Acyclic-Asn-Trp-Thr-Phe(4-NH₂) (S19):

Current Data Parameters
NAME  KL-5-127
EXPNO  1
PROCNO  1

F2 - Acquisition Parameters
Date  20130209
Time  15.55
INSTRIM  av500
PROBHD  5 mm DCH C-13
PULPROG  zg30
TD  65536
SOLVENT  DMSO
NS  8
DS  0
SNM  10000.000 Hz
FIDRES  0.152588 Hz
AQ  3.2767999 sec
RG  11
DW  50.000 usec
DE  10.00 usec
TE  298.0 K
D1  2.00000000 sec
D0  1

F2 - Processing parameters
SI  65536
SF  500.1330008 MHz
NEX1  1
P1  1.00 usec
PLw1  13.50000000 W

F2 - Processing parameters
SI  65536
SF  500.1300146 MHz
NEX1  1
P1  1.00 usec
PLw1  13.50000000 W

== CHANNEL f1 =========

F2 - Acquisition Parameters
Date  20130209
Time  15.55
INSTRIM  av500
PROBHD  5 mm DCH C-13
PULPROG  zg30
TD  65536
SOLVENT  DMSO
NS  8
DS  0
SNM  10000.000 Hz
FIDRES  0.152588 Hz
AQ  3.2767999 sec
RG  11
DW  50.000 usec
DE  10.00 usec
TE  298.0 K
D1  2.00000000 sec
D0  1

F2 - Processing parameters
SI  65536
SF  500.1300146 MHz
NEX1  1
P1  1.00 usec
PLw1  13.50000000 W

F2 - Processing parameters
SI  65536
SF  500.1300146 MHz
NEX1  1
P1  1.00 usec
PLw1  13.50000000 W

== CHANNEL f1 =========

F2 - Acquisition Parameters
Date  20130209
Time  15.55
INSTRIM  av500
PROBHD  5 mm DCH C-13
PULPROG  zg30
TD  65536
SOLVENT  DMSO
NS  8
DS  0
SNM  10000.000 Hz
FIDRES  0.152588 Hz
AQ  3.2767999 sec
RG  11
DW  50.000 usec
DE  10.00 usec
TE  298.0 K
D1  2.00000000 sec
D0  1

F2 - Processing parameters
SI  65536
SF  500.1300146 MHz
NEX1  1
P1  1.00 usec
PLw1  13.50000000 W

F2 - Processing parameters
SI  65536
SF  500.1300146 MHz
NEX1  1
P1  1.00 usec
PLw1  13.50000000 W

== CHANNEL f1 =========
Acyclic-Asn-Trp-Thr-Phe(4-NH$_2$) (S19):

Current Data Parameters
NAME: KL-5-127
EXPNO: 2
PROCNO: 1

F2 - Acquisition Parameters
Date: 20130209
Time: 15.58
INSTRUM: av500
PROBHD: 5 mm DCH 13C-1
PULPROG: zgpg30
TD: 65536
SOLVENT: DMSO
NS: 66
DS: 2
SNR: 31250.000 Hz
FIDRES: 0.476837 Hz
AQ: 1.0485760 sec
RG: 202.91
DW: 16.000 usec
DE: 18.00 usec
TE: 298.0 K
D1: 2.00000000 sec
D11: 0.03000000 sec
TD0: 1

-------- CHANNEL f1 --------
SFO1: 125.7722511 MHz
NUC1: 13C
PLW1: 23.00000000 W
PLW11: 0.21094000 W
PLW13: 0.13500001 W

-------- CHANNEL f2 --------
SFO2: 500.1330008 MHz
NUC2: 1H
CFDPPG[2: waltz16
PCPD2: 80.00 usec
PLMW: 13.50000000 W
PLMW1: 0.21094000 W
PLMW3: 0.13500001 W

F2 - Processing parameters
SI: 131072
SF: 125.7577892 MHz
WDM: EM
SSB: 0
LB: 1.00 Hz
GB: 0
PC: 1.40
Acyclic-Ala-Leu-Glu-Tyr (15):

![Chemical Structure](image)

Current Data Parameters
NAME: KL-III-283
EXPNO: 1
PROCNO: 1

F2 - Acquisition Parameters
Date: 20110830
Time: 17.22
INSTRUM: av600
PROBHHD: 5 mm BB5
PULPJOB: zg30
TD: 65536
SOLVENT: DMSO
NS: 8
DS: 0
SWH: 12376.237 Hz
FIDRES: 0.188846 Hz
AQ: 2.6476543 sec
RG: 71.8
DW: 40.400 usec
DE: 6.50 usec
TE: 294.7 K
TD0: 2.0000000 sec

F2 - Processing parameters
SI: 65536
SF: 600.1300273 MHz
WDW: EM
SSB: 0
LB: 0.30 Hz
PC: 1.00
Acyclic-Ala-Leu-Glu-Tyr (15):

![Chemical Structure]

Current Data Parameters
NAME         KL-III-283
EXPNO                 2
PROCNO                1

F2 - Processing parameters
SI                65536
SF                  70.9028319 MHz
WDW                  EM
SSB                 0
LB                 1.00 Hz
GR                 0
PC                 1.40
Acyclic-Phe-Leu-Hyp (S21):

Current Data Parameters
NAME: KL-5-11
EXPNO: 1
PROCNO: 1

F2 - Acquisition Parameters
Date: 20120821
Time: 17.09
INSTRIUM: av500
PROC HD: 5 mm DCH 13C-1
PULPROG: zg30
TD: 65536
SOLVENT: DMSO
NS: 8
DS: 0
SNM: 10000.000 Hz
FIDRES: 0.152588 Hz
AQ: 3.2767999 sec
RG: 129.78
DW: 50.000 usec
TE: 298.0 K
D1: 2.00000000 sec
TD0: 1

====== CHANNEL f1 ======
NEX: 1H
P1: 10.00 usec
PLH1: 13.5000000 W
SPW1: 500.1330008 MHz

F2 - Processing parameters
SI: 65536
SF: 500.1300146 MHz
FW: 1M
SSB: 1 Hz
LB: 0.30 Hz
GR: 0
PC: 1.00
Acyclic-Phe-Leu-Hyp (S21):
Acyclic-Gly-Val-Trp (S22):
Acyclic-Gly-Val-Trp (S22):
Acyclic-Ala-Val-Pro-His-OH (S23):
Acyclic-Ala-Val-Pro-His-NH₂ (S24):

Current Data Parameters
NAME          ICON-W-B5
EXPNO                1
PROCNO                1

F2 - Acquisition Parameters
Date_          20121013
Time              13.40
INSTRUM           av500
PROBHDP   5 mm DCH 13C-1
PULPSEG            zg30
TD                65536
SOLVENT           DMSO
NS                8
DS                  0
SNH            10000.000 Hz
FIDRES         0.152588 Hz
AQ                 3.2767999 sec
RG              11
DW                50.000 usec
DE                10.00 usec
TE                298.0 K
DI               2.0000000 sec
TD0               1

======== CHANNEL f1 ========
NXXi                1H
P1                10.00 usec
PLH1           13.5000000 W
SF01         500.1330000 MHz

F2 - Processing parameters
SI                65536
SF            500.1300000 MHz
WMW              00
SSB              0
LB                0.30 Hz
GR              0
PC                1.00
Acyclic-Ala-Val-Pro-His-NH$_2$ (S24):
Acyclic-Ala-Arg-His-Phe-NH₂ (S25):

Current Data Parameters
NAME             HIS_A5
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20121130
Time              17.23
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                    8
DS                0
SNM           10000.000 Hz
FIDRES         0.152588 Hz
AQ                3.2767999 sec
RG                11
DM           50.000 usec
dE                10.00 usec
tE                298.0 K
tD0                   1

====== CHANNEL f1 ======
SFO1        500.1330008 MHz
NUC1                 1
PLW1        13.50000000 W

F2 - Processing parameters
SI                65536
SF    500.1300146 MHz
WMW             1H
SSB                0
LB                0.30 Hz
GB                0
PC                1.00
Acyclic-Ala-Arg-His-Phe-NH$_2$ (S25):

Current Data Parameters
NAME ICON-W-A5
EXPN0 2
PROCNO 1
F2 - Processing parameters
SI 131072
SF 125.7578519 MHz
WDW EM
SSB 0
LR 1.00 Hz
GR 0
PC 1.40
Acyclic-Ala-Ile-His-Phe-NH$_2$ (S26):

\[
\text{Current Data Parameters}
\]

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**F2 - Acquisition Parameters**

- **Date**: 20121130
- **Time**: 17:41
- **INSTRUM**: av500
- **PROBHD**: 5 mm DCH 13C-1
- **PULPROG**: zg30
- **TD**: 65536
- **SOLVENT**: DMSO
- **NS**: 8
- **DS**: 0
- **SNR**: 10000.000 Hz
- **FIDRES**: 0.152588 Hz
- **AQ**: 3.2767999 sec
- **RG**: 11
- **DW**: 50.000 usec
- **DE**: 10.00 usec
- **TE**: 298.0 K
- **D1**: 2.0000000 sec
- **TD0**: 1

**F2 - Processing parameters**

- **SI**: 65536
- **SF**: 500.1300146 MHz
- **WDW**: EMSSB
- **LB**: 0.30 Hz
- **GB**: 0
- **PC**: 1.00

243
Acyclic-Ala-Ile-His-Phe-NH₂ (S26)
Acyclic-β-Ala-Pro[4-(2-methoxy-4-methylphenoxy)]-His (S27):
Acyclic-β-Ala-Pro[4-(2-methoxy-4-methylphenoxy)]-His (S27):
Acyclic-Val-Gln-Tyr-His-NH₂ (18):

Current Data Parameters
NAME     KL-5-151_AV600
EXPNO     2
PROCNO    1

F2 - Acquisition Parameters
Date_      20130429
Time       17.41
INSTRUM    av600
PROBHD     5 mm TBI5
PULPORG    zgpr
TD         65536
SOLVENT    DMSO
NS         32
DS         0
SWM        12376.237 Hz
FIDRES     0.188846 Hz
AQ         2.6476543 sec
RG         90.5
DM         40.400 usec
DE         6.50 usec
TE         293.9 K
D1         2.00000000 sec
D12        0.00002000 sec
TDD        1

====== CHANNEL f1 ======
NUC1       1
HP1        9.75 usec
PL1        -2.00 dB
PL9        52.20 dB
PL1W       39.81071854 W
PL9W       0.00015136 W
SP01       600.1320825 MHz

F2 - Processing parameters
SI         65536
SF         600.1300273 MHz
WDW        EM
LB         0
GB         0.30 Hz
PC         1.40
Acyclic-Val-Gln-Tyr-His-NH₂ (18):

Current Data Parameters
NAME KL-5-151
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date 20130424
Time 15.43
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPGRG zgpg30
TD 65536
SOLVENT DMSO
NS 126
DS 2

SNH 31250.000 Hz
FIDRES 0.476837 Hz
AQ 1.0485760 sec
RG 202.91

DW 16.000 usec
DE 18.000 usec

TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 125.7722511 MHz
NUC1 13C
PLW1 23.00000000 W

======== CHANNEL f2 ========
SFO2 500.1330008 MHz
NUC2 1H

PCPD2 80.00 usec
PLW2 0.21094000 W
PLW12 0.13500001 W
PLW13 0.21094000 W

F2 - Processing parameters
SI 131072
SF 125.7577892 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
Acyclic-Val-Orn-Met-Tyr (S30):

Current Data Parameters
NAME        KL-5-153_deprot
EXPNO         1
PROCNO        1

F2 - Acquisition Parameters
Date          20130409
Time            12.12
INSTRUM    av500
PROBHD           5 mm DCH 13C-1
PULPROG       zg30
TD              65536
SOLVENT          DMSO
NS              8
DS           0
SNR         10000.000 Hz
FIDRES    0.152588 Hz
AQ           3.2767999 sec
RG              11
DM         50.000 usec
DE           10.00 usec
TE              298.0 K
TD0            2.00000000 sec

======== CHANNEL f1 ========
SFO1        500.1330008 MHz
NUC1            1
HP1             10.00 usec
PLW1         13.50000000 W

F2 - Processing parameters
SI            65536
SF           500.1300146 MHz
WWW           13.50000000
SSB            0
LB               0.30 Hz
GR            0
PC              1.00
Acyclic-Val-Orn-Met-Tyr (S30):

Current Data Parameters
NAME  KL-5-153_deprot
EXPNO  2
PROCNO  1

F2 - Acquisition Parameters
Date  20130409
Time  12.15
INSTRUM  av500
PROBHD  5 mm DCH 13C-1
PULPROG  zgsg30
TD  65536
SOLVENT  DMSO
NS  85
DS  2
SNM  31250.000 Hz
FIDRES  0.476837 Hz
AQ  1.0485760 sec
RG  202.91
DW  16.000 usec
DE  18.00 usec
TE  298.0 K
D1  2.00000000 sec
D11  0.03000000 sec
TD0  1

======== CHANNEL f1 ========
SFO1  125.7722511 MHz
NUC1  1H
PLW1  23.00000000 W
P1  9.63 usec

======== CHANNEL f2 ========
SFO2  500.1330008 MHz
NUC2  1H
CFDPRG2  waltz16
PCPD2  80.00 usec
PLM2  13.50000000 W
PLM12  0.21094000 W
PLM13  0.13500001 W

F2 - Processing parameters
SI  131072
SF  125.7577892 MHz
WDM  EM
SSB  0
LB  1.00 Hz
GR  0
PC  1.40
Acyclic-Orn-Thr-Tyr (S35):

Current Data Parameters
NAME TR4-128
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 20130322
Time 20.59
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 0
SNM 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 11
DM 50.000 usec
DE 10.000 usec
TE 298.0 K
D1 2.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 500.1330008 MHz
NUC1 1
HP1 10.000 usec
PLW1 13.50000000 W

F2 - Processing parameters
SI 65536
SF 500.1300146 MHz
WMW 13
SSB 0
LB 0.10 Hz
GR 0
PC 1.00
Acyclic-Orn-Thr-Tyr (S35):

Current Data Parameters
NAME: TR4-128
EXPNO: 2
PROCNO: 1

F2 - Acquisition Parameters
Date: 20130322
Time: 21.02
INSTRUM: av500
PRORD: 5 mm DCH 13C-1
PULPROG: zgpg30
TD: 65536
SOLVENT: DMSO
NS: 128
DS: 2
SNM: 31250.000 Hz
FIDRES: 0.476837 Hz
AQ: 1.0485760 sec
RG: 15.53
DM: 16.000 usec
DE: 18.00 usec
TE: 298.0 K
D1: 0.00000000 sec
D11: 0.00000000 sec
TD0: 1

======== CHANNEL f1 ========
SFO1: 125.7722511 MHz
NUC1: 13C
PLW1: 23.00000000 W
PLW12: 0.21094000 W
PLW13: 0.13500001 W

======== CHANNEL f2 ========
SFO2: 500.1330008 MHz
NUC2: 1H
PLM2: 13.50000000 W
PLM12: 0.21094000 W
PLM13: 0.13500001 W

F2 - Processing parameters
SI: 131072
SF: 125.7577892 MHz
WDW: EM
SSB: 0
LB: 1.00 Hz
PC: 1.00
Acyclic-Gly-Thi-Trp-5HT (S31):

---

Current Data Parameters

**NAME**
KL-4-46

**EXPNO**
2

**PROCNO**
1

F2 - Acquisition Parameters

**Date**
20131012

**Time**
13.55

**INSTRUM**
av600

**PROBHD**
5 mm BB5

**PULPROG**
zg30

**TD**
65536

**SOLVENT**
DMSO

**NS**
4

**DS**
0

**SNH**
12376.237 Hz

**FIDRES**
0.188846 Hz

**AQ**
2.6476543 sec

**RG**
90.5

**DM**
40.400 usec

**DE**
6.50 usec

**TE**
300.5 K

**DI**
2.000000 sec

**TD0**
1

--- CHANNEL f1 ---

**NUC1**
1H

**P1**
14.00 usec

**PL1**
-1.00 dB

**PL1W**
31.62276034 MHz

**SP01**
600.1336008 MHz

F2 - Processing Parameters

**SI**
65536

**SP**
600.130027 MHz

**WG**
EM

**SSB**
0

**LB**
0.30 Hz

**PC**
1.00
Acyclic-Gly-Thi-Trp-5HT (S31):
Acyclic-Ala-Phe-Ser-Val-Pro-Gly-Val-Trp-Ile-Ser-Tyr-Val (S32):
Acyclic-Ala-Phe-Ser-Val-Pro-Gly-Val-Trp-Ile-Ser-Tyr-Val (S32):
Acyclic-Trp-Leu-Gln-Met-Thr-Gly-Phe-Tyr (S33):
Acyclic-Trp-Leu-Gln-Met-Thr-Gly-Phe-Tyr (S33):
Acyclic-Thr-Ala-Trp-Ile-Pro-Tyr-His-Asn-Val (S34):
Cyclic-Ala-Trp-Thr-Tyr (4):
Cyclic-Ala-Trp-Thr-Tyr (4):
Cyclic-Ser-Met-Tyr (5):

Current Data Parameters
NAME            KL-4-16
EXPNO                1
PROCNO                1

F2 - Acquisition Parameters
Date_          20110926
Time              16.58
INSTRUM           av600
PROBHD   5 mm TBI
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                    8
DS                0
SWM           12376.237 Hz
FIDRES      0.188846 Hz
AQ                  2.6476543 sec
RG                181
DW               40.400 usec
DE                6.50 usec
TE                294.0 K
D1           2.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                9.10 usec
PL1              -2.00 dB
PL1W        39.81071854 W
SP01         600.1336008 MHz

F2 - Processing parameters
SI                65536
SP             600.1300273 MHz
WDW          EM
SSB                0
LB                0.30 Hz
GP                1.00
Cyclic-Ser-Met-Tyr (5):
### Cyclic-Ile-Trp-Tyr (6):

**Current Data Parameters**

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**F2 - Acquisition Parameters**

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<td>3.2767999 sec</td>
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**F2 - Processing parameters**

| SF01  | 500.1317204 MHz |
| NOC1  | 1H |
| PI    | 10.00 usec |
| PLW1  | 13.50000000 W |
| PLW9  | 0.00005400 W |
| SF    | 500.1300146 MHz |
| WDN   | EM |
| SSB   | 0 |
| LB    | 0.30 Hz |
| GB    | 0 |
| PC    | 1.00 |
Cyclic-Ile-Trp-Tyr (6):

Current Data Parameters
NAME  INW-Cy
EXPNO  6
PROCNO  1

F2 - Acquisition Parameters
Date  20130518
Time  3:28
INSTRM  av500
PRORID  5 mm DCH 13C-1
PULPROG  zgpg30
TD  65536
SOLVENT  DMSO
NS  8192
DS  2
SNR  31250.000 Hz
FIDRES  0.476837 Hz
AQ  1.0485760 sec
RG  202.91
DW  16.000 usec
DE  18.000 usec
TE  298.0 K
D1  2.00000000 sec
D11  0.03000000 sec
TDO  1

F2 - Processing parameters
SI  131072
SF  125.7577892 MHz
WDW  EM
SGB  0
LR  1.00 Hz
PC  1.00
Cyclic-Trp-Ile-Gln-Tyr (8):
Cyclic-Trp-Ile-Gln-Tyr (8):

Current Data Parameters
NAME          KL-5-117b
EXPNO                     4
PROCNO                  1

F2 - Acquisition Parameters
Date            20130204
Time            19.00
INSTRUM           av500
PROBHHD          5 mm DCH 13C-1
PULPROG          zgpg30
TD                65536
SOLVENT           DMSO
NS                  861
DS                2
SNM            31250.000 Hz
FIDRES          0.476837 Hz
AQ                1.0485760 sec
RG             202.911 sec
E               16.000 usec
DE                18.00 usec
TE                298.0 K
D1            2.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1       125.7722511 MHz
NUC1                 13C
PLW1        23.00000000 W

======== CHANNEL f2 ========
SFO2       500.1330008 MHz
NUC2                 1H
CPDG2          80.00 usec
PCPD2        13.5000000 W
PLM2          0.01094000 W
PLM1 0.13500001 W

F2 - Processing parameters
SI                131072
SF            125.7577892 MHz
WDM           EM
SSB                  0
LB                1.00 Hz
GB                  0
PC                1.40
Cyclic-Val-Met-Phe-Tyr (9):
Cyclic-Val-Met-Phe-Tyr (9):
Cyclic-Gly-Thi-Trp-5HT (10):

Current Data Parameters
NAME: KL-4-171B
EXPNO: 1
PROCNO: 1

F2 - Acquisition Parameters
Date: 20120409
Time: 19.19
INSTRUM: av600
PROBHD: 5 mm TBI5
PULP: zg30
TD: 65536
SOLVENT: DMSO
NS: 8
DS: 0
SNH: 12376.237 Hz
FIDRES: 0.188846 Hz
AQ: 2.6476543 sec
RG: 181
DW: 40.400 usec
DE: 6.50 usec
TE: 294.6 K
D1: 2.00000000 sec
TD0: 1

F2 - Processing parameters
SI: 65536
SF: 600.1300273 MHz
WDW: EM
SSB: 0
LB: 0.30 Hz
GC: 1.00
**Cyclic-Gly-Thi-Trp-5HT (10):**

![Chemical Structure]

Current Data Parameters

NAME: KL-4-171A_500A
EXPNO: 2
PROCNO: 1

F2 - Acquisition Parameters

Date: 20120411
Time: 18.26

INSTRUM: av500
PROBHD: 5 mm DCH 13C-1
PULPROG: zgpg30
TD: 65536
SOLVENT: DMSO
NS: 600
DS: 2
SNR: 31250.000 Hz
FIDRES: 0.476837 Hz
AQ: 1.0485760 sec
DG: 202.91
DW: 16.000 usec
DE: 18.00 usec
TE: 296.0 K
TD0: 1
SFO1: 125.7722511 MHz
NUC1: 13C
PLW1: 23.00000000 W
CPDG[2]: waltz16
PCPD2: 80.00 usec
PLM2: 13.50000000 W
PLM1: 0.21094000 W
PLM1: 0.13500001 W

F2 - Processing parameters

SI: 131072
SF: 125.7577892 MHz
WDW: EM
GB: 0
LB: 1.00 Hz
PC: 1.40
Cyclic- Leu-Ala-Arg-Tyr (11):

[Image of the cyclic peptide structure]
Cyclic- Leu-Ala-Arg-Tyr (11):
Cyclic-Ile-Met-Ser-Tyr-Trp (12):
Cyclic-Ile-Met-Ser-Tyr-Trp (12):
Cyclic-Ile-Met-Ser-Tyr-Trp (12):

Current Data Parameters
NAME            KL-4-57
EXPNO                1
PROCNO                1

F2 - Acquisition Parameters
Date_          20111019
Time              19.25
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                    8
DS               0
SNM           10000.000 Hz
FIDRES          0.152588 Hz
AQ                3.2767999 sec
RG                20.17
DM           50.000 usec
DE                10.00 usec
TE            301.0 K
DI        2.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PLW1        13.50000000 MHz
SP1          500.1330008 MHz

F2 - Processing parameters
SI                65536
SF               500.1300146 MHz
WDM             1M
SSB                0
LB            0.30 Hz
GB                0
PC                1.00
Cyclic-Ile-Met-Ser-Tyr-Trp (12):
Cyclic- Ala-Phe-Thr-Ile-Tyr (13):
Cyclic- Ala-Phe-Thr-Ile-Tyr (13):

![Chemical Structure Image]
Cyclic-Gly-Ser-Phe-Asn-Tyr (14):
**Cyclic-Ala-Leu-Glu-Tyr (16):**

Current Data Parameters
NAME       KL-4-50_f92
EXPNO      1
PROCNO     1

F2 - Acquisition Parameters
Date        20111008
Time        19.54
INSTRUM     av600
PROBHD      5 mm TBI5
PULPROG     zg30
TD          65536
SOLVENT     DMSO
NS          8
DS          0
SNW         12376.237 Hz
FIDRES      0.188846 Hz
AQ          2.6476543 sec
RG          181
DM          40.400 usec
DE          6.50 usec
TE          295.7 K
TD0         2.00000000 sec

========== CHANNEL f1 =========
NXXi       1H
P1         9.10 usec
PL1        -2.00 dB
PL1W       39.81071854 W
SP01       600.1336008 MHz

F2 - Processing parameters
SI          65536
SF          600.1300273 MHz
WDW        EM
SSB         0
LB          0.30 Hz
PC          1.00
Cyclic-Ala-Leu-Glu-Tyr (16):
Cyclic-Ala-Leu-Glu-Tyr (17):
Cyclic-Val-Gln-Tyr-His (19):
Cyclic-Val-Gln-Tyr-His (20):
### Current Data Parameters

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#### F2 - Acquisition Parameters

- **Date:** 20130416
- **Time:** 19.54
- **INSTRUM:** av500
- **PROBHD:** 5 mm DCH 13C-1
- **PULPROG:** zgpg30
- **TD:** 65536
- **SOLVENT:** DMSO
- **NS:** 128
- **DS:** 2
- **SWH:** 31250.000 Hz
- **FIDRES:** 0.476837 Hz
- **AQ:** 0.476837 Hz
- **RG:** 202.91
- **DM:** 16.000 usec
- **DE:** 18.00 usec
- **TE:** 298.0 K
- **DW:** 16.000 usec
- **D1:** 2.00000000 sec
- **D11:** 0.03000000 sec
- **TDO:** 1

### CHANNEL f1

- **SFO1:** 125.7722511 MHz
- **NUC1:** 13C
- **PLW1:** 23.00000000 W

### CHANNEL f2

- **SFO2:** 500.1330008 MHz
- **NUC2:** 1H
- **CPDPRG[2:** waltz16
- **PCPD2:** 80.00 usec
- **PLW2:** 0.21094000 W
- **PLW12:** 0.13500001 W
- **PLW13:** 0.13500001 W

#### F2 - Processing parameters

- **SI:** 131072
- **SF:** 125.7577892 MHz
- **WDM:** EM
- **SSB:** 0
- **LB:** 1.00 Hz
- **GR:** 0
- **PC:** 1.40

---

**Cyclic-Val-Gln-Tyr-His (20):**

![Cyclic-Val-Gln-Tyr-His (20)](image-url)
Cyclic-Gly-Val-Trp (21):
Cyclic-Phe-Leu-Hyp (22):

Current Data Parameters
NAME  KL-5-12_AV500
EXPSN  1
PROCNO  1

F2 - Acquisition Parameters
Date    20120821
Time    17.22
INSTRUM    av500
PROBHD  5 mm DCH 13C-1
PULPROG  zg30
TD     65356
SOLVENT  DMSO
NS      8
DS      0
SWH      10000.000 Hz
NS       8
DS       0
DMS      10000.000 Hz
AQ      0.152588 Hz
AF      3.2767999 sec
RG      202.91
DW      50.000 usec
DE      10.00 usec
TE      298.0 K
D1     2.00000000 sec
TDD     1

======== CHANNEL f1 ========
NUC1    1H
P1      10.00 usec
PLW1     13.50000000 MHz
FR1     500.133000 MHz

F2 - Processing parameters
SI     65356
SF    500.1300146 MHz
WDM    1M
SSW    0
LB     0.30 Hz
GB     0
PC     1.00
Cyclic-Ala-Val-Pro-His-OH (23):
Cyclic-Ala-Val-Pro-His-OH (23):
Cyclic-Ala-Val-Pro-His-NH₂ (24):

![Chemical Structure of Cyclic-Ala-Val-Pro-His-NH₂ (24)]

Current Data Parameters

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F2 - Acquisition Parameters

- **Date**: 20120731
- **Time**: 12.41
- **INSTRUM**: av500
- **PROBHD**: 5 mm DCH 13C-1
- **PULPROG**: zg30
- **TD**: 65536
- **SOLVENT**: DMSO
- **NS**: 8
- **DS**: 0
- **SNM**: 10000.000 Hz
- **FIDRES**: 0.152588 Hz
- **AQ**: 3.2767999 sec
- **RG**: 202.91
- **DW**: 50.000 usec
- **DE**: 10.00 usec
- **TE**: 296.0 K
- **D1**: 2.00000000 sec
- **TD0**: 1

F2 - Processing parameters

- **SI**: 65536
- **SF**: 500.1300146 MHz
- **WDW**: EMSSB 0
- **LB**: 0.30 Hz
- **PC**: 1.00

---

**ppm**

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---
Cyclic-Ala-Val-Pro-His-NH₂ (24):
Cyclic-Gly-Thr-His-Tyr-NH$_2$ (25):
**Cyclic-Gly-Thr-His-Tyr-NH₂ (25):**

![Chemical Structure](image)

---

**Current Data Parameters**

**NAME**  His_A2_F17  
**EXPNO**  6  
**PROCNO**  1  

**F2 - Acquisition Parameters**

- **Date**: 20121220  
- **Time**: 17.18  
- **INSTRUM**: av500  
- **PROBHD**: 5 mm DCH 13C-1  
- **PULPROG**: zgpg30  
- **TD**: 65536  
- **SOLVENT**: DMSO  
- **NS**: 256  
- **DS**: 2  
- **SN**: 31250.000 Hz  
- **FIDRES**: 0.476837 Hz  
- **AQ**: 1.0485760 sec  
- **RG**: 202.91  
- **DW**: 16.000 usec  
- **DE**: 18.00 usec  
- **TE**: 298.0 K  
- **D1**: 2.00000000 sec  
- **D11**: 0.03000000 sec  
- **TD0**: 1  

---

**CHANNEL f1**

- **SFO1**: 125.7722511 MHz  
- **NUC1**: 13C  
- **PLW1**: 23.00000000 W  

---

**CHANNEL f2**

- **SFO2**: 500.1330008 MHz  
- **NUC2**: 1H  
- **PCPD2**: waltz16  
- **PLM1**: 23.00000000 W  

---

**F2 - Processing parameters**

- **SI**: 131072  
- **SF**: 125.7577892 MHz  
- **WDW**: EM  
- **SSB**: 1.00 Hz  
- **PC**: 1.40
Cyclic-β-Ala-Pro[4-(2-methoxy-4-methylphenoxy)]-His (26):
Cyclic-Ala-Ile-His-Phe-NH$_2$ (27):
Cyclic-Ala-Ile-His-Phe-NH$_2$ (27):
**Cyclic-Ala-Arg-His-Phe-NH\(_2\) (28):**

![Chemical Structure Image]

---

**Current Data Parameters**
- **NAME**: His_A5_F24
- **EXPNO**: 1
- **PROCNO**: 1

**F2 - Acquisition Parameters**
- **Date**: 20121207
- **Time**: 17.25
- **INSTRUM**: av600
- **PROBHD**: 5 mm TBI5
- **PULPROG**: zg30
- **TD**: 65536
- **SOLVENT**: DMSO
- **NS**: 16
- **DS**: 0
- **SWH**: 12376.237 Hz
- **FIDRES**: 0.188846 Hz
- **AQ**: 2.6476543 sec
- **RG**: 256
- **DW**: 40.400 usec
- **DE**: 6.50 usec
- **TE**: 294.1 K
- **TD0**: 1

**F2 - Processing parameters**
- **SI**: 65536
- **SF**: 600.1300273 MHz
- **WDW**: EM
- **SSB**: 0
- **LB**: 0.30 Hz
- **PC**: 1.00

---

**ppm Scale**

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0
Cyclic-Ala-Arg-His-Phe-NH$_2$ (28):

Current Data Parameters
NAME    His_A5_F24
EXPNO   2
PROCNO  1

F2 - Acquisition Parameters
Date    20130122
Time    10.40
INSTRUM av500
PROBHD  5 mm DCH 13C-1
PULPROG zgpg30
TD      65536
SOLVENT DMSO
NS      472
DS      2
SWH     31250.000 Hz
FIDRES  0.476837 Hz
AQ      1.0485760 sec
RG      202.91
DM      16.000 usec
DE      18.00 usec
TE      298.0 K
D1      2.00000000 sec
D11     0.03000000 sec
TD0     1

======== CHANNEL f1 ========
SFO1    125.7722511 MHz
NUC1    13C
PLW1    23.00000000 W
PLW11   9.63 usec

======== CHANNEL f2 ========
SFO2    500.1330008 MHz
NUC2    1H
CPD2    80.00 usec
PLW2    13.50000000 W
PLW21   0.21094000 W
PLW23   0.13500001 W

F2 - Processing parameters
SI      131072
SF      125.7577892 MHz
WDW     EM
SSB     0
LB      1.00 Hz
PC      1.40
Cyclic-Thr-Ala-Trp-Ile-Pro-Tyr-His-Asn-Val (29):
Cyclic-Thr-Ala-Trp-Ile-Pro-Tyr-His-Asn-Val (29):

![Chemical Structure Image]

Current Data Parameters
NAME K1-4-184B
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20120419
Time 19.18
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 272
DS 2
SNM 31250.000 Hz
FIDRES 0.476837 Hz
AQQ 1.0485760 sec
Rg 202.91
DE 16.000 usec
TE 296.0 K
TD0 1
SFO1 125.7722511 MHz
NUC1 13C
PLW1 9.63 usec
PLW1 23.00000000 W
SFO2 500.1330008 MHz
NUC2 1H
CPDPKG1[2] waltz16
PCPD2 40.00 usec
PLM2 13.50000000 W
PLM1 0.21094000 W
PLM1 0.13500001 W

F2 - Processing parameters
SI 131072
SF 125.7577892 MHz
WDW EM
GB 0
LB 1.00 Hz
PC 1.40
Cyclic-Asn-Trp-Thr-Phe(4-NH₂) (30):

Current Data Parameters
NAME           KL-5-158
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20130416
Time              19.41
INSTRUM           av500
PROBHD           5 mm DCH 13C-1
PULPROG            zg30
TD                65536
SOLVENT           DMSO
NS                    8
DS                    0
SWM           10000.000 Hz
FIDRES         0.152588 Hz
AQ                3.2767999 sec
RG                    11
DM       50.000 usec
DE                10.00 usec
TE                298.0 K
D1           2.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        500.1330008 MHz
NUC1                 1
HP1                10.00 usec
PLW1        13.50000000 W

F2 - Processing parameters
SI                65536
SF       500.1300146 MHz
WMW              1W
SSB             0
LB                0.30 Hz
GR                    0
PC                    1.00
Cyclic-Asn-Trp-Thr-Phe(4-NH₂) (30):

Current Data Parameters
NAME          KL-5-158
EXPNO         2
PROCNO        1

F2 - Acquisition Parameters
Date           20130416
Time            19.45
INSTRUM       av500
PRORHD       5 mm DCH 13C-1
PULPROG     zgpg30
TD             65536
SOLVENT      DMSO
NS            82
DS            2
SNR          31250.000 Hz
FIDRES      0.476837 Hz
AQ            1.0485760 sec
RG           202.91
DW            16.000 usec
DE            18.00 usec
TE           298.0 K
D1           2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1        125.7722511 MHz
NUC1                13CP1                9.63 usec
PLW1        23.00000000 W
PLW12        0.21094000 W
PLW13        0.13500001 W

======== CHANNEL f2 ========
SFO2        500.1330008 MHz
NUC2                1HCPDPRG[2      waltz16
PCPD2             80.00 usec
PLM2       13.50000000 W
PLM12        0.21094000 W
PLM13        0.13500001 W

F2 - Processing parameters
SI            131072
SF       125.7577892 MHz
WDM          EM
SSB            0
LB            1.00 Hz
GR            0
PC            1.40
Current Data Parameters
NAME     XL-5-158
EXPNO 6
PROCNO 1

P2 - Acquisition Parameters
Date     20130417
Time     18.34
INSTRUM  av500
PROBHD   5 mm DCH 13C-1
FIDPROG  hnqedtgp
TD       2048
SOLVENT  DMSP
NS       2
DS       16
SWM      5000.000 kHz
FIDRES   2.441406 Hz
AQ       0.2048000 s
RG       202.91
DM       100.000 u
DE       10.00 s
TE       298.0 K
CNST2    145.0000000
D0       0.000000000
D1       1.000000000
D4       0.001724140
D11      0.030000000
D13      0.000000000
D16      0.000020000
D21      0.003450000
INO      0.000019900
ZGOPTNS

------- CHANNEL 1 -------
SP01    500.1325007 MHz
NUC1    1H
P1      9.50 u
P2      19.00 u
P28     0 usec
PW1     13.5000000 MHz

------- CHANNEL 2 -------
SP02    125.7678496 MHz
NUC2    13C
CPDPRG(2 garp
P3      9.63 u
P4      19.26 u
Current Data Parameters
NAME     KL-5-156c_NV600
EXPNO                1
PROCNO                1

F2 - Acquisition Parameters
Date_          20130411
Time              20.12
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                    8
DS                0
SWH           12376.237 Hz
FIDRES         0.188846 Hz
AQ            2.6476543 sec
RG                181
DW               40.400 usec
DE                6.50 usec
TE                294.1 K
D1            2.00000000 sec
TD0                1

====== CHANNEL f1 ======
NXYc               1H
P1               9.75 usec
PL1             -2.00 dB
PL1W          39.81071854 W
SP01        600.1336008 MHz

F2 - Processing parameters
SI                65536
SP            600.1300273 MHz
WDM            600.1300273 MHz
SSB                0
LB                0.30 Hz
PC                1.40
Cyclic-Val-Orn-Met-Try (32):
Cyclic-Val-Orn-Met-Try (33):
Cyclic-Orn-Thr-Try (35):

Current Data Parameters
NAME       TR4-169A_2
EXPNO       4
PROCNO      1

F2 - Acquisition Parameters
Date_       20130428
Time         18.14
INSTROM      av600
PROBHD       5 mm TBI5
FURLPROG     zgpr
TD           65536
SOLVENT      DMSONS
NS           8
DS           0
SWH          6009.615 Hz
FIDRES       0.091689 Hz
AQ           5.4525952 sec
RG           64
DW           83.200 usec
DE           6.50 usec
TE           298.0 K
D1           2.00000000 sec
D12          0.00002000 sec
TDO          1

======== CHANNEL f1 ========
NUC1         1H
PL1          -2.00 dB
PL9          52.24 dB
PL1W         39.81071854 W
PL9W         0.00014997 W
SF01         600.1321531 MHz

F2 - Processing parameters
SI           65536
SF           600.1300273 MHz
WDW          0T
SBR          0
LB           0.30 Hz
PC           1.00
Cyclic-Ser-Phe-Phe(4-NH₂) (37):
Cyclic-Ser-Phe-Phe(4-NH₂) (37):

Current Data Parameters
NAME            KL-5-10
EXPMO            12
PROCNO            1
F2 - Processing parameters
SI               131072
SF                125.7577892 MHz
WDW                  EM
SSB               0
LB                1.00 Hz
GR               0
PC                1.40
Cyclic-Ala-Phe-Ser-Val-Pro-Gly-Val-Trp-Ile-Ser-Tyr-Val (38):

[Chemical structure image]

Current Data Parameters
NAME            KL-4-44
EXPNO                1
PROCNO                1

F2 - Acquisition Parameters
Date_          20111006
Time              18.36
INSTRM           av600
PROBHD   5 mm TBI5
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                    8
DS                    0
SNH    12376.237 Hz
FIDRES      0.188846 Hz
AQ                2.647654 sec
RG                181
DW         40.400 usec
DE                6.50 usec
TE                295.8 K
D1  2.00000000 sec
TD0                   1

F2 - Processing parameters
SI                65536
SP     600.1300273 MHz
WDM       0
DSB                   0
LB            0.30 Hz
PC                1.00
Cyclic-Trp-Leu-Gln-Met-Thr-Gly-Phe-Tyr (39):

![Chemical Structure Diagram]

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F2 - Processing parameters

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<td>PC</td>
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Cyclic-Trp-Leu-Gln-Met-Thr-Gly-Phe-Tyr (39):
Current Data Parameters

NAME               TR4-129
EXPNO              21
PROCNO             1

F2 - Acquisition Parameters

Date              20130403
Time              22.13
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG          zgesgp
TD                65536
SOIVENT           H2O+D2O
NS                8DS                    4
SWH            8389.262 Hz
FIDRES         0.128010 Hz
AQ                3.9059956 sec
RG                 128
DW               59.600 usec
DE                6.50 usec
TE               298.0 X
D1                1.000000000 sec
D12                0.0020000 sec
D14                0.0020000 sec
TD0                1

------- CHANNEL f1 --------
P1               9.82 usec
P2              19.64 usec
P12             3000.00 usec
P10              320.00 db
P11                -2.00 db
P12W                0 W
P12W                38.6107864 W
SP1               41.68 dB
SPNAM1     Squa100.100
SPOAL1            1.000
SPOOFFS1        -1235.04 Hz

------- GRADIENT CHANNEL ----- 
SPGR1               100.00 dB
SPGR2               100.00 Hz
SPGR3               100.00 Hz
SPGR4               100.00 Hz

F2 - Processing parameters

SI                65536
SP 600.131313 MHz
WDW                EM
SSB                0
LB                0.30 Hz
NB                0
PB                1.00

Compound S33
Current Data Parameters
NAME            TR4-129EXPNO                13
PROCNO                1

F2 - Acquisition Parameters
Date_          20130326
Time              22.05
INSTRUM           av600
PROBHD   5 mm TBI
PULPROG      mlevesgpph
TD                 2048
SOLVENT         H2O+D2O
NS                    2
DS                   16
SWH            8389.262 Hz
FIDRES         4.096319 Hz
AQ            0.1221108 sec
RG                  362
DW               59.600 usec
DE                 6.50 usec
TE                323.0 K
D0           0.00003310 sec
D1           1.00000000 sec
D9           0.06000000 sec
D12          0.00002000 sec
D16          0.00020000 sec
IN0          0.00011920 sec
L1                   24

== CHANNEL f1 ========
NUC1                 1
HP1                10.21 usec
P2                20.42 usec
P5                26.68 usec
P6                40.00 usec
P7                80.00 usec
P12             2000.00 usec
P17             2500.00 usec
PL0              120.00 dB
PL1               -2.00 dB
PL10               9.86 dB
PL0W     0 W
PL1W       39.81071854 W
PL10W      2.59417963 W
SFO1        600.1348010 MHz
SP1               37.82 dB
SPNAM1     Squa100.1000
SPOAL1            1.000
SPOFFS1        -1345.04 Hz

== GRADIENT CHANNELS ====
GPNAM1         SINE.100
GPNAM2         SINE.100
GPZ1              31.00 %
GPZ2              11.00 %
P16             1000.00 usec

F1 - Acquisition parameters
TD                  256
SFO1           600.1348 MHz
FIDRES        32.770554 Hz
SW            13.979 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                 4096
SF          600.1310113 MHz
WDW               QSINESSB                   2
PC                 1.00

F1 - Processing parameters
SI                 4096
MC2         States-TPPI
SF          600.1310119 MHz
WDWSB                   2

Compound S33

ppm

ppm
Current Data Parameters
NAME            XL4-44
EXPNO             15
PROCNO            1

F2 - Acquisition Parameters
Date              20130317
Time             13.21
INSTRUM          av600
PROBHD   5 mm TBI5
PULPROG          zgesgp
TD              65536
SOLVENT       H2O+D2O
NS                    8DS                    4
SWH            8389.262 Hz
FIDRES         0.128010 Hz
AQ                  3.9059956 sec
RG                  256
DW                 5.600 usec
TE                298.0 K
D1           1.00000000 sec
D12          0.00002000 sec
D16          0.00002000 sec
TDD            1

------- CHANNEL f1 -------
P1C1             1.0
P1                9.75 usec
P2                30.00 usec
P12                 20.00 dB
P15                 -2.00 dB
SLOW              0.0 W
SLIM          39.81071854 W
SP1               600.1352691 MHz
SFO1       600.1352691 MHz
SPNAM1     Squa100.1000
SPOAL1            1.000
SPOFFS1        -1709.04 Hz

------- GRADIENT CHANNEL ------
GPNAM1         SINE.100
GPNAM2         SINE.100
GPZ1             31.00 %
GPZ2             11.00 %
P16                1000.00 usec

F2 - Processing parameters
SI              65536
SF          600.1313336 MHz
WDW                  EM
SSB         0
LB                 1.00 Hz
GB       0
PC                 1.00

--- 383 ---

Compound 38
383

--- End of Document ---
Current Data Parameters
NAME             KL4-44EXPNO                16PROCNO                1
F2 - Acquisition Parameters
Date_          20130317Time              13.24
INSTRUM           av600
PROBHD   5 mm TBI5PULPROG     noesyesgpphTD                 4096
SOLVENT         H2O+D2O
NS                    8DS                   16SWH            8389.262 Hz
FIDRES         2.048160 Hz
AQ            0.2441716 secRG               1625.5DW               59.600 usec
DE                 6.50 usec
TE                298.0 KD0           0.00004719 secD1           2.00000000 sec
D8           0.30000001 secD11          0.03000000 secD12          0.00002000 secD16          0.00020000 sec
IN0          0.00011920 sec
======== CHANNEL f1 ========
NUC1                 1H
P1                 9.75 usec
P2                19.50 usecP12             3000.00 usec
PL0              120.00 dBPL1               -2.00 dB
PL0W     0 W
PL1W        39.81071854 W
SFO1        600.1352691 MHz
SP1               41.74 dB
SPNAM1     Squa100.1000
SPOAL1            1.000SPOFFS1        -1710.14 Hz
====== GRADIENT CHANNEL =====
GPNAM1         SINE.100
GPNAM2         SINE.100
GPZ1              31.00 %
GPZ2              11.00 %
P16             1000.00 usec
F1 - Acquisition parameters
TD                  256
SFO1           600.1353 MHzFIDRES        32.770554 HzSW               13.979 ppm
FnMODE      States-TPPI
F2 - Processing parameters
SI                 4096
SF          600.1313328 MHz
WDW                   QSINE
SSB                   2PC                 1.00
F1 - Processing parameters
SI                 4096
MC2         States-TPPI
SF          600.1313335 MHz
WDWSSB                   3

Compound 38
Current Data Parameters
NAME             KL4-44
EXPNO                18
PROCNO                1

F2 - Acquisition Parameters
Date_          20130402
Time              22.01
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG    hsqcetgpsisp
TD                 2048
SOLVENT         H2O+D2O
DS                   8
DS                   16
DS                   32
DS                   64
DS                   128
DS                   256
DS                   512
DS                   1024
SW              4921.260 Hz
FIDRES         2.402959 Hz
AQ            0.2081268 sec
RG                 8192
DW              101.600 usec
DE                 6.00 usec
TE                283.0 KCNST2       145.00000008 a0
D1           1.00000000 sec
D4           0.00172414 sec
D11          0.03000000 sec
D16          0.00020000 sec
IN0          0.00002070 sec

ZGOPTNS

======== CHANNEL f1 ========
NUC1                 1
P1                 9.96 usec
P2                19.92 usec
P28             1000.00 usec
PL1               -2.00 dB
PL1W                39.81071854 W
WSFO1        600.1340570 MHz

======== CHANNEL f2 ========
CPDG2            garp
NUC2                13C
P3                19.52 usec
P4                39.04 usec
P14             1000.00 usec
PCPD2             65.00 usec
PL0              120.00 dB
PL2               -3.00 dB
PL12               7.45 dB
PL0W        0 W
PL2W       150.35617065 W
PL12W       13.55567932 W
WSFO2        150.9133722 MHz
SP3                4.12 dB
SPNAM3   Crp80,0.5,20.1
SPOAL3            0.500
SPOFFS3  0 Hz

====== GRADIENT CHANNEL =====
GPNAM1         SINE.100
GPNAM2         SINE.100
GPZ1              80.00 %
GPZ2              20.10 %
P16             1000.00 usec

F1 - Acquisition parameters
TD                  134
SFO1           150.9134 MHz
FIDRES       180.195068 Hz
SW              160.000 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 4096
SF          600.1313293 MHz
WDW                  EM
SSB      0
LB                 3.00 Hz
GB       0
PC                 1.40

F1 - Processing parameters
SI                 4096
MC2       echo-antiecho
SF          150.9031686 MHz
WDWSSB                2.5
LB                 3.00 Hz
GB       0
PC                 1.40
Current Data Parameters
NAME            TR4-133
EXPNO                18
PROCNO                1

F2 - Acquisition Parameters
Date_          20130403
Time              18.45
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG          zgesgp
TD                65536
SOLVENT         H2O+D2O
NS                    8DS                    4
SWH            8389.262 Hz
FIDRES         0.128010 Hz
AQ                  3.9059956 sec
RG                  256
DW                59.600 usec
DE                6.50 usec
TE               281.0 K
DI 1.000000000 sec
DI2 0.000000000 sec
DI4 0.000000000 sec
TD0               1

======== CHANNEL f1 ========
NUC1                 1H
P1                10.10 usec
P2                20.20 usec
P12            3000.00 usec
P40               1.00 db
P41                2.00 db
PLOW               0 W
PS1W               39.81071654 W
SPF1          400.1348010 MHz
SP1               41.43 dB
SPNAM1     Squa100.1000
SPOAL1            1.000
SPOFFS1       -1171.44 Hz

====== GRADIENT CHANNEL ======
GP1M1         SINE.100
GP1M2         SINE.100
GP1Z1              31.00 %
GP1Z2              11.00 %
PI6            1000.00 usec

F2 - Processing parameters
SI                65536
SF          600.1313335 MHz
WDW                  EM
SSB                 0
LB                 1.00 Hz
GB                 0
PC                 1.00
Acyclic - Ac-QSQQTFDapNLWRLHQN-NH₂

Current Data Parameters
NAME     p56_A1_acyclic
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121206
Time_ 17.04
INSTRUM av500
PROBHD 5 mm DCI 13C-1
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 19
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 11
DW 50.000 usec
DE 10.00 usec
TE 298.0 K
D1 2.0000000 sec
TDO 1

======== CHANNEL f1 ========
SFO1 500.1330008 MHz
NUC1 1H
PT 10.00 usec
PLW1 13.5000000 W

F2 - Processing parameters
SI 65536
SF 500.1300146 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
Acyclic - Ac-QSQQTF(Dap)NLWRLHQN-NH₂

Current Data Parameters
NAME      p56_A1_acyclic
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20121206
Time              17.06
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                  125
DS                    2
SWH            31250.000 Hz
FIDRES            0.476837 Hz
AQ               1.0485760 sec
RG               202.91
DW                16.000 usec
DE                18.000 usec
TE                298.0 K
D1             2.0000000 sec
D11          0.03000000 sec
T00                   1

======== CHANNEL f1 ========
SFO1        125.7722511 MHz
NUC1                13C
P1                 9.63 usec
PLWL            23.0000000 W

======== CHANNEL f2 ========
SFO2        500.1330008 MHz
NUC2                1H
CPIP[2       waltz16
PCPD2          80.000 usec
PLW2          3.50000000 W
PLW12         0.021094000 W
PLW13        0.13500001 W

F2 - Processing parameters
ST               131072
SF               125.7577892 MHz
WDW                  EM
SSB             0
LB                1.00 Hz
CH                n
Acyclic - Ac-QSQQTFOreNLWRLLHQN-NH₂

Current Data Parameters
NAME     p53_A2_acyclic
EXPNO                10
PROCNO                1

F2 - Acquisition Parameters
Date_          20121206
Time              17.19
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                    8
DS                    0
SWH           10000.000 Hz
FIDRES         0.152588 Hz
AQ            3.2767999 sec
RG                   11
DW               50.000 usec
DE                10.00 usec
TE                298.0 K
D1           2.00000000 sec
TDO                   1

======== CHANNEL f1 ========
SFO1        500.1330008 MHz
NUCL                 1H
PL                    10.00 usec
PLWL        13.50000000 W

F2 - Processing parameters
SI                65536
SF    500.1300146 MHz
WDW                  EM
SSB           0.30 Hz
LB                    0
GB                    0
PC                1.00
Acyclic - Ac-QSQQTF(Orn)NLWRLLHQ-NH₂

Current Data Parameters
NAME     p53_A2_acyclic
EXPNO                11
PROCNO                1

F2 - Acquisition Parameters
Date              20121206
Time              18.14
INSTRUM           av500
PROBHD         5 mm DCH 13C-1
PULPROG          zgpg30
TD                65336
SOLVENT           DMSO
NS                 1024
DS                  2
SWH                   3250.000 Hz
FIDRES       0.476837 Hz
AQ            1.0485760 sec
RG              202.91
DW             16.000 us
DE                18.00 us
TR              298.0 K
D1           2.00000000 sec
D11          0.03000000 sec
D0                   1

======== CHANNEL f1 ========
SFO1       125.7722511 MHz
NUC1                 13C
P1        9.63 usec
PLW1       23.00000000 W

======== CHANNEL f2 ========
SFO2       500.1330008 MHz
NUC2                 1H
CPDPRG[2        waltz16
PCPD2          80.00 usec
PLW2       13.50000000 W
PLW12        0.21094000 W
PLW13        0.13500001 W

F2 - Processing parameters
SI                131072
SF        125.7577892 MHz
WDWM             EM
SSB                 0
LB               1.00 Hz

Acyclic - Ac-QSQQTF(Orn)NLWRLLHQ-NH₂
Acyclic - Ac-QSQQT(Dap)NLWRLLYQN-NH₂

Current Data Parameters
NAME p53_A3_acyclic
EXPNO 11
PROCNO 1

F2 - Acquisition Parameters
Date 20121206
Time 19.12
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 2
SWH 31250.000 Hz
FIDRES 0.476837 Hz
AQ 1.0485760 sec
RG 202.91
DW 16.000 usec
DE 18.00 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

-------- CHANNEL f1 --------
SFO1 125.7722511 MHz
NUC1 13C
P1 9.63 usec
PLW1 23.00000000 W

-------- CHANNEL f2 --------
SFO2 500.1330008 MHz
NUC2 1H
CPDPRG[2] waltz6
PCEP2 80.00 usec
PLW2 13.50000000 W
PLW12 0.21094000 W
PLW13 0.13500001 W

F2 - Processing parameters
SI 131072
SF 125.757892 MHz
WDW EM
SSB 0
LB 1.00 Hz
n
Acyclic - Ac-QSQQTFO(Orn)NLWRLLYQN-NH₂
Acyclic - Ac-QSQQTF(Orn)NLWRLLYQN-NH₂

Current Data Parameters
NAME     p53_A4_acyclic
EXPNO                11
PROCNO                1

F2 - Acquisition Parameters
Date_        20121206
Time              20.09
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                 1024
DS                2
SWH            31250.000 Hz
FIDRES        0.476837 Hz
AQ               1.0485760 sec
RG               202.91
DW               16.000 usec
DE               18.000 usec
TE                298.0 K
D1            2.00000000 sec
D11          0.03000000 sec
TDO                   1

 CHANNEL f1
SFO1        125.7722511 MHz
NUC1                13C
P1                9.63 usec
PLW1            23.00000000 W

 CHANNEL f2
SFO2        500.1330008 MHz
NUC2                1H
CPDPRG[2       waltz16
PCPD2            80.00 usec
PLW2            13.50000000 W
PLW12          0.21094000 W
PLW13        0.13500001 W

F2 - Processing parameters
SI               131072
SP              125.7577892 MHz
WDM                  EM
SSB                  0
LB                1.00 Hz
ch n
Acyclic - Ac-QSQETF(Orn)NLWRLLYQN-NH₂

Current Data Parameters
NAME         p53_B6_acy
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_    20130509
Time       11.27
INSTRUM     av500
PROBHD    5 mm DCH 13C-1
PULPROG        zg30
TD         65536
SOLVENT     DMSO
NS            8
DS               0
SWH    10000.000 Hz
FIDRES     0.152588 Hz
AQ        3.2767999 sec
RG           22.82
DW          50.000 usec
DE            10.00 usec
TE         298.0 K
D1         2.0000000 sec
TD0                   1

------- CHANNEL f1 -------
SFO1    500.1330008 MHz
NUC1            1H
P1          10.00 usec
PLW1    13.5000000 W

F2 - Processing parameters
SI        65536
SF   500.1300146 MHz
WDM           EM
SSB             0
LB            0.30 Hz
GB             0
PC            1.00
Acyclic - Ac-QSQETF(Orn)NLWRLLYQN-NH$_2$

Current Data Parameters
NAME         p53_B6_acy
EXPMO        2
PROCNO       1

F2 - Acquisition Parameters
Date_         20130509
Time           11.30
INSTRUM       av500
PROBHD   5 mm DCH 13C-1
PULPROG      zgpg30
TD            65536
SOLVENT       DMSO
NS            87
DS            2
SWH          31250.000 Hz
FIDRES       0.476837 Hz
AQ             1.0485760 sec
RG            202.91
DW           16.000 usec
DE            16.000 usec
TE            298.0 K
D1            2.00000000 sec
D11        0.03000000 sec
TD0              1

== CHANNEL f1 ==
SFO1        125.7722511 MHz
NUC1              13C
P1           9.63 usec
PLW1       23.00000000 W

== CHANNEL f2 ==
SFO2      500.1330008 MHz
NUC2              1H
CPDPRG[2    waltz16
PCPD2         80.00 usec
PLW2      13.50000000 W
PLW12    0.21094000 W
PLW13   0.13500001 W

F2 - Processing parameters
ST           131072
SF           125.7577892 MHz
WDW            EM
SSB             0
LB            1.00 Hz
CH            n
Cyclic - Ac-QSQTF(Dap)NLWRLLHQN-NH₂

Current Data Parameters
NAME     p53_A1_cycle
EXPNO     3
PROCNO     1

F2 - Acquisition Parameters
Date       20130122
Time       18.59
INSTRUM    av500
PROBHD     5 mm DCH 13C-1
PULPROG    zg
TD         65536
SOLVENT    DMSO
NS         8
DS         0
SWH       10000.000 Hz
FIDRES     0.152588 Hz
AQ         3.2767999 sec
RG         11
DW         50.000 usec
DE         10.00 usec
TE         298.0 K
D1        2.00000000 sec
TDO        1

----- CHANNEL f1 -----  
SP01      500.1330008 MHz
NUC1      1H
PI         10.00 usec
PLW1      13.50000000 W

F2 - Processing parameters
SI         65536
SF         500.1300146 MHz
WDW        EM
SSB        0
LB         0.30 Hz
GB         0
PC         1.40
Cyclic - Ac-QSQQTF(Dap)NLWRLHHQN-NH₂

TOCSY
Cyclic - Ac-QSQQTF(Orn)NWRLHQNNH₂

Current Data Parameters
NAME      p53_A2b_cycle
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20121211
Time              17.15
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                   64
DS                    0
SWH           10000.000 Hz
FIDRES             0,152588 Hz
AQ                   3,276999 sec
RG                   11
DW                50.000 usec
TE                298.0 K
D1           2.00000000 sec
D0                   1

======== CHANNEL f1 ========
SFO1     500.1330008 MHz
NUC1                   1H
P1                    10.00 usec
PLW1           13.50000000 W

F2 - Processing parameters
SI                  65536
SF           500.1300146 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                   0
PC                   1.40
### Current Data Parameters

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#### F2 - Acquisition Parameters

- **Date**: 20121211
- **Time**: 17:15
- **INSTRUM**: av500
- **PROBHD**: 5 mm DCH 13C-1
- **PULPROG**: cosygpmfph
- **TD**: 4096
- **SOLVENT**: DMSO
- **NS**: 2
- **DS**: 8
- **SWH**: 5498.534 Hz
- **AQ**: 0.3724629 sec
- **TE**: 298.0 K
- **RG**: 202.91
- **DW**: 90.933 usec
- **DE**: 10.00 usec
- **D0**: 0.00007817 sec
- **D1**: 2.00000000 sec
- **D13**: 0.00000400 sec
- **D16**: 0.00020000 sec
- **IN0**: 0.00018180 sec

#### CHANNEL f1

- **SFO1**: 500.1327507 MHz
- **NUC1**: 1H
- **P1**: 10.00 usec
- **P2**: 20.00 usec
- **PLW1**: 13.50000000 W

#### GRADIENT CHANNEL

- **GPZ1**: 10.00 %
- **GPZ2**: 20.00 %
- **P16**: 1000.00 usec

#### F1 - Acquisition Parameters

- **TD**: 256
- **SFO1**: 500.1328 MHz
- **FTIFRES**: 21.486525 Hz
- **SN**: 10.998 ppm
- **F2 - Processing parameters**

#### CHANNEL f2

- **SI**: 2048
- **SF**: 500.1300135 MHz
- **WDW**: SIN
- **LB**: 0 Hz
- **GB**: 0
- **FC**: 1.00

#### F1 - Processing parameters

- **SI**: 2048
- **MC2**: States-TPPI
- **SF**: 500.1300320 MHz
- **WDW**: SIN
- **GB**: 0
- **LB**: 0 Hz
- **GB**: 0
Cyclic - Ac-QSQQTF(Orn)NLWRLLHQN-NH₂

HMBC
References


Chapter 4 - Diverse macrocyclic peptidomimetics through Friedel-Crafts alkylations of tryptophan and tyrosine

adapted in part from

Template-induced macrocycle diversity through large-ring forming alkylations of tryptophan

Kenneth V. Lawson, Tristan E. Rose, Patrick G. Harran

_Tetrahedron_ 2013, 69 (36), 7683-7691

4.1. Introduction

As opportunities in biological research and drug discovery expand, there is considerable need for synthetic methods that form new types of complex small molecules. Conventional screening libraries often fail to produce viable lead structures when challenged with demanding targets. These include receptors with relatively large, dynamic, or solvent exposed ligand binding sites and protein-protein interaction surfaces. Recent drug discovery efforts aimed at such targets have benefited from biophysical studies highlighting ‘hot spots’ within these larger binding motifs. Focused libraries that incorporate structures able to interact selectively and avidly with such sites would be valuable. Molecules that recapitulate the three-dimensional display of functional groups found in native binding partners while possessing favorable pharmacological properties would be ideal.

Peptides are intrinsically relevant to this goal. They are a logical starting point to identify ligands for protein surfaces. However, peptides frequently exhibit poor bioavailability and limited stability in vivo. Numerous strategies have been developed to mitigate these problems, including the incorporation of D-configured and non-proteinogenic amino acids, pseudo-peptide bonds and conformational constraints. Each of these features is seen in peptide-derived macrocyclic natural products, which often possess markedly different properties relative
to their acyclic precursors. With macrocycles as a central theme, we have sought to expand upon existing methods for large ring formation.

In a previous report, we outlined elements of a program aimed at systematically generating complex peptidomimetics. These experiments used designed templates (Fig. 1B) to form composite structures with peptides. Our current templates capitalize on reactivity of the cinnamyl cation, and transiently formed palladium complexes thereof, to efficiently promote large ring-forming substitution reactions involving aromatic rings and heteroatom nucleophiles. While numerous methods exist to prepare peptidic macrocycles, most require tailored reacting partners. Our template chemistry exploits reactivity inherent to a subset of natural amino acid side chains.

![Figure 1.](image)

For example, we used the allylic carbonate in template 1 (Fig. 1B) to form macrocyclic ethers by engaging the phenol of tyrosine in palladium catalyzed substitution reactions. In the context of peptides harboring other aromatic residues, we observed that acid treatment caused these ethers to rearrange, wherein the cinnamyl unit migrated to adjacent tryptophan residues forming stable carbon-carbon bonded products. This was an exciting discovery. To
probe this reactivity in greater detail, and in systems not complicated by competing rearrangements of the diene-yne appendage in 1, we synthesized template 2.\textsuperscript{17} Using simple, straightforward chemistry, composites of 2 participate in remarkable reactions that alter the structure and properties of linear peptide motifs (vide infra).

Towards the goal of rapidly accessing diverse, natural product-like structures, we demonstrate use of 2 in a divergent process to prepare mixtures of macrocyclic products displaying a peptidic binding epitope.\textsuperscript{18} In two synthetic steps, template 2 transforms a peptide harboring multiple nucleophilic side-chains (X, Y, Z Fig. 1A) into constitutionally isomeric macrocycles through competing reaction pathways. The resulting products differ in core ring size and conformation, each dictating a unique display of side chains.\textsuperscript{19} The structural diversity derived from this process arises from the nature of the starting peptide and the reactivity of the template. Processes of this kind have potential to create composite macrocycles with inherent complementarity to protein surfaces.

4.2. Results and Discussion

4.2.1. Preparation of Cyclic and Acyclic Acidolysis Precursors

Template 2 was prepared from commercial 3-(3-bromophenyl)propionic acid in 6 steps and 51% overall yield.\textsuperscript{17} This material acylated the N-terminus of synthetic Trp-Trp-Tyr-NH₂.

![Figure 2](image-url)  
Figure 2. Reaction conditions: a) H-Trp-Trp-Tyr • TFA (1 eq.), template 2 (1 eq.), iPr₂NEt (4 eq.), DMF (0.1M). b) Pd(PPh₃)₄ (5 mol %), DMF (5 mM, degassed).
without incident, providing composite product 4 in good yield (Fig. 2). Analogous to previous work, exposure of 4 to 5 mol% Pd(PPh₃)₄ catalyzed efficient macrocyclization to give tyrosine O-linked cinnamyl ether 5. Treatment of 5 with 15 equiv. methanesulfonic acid in anhydrous nitromethane at room temperature provided a mixture of three isolable products (Fig. 3A and 5B). These proved to be analogous to the four macrocyclic core structures observed previously from reactions of template 1 with Trp-Trp-Tyr-NH₂. Close inspection of HPLC-MS ion chromatograms indicated the presence of five additional minor isomers (vide infra). Combined,
those eight products accounted for >95% of the total peak area (HPLC-UV at 254 nm). This confirmed that template 2 was an excellent model for further study.

### 4.2.2. Purification and Characterization

Acidolysis products 6-12 were readily separated by reverse phase preparative HPLC (Fig. 5). From macrocyclic ether 5, we initially isolated only 6, 7, and 11 in sufficient quantities for NMR analyses. Upon refining the reaction conditions (see Sect. 2.3 and Table 1), initially trace components 8, 9, 10 and 12 were also isolated. Compounds 6-9, 11 and 12 were each obtained in >95% purity. Only fraction 10 was isolated as a mixture of closely related regioisomers 10a and 10b, which were characterized together.

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Table 1. Effect of substrate and acid promoter on product distribution in rearrangement reactions of cyclic ether 5 and direct large-ring closure reactions of acyclic mixed carbonate 4. Reaction conditions: substrate (5 mM) in indicated solvent, 2 hours unless otherwise noted.⁺16 hour reaction time. Decomposition to non-isomeric products observed. 30 minute reaction time.

The planar structures of compounds 6-12 (Fig. 3A) were determined by complete assignment of their proton and carbon connectivities on the basis of homo- and heteronuclear correlations obtained from 2D and selective 1D NMR experiments (see supplementary information). Structural elucidation involved 1) sequential assignment of the peptide backbone, 2) correlation of backbone atoms to their corresponding side chain aromatic ring, and 3) determination of the connectivity of the cinnamyl moiety to an aromatic side chain.
In this model peptide, complete resonance assignment of the peptide was required to differentiate between the two tryptophan residues. Sequential assignment of the amide backbone was made by H\textsuperscript{N}-C(O) and H\textsuperscript{\alpha}-C(O) correlations observed by HMBC\textsuperscript{20} or by H\textsuperscript{\alpha} - H\textsuperscript{N+1} NOE where ambiguities arose from weak correlations or overlapping carbonyl resonances\textsuperscript{21}. Assignment of residue specific H\textsuperscript{N}–H\textsuperscript{\alpha}–H\textsuperscript{\beta} spin systems from TOCSY spectra was then possible\textsuperscript{22}, and connectivity of H\textsuperscript{\beta} to the aromatic portion of the side chain was established from reciprocal HMBC correlations.

The ansa bridge motif arising from electrophilic aromatic substitution causes a characteristic loss of one proton relative to the parent \textsuperscript{1}H spin system of the aromatic amino acid side chains which was apparent by TOCSY. The precise position of substitution was deduced from careful analysis of 2,3,4,\textsubscript{\text{CH}}\textsubscript{4} correlations observed in HMBC experiments (e.g. Fig. 4A). In general, heteronuclear correlations from the cinnamyl methylene to aromatic resonances of the substituted ring, and the reciprocal thereof, allowed unambiguous structural assignment. In cases where HMBC correlations were either unclear or not observed, the connectivity of the cinnamyl unit was inferred from NOE correlations between the two proximal spin systems observed by TOCSY (Fig. 4B).

The isomeric products obtained from acidolysis of macrocyclic ether 5 comprised three of the four outcomes anticipated from previous work. We obtained compound 6, arising from rearrangement of the O-linked macrocyclic ether to the phenolic \textit{ortho} position, as the
predominant product. The next most abundant outcomes derived from alkylation of tryptophan at indole C5. Substitution of Trp1 (11) and Trp2 (7) at indole C5 comprised 17% and 7% of the product mixture, respectively. The absence of branched isomers observed previously from alkylation at indole C2 likely reflects a subtle difference between the conformational preferences of templates 1 and 2.\textsuperscript{12}

4.2.3. Unprecedented large ring-forming Friedel-Crafts alkylations

We next investigated what role the cinnamyl ether in 5 played in the formation of carbon-carbon bonded isomers. Acid promoted rearrangement of cyclic ether 5 to isomers 6-12 is, for this substrate, a set of competing ring contractions. It was possible that starting from a pre-organized cyclic template like 5 was necessary to observe such outcomes. Large ring-forming Friedel-Crafts alkylations are virtually absent from the literature.\textsuperscript{23,24} To test this idea, we

![Figure 5. HPLC traces of large-ring forming reactions: A) 4 with MeSO\textsubscript{3}H (conditions: Table 1, entry 11), B) 5 with MeSO\textsubscript{3}H (conditions: Table 1, entry 3), C) 4 with Sc(OTf)\textsubscript{3} (conditions: Table 1, entry 17). Conditions: RP-C18, MeCN/H\textsubscript{2}O, 0.1% TFA (see supplementary information).]
subjected acyclic mixed carbonate 4 to the same reaction conditions that caused isomerizations of 5. Remarkably, the reaction afforded a mixture of products that co-chromatographed with those derived from 5, varying only in their relative abundance (Fig. 5A). From this more evenly distributed mixture, minor products 8, 9, 10a/b, and 12 were readily isolated and characterized. Structure elucidation by NMR methods led to the assignment of five novel macrocycles arising from alkylation of tryptophan at indole N1, C3, C6 and C7. Products of C5 alkylation of Trp1 (11) and Trp2 (7) were obtained as the major products, consistent with the relatively high reactivity of this position observed in rearrangement of 5, and in related bimolecular reactions. Tyrosine alkylation product 6, the major product from 5, now comprised only 12% of the product mixture. Lesser products arising from alkylation at C7 of Trp1 (8) and Trp2 (10b), C6 of Trp2 (10a), and N1 of Trp2 (9) were also obtained. Product 12, comprising the final 12% of the mixture, was determined to be a macrocyclic pyrroloindoline arising from indole C3 alkylation of Trp2 and trapping of the resultant indolium ion by the proximal amide nitrogen (Fig. 6). 

Figure 6. Plausible mechanism for the formation of 12 involving initial alkylation of C3 of tryptophan followed by internal capture of the incipient iminium ion.
Template 2 illustrates the utility of the cinnamyl cation to access diverse macrocycles by direct engagement of aromatic amino acid side chains. From a single reaction, we isolated eight unique macrocyclic cores comprising 15, 16, 17, 18, 19, 20 and 21-membered rings (see Fig. 3B). Isomeric structures 6-12 exhibit varying polarity as evidenced by their elution order in HPLC, and distinct conformations as evidenced by large chemical shift differences observed between conserved motifs (see supplementary information). These results bode well for accessing molecular diversity by template-induced macrocyclization of oligomers containing other π-basic aromatic residues.

4.2.4. Affects of acid catalyst, solvent and pre-cyclization

Counterion and solvent effects are known to perturb the reaction rate and product distributions of Friedel-Crafts alkylation and rearrangement reactions. Accordingly, we examined alternative conditions to promote large ring-forming reactions of mixed carbonate 4 and cyclic cinnamyl ether 5.

The nature of the acidic counterion was examined using a range of Brønsted and Lewis acids in both polar and non-polar solvents, the results of which are summarized in Table 1. Strong organic acids, including methanesulfonic acid and trifluoroacetic acid (TFA) were superior in promoting clean conversion to products 6-12 by ring contractions of 5 (entries 1-10) and direct large-ring formations from 4 (entries 11-17). Weaker acids, such as aqueous acetic acid (not shown) and formic acid, returned only starting material. Using methanesulfonic acid, but changing the solvent from MeNO₂ to CH₂Cl₂, led to intractable decomposition of 4 as observed by HPLC-MS. Consistent with previous studies by Olah and others, nitromethane likely stabilizes ion-paired intermediates along the reaction pathway. In CH₂Cl₂, stoichiometric amounts of TFA reacted only slowly, whereas higher concentrations of TFA rapidly converted both 4 and 5 to well-distributed mixtures comparable to those seen in reactions of 4 with methanesulfonic acid in nitromethane. Superacids showed mixed results. Stoichiometric triflic
acid caused decomposition of 4 to non-isomeric products, even in MeNO₂ solvent. On the other hand, two equivalents of bistriflimide caused rapid reaction of 4, and doubled the relative abundance of pyrroloindoline 12. Lewis acids also efficiently promoted these reactions. Relative to Brønsted acids, metal triflates such as Sc(OTf)₃ enhanced the conversion of acyclic precursor 4 to Trp1 indole C5 alkylation product 11 (see Fig. 5C and Fig. S2). The product distribution from reactions of 4 is tunable with choice of acid promoter and solvent.

Under certain reaction conditions, significantly different product distributions were observed when starting from cyclic ether 5 relative to 4. Reaction of 5 with dilute TFA in CH₂Cl₂ at room temperature (entry 9, Table 1), while sluggish, selectively formed tyrosine alkylation product 6, exhibiting a prominent reversal of selectivity relative to that of 4 (entry 13).²⁹ This selectivity was lost at high concentrations of TFA. Similar trends were observed with methanesulfonic acid. Using only 5 equivalents of methanesulfonic acid in nitromethane at -20 °C, 6 was formed in a 20:1 ratio relative to all other isomers. These dramatic differences appear to reflect the influence of conformational pre-organization in 5 on the resulting reaction pathways.

One way to rationalize these results is in terms of a qualitative least motion argument.³⁰ All else considered equal, the conformationally pre-organized template in 5 rearranges more selectively, with the cinnamyl unit migrating to electron rich positions adjacent to the original attachment site.³¹ In contrast, ionization of acyclic carbonate 4 occurs in the context of a complex ensemble of peptide conformations, providing ample opportunity for the solvated cinnamyl ion pair to approach multiple internal reactive sites, wherein less selectivity is manifest and a more diverse mixture results.³² The attenuated selectivity observed from 5 in higher concentrations of acid may reflect accelerated ion pair return or altered solvation thereby permitting relaxation away from the cyclic conformation and leading to products by similar pathways as 4.³³
While the initial acidolysis conditions using methanesulfonic acid gave a desirable, evenly-distributed product mixture, there are reasons to perturb this outcome. To retain tractability in biological screening exercises, a mixture should optimally contain an equal concentration of products so as to minimize the incidence of false negatives. Conversely, in the event that a single component becomes desirable as a result of either structure or function, it may be possible to enhance its abundance by subtle changes in reaction conditions, rather than undertaking a target-oriented synthesis. We have shown this is possible by biasing the template-induced macrocyclization towards the 15-membered macrocyclic pyrroloindoline 12, 16-membered ring 11, or 21-membered ring 6. Cyclic cinnamyl ether 5 was essential in this regard. While we were successful in biasing the product distribution in favor of initially abundant compounds 6, 11 or 12, it is not yet clear this can be accomplished for minor constituents to the same degree. Further experiments on a variety of substrates are ongoing.

4.2.5. Scope of selective tyrosine ortho-alkylation

With conditions established which strongly favor intraresidue O-C\textsubscript{ortho} migration, we prepared a set of macrocyclic ethers derived from 2 and set of peptides with varied functional groups. For example, treatment of macroether 13 with 15 equivalents of trifluoroacetic acid in CH\textsubscript{2}Cl\textsubscript{2} provided tyrosine ortho-alkylated macrocycle 14 in 69% isolated yield. Polar functionality including alcohols, thioethers, and guanidines were well-tolerated in peptides possessing three to five amino acids (Table 2). These data bode well for the application of this method in more complex setting or library construction efforts.
Under these conditions intraresidue cinnamyl migration is strongly favored and in the case of Trp-Trp-Tyr the product distribution is greatly altered relative to acidolysis of the corresponding acyclic carbonate. In other settings, where 1,3 migration is not a possible migratory pathway, the relative distribution from cationic rearrangements in cyclic vs acyclic precursors is unclear. To investigate one such scenario, macrolactone 19 was prepared from Pd-catalyzed cyclization of Gly-Val-Trp-OH with template 2. Macrolactone 19 possesses numerous indole nucleophilic sites at varied distance from the ionizable C-O bond. However, acidolysis of 19 has no discernible effect on product distribution when compared to acidolysis of acyclic carbonate 18 under identical conditions. This data suggests pre-organization in a macrocyclic conformation only effects product distribution where directly adjacent sites are apt to capture the forming electrophile (e.g. tyrosine O-C<sub>ortho</sub> migration).

Table 2. Macrocycles derived from TFA promoted O-C<sub>ortho</sub> migrations. The indicated unprotected peptides precursors are listed above product. Isolated yield from preparative HPLC indicated in parentheses.

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<td><img src="image2.png" alt="Structure 16" /> (84 %)</td>
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Figure 7. TFA promoted O-C<sub>ortho</sub> migration within LMSYW derived macroether.
4.2.6. Deuterium labeling - Mass spectrometry assay

The process of isolation and characterization of individual products derived from divergent acidolyses becomes challenging with increasingly sophisticated templates. Accordingly, we sought to develop sensitive analytical means to assess product distribution and the efficiency of large ring formations. In principle, perdeuteration of selected aromatic amino acid side-chains would provide a characteristic molecular mass shift upon electrophilic aromatic substitution by loss of $^2$H$^+$ upon re-aromatization (Fig. 9A). The high sensitivity of HPLC-MS would allow analytical separation of small-scale reactions. Successful aromatic substitution of the $^2$H labeled amino acid would result in a molecular mass of [M-1].

To examine the viability of this approach, the tripeptide Trp-Trp-Tyr was again employed as a model substrate to allow comparison with the structures determined by NMR (vide supra). Isotopologues Trp($d_5$)-Trp-Tyr

Figure 8. Comparison to acidolysis of acylic carbonate 18 and macrolactone 19. The major product of acidolysis is 20 from both 18 and 19. Inset: Nucleophilic indolyl positions vary in distance from ionizing bond. Conditions: a) Pd(PPh$_3$)$_4$ (5 mol%), DMF (5 mM), 1h; b) 15 eq. TFA, CH$_2$Cl$_2$ (5 mM), 48h. Chromatograms A and B recorded on different instrument.
and Trp-Trp(d$_5$)-Tyr were synthesized using solution-phase chemistry to incorporate Fmoc-Trp(d$_5$)-OH in high isotopic purity.$^{35}$ Subsequent acylation with template 2 afforded acyclic mixed carbonates 21 and 22 (Fig. 9B). After purification, MS analysis showed > 95 % average $^2$H incorporation at positions indicated in Figure 7B.

Acidolyses of 21 and 22 under the standard conditions with MeSO$_3$H proceeded to product mixtures which were, by HPLC-UV, identical to that observed with unlabeled substrate 4. To avoid potential complications arising from scrambling of the labeling pattern, reactions were analyzed at partial and full conversion, and also under Lewis acidic conditions. The rate of product formation appeared to outcompete scrambling.$^{36}$ As anticipated, alkylation of Trp1(d$_5$) leading to products 8 and 11 was revealed as [M-1] by HPLC-MS analysis of the reaction of 21. This characteristic mass signature was also observed for products 7, 10a and 10b arising from alkylation of Trp2(d$_5$) in the reaction of 22. While complete retention of deuterium was observed as expected for product 12, an unexpected loss of two deuterium was found for Trp2 N-alkylated product 9 from the acidolysis of 22. Whether this loss is mechanism based or due to increased exchange rate in the product is not yet known. N-alkylation of indole may accelerate deuterium/hydrogen exchange by enhancing the basic character of the resulting aromatic system.$^{37}$ Although this non-diagnostic outcome limits the accuracy of deuterium labeling in probing macrocycle connectivity, this result remains characteristic of substitution at Trp2.
These data demonstrate the utility of deuterium labeled tryptophan in predicting large ring structures arising from aromatic substitution using templates such as 2 without the need for purification and characterization. This analytical approach may be particularly useful when investigating peptide sequences harboring multiple aromatic amino acids, where spectral overlap can complicate structural assignment. Future development of electrophilic templates incorporating novel or multiple reactive centers may also benefit from similar mass spectrometry-based pre-screens in the search for unique structures.

4.2.7. Stereochemical assignment and NMR solution structure of pyrroloindoline 12

Macrocyclic pyrroloindoline 12 bears structural resemblance to a large family of natural products possessing these motifs.\textsuperscript{38} To our knowledge 12 is the first example possessing an all carbon quaternary center at the core 5,5 ring juncture (Fig. 10A). A number of both naturally and synthetically derived pyrroloindolines have been studied spectroscopically and computationally...
in an effort to characterize the stability and conformational equilibria of this ring system.\textsuperscript{39} Intrigued by this heterocyclic motif in the context of macrocycle 12, we further examined its structure and three-dimensional conformation using NMR.

![Diagram of 12](image)

**Figure 10.** a) Numbering scheme used in the annotation of spectra for 12. b) Selected slices from 2D-NOESY of compound 12 highlighting intraresidue (purple boxes) and key long-range (red) correlations. Black lines denote the diagonal.

The conformation of 12 in solution appeared to be relatively homogenous. The core pyrroloindoline was clearly observed as a methine, weakly split by the adjacent H31, with a carbon chemical shift of 81.1 ppm characteristic of an aminal. Heteronuclear correlations codified connectivity of the cinnamyl moiety at bridging quaternary center C29. As anticipated,
the 5,5 ring juncture was formed with the thermodynamically preferred cis relationship, which was readily established from NOE correlation of methine H30 to the geminal pair H1/1’. Spectral overlap in the aliphatic region, and of H27, H31 and H41 frustrated the use of correlations to H1/1’ in assigning the ansa bridge stereochemistry relative to the 27S stereocenter, preserved from L-tryptophan. Stereospecific assignment of the geminal pair H28/28’ was tenuous, with no significant difference observed by NOE to H30. Analysis of $^3J_{27-28}$ and $^3J_{27-28’}$ suggested an endo orientation of H28’, which appeared contradictory to their relative chemical shift in comparison to related systems.\(^\text{39}\) We viewed a distinct possibility that the macrocyclic motif and/or tyrosine residue could distort this pyrrolidine ring, leading to atypical J-values.\(^\text{40}\) A single unambiguous long-range NOE from H2 to H27 led to the tentative assignment of the C38-endo 27S,29R,30R stereochemistry, as shown. Careful analysis of selective 1D-NOESY, 2D-NOESY and 2D-ROESY spectra obtained in DMSO or DMSO/D$_2$O supported this configuration, revealing seven prominent long-range correlations. Notably, strong NOEs within the tetrad H14, H30, H9 and H2

**Figure 11.** a) $^1$H NMR spectrum of compound 12 (DMSO-d$_6$, 600 MHz) b) Overlay of the five lowest energy conformers calculated using NOE distance constrained molecular mechanics simulation and c) the lowest energy conformer obtained from this analysis. Spectral annotations correspond to numbering scheme in Figure 10A.
indicated arrangement of these positions along the interior of the macrocycle. An initial model generated from a conformational search incorporating these constraints facilitated assignment of 29 additional long-range NOEs, and calculation of a refined structural ensemble (Fig. 11B) showing agreement with experimental NOEs (see Table S4).

The solution structure revealed several notable features induced by template 2. Planarity of the cinnamyl unit was retained, as evidenced by strong NOE of H3 to H5, and H2 to H9, thereby limiting the overall conformational flexibility of the 15-membered ring. The Trp1 side chain appeared to populate a single rotamer resulting in a close proximity of the indole ring to the benzene ring of the pyrroloindoline, which was supported by NOE observed between H20 and H33. While side chain torsions were indirectly restrained by long-range NOEs, the calculated rotamer preferences of Trp1 (g^2t^3) and Tyr3 (t^2g^3) agreed only loosely with observed coupling constants (±30°), suggesting potential motional averaging at these side chains.41

The bridged pyrroloindoline motif formed from cyclization of Trp2 onto the backbone effectively acts as a proline mimic. The backbone amide at this position retains the trans conformation, and the highly puckered endo pyrroloindoline induces a turn conformation, analogously to proline, yielding a potential hydrogen bond between the Trp1-C(O) and Tyr3 carboxamide. The anomalous J-values associated with H28/28' were rectified on basis of long-range NOEs from H28 to H43 and H44 indicating a syn relationship of H28 to the C-terminal tyrosine residue, though details of the pyrrolidine ring conformer were not revealed from these force field calculations.41 These data suggest that compound 12 occupies a relatively ordered conformation in solution that is enforced by both the macrocyclic and pyrroloindoline motifs.

4.3. Conclusion

In this pilot study, we have demonstrated a template-based approach to form composite macrocyclic peptidomimetics by unique large ring-forming Friedel-Crafts alkylations of tryptophan and tyrosine. A single reaction efficiently accessed eight macrocyclic structures. The
product distribution showed a strong dependence on acid promoter and substrate geometry. Rearrangement within a conformationally pre-organized tyrosine O-linked cinnamyl macrocyclic ether favored alkylation ortho to the phenol. By reducing the concentration of acid, this product was formed in 20:1 ratio relative to all other isomers. The ability to enhance the formation of specific isomers by tuning the reaction conditions allows rapid access to individual constituents for further study. It should be emphasized that, any one of products 6-12 could likely be selectively synthesized de novo utilizing established methodologies.42

The peptide domain was found to be conformationally restricted as a result of template-induced macrocycle formation. This was demonstrated in the NMR solution structure of novel endo-pyrroloindoline 12 possessing an all-carbon quaternary center at ansa bridgehead C29. These results suggest that the divergent reactivity of templates such as 2 is an effective means of accessing molecular diversity. Isomeric products inherently possess the same primary peptide sequence, but likely vary substantially in their spatial display of side chains. Products derived from 2, formed from carbon-carbon sigma bonding, also display improved physicochemical properties. These macrocycles have polar surface area comparable to the linear peptide, but much improved solubility in organic solvents and minimal propensity to aggregate.

We believe divergent strategies such as those described herein will prove valuable in a broader context of preparing structurally complex peptidomimetics. The particular utility of template 2 is demonstrated by the ability to transform a single peptide, Trp-Trp-Tyr, in two steps into eight isomeric macrocycles that would be otherwise time consuming to prepare. Rapid, efficient synthesis of diverse, composite macrocyclic peptidomimetics has the potential to identify small molecules effective against challenging targets where traditional libraries are often unsuccessful. We anticipate methods to generate shape diversity will prove valuable in efforts to recapitulate key motifs within larger folded polypeptides and to target surfaces involved in protein-protein interactions.
# Chapter 4 - Supporting Information

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General
Reactions were performed under ambient atmosphere, unless otherwise noted. Dichloromethane was deoxygenated and dried by passing through an activated alumina solvent drying system. Anhydrous N,N-dimethylformamide (EMD DriSolv®) was used without further purification. Nitromethane was dried over 4Å molecular sieves for at least 24 hr before use. Methanesulfonic acid (≥99.5%, Sigma Aldrich) was used without further purification. Column chromatography was performed on silica gel 60 (SiliCycle, 240-400 mesh). Thin layer chromatography (TLC) utilized pre-coated plates (Sorbent Technologies, silica gel 60 PF254, 0.25 mm) visualized with UV 245 nm, iodine, or basic potassium permanganate stain.

Purification of acidolysis products employed an Agilent 1100/1200 HPLC system equipped with G1361A preparative pumps, a G1314A autosampler, a G1314A VWD, and a G1364B automated fraction collector. Analytical HPLC was performed using the same system, but with a G1312A binary pump. Mass spectra were recorded using an Agilent 6130 LC/MS system equipped with an ESI source.

NMR methods:
NMR spectra were recorded on Bruker Avance (300, 500 or 600 MHz), DRX (500 MHz) and ARX (400 MHz) spectrometers. Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration), and are referenced to a residual protonated solvent peak.$^1$ $^{13}$C resonances are reported in terms of chemical shift (δ ppm) as referenced to the residual DMSO peak. For mass-limited samples, solvent magnetic susceptibility matched Shigemi tubes were used with a sample volume of ~300 µL. Optimization of on-axis shims was accomplished using the TopShim automated tool within Bruker Topspin™ 2.1. Optimization of off-axis shims was performed manually.$^2$ $^1$H 90º transmitter pulse lengths were calibrated by back calculation from the 360º or 180º null.$^3$ The pulse width or power level for soft pulses and shaped pulses were calculated using the Shape Tool within TopSpin™ 2.1. $^1$H-$^1$H COSY spectra were recorded using a phase sensitive, gradient enhanced double-quantum-filtered experiment, using States-TPPI acquisition.$^4$ TOCSY spectra were recorded using a sensitivity improved, phase sensitive experiment using a 60ms DIPSI-2 pulse train for homonuclear Hartman-Hahn transfer.$^5$ NOESY spectra were recorded using a phase sensitive experiment with selection gradients during the mixing time.$^6$ ROESY spectra were recorded using a phase sensitive experiment with selection gradients and water suppression with excitation sculpting.$^7$

HMBC spectra for non-protonated carbons. $^1$H-$^{13}$C HSQC spectra were recorded using a sensitivity improved phase sensitive experiment using an adiabatic shape pulse for $^{13}$C inversion, and $^{13}$C decoupling during acquisition.\(^8\) Experimental parameters were optimized for $^1J_{CH} = 145$Hz. $^1$H-$^{13}$C HMBC spectra were recorded using a gradient selected experiment with a two-fold J-filter optimized for $^1J_{CH} = 125$-$165$Hz. Experimental parameters were optimized for long range $^1J_{CH} = 8$Hz.

**Figure S1.** a) Products 6-12 derived from acidolysis of Trp-Trp-Tyr. b) Core macrocyclic substructures of 6-12.

Acylation of Trp-Trp-Tyr with template 2

An oven-dried, screw-capped scintillation vial was charged with Trp-Trp-Tyr•TFA (343 mg, 0.515 mmol) and N-hydroxysuccinimidyl ester 2 (208 mg, 0.515 mmol) followed by addition of anhydrous DMF (10 ml) and iPr₂NET (359 μl, 2.06 mmol). The reaction was allowed to stir at room temperature for 3 hours. The DMF was removed by rotary evaporation and the residue was dissolved in MeCN/CHCl₃ (1:3) and purified by column chromatography (SiO₂, gradient 0-10% MeOH/CHCl₃) to give 4 as a white solid (337 mg, 0.402 mmol, 78%).

$^1$H NMR (DMSO-d₆, 600 MHz): δ 10.79 (br. s, 1H), 10.7 (br. s, 1H), 9.13 (br. s, 1H), 8.07 (d, J = 6.8 Hz, 1H), 8.01 (d, J = 7.4 Hz, 1H), 7.82 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.26-7.31 (m, 2H), 7.11-7.25 (m, 4H), 6.99-7.08 (m, 5H), 6.90-6.99 (m, 5H), 6.62 (d, J = 8.1 Hz, 2H), 6.56 (d, J = 15.7 Hz, 1H), 6.28 (dt, J = 15.4, 7.4 Hz, 1H), 4.60-4.64 (m, 2H), 4.42-4.53 (m, 2H), 4.31-4.37 (m, 1H), 3.01-3.07 (m, 2H), 2.93 (dd, J = 12.1, 11.3 Hz, 1H), 2.79-2.86 (m, 2H), 2.71 (dd, J = 10.2, 10.2 Hz, 1H), 2.56-2.62 (m, 2H), 1.4 (s, 9H). $^{13}$C NMR (DMSO-d₆, 150 MHz): δ 173.0, 172.6, 172.1, 171.5, 170.4, 157.2, 153.3, 142.1, 136.5, 136.3, 133.9, 130.7, 129.1, 128.4, 127.8, 126.9, 124.7, 124.1, 123.8, 121.3, 119.0, 118.6, 118.3, 115.9, 111.7, 110.6, 82.0, 67.4, 67.0, 58.5, 54.5, 54.0, 52.7, 40.9, 40.6.

MS (ESI) Calculated for C₄₈H₅₂N₆O₈ [M+H]+: 841.4, found 841.1.
Palladium-catalyzed macrocyclization

A solution of acyclic carbonate 4 (109 mg, 0.130 mmol) in DMF (26 ml, 5mM) was sparged with Argon for 15 minutes. The septa was removed briefly to allow the addition of Pd(PPh₃)₄ (8 mg, 0.0065 mmol, 5 mol %). The mixture was stirred for 1 hour at which point analysis by HPLC/UV showed complete conversion of 4 to 5. Silica bound thiol (Si-Thiol, silicycle, 1.29 mmol/gram, ~25 mg) was added to the reaction mixture, mixed for 5 minutes, and filtered (syringe filter, 0.45 μ). DMF was removed by rotary evaporation with a high vacuum oil pump. The residual oil was taken up in CHCl₃/MeCN and purified by column chromatography (SiO₂, gradient 0-10% MeOH/CHCl₃) to give 5 as a white solid (67 mg, 0.092 mmol, 71%).

^1H NMR (DMSO-d₆, 500 MHz): δ 10.7 (d, J = 2.0 Hz, 1H), 10.64 (d, J = 2.0 Hz, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.28 (br. d, J = 3.7 Hz, 1H), 7.26 (br. d, J = 3.9 Hz, 1H), 7.10-7.13 (m, 3H), 6.99-7.10 (m, 6H), 6.90-6.96 (m, 3H), 6.74 (d, J = 8.9 Hz, 2H), 6.6 (d, J = 2.5 Hz, 1H), 6.47 (br. d, J = 16.1 Hz, 1H), 6.21 (dt, J = 15.9, 5.9 Hz, 1H), 4.68 (dd, J = 15.3, 6.3 Hz, 1H), 4.6 (dd, J = 14.3, 5.6 Hz, 1H), 4.51 (ddd, J = 7.6, 7.6, 5.9 Hz, 1H), 4.34 (ddd, J = 10.9, 8.1, 2.8 Hz, 1H), 4.22 (app q, J = 7.5 Hz, 1H), 3.02 (dd, J = 14.8, 5.5 Hz, 1H), 2.92 (dd, J = 13.8, 2.6 Hz, 1H), 2.84 (dd, J = 14.7, 6.0 Hz, 1H), 2.70-2.77 (m, 4H), 2.59 (dd, J = 14.8, 7.8 Hz, 1H), 2.42-2.47 (m, 1H). ^13C NMR (DMSO-d₆, 125 MHz): δ 173.8, 171.9, 171.4, 171.2, 157.0, 141.6, 136.4, 136.3, 133.4, 130.6, 130.3, 128.8, 127.9, 127.8, 126.1, 125.4, 124.8, 124.1, 124.0, 121.3, 121.2, 118.9, 118.8, 118.6, 115.1, 111.69, 111.65, 110.5, 110.3, 68.2, 54.8, 54.1, 53.5, 36.8, 36.3, 35.8, 31.2, 30.6. MS (ESI) Calculated for C₄₃H₄₂N₆O₅ [M+H]⁺: 723.3, found 723.0.
Acidolysis of macrocycle 5

Tyrosine macroether (5) (80 mg, 0.11 mmol) was suspended in dry nitromethane (22 ml, 5 mM) under argon atmosphere, and treated with methanesulfonic acid (108 μl, 1.66 mmol, 15 eq.) at room temperature, which caused complete dissolution of the starting material. After 2 hours the reaction was partitioned between EtOAc and saturated NaHCO₃. The organic phase was washed with saturated NaHCO₃ (x2) and brine, then dried over Na₂SO₄ and concentrated. The product mixture was reconstituted in N,N-DMF and purified by semi-preparative RP-HPLC (Sunfire C18, 5 μ, 10x250 mm, gradient: 41-48% MeCN/H₂O, 0.1% TFA, 21 minutes). Fractions were pooled and evaporated under reduced pressure.

Acidolysis of acyclic carbonate 4

Acyclic cinnamyl carbonate (4) (330 mg, 0.39 mmol) was suspended in dry nitromethane (78 ml, 5 mM) under argon atmosphere, and treated with methanesulfonic acid (382 μl, 5.89 mmol, 15 eq.) at room temperature, which caused complete dissolution of the starting material. After 2 hours the reaction was partitioned between EtOAc and saturated NaHCO₃. The organic phase was washed with saturated NaHCO₃ (x2) and brine, then dried over Na₂SO₄ and concentrated. The product mixture was reconstituted in N,N-DMF and purified by semi-preparative RP-HPLC (Sunfire C18, 5 μ, 10.0x250 mm, gradient: 41-
48% MeCN/H$_2$O, 0.1% TFA, 21 minutes). Fractions were pooled and evaporated under reduced pressure.

**Screening acidolysis conditions**

The tyrosine macroether or acyclic cinnamyl carbonate (~5 mg) in a 1 dr vial was dissolved or suspended in indicated solvent (5 mM) under ambient atmosphere, and treated with acid. All reactions were stopped at two hours unless otherwise noted in the table below. MeSO$_3$H/CF$_3$CO$_2$H was transferred to the reaction vial via a micropipet using polypropylene tips. Bistriflimide was weighed under an Argon atmosphere and a 10 mM solution in anhydrous MeNO$_2$ was prepared and transferred to the reaction vessel via syringe. Volumetric solutions of 50% TFA, HCO$_2$H or AcOH in their respective solvents were prepared and transferred to a reaction vessel containing acidolysis substrate. Metal triflates were weighed under ambient atmosphere and transferred to a suspension of acidolysis substrate. Sc(OTf)$_3$ uniquely promoted complete dissolution of substrate/acid in the reaction media. Other metal triflates were heterogeneous throughout the reaction which resulted in increased reaction time (16 hours). Reactions performed below ambient temperatures were performed in a cool aluminum block and the temperature was equilibrated for 30 minutes prior to addition of acid. Aliquots for HPLC/MS analysis were removed and quenched with a methanolic solution of Et$_3$N, evaporated under high vacuum, and reconstituted in DMSO prior to injection. Relative yields were determined by integration at UV 254 nm and were not standardized.

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*Table S1.* Effect of substrate and acid promoter on product distribution
Figure S2. Analytical HPLC of the reaction of various metal triflates with acyclic carbonate 4. Little perturbation of product distribution was observed. HPLC conditions: Sunfire C18, 4.6x250 mm, 5.0 μ. 45-55% MeCN/H2O, 0.1% TFA, 35 minute run time.

Acidolysis of selectively deuterated Trp-Trp-Tyr

L-Tryptophan(d5)+HCl: Prepared according to Oba, et al.\textsuperscript{9} To a degassed solution of H-Trp-OH (3.0 g, 14.7 mmol) in D\textsubscript{2}O (20.0 ml) was added mercaptoacetic acid (0.4 ml, 5.9 mmol) followed by 4M DCI (30 wt% in D\textsubscript{2}O). The solution was heated to 100 °C (oil bath) for 5 hours then cooled to room temperature and extracted with EtOAc. The aqueous layer was lyophilized to give a white powder which was re-subjected to the conditions above. The DCI/D\textsubscript{2}O solution of Trp(d5) was diluted with H\textsubscript{2}O (250 ml) and lyophilized to give a white powder (3.01 g, 14.4 mmol, 98%). Analysis by MS (ESI+) showed > 95 % average incorporation at each position ( ~ 75% d\textsubscript{5}). The percent deuterium at each position was determined by \textsuperscript{1}H NMR.\textsuperscript{10} The residual Ar-H signals were integrated relative to C\textsubscript{α}-H to give C2-\textsuperscript{2}H (98%), C4-\textsuperscript{2}H (90%), C5-\textsuperscript{2}H (97%), C6-\textsuperscript{2}H (98%), C7-\textsuperscript{2}H (96%). \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 500 MHz): δ 7.58 (s, 0.10H), 7.34 (s, 0.04H), 7.25 (s, 0.02H),

7.06 (s, 0.03H), 6.98 (s, 0.02H), 4.09 (t, J = 6.0 Hz, 1H), 3.29 (d, J = 6.3 Hz, 2H). MS (ESI) Calculated for C_{11}H_{7}D_{5}N_{2}O_{2} [M+H]^+: 210.1, found 210.1.

Fmoc-L-Trp(d5)-OH: To a suspension of H-Trp(d5)-OH (1.79 g, 8.53 mmol) in sat. aq. NaHCO_{3} (25 ml) and THF (25 ml) was added Fmoc-OSu (3.45 g, 10.24 mmol, 1.2 equiv.) in one portion. The reaction was stirred for 2 hours at room temperature. The THF was evaporated by rotary evaporation to give a white aqueous suspension was diluted with sat. NaHCO_{3} (25 ml) and extracted with diethyl ether (2X) to remove excess Fmoc-OSu. The aqueous layer was acidified with 1.0N HCl to pH < 3 and extracted with EtOAc (2X) to give Fmoc-L-Trp(d5)-OH as a tan solid (3.09 g, 7.17 mmol, 84%). MS analysis showed no loss of isotopic purity. \[\text{\textsuperscript{1}H NMR (DMSO-\textit{d}_{6}, 600 MHz): mixture of rotamers. } \delta \text{ 12.67 (s, 1H), 10.82 (s, 1H), 7.84 (br. d, J = 7.6 Hz, 2H), 7.68 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.32-7.40 (m, 2H), 7.28 (ddd, J = 7.6, 7.6, 0.7 Hz, 1H), 7.24 (ddd, J = 7.6, 7.6, 0.7 Hz, 1H), 4.12-4.23 (m, 4H), 3.17 (dd, J = 14.6, 4.5 Hz, 1H), 3.00 (dd, J = 14.6, 9.9 Hz, 1H). MS (ESI) Calculated for C_{26}H_{17}D_{5}N_{2}O_{4} [M+H]^+: 432.2, found 432.1.}\]

Peptide synthesis:

Peptides were prepared using solution phase techniques with the Fmoc- protection strategy. Couplings were performed with O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) (1.2 equivalent), Fmoc-AA-OH (1.2 eq), iPr_{2}NEt (5 eq.) in DMF (0.1M). Coupling were complete within 2 hours and diluted with EtOAc and washed sequentially with 1.0N HCl, sat. NaHCO_{3}, H_{2}O and brine. Fmoc deprotection was performed was achieved with DBU (1.0 eq) in THF (0.2M) in the presence of octanethiol (5 equiv).\textsuperscript{11} After deprotection, the unprotected peptide was precipitated with Et_{2}O and pelleted by centrifugation. The peptide was repeatedly suspended in Et_{2}O and collected by centrifugation to completely remove residual octanethiol and DBU. After final deprotection the peptide was purified via reverse-phase HPLC (C18, MeCN/H_{2}O, 0.1%TFA). Fractions were pooled and lyophilized. Under these coupling/purification conditions no significant loss of isotopic purity was observed.

**Acidolysis of Trp-Trp(d)5-Tyr**

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**Table S2.** MS analysis of acidolysis products derived from 13.
ESI (pos. mode) mass spectra of peaks corresponding to compounds 6-12 derived from acidolysis of 13.
Acidolysis of Trp(d$_5$)-Trp-Tyr

<table>
<thead>
<tr>
<th>Structure</th>
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<th>Observed mass</th>
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**Table S2.** MS analysis of acidolysis products derived from 14.
ESI (pos. mode) mass spectra of peaks corresponding to compounds 6-12 derived from acidolysis of 14.
Selective O-C<sub>ortho</sub> acidolyses:

The macrocyclic ether starting materials were characterized in chapter 4.

Cyclic-Ile-Met-Ser-Tyr-Trp (14) - To a solution of macrocycle 13 (5.2 mg, 5.9 μmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.2 ml) was added CF<sub>3</sub>CO<sub>2</sub>H (6.3 μl, 82.5 μmol, 15 equiv.). The reaction was stirred at room temperature for 24 hours at which point HPLC shows complete consumption of macrocyclic ether. The reaction was concentrated without heating, reconstituted in DMSO (400 μL) and purified by preparative reverse phase HPLC (C18, XBridge RP18, 19x250mm). Concentration afforded 3.6 mg (69%). The product was characterized by mass and <sup>1</sup>H NMR analysis for loss of symmetry about tyrosine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500 MHz): δ 10.77 (d, J = 2 Hz, 1H), 9.15 (s, 1H), 8.08 (d, J = 6.8 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.38 (br. s, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.08-7.20 (m, 5H), 7.00-7.05 (m, 2H), 6.94-6.99 (m, 3H), 6.87 (dd, J = 8.3, 1.9 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.41 (d, J = 15.9 Hz, 1H), 6.31 (dt, J = 15.9, 6.8 Hz, 1H), 5.24 (dd, J = 5.4, 5.4 Hz, 1H), 4.4 (ddd, J = 8.2, 8.2, 5.3 Hz, 1H), 4.34 (ddd, J = 6.4, 6.4, 6.4 Hz, 1H), 4.23-4.31 (m, 2H), 4.03 (dd, J = 8.4, 6.1 Hz, 1H), 3.63 (ddd, J = 10.9, 5.5, 5.5 Hz, 1H), 3.57 (ddd, J = 11.0, 5.5, 5.5 Hz, 1H), 3.48 (dd, J = 15.6, 6.2 Hz, 1H), 3.25-3.30 (m, 1H), 3.14 (dd, J = 14.6, 5.1 Hz, 1H), 2.9 (dd, J = 14.9, 8.6 Hz, 1H), 2.74-2.84 (m, 3H), 2.49-2.59 (m, 3H), 2.33-2.45 (m, 3H), 1.94 (s, 3H), 1.83-1.90 (m, 1H), 1.74-1.82 (m, 1H), 1.65-1.76 (m, 1H), 1.17-1.25 (m, 2H), 0.95-1.03 (m, 1H), 0.66-.074 (m, 6H). (ESI) Calculated for C<sub>46</sub>H<sub>57</sub>N<sub>7</sub>O<sub>8</sub>S [M+H]<sup>+</sup>: 868.4, found 868.7

Cyclic-Ser-Met-Tyr (15) - To a solution of macrocycle S1 (3.3 mg, 5.8 μmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.16 ml) was added CF<sub>3</sub>CO<sub>2</sub>H (6.7 μl, 87.0 μmol, 15 equiv.). The reaction was stirred at room temperature for 24 hours at which point HPLC shows complete consumption of macrocyclic ether. The reaction was concentrated without heating, reconstituted in DMSO (400 μL) and purified by preparative reverse phase HPLC (C18,
XBridge RP18, 19x250mm). Concentration afforded 2.5 mg (77 %). The product was characterized by mass and $^1$H NMR analysis for loss of symmetry about tyrosine. $^1$H NMR (DMSO-d$_6$, 500 MHz): δ 9.1 (s, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.39 (br. s, 1H), 7.2 (br. d, J = 7.9 Hz, 1H), 7.15 (dd, J = 7.6, 7.6 Hz, 1H), 7.1 (br. s, 1H), 7.03 (br. s, 1H), 6.98-7.02 (m, 2H), 6.84 (dd, J = 8.2, 2.0 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 6.41 (dt, J = 15.8, 6.6 Hz, 1H), 6.21 (d, J = 15.6 Hz, 1H), 4.39 (ddd, J = 9.5, 9.5, 3.7 Hz, 1H), 4.21 (ddd, J = 8.3, 5.6, 5.6 Hz, 1H), 4.16 (ddd, J = 7.8, 7.8, 5.2 Hz, 1H), 3.47-3.50 (m, 2H), 3.31-3.42 (m, 1H), 2.89 (ddd, J = 9.3, 9.3, 4.0 Hz, 1H), 4.26 (dq, J = 7.1, 7.1 Hz, 1H), 3.82 (dt, J = 7.9 Hz, 1H), 2.89-2.97 (m, 1H), 2.82 (dd, J = 13.9, 3.8 Hz, 1H), 2.64-2.74 (m, 2H), 2.36-2.43 (m, 2H), 1.62 (app dq, J = 6.8, 6.8 Hz, 1H), 0.99 (d, J = 7 Hz, 3H), 0.49 (t, J = 6.7 Hz, 6H). (ESI) Calculated for C$_{29}$H$_{36}$N$_4$O$_6$ [M+H]$^+$: 569.2, found 569.5

Cyclic-Ala-Leu-Tyr (16) - To a solution of macrocycle S2 (1.1 mg, 2.1 μmol) in CH$_2$Cl$_2$ (0.41 ml) was added CF$_3$CO$_2$H (2.4 μl, 31 μmol, 15 equiv.). The reaction was stirred at room temperature for 24 hours at which point HPLC shows complete consumption of macrocyclic ether. The reaction was concentrated without heating, reconstituted in DMSO (400 μL) and purified by preparative reverse phase HPLC (C18, XBridge RP18, 19x250mm). Concentration afforded 0.9 mg (84 %). The product was characterized by mass and $^1$H NMR analysis for loss of symmetry about tyrosine. $^1$H NMR (DMSO-d$_6$, 500 MHz): δ 9.09 (s, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.25 (br. s, 1H), 7.12-7.19 (m, 3H), 7.02 (br. s, 1H), 6.96-7.01 (m, 2H), 6.84 (dd, J = 8.3, 2.0 Hz, 1H), 6.65 (d, J = 8.6 Hz, 1H), 6.27-6.37 (m, 2H), 4.42 (ddd, J = 9.3, 9.3, 4.0 Hz, 1H), 4.26 (dq, J = 7.1, 7.1 Hz, 1H), 3.82 (dt, J = 7.9 Hz, 1H), 2.89-2.97 (m, 1H), 2.82 (dd, J = 13.9, 3.8 Hz, 1H), 2.64-2.74 (m, 2H), 2.36-2.43 (m, 2H), 1.62 (app dq, J = 6.8, 6.8 Hz, 1H), 0.99 (d, J = 7 Hz, 3H), 0.49 (t, J = 6.7 Hz, 6H). (ESI) Calculated for C$_{30}$H$_{38}$N$_4$O$_5$ [M+H]$^+$: 534.3, found 534.6
Cyclic-Leu-Ala-Arg-Tyr (14) - To a solution of macrocycle S3 (6.0 mg, 8.7 μmol) in CH₂Cl₂ (1.74 ml) was added CF₃CO₂H (9.9 μl, 130 μmol, 15 equiv.). The reaction was stirred at room temperature for 24 hours at which point HPLC shows complete consumption of macrocyclic ether. The reaction was concentrated without heating, reconstituted in DMSO (400 uL) and purified by preparative reverse phase HPLC (C18, XBridge RP18, 19x250mm). Concentration afforded 4.4 mg (74 %). The product was characterized by mass and ¹H NMR analysis for loss of symmetry about tyrosine. ¹H NMR (DMSO-d₆, 500 MHz): δ 9.18 (br. s, H), 8.08 (d, J = 7.6 Hz, H), 7.88 (d, J = 8.1 Hz, H), 7.84 (d, J = 6.3 Hz, H), 7.75 (d, J = 7.9 Hz, H), 7.42 (dd, J = 5.7, 5.7 Hz, H), 7.32 (br. s, H), 7.27 (br. s, H), 7.16 (dd, J = 7.6, 7.6 Hz, H), 7.04-7.11 (m, H), 7 (br. d, J = 7.5 Hz, H), 6.94 (br. s, H), 6.89 (dd, J = 8.2, 1.8 Hz, H), 6.69 (d, J = 8.1 Hz, H), 6.41 (d, J = 15.7 Hz, H), 6.32 (dt, J = 15.7, 6.8 Hz, H), 4.29 (ddd, J = 8.5, 8.5, 4.1 Hz, H), 4.21 (ddd, J = 8.0, 8.0, 5.0 Hz, H), 4.04-4.12 (m, H), 3.97 (dd, J = 15.9, 6.7 Hz, H), 3.29 (dd, J = 15.6, 6.5 Hz, H), 3.03 (dd, J = 12.8, 6.5 Hz, H), 2.9 (dd, J = 14.2, 3.7 Hz, H), 2.74-2.84 (m, H), 2.66 (dd, J = 14.2, 9.2 Hz, H), 2.53 (dd, J = 14.6, 7.3, 7.3 Hz, H), 2.4 (ddd, J = 14.0, 6.9, 6.9 Hz, H), 1.61-1.71 (m, H), 1.48-1.58 (m, H), 1.30-1.45 (m, H), 1.12 (d, J = 7.4 Hz, H), 0.77 (d, J = 6.1 Hz, H), 0.7 (d, J = 6.1 Hz, H). (ESI) Calculated for C₃₆H₅₀N₈O₆ [M+H]⁺: 691.4, found 691.7

Cyclic-Leu-Ala-Arg-Tyr (14) - To a solution of macrocycle S3 (2.4 mg, 4.5 μmol) in CH₂Cl₂ (0.90 ml) was added CF₃CO₂H (5.2 μl, 68 μmol, 15 equiv.). The reaction was stirred at room temperature for 24 hours at which point HPLC shows complete consumption of macrocyclic ether. The reaction was concentrated without heating, reconstituted in DMSO (400 uL) and purified by preparative reverse phase HPLC (C18, XBridge RP18, 19x250mm). Yield not determined. The macrocyclic linkage was assigned by a combination of TOCSY, COSY, HSQC. ¹H NMR (DMSO-d₆, 500 MHz): δ 12.58 (s, 1H), 10.75 (d, J = 2 Hz, 1H), 8.31 (d, J = 7.6 Hz, 1H), 8.11 (t, J = 5.9 Hz, 1H), 7.49-7.56 (m, 2H), 7.27 (br. s, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.13-7.18
(m, 3H), 7.06-7.10 (m, 2H), 6.97-7.00 (m, 1H), 6.89 (dd, J = 8.2, 1.6 Hz, 1H), 6.48-6.56 (m, 1H), 6.4 (d, J = 15.6 Hz, 1H), 4.46 (ddd, J = 8.0, 8.0, 5.5 Hz, 1H), 4.25 (dd, J = 9.0, 5.8 Hz, 1H), 3.84 (dd, J = 16.5, 6.6 Hz, 1H), 3.49-3.57 (m, 4H), 3.09 (dd, J = 14.5, 5.5 Hz, 1H), 2.99 (dd, J = 14.2, 7.8 Hz, 1H), 2.76-2.91 (m, 3H), 2.38-2.44 (m, 1H), 1.99 (dddd, J = 13.2, 13.2, 6.6, 6.6 Hz, 1H), 0.78 (d, J = 6.5 Hz, 3H), 0.71 (d, J = 6.9 Hz, 3H). (ESI) Calculated for C₃₀H₃₄N₄O₅ [M+H]⁺: 531.3, found 531.6
Tabulated data for compounds 6 - 12:

**Compound 6 - Tabulated data**

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### Compound 7 - Tabulated data

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<td>HMBC 1$\rightarrow$3,21,22,23</td>
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<td>129.4</td>
<td>6.47 (dt, $J = 15.6, 6.4$ Hz, 1H)</td>
<td>COSY 2$\rightarrow$1 HMBC 2$\rightarrow$4</td>
</tr>
<tr>
<td>3</td>
<td>130.6</td>
<td>6.27 (d, $J = 15.6$ Hz, 1H)</td>
<td>HMBC 3$\rightarrow$4,5,9</td>
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<td>7.13 - 7.17 (m, 1H) overlap</td>
<td>HMBC 5$\rightarrow$3,7,9</td>
</tr>
<tr>
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<td>127.8</td>
<td>7.13 - 7.17 (m, 1H) overlap</td>
<td>HMBC 6$\rightarrow$4,8</td>
</tr>
<tr>
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<td>127.0</td>
<td>6.97 - 7.00 (m, 1H) overlap</td>
<td>HMBC 7$\rightarrow$5,8,9</td>
</tr>
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<td>9</td>
<td>124.7</td>
<td>7.13 - 7.17 (m, 1H) overlap</td>
<td>HMBC 9$\rightarrow$7</td>
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<td>2.64 (dd, $J = 13.4, 8.0$ Hz, 1H), 2.93 - 2.99 (m, 1H) overlap</td>
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<td>2.70 - 2.76 (m, 1H) overlap, 2.86 - 2.94 (m, 1H) overlap</td>
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<td>16</td>
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<td>6.96 - 6.99 (m, 1H) overlap</td>
<td>HMBC 17$\rightarrow$16,19</td>
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<td>10.72 (s, 1H) or 10.63 (s, 1H)*</td>
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### Compound 8 - Tabulated data

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<td>HMBC 1→2,3,19,20,21</td>
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<td>6.13 (ddd, J = 16.4, 5.5, 2.8 Hz, 1H)</td>
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<td>5.62 (s, 1H)</td>
<td>HMBC 9→5,3,10,7</td>
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* indole N-H not assigned
| 10 | 26.9 | 2.32 (dd, J = 14.9, 7.3 Hz, 1H), 3.05 (dd, J = 14.9, 11.9 Hz, 1H) | HMBC 10→8,12 |
| 11 | 34.3 | 2.07 (dd, J = 15.5, 11.9 Hz, 1H), 2.24 (dd, J = 15.5, 7.3 Hz, 1H) | HMBC 11→8,12 |
| 12 | 171.9 | - | - |
| 13 | - | 8.05 (d, J = 7.8 Hz, 1H) | HMBC 13→12 |
| 14 | 53.6 | 4.36 (ddd, J = 12.8, 7.8, 3.1 Hz, 1H) | - |
| 15 | 26.7 | 2.75 (dd, J = 13.9, 12.8 Hz, 1H), 3.23 (dd, J = 13.9, 3.1 Hz, 1H) | HMBC 15→16,17 |
| 16 | 109.6 | - | - |
| 17 | 124.7 | 7.19 (d, J = 2.4 Hz, 1H) overlap | - |
| 18 | - | 10.28 (br s, 1H) | HMBC 18→17,19 |
| 19 | 135.7 | - | - |
| 20 | 123.5 | - | - |
| 21 | 121.5 | 6.93 (d, J = 6.8 Hz, 1H) | HMBC 21→1 |
| 22 | 118.3 | 6.97-7.01 (m, 1H) overlap | HMBC 22→20,24 |
| 23 | 117.1 | 7.68 (d, J = 7.8 Hz, 1H) | TOCSY 23→22,21 |
| 24 | 126.1 | - | - |
| 25 | 172.3 | - | - |
| 26 | - | 8.18 (d, J = 7.4 Hz, 1H) | TOCSY 26→27,28 HMBC 26→25 |
| 27 | 53.5 | 4.52 (ddd, J = 8.5, 7.4, 5.0 Hz, 1H) | HMBC 27→29,37 |
| 28 | 27.0 | 3.05 (dd, J = 14.9, 8.5 Hz, 1H), 3.15 (dd, J = 14.9, 5.0 Hz, 1H) | HMBC 28→29,30 |
| 29 | 109.7 | - | - |
| 30 | 1232.0 | 7.14 (d, J = 2.0 Hz, 1H) | HMBC 30→29,32,37 |
| 31 | - | 10.84 (br d, J = 2.0 Hz, 1H) | HMBC 31→30 |
| 32 | 135.8 | - | - |
| 33 | 111.0 | 7.32 (d, J = 7.4 Hz, 1H) overlap | - |
| 34 | 120.6 | 7.06 (d, J = 7.4, 7.4 Hz, 1H) overlap | HMBC 34→32,36 |
| 35 | 118.2 | 6.97-7.01 (m, 1H) overlap | HMBC 35→33,37 |
| 36 | 118.1 | 7.56 (d, J = 7.8 Hz, 1H) | TOCSY 36→33,34,35 |
| 37 | 127.1 | - | - |
| 38 | 170.8 | - | - |
| 39 | - | 7.84 (d, J = 8.0 Hz, 1H) | TOCSY 39→40,41 HMBC 39→38 |
| 40 | 53.6 | 4.40 (ddd, J = 8.0, 7.9, 5.7 Hz, 1H) | HMBC 40→38,47 |
| 41 | 36.6 | 2.77 (dd, J = 13.8, 7.9 Hz, 1H), 2.89 (dd, J = 13.8, 5.7 Hz, 1H) | HMBC 41→47 |
| 42 | 127.4 | - | - |
| 43 | 129.9 | 7.02 (d, J = 8.5 Hz, 2H) | HMBC 43→41,45 |
| 44 | 114.6 | 6.66 (d, J = 8.5 Hz, 2H) | HMBC 44→42,45 COSY 44→43 |
| 45 | 155.6 | - | - |
| 46 | - | 9.15 (br s, 1H) | - |
| 47 | 172.5 | - | - |
| 48 | - | 7.09 (br s, 1H), 7.31 (br s, 1H) overlap | HMBC 48→47 |
### Compound 9 - Tabulated data

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<td>6.98-7.01 (m, 1H)</td>
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29 | 109.7 | - | -
30 | 124.0 | 7.20 (d, J = 1.7 Hz, 1H) | HMBC 30→29,32,37 ROESY 30→27,28
31 | - | 10.54 (br s, 1H) | ROESY 31→1,2,3 COSY 31→30
32 | 134.9 | - | -
33 | 122.0 | - | -
34 | 120.9 | 6.86-6.89 (m, 1H) | ROESY 34→1 HMBC 34→1
35 | 118.1 | 6.90-6.95 (m, 1H) | -
36 | 116.6 | 7.57 (d, J = 8.0 Hz, 1H) | HMBC 36→32,34
37 | 126.7 | - | -
38 | - | - | -
39 | - | 7.92 (d, J = 7.7 Hz, 1H) | TOCSY 39→40,41
40 | 53.6 | 4.49-4.54 (m, 1H) | HMBC 40→42,47 ROESY 40→48
41 | 36.8 | 2.81-2.87 (m, 1H), 2.94-2.99 (m, 1H) | HMBC 41→47
42 | 127.4 | - | -
43 | 129.9 | 7.05-7.09 (m, 2H) | HMBC 43→45,41
44 | 114.6 | 6.66-6.69 (m, 2H) | HMBC 44→42,45
45 | 155.7 | - | -
46 | - | 9.17-9.19 (m, 1H) | HMBC 46→45
47 | 172.6 | - | -
48 | - | 7.11 (br s, 1H), 7.48 (br s, 1H) | TOCSY 48→48'

**Compound 10b - Tabulated data**

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* indole N-H not assigned
### Compound 12 - Tabulated data

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**Solution structure:**

The solution conformation of pyrroloindoline # was determined from NMR spectra of 7 acquired in DMSO to permit the observation of exchangeable protons. ROESY was also acquired in DMSO:D$_2$O (9:1) to resolve potential signal overlap arising from exchangeable protons. The relative stereochemistry of the pyrroloindoline ring juncture was determined by careful analysis of long range inter-residue correlations observed by NOESY and ROESY (see text). Distance restraints were obtained from pairs of NOE correlations from a 100ms $^1$H-$^1$H NOESY experiment. The fixed reference distance H18-H20 (2.8 Å)$^{12}$ was corroborated by distance H30-H31$^{13}$ and all geminal pairs, suggesting sufficiently linear NOE buildup for stratification of the larger dataset. Volume integrals were grouped into bins, and classified as strong (<2.5 Å), medium (<3.5 Å) and weak (<4.5 Å), based on the relationship of $r^−6$. An initial model was generated by a Mixed Monte-Carlo low-mode conformational search incorporating 7 key long-distance NOE distance restraints. From this model, an additional 29 NOEs were defined, and prochiral methylenes H1 (pro-R), H1’ (pro-S) and H28 (pro-S), H28’ (pro-R) were defined. Equivalent NOE correlations arising from unassigned prochiral methylenes at C10, C11, C15 and C41, where present, were assigned the weaker of the two restraint bins. No torsional constraints were utilized. Structure calculations were carried out using Macromodel 9.8 (Schrödinger, Inc., San Diego, CA) using the OPLS-2005 force field with implicit GB/SA solvation and a constant dielectric ($\varepsilon = 1.0$). A 5,000 step restrained Mixed Monte-Carlo low-mode conformational search was used. Amide bonds rotations were not restrained. Redundant conformers were filtered within a heavy atom RMSD cutoff of 1.0 Å, which converged to 5 structures within 11 kcal/mol of the global minimum. The global minimum was located 150 times.

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Figure S3. Conformational ensemble and average RMSDs of pyrroloindoline 12 derived from constrained simulations using 36 distances measured by NOE. Rendered with PyMol.

**Average RMSD (Å) for:**

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Figure S4. Lowest energy conformational and peptide torsional angles of pyrroloindoline 12. Rendered with CYLview.\textsuperscript{14}

Table S2. Internuclear distances determined from NOESY, and distances from calculated solution conformation.

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\textsuperscript{14} "CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009 (http://www.cylview.org)"

\textsuperscript{15} Correlation which is greater than three bonds, and which is not geometrically fixed due to small rings, etc.

\textsuperscript{16} Distance restraints used in generating a preliminary model (see text).

\textsuperscript{17} Long range correlations used in final calculation of solution conformation.

\textsuperscript{18} See numbering scheme, above.

\textsuperscript{19} Internuclear distance calculated from experiment NOE.

\textsuperscript{20} Bins were defined as strong (s, <2.5 Å), medium (m, <3.5 Å) and weak (w, <4.5 Å).

\textsuperscript{21} Internuclear distance measured from lowest energy conformer.

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<sup>23</sup> Anomalous distance. Violates constraint from NOE measured distance.
Compound 6

Current Data Parameters
NAME  KL-4-251_AV500
PROCNO  1

F2 - Acquisition Parameters
Date_  20120612
Time  16.37
INSTRUM  av500
PROBHD  5 mm DCH 13C-1
PULPROG  zg30
TD  65536
SOLVENT  DMSO
NS  8
DS  0
SWHN  10000.000 Hz
FIDRES  0.152588 Hz
AQ  3.2768500 sec
RG  202.91
DW  50.000 usec
DE  10.00 usec
TE  29.60 K
D1  2.00000000 sec
TD0  1

======== CHANNEL f1 ========
NUC1  1H
P1  10.00 usec
PLW1  13.50000000 W
SF01  500.1330008 MHz

F2 - Processing parameters
SI  65536
SF  500.1300055 MHz
WDW  EMSSB  0
LB  0.30 Hz
GB  0
PC  1.00
Compound 6

Current Data Parameters
NAME     KL-4-251_AV500
EXPRO     8
PROCNO     3

F2 - Acquisition Parameters
Date_          20120613
Time              19.41
INSTRUM           av500
PROBHD   5 mm DCH 13C
PULPROG     mlevetgp.js
SOLVENT            DMSO
NS                    2
DS                    8
SN                 5151.099 Hz
FIDRES         2.515185 Hz
AQ                0.1988425 sec
NS                    79.91
D0             97.067 usec
dt             296.0 K
D1                    0.00000300 sec
d9                    0.00000000 sec
d11                 0.03000000 sec
d12                 0.00002000 sec
d16                 0.00020000 sec
dh0                 0.00019415 sec
L1                   24

F1 - Acquisition Parameters
TD                  256
FIDRES        500.1324 MHz
SN           5151.099 Hz
FIDRES     20.121468 Hz
SM               10.299 ppm
F1 - Processing parameters
SI                 4096
SF        500.1300135 MHz
MDW            QSINX
SDS     2
LB                0 Hz
GF                    0
PC                 1.00

F1 - Processing parameters
SI                 4096
MC2        echo-anti-echo
SF        500.1300135 MHz
MDW            QSINX
SSB     2
LB                0 Hz
GB                    0

467
Compound 6

Current Data Parameters
NAME: KL-4-251_AV500
PROCNO: 1

F2 - Acquisition Parameters
Date: 20120613
Time: 19.00
INSTRUM: av500
PROBHD: 5 mm DCH 13C
PULPROG: hmbcgpl2ndqf
TD: 256
FIDRES: 98.257607 Hz
SW: 199.999 ppm
FnMODE: QF

F2 - Processing parameters
SI: 4096
SF: 500.1300135 MHz
WDW: QSINESSB = 2
LB = 0 Hz
GB = 0
PC = 1.00

F1 - Processing parameters
SI: 4096
SF: 125.7947 MHz
NCH: QC

Notes:

- F1 - Acquisition parameters
  TD: 256
  SFQ: 125.7947 MHz
  FIDRES: 199.999 ppm
  FNMODE: QF

- F2 - Processing parameters
  SI: 4096
  SF: 500.1300135 MHz
  WDW: QSINESSB = 2
  LB = 0 Hz
  GB = 0
  PC = 1.00

- F1 - Processing parameters
  SI: 4096
  SF: 125.7947 MHz
  NCH: QC
Compound 6

Current Data Parameters
NAME     KL-4-251_AV500
EXPNO                 7
PROCNO                1

F1 - Acquisition Parameters
Date_          20120613
Time              19.20
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG      hsqcedetgp
TD                 2048
SOLVENT            DMSONS                    2
DS                   16
SWH            5000.000 Hz
FIDRES         2.441406 Hz
AQ            0.2048500 secRG               202.91
DW              100.000 usec
DN                10.00 usec
TC                296.0 K
CMPT2            145.0000000
D0              0.00000000 sec
D1              1.55000000 sec
D4              0.00172414 sec
D11             0.00000000 sec
D13             0.00000000 sec
D15             0.00000000 sec
D16             0.00000000 sec
I11             0.00000000 sec
I13             0.00000000 sec
I16             0.00000000 sec
ZGOPTNS

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
P2                20.00 usec
PC2A              0 usec
PLW1        13.00000000 W
FPO1        500.1305097 MHz

-------- CHANNEL f2 --------
CPDPRG2            garp
NUC2                13CP
P4                19.26 usec
PCPD2             70.00 usec
PLW2        23.01399994 W
FPO2        125.7678496 MHz

====== GRADIENT CHANNEL =====
GPNAM1       SMSQ10.100
GPNAM2       SMSQ10.100
GPZ1              80.00 %
GPZ2              20.10 %
P16             1000.00 usec

F2 - Processing parameters
SI                 4096
SF          500.1301145 MHz
QSW               QSINE
GSB               2
LS                0 Hz
OB                0
PC                1.00

F1 - Processing parameters
SI                 4096
SF          500.1301145 MHz
QSW               QSINE
GSB               2
LS                0 Hz
OB                0
PC                1.00

ppm

Compound 6

Current Data Parameters
NAME     KL-4-251_AV500
EXPNO                 7
PROCNO                1

F1 - Acquisition Parameters
Date_          20120613
Time              19.20
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG      hsqcedetgp
TD                 2048
SOLVENT            DMSONS                    2
DS                   16
SWH            5000.000 Hz
FIDRES         2.441406 Hz
AQ            0.2048500 secRG               202.91
DW              100.000 usec
DE                10.00 usec
TE                296.0 K
CMPT2            145.0000000
D0              0.00000000 sec
D1              1.55000000 sec
D4              0.00172414 sec
D11             0.00000000 sec
D13             0.00000000 sec
D15             0.00000000 sec
D16             0.00000000 sec
I11             0.00000000 sec
I13             0.00000000 sec
I16             0.00000000 sec
ZGOPTNS

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
P2                20.00 usec
PC2A              0 usec
PLW1        13.00000000 W
FPO1        500.1305097 MHz

-------- CHANNEL f2 --------
CPDPRG2            garp
NUC2                13CP
P4                19.26 usec
PCPD2             70.00 usec
PLW2        23.01399994 W
FPO2        125.7678496 MHz

====== GRADIENT CHANNEL =====
GPNAM1       SMSQ10.100
GPNAM2       SMSQ10.100
GPZ1              80.00 %
GPZ2              20.10 %
P16             1000.00 usec

F2 - Processing parameters
SI                 4096
SF          500.1301145 MHz
QSW               QSINE
GSB               2
LS                0 Hz
OB                0
PC                1.00

F1 - Processing parameters
SI                 4096
MC2       echo-antiecho
SF          125.7578472 MHz
WDW
QSW               2
LB                0 Hz
GB                0
PC                1.00

ppm
## Current Data Parameters

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### F2 - Acquisition Parameters

- **Date_**: 20120209
- **Time**: 19.31
- **INSTRUM**: av600
- **PROBHD**: 5 mm TBI5
- **PULPROG**: zgTD
- **SOLVENT**: DMSO
- **NS**: 8
- **DS**: 0
- **SWH**: 12376.237 Hz
- **FIDRES**: 0.188846 Hz
- **AQ**: 2.6477044 sec
- **RG**: 90.5
- **DW**: 40.400 usec
- **DE**: 6.50 usec
- **TE**: 294.4 KD1
- **TD0**: 1

### CHANNEL f1

- **NUC**: 1H
- **P**: 9.40 usec
- **PL1**: -2.00 dB
- **PL1W**: 39.81071854 W
- **SFO**: 600.1336008 MHz

### F2 - Processing parameters

- **SI**: 65536
- **SF**: 600.1300078 MHz
- **WDW**: EM
- **SSB**: 0
- **LB**: 0 Hz
- **GB**: 0
- **PC**: 1.00
Compound 7

Current Data Parameters

NAME: ZI-4-103-4-1
EXPNO: 1
PROCNO: 1

F2 - Acquisition Parameters

Date: 20120209
Time: 19.25
INSTRUM: av600
PROBHD: 5 mm TBI
POLYMS: kosygmpf
TO: 4096
SOLVENT: DMSO
D1: 1.00 sec
D2: 0.0000800 sec
D12: 0.00000400 sec
D13: 0.00000400 sec
D16: 0.00000400 sec

======== CHANNEL f1 ========

NUC1: 1
HP1: 9.40 usec
P2: 18.80 usec
PL1: -2.00 dB
PL1W: 39.81071854 W
FSO1: 600.1327 MHz

====== GRADIENT CHANNEL =====

GPNAM1: SINE.100
GPNAM2: SINE.100
GPZ1: 10.00 %
GPZ2: 20.00 %
P16: 1000.00 usec

F1 - Acquisition parameters

TD: 512
FIDRES: 10.523297 Hz
SW: 8.978 ppm
FnMODE: States-TPPI

F2 - Processing parameters

SI: 8192
SF: 600.1300115 MHz
WDW: QSINESSB: 2
LB: 0 Hz
GB: 0
PC: 1.00

F1 - Processing parameters

SI: 8192
MC1: States-TPPI
SF: 600.1300071 MHz
WDW: 2
LB: 0 Hz
GB: 0

...
Compound 7

Current Data Parameters

NAME: NL-4-103-4-1
EXPERIMENT: 4
PROCEDURE: 1

F2 - Acquisition Parameters

Date: 2012-02-10
Time: 20:58
Instruments: av600

PROB HD Recommended:

- TBI5
- mlevetgp.js
- ...
- TD: 0.03000000 sec
- D12: 0.00002000 sec
- D16: 0.00020000 sec
- IN0: 0.00015720 sec
- L1: 24

--- CHANNEL f1 ---

- NUC1: 1H
- HP1: 9.40 usec
- P2: 18.80 usec
- P5: 26.68 usec
- P6: 40.00 usec
- P7: 50.00 usec
- PL1: 3.00 GB
- PI: 1000.00 usec
- SFO1: 600.1327006 MHz

--- GRADIENT CHANNEL ---

- GPNAM1: SINE.100
- GPNAM2: SINE.100
- GPZ1: 30.00 %
- GPZ2: 30.00 %
- P16: 1000.00 usec
- F1: Acquisition parameters
  - SFO1: 600.1327 MHz
  - FIDRES: 10.602203 Hz
  - SW: 10.600 ppm

F2 - Processing parameters

- SI: 4096
- SF: 600.1300081 MHz
- WD: 0 Hz
- L: 0
- GB: 0

--- CHANNEL f2 ---

- NUC2: 1H
- HP2: 9.40 usec
- P2: 18.80 usec
- P5: 26.68 usec
- P6: 40.00 usec
- P7: 50.00 usec
- PL1: 3.00 GB
- PI: 1000.00 usec
- SFO1: 600.1327006 MHz

--- GRADIENT CHANNEL ---

- GPNAM1: SINE.100
- GPNAM2: SINE.100
- GPZ1: 30.00 %
- GPZ2: 30.00 %
- P16: 1000.00 usec
- F1: Acquisition parameters
  - SFO1: 600.1327 MHz
  - FIDRES: 10.602203 Hz
  - SW: 10.600 ppm

F2 - Processing parameters

- SI: 4096
- SF: 600.1300034 MHz
- WD: 0 Hz
- L: 0
- GB: 0
Compound 8

Current Data Parameters
NAME: KL4-103-5-1
EXPNO: 2
PROCNO: 1

F2 - Acquisition Parameters
Date: 20130201
Time: 18:19
INSTRUM: av600
PROBHD: 5 mm TBI1
PULPROG: zg
TD: 65536
SOLVENT: DMSO
NS: 8
DS: 0
SN: 12376.237 Hz
FIDRES: 0.188846 Hz
AQ: 2.6477944 sec
RG: 128
DW: 40.400 usec
DE: 6.50 usec
TE: 298.0 K
D1: 2.00000000 sec
TD0: 1

====== CHANNEL f1 ======
NUC1: 1H
P1: 9.48 usec
PL1: 2.00 da
PL1W: 39.81071854 W
SF01: 600.1336008 MHz

F2 - Processing parameters
SI: 65536
SF: 600.1300070 MHz
MIN: EM
SSB: 0
LB: 0 Hz
GB: 0
FC: 1.00
Compound 8

Current Data Parameters
NAME       XL-103-9-1
EXPER   4
PROCNO   5

F2 - Acquisition Parameters
Date       20130201
Time       18.43
INSTRUM    av600
PROBHD     5 mm TBI5
PULPROG    dipsi2etgpsi
TD         2048
SFOMODE    D2ref

---- CHANNEL f1 -----
NUC1               1
HP1                9.48 usec
P2                  18.96 usec
P6                 40.00 usec
PL1              -2.00 dB
PL10               10.51 dB
PL1W          39.81071854 W
PL10W         2.23357201 W
SFO1       600.1336008 MHz

F1 - Acquisition parameters
TD        128
SFO1       600.1336 MHz
FIDRES   60.845032 Hz
SW            12.977 ppm
FnMODE     Echo-Antiecho

F2 - Processing parameters
SI        4096
SF          600.1300059 MHz
WDWSSB       2
LB       0 Hz
GB       0
PC          1.00

F1 - Processing parameters
SI        4096
MC2  echo-Antiecho
ZF       600.1300056 MHz
NOW       0 Hz
SSB       2
LB       0 Hz
GB       0
## Compound 8

**Current Data Parameters**

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<tr>
<td>Time</td>
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<td>INSTRUM</td>
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<tr>
<td>PROBHD</td>
<td>5 mm TBI</td>
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<tr>
<td>SOLVENT</td>
<td>DMSONS</td>
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<tr>
<td>DS</td>
<td>24</td>
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<tr>
<td>SW</td>
<td>7183.908 H</td>
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<td>FIDRES</td>
<td>3.507768 H</td>
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<tr>
<td>AQ</td>
<td>0.1425908 s</td>
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<tr>
<td>RG</td>
<td>2600</td>
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<tr>
<td>DW</td>
<td>69.600 u</td>
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<tr>
<td>DE</td>
<td>6.060 u</td>
</tr>
<tr>
<td>TR</td>
<td>197.9 X</td>
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<tr>
<td>CNH7</td>
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<td>CNH9</td>
<td>149.00000000</td>
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<td>DCS</td>
<td>0.000000005 s</td>
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<tr>
<td>D1</td>
<td>1.350000005 s</td>
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<tr>
<td>D2</td>
<td>0.000000005 s</td>
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<td>D16</td>
<td>0.000000005 s</td>
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<td>D9</td>
<td>0.000000005 s</td>
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--- CHANNEL f1 ---

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<tbody>
<tr>
<td>NUC1</td>
<td>1H</td>
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<tr>
<td>P1</td>
<td>9.044 u</td>
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<tr>
<td>PL1</td>
<td>7.066 dB</td>
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<tr>
<td>PLW</td>
<td>39.81071854 W</td>
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<tr>
<td>EFGQ</td>
<td>600.1332007 MHz</td>
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--- CHANNEL f2 ---

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<tr>
<td>NUC2</td>
<td>13C</td>
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<tr>
<td>P3</td>
<td>18.96 u</td>
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<tr>
<td>PL2</td>
<td>-3.00 dB</td>
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<tr>
<td>SFO2</td>
<td>150.9156357 MHz</td>
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--- GRADIENT CHANNEL ---

### F1 - Acquisition parameter

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<tr>
<td>TO</td>
<td>0 Hz</td>
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<tr>
<td>STDS</td>
<td>150.9156 MHz</td>
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<tr>
<td>PSHSS</td>
<td>94.033469 Hz</td>
</tr>
<tr>
<td>SW</td>
<td>180.002 Hz</td>
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<tr>
<td>PSHGD</td>
<td>180.002 Hz</td>
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### F2 - Acquisition parameter

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<td>0 Hz</td>
</tr>
<tr>
<td>STDS</td>
<td>150.9156 MHz</td>
</tr>
<tr>
<td>PSHSS</td>
<td>94.033469 Hz</td>
</tr>
<tr>
<td>SW</td>
<td>180.002 Hz</td>
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<tr>
<td>PSHGD</td>
<td>180.002 Hz</td>
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### F1 - Processing parameter

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<tr>
<td>SI</td>
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</tr>
<tr>
<td>SF</td>
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<tr>
<td>WDW</td>
<td>QSINESSB</td>
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### F2 - Processing parameter

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<tr>
<td>WDW</td>
<td>QSINESSB</td>
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### Current Data Parameters

<table>
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### F2 - Acquisition Parameters

- **Date:** 20130209
- **Time:** 16:03
- **INSTRUM:** av500
- **PROBHD:** 5 mm DCH 13C-1
- **PULPROG:** zg30
- **TD:** 65536
- **SOLVENT:** DMSO
- **NS:** 16
- **DS:** 0
- **SWN:** 10000.000 Hz
- **FIDRES:** 0.152588 Hz
- **AQ:** 3.2768500 sec
- **RG:** 29.99
- **DW:** 50.000 usec
- **DE:** 10.00 usec
- **TE:** 298.0 K
- **TD0:** 1

#### CHANNEL f1

- **SFO:** 500.1330008 MHz
- **NUC:** 1H
- **PLW:** 13.5000000 W

### F2 - Processing parameters

- **SI:** 65536
- **SF:** 500.1300146 MHz
- **WDW:** EMSSB 0
- **LB:** 0.30 Hz
- **GB:** 1.00
### Current Data Parameters

<table>
<thead>
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<th>NAME</th>
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### F2 - Acquisition Parameters

<table>
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<tbody>
<tr>
<td>Date</td>
<td>20120214</td>
</tr>
<tr>
<td>Time</td>
<td>18.39</td>
</tr>
<tr>
<td>INSTRUM</td>
<td>av600PROBHD</td>
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<tr>
<td>PROBHD</td>
<td>5 mm TBI</td>
</tr>
<tr>
<td>PULPROG</td>
<td>cosygmfph</td>
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<tr>
<td>TD</td>
<td>4096</td>
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<tr>
<td>SOLVENT</td>
<td>DMSON</td>
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<td>DS</td>
<td>4</td>
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<td>NM</td>
<td>2</td>
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<tr>
<td>SWH</td>
<td>5387.93 Hz</td>
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<td>FIDRES</td>
<td>1.3154 Hz</td>
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<tr>
<td>AQ</td>
<td>0.3801588 sec</td>
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<td>RG</td>
<td>181</td>
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<td>DW</td>
<td>90.800 usec</td>
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<td>DE</td>
<td>6.50 usec</td>
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<td>TE</td>
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<td>D0</td>
<td>0.000000000 sec</td>
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<td>D1</td>
<td>2.000000000 sec</td>
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<tr>
<td>D13</td>
<td>0.000000000 sec</td>
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<tr>
<td>D16</td>
<td>0.000000000 sec</td>
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<tr>
<td>IN0</td>
<td>0.000018560 sec</td>
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### CHANNEL f1

<table>
<thead>
<tr>
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<th>Value</th>
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<tbody>
<tr>
<td>NUC1</td>
<td>1H</td>
</tr>
<tr>
<td>P1</td>
<td>9.35 usec</td>
</tr>
<tr>
<td>P2</td>
<td>18.70 usec</td>
</tr>
<tr>
<td>PL1</td>
<td>-2.00 dB</td>
</tr>
<tr>
<td>PL2</td>
<td>39.81071854 W</td>
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<tr>
<td>SF01</td>
<td>600.1327006 MHz</td>
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### CHANNEL Gradient

<table>
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<tr>
<td>GPX2</td>
<td>0 %</td>
</tr>
<tr>
<td>GPY1</td>
<td>0 %</td>
</tr>
<tr>
<td>GPY2</td>
<td>0 %</td>
</tr>
<tr>
<td>GPZ1</td>
<td>10.00 %</td>
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<tr>
<td>GPZ2</td>
<td>20.00 %</td>
</tr>
<tr>
<td>P16</td>
<td>1000.00 usec</td>
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</table>

### F1 - Acquisition parameters

<table>
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<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>TD</td>
<td>512</td>
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<tr>
<td>SF01</td>
<td>600.1327 MHz</td>
</tr>
<tr>
<td>FIDRES</td>
<td>10.523297 Hz</td>
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<tr>
<td>SW</td>
<td>8.978 ppm</td>
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<td>FnMODE</td>
<td>States-TPPI</td>
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### F2 - Processing parameters

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<td>SF</td>
<td>600.1300273 MHz</td>
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<tr>
<td>WDM</td>
<td>QSINE</td>
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<tr>
<td>LB</td>
<td>0 Hz</td>
</tr>
<tr>
<td>GB</td>
<td>0</td>
</tr>
<tr>
<td>PC</td>
<td>1.00</td>
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### F1 - Processing parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>SI</td>
<td>2048</td>
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<tr>
<td>MC2</td>
<td>States-TPPI</td>
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<tr>
<td>SF</td>
<td>600.1300273 MHz</td>
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<tr>
<td>WDM</td>
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<td>LB</td>
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<td>GB</td>
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Compound 9

**Current Data Parameters**

**NAME**       KL-4-103-6-2EXPNO                 5
PROCNO                1

**F2 - Acquisition Parameters**

**Date_**          20120214
**Time**              20.30
**INSTRUM**           av600
**PROBHD**   5 mm TBI5
**PULPROG**    hsqcetgpsisp
**TD**                 2048
**SOLVENT**            DMSONS
**DS**                   16
**SWH**            5387.931 Hz
**FIDRES**         2.630826 Hz
**AQ**            0.1901044 sec
**RG**                26008
**DW**               92.800 usec
**DE**                6.00 usec
**TE**                297.2 K
**CNST2**       145.0000000 D0
**D1**           1.20000005 sec
**D4**           0.00172414 sec
**D11**          0.03000000 sec
**D16**          0.00020000 sec
**IN0**          0.00001840 sec

**ZGOPTNS**

-chan- f1

**NUC1**                 1
**HP1**                 9.35 usec
**P2**                18.70 usec
**P1**               1000.00 usec
**PL1**               -2.00 dB
**PL1W**        39.81071854 W
**WSFO1**        600.1327006 MHz

-chan- f2

**CPDPRG2**            garp
**NUC2**                13
**CP3**                18.50 usec
**P4**                37.00 usec
**P14**              1500.00 usec
**PCPD2**              65.00 usec
**PL0**              120.00 dB
**PL2**              -3.00 dB
**PL12**             7.91 dB
**PL0W**          0 W
**PL2W**         150.35617065 W
**PL12W**       12.19330025 W
**WSFO2**        150.9133722 MHz
**SP3**                6.35 dB
**SPNAM3**      Wurst. ret
**SPOAL3**            0.500
**SPOFFS3**   0 Hz

-grad-

**GPNAM1**         SINE.100
**GPNAM2**         SINE.100
**GPZ1**            80.00 %
**GPZ2**            20.10 %
**P16**          1000.00 usec

-chan- f1

**TD**                  256
**FIDRES**       150.9134 MHz
**SW**              180.000 ppm
**FnMODE**       Echo-Antiecho

-chan- f2

**SI**                 4096
**SF**          600.1300273 MHz
**WDW**                  2
**LB**            0 Hz
**GB**            0

-chan- f1

**SI**                 4096
**MC2**       echo-antiecho
**SF**          150.9028800 MHz
**WDWSSB**                  2
**LB**            0 Hz
**GB**            0
Compound 10a/b

Current Data Parameters
NAME          KL5-116-7-1
EXPN0         12
PROCNO        1

F2 - Acquisition Parameters
Date_          20130209
Time            19.24
INSTRM          av600
PROBHD          5 mm TBI
PULPROG         zg
TD             65536
SOLVENT        DMSO
NS            8
DS            0
SWR           12176.297 Hz
FIDRES         0.188846 Hz
AQ             2.6477344 sec
RG             128
DW            40.400 usec
DE              6.50 usec
TE             298.0 K
D1            2.00000000 sec
TD0           1

====== CHANNEL f1 ======
NUC1          1H
P1            9.27 usec
PL1            2.00 da
PL1W          39.81071854 W
SFO1          600.1336008 MHz

F2 - Processing parameters
S1             65536
SF          600.1300070 MHz
DWW              EM
SSB            0
LB              0.30 Hz
GB            0
FC            1.00
Compound 10a/b

Current Data Parameters
NAME KL5-116-7-1
EXPNO 5
PROCNO 1

F2 - Acquisition Parameters
Date 20130207
TIME 19.26
INSTRUM av600PROBHD
PULPROG cosygpmfph
TD 2048
SOLVENT DMSO
NS 16
DS 16
SW 6887.052 Hz
FIDRES 3.362818 Hz
AQ 0.1487348 sec
RG 128
DW 72.600 usec
GE 6.50 usec
TE 8.5 C
D0 0.00000000 sec
D1 1.50000000 sec
D13 0.00000000 sec
D16 0.00000000 sec
IN0 0.00014520 sec

--------------- CHANNEL f1 ---------------
NUC1 1H
P1 9.16 usec
P2 18.72 usec
PL1 -2.00 dB
PLW 39.81071854 W
SFO1 600.1333007 MHz

----- GRADIENT CHANNEL ------
GRAN1 SINE.100
GRAN2 SINE.100
GPK1 0 %
GPK2 0 %
GPV1 0 %
GPV2 0 %
GPE1 0.00 %
GPE2 0.00 %
P16 1000.00 usec

F1 - Acquisition parameters
TD 512
SFO1 600.1333 MHz
FIDRES 13.451260 Hz
SM 11.4476 ppm
FREQUENCY States-TPPI

F2 - Processing parameters
SI 4096
SF 600.1300026 MHz
WDM QSINE
LSB 2
LB 0 Hz
Q 0
PC 1.00

F1 - Processing parameters
SI 4096
SF 600.1300026 MHz
WDM QSINE
LSB 2
LB 0 Hz
Q 0
PC 1.00
Compound 10a/b

Current Data Parameters
NAME KL5-116-7-1
EXINFO 6
PROCINFO 1

F2 - Acquisition Parameters
Date 20130207
TIME 21:21
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG dipsi2etgpsi
TD ... DMSONS                    8
DS                   16
D11          0.00020000 sec
D21          0.00001000 sec
DN0          0.00012840 sec
L1           14

======== CHANNEL f1 ========
NUC1                 1
P1                 9.36 usec
P2                 18.72 usec
P6                 40.00 usec
P11                -2.00 dB
P10                 10.62 dB
P1W        39.81071854 W
PL10W        2.17770982 W
SFO1        600.1336008 MHz

====== GRADIENT CHANNEL =====
GPNAM1         SINE.100
GPNAM2         SINE.100
GPZ1              30.00 %
GPZ2              30.00 %
P16             1000.00 usec

F1 - Acquisition parameters
TD      512
SFO1    600.1336 MHz
FIDRES  15.211258 Hz
SW      12.977 ppm
FnMODE    Echo-Antiecho

F1 - Processing parameters
SI        4096
SF        400.1300 MHz
MEM      2
SBS      2
LB      0 Hz
GB      0
PC      1.00

F1 - Processing parameters
SI        4096
MC2    echo-antiecho
SF        400.1300 MHz
MEM      2
SBS      2
LB      0 Hz
GB      0
Compound 10a/b

Current Data Parameters

F1 - Acquisition Parameters
       TD: 312
       SW: 600.1339 MHz
       FIDRES: 15.21128 Hz
       Sw: 13.277 ppm

F1 - Processing parameters
       SF: 4096
       SW: 600.133000 MHz
       WCM: 2
       LB: 0 Hz
       DB: 0
       FC: 1.00

F1 - Acquisition parameters
       TD: 312
       SW: 600.1339 MHz
       FIDRES: 15.21128 Hz
       Sw: 13.277 ppm

F1 - Processing parameters
       SF: 4096
       SW: 600.133000 MHz
       WCM: 2
       LB: 0 Hz
       DB: 0
       FC: 1.00

F1 - Processing parameters
       SF: 4096
       SW: 600.133000 MHz
       WCM: 2
       LB: 0 Hz
       DB: 0
       FC: 1.00
Compound 11

Current Data Parameters
NAME        KL-4-103-8
EXPNO          2
PROCNO          1

F2 - Acquisition Parameters
Date_        20120131
Time          12.13
INSTRUM        av600
PROBHD        5 mm TBI
PULPROG       zg
TD            65536
SOLVENT       DMSO
NS            8
DS             0
SNH          12376.237 Hz
FIDRES        0.18846 Hz
AQ            2.647794 sec
RG            28.5
DW           40.450 usec
DE             6.50 usec
TE            295.0 K
D1        2.00000000 sec
TD0            1

======== CHANNEL f1 ========
NUC1          1H
P1            10.15 usec
PL1         2.00 dm
PL1W     39.81071854 W
FRO1     600.1336008 MHz

F2 - Processing parameters
S1          65536
SF        600.1300273 MHz
WINM         EM
SSB         0
LB            0.30 Hz
GB            0
PC            1.00
Compound 11

Current Data Parameters
NAME          KL-4-103-8
EXPNO          3
PROCNO          1

F2 - Acquisition Parameters
Date           20120131
Time             12.16
INSTRUM          av600PROBHD
PULPROG        cosygpmfph
TD             4096
SOLVENT        DMSO

F1 - Acquisition parameters
TD             512
F2             2048

F2 - Processing parameters
SI            2048
MC2     States-TPPI
SF     600.1300273 MHz

F1 - Processing parameters
SI            2048
MC2     States-TPPI
SF     600.1300273 MHz
Compound 11

Current Data Parameters
NAME         KL-4-103-8
EXPNO                7
PROCNO                1

F2 - Acquisition Parameters
Date_          20120202
Time              11.13
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG     mlevetgp.js
TD                 4096
SOLVENT            DMSONS
NS                2
DS                16
DM6S            5350.974 Hz
FIDRES            1.360395 Hz
AQ            0.3703284 sec
BO                128
DW               90.400 ussec
TE              284.2 kHz
DG            0.000000100 sec
D1               2.00000005 sec
D2            0.00000000 sec
D11            0.00000200 sec
D12            0.00000200 sec
D16            0.000015720 sec
L1                24

====== CHANNEL f1 ======
NUC1                 1
P1                 10.50 ussec
P2                21.00 ussec
P5                26.68 ussec
P6                40.00 ussec
P7                80.00 ussec
P17            2500.000 ussec
PL1            -2.00 dB
PL10            9.54 dB
PL1W        39.81071854 W
PL10W          2.79254389 W
SF01        600.1327006 MHz

====== GRADIENT CHANNEL ======
GPNAM1         SINE.100
GPNAM2         SINE.100
GPZ1            30.00 %
GPZ2            30.00 %
P16            1000.000 ussec
F1 - Acquisition parameters
TD              600
SF01        600.1327006 MHz
FIDRES            10.600 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI              1024
SF        600.1300273 MHz
WDM           QUITINE
SSB                2
LB              0 Hz
GB                0 Hz
PC               1.00

F1 - Processing parameters
SI              1024
WDM           echo-antiecho
SF        600.1300273 MHz
WDM           QUITINE
SSB                2
LB              0 Hz
GB                0 Hz
Compound 11

Current Data Parameters
NAME: KL5-126-5
EXPNO: 10
PROCNO: 1

F2 - Acquisition Parameters
Date: 20130214
Time: 20.02
INSTRUM: av600
PROBHD: 5 mm TBI
PULPROG: roesyesgppp
SOLVENT: DMSO
NS: 10
DS: 10
FIDRES: 3.507768 Hz
SW: 7183.908 Hz
AQ: 0.1425908 sec
dm: 49.600 usec
tE: 298.0 K
D0: 0.00005978 sec
d12: 0.00002000 sec
D16: 0.00020000 sec

======== CHANNEL f1 ========
NUC1: 1H
P1: 9.14 usec
P2: 18.28 usec
P15: 200000.00 usec
PL0: 120.00 dB
PL1: -2.00 dB
PL11: 18.78 dB
PL0W: 0 W
PL1W: 39.81071854 W
PL11W: 0.33265951 W
SFO1: 600.1336008 MHz
SP10: 38.78 dB
SPNAM10: Squa10.00
SPOAL10: 0.500
SPOFFS10: -1601.48 Hz

==== GRADIENT CHANNEL ====
GPNAM1: SINE.100
GPNAM2: SINE.100
GPZ1: 31.00 %
GPZ2: 11.00 %
P16: 1000.00 usec

F1 - Acquisition parameters
TD: 554
FIDRES: 11.971 ppm
F2 - Processing parameters
SI: 4096
SF: 600.1336 MHz
WDM: 1.00

F1 - Processing parameters
SI: 4096
SF: 600.1336 MHz
WDM: 1.00
### Compound 12

**Current Data Parameters**

<table>
<thead>
<tr>
<th>NAME</th>
<th>KLS-103-9-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROCNO</td>
<td>11</td>
</tr>
</tbody>
</table>

**F2 - Acquisition Parameters**

<table>
<thead>
<tr>
<th>Date_</th>
<th>20130218</th>
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<tbody>
<tr>
<td>Time</td>
<td>17:29</td>
</tr>
<tr>
<td>INSTRUM</td>
<td>av600</td>
</tr>
<tr>
<td>PROBHD</td>
<td>5 mm TBI5</td>
</tr>
<tr>
<td>PULPROG</td>
<td>zg</td>
</tr>
<tr>
<td>TD</td>
<td>65516</td>
</tr>
<tr>
<td>SOLVENT</td>
<td>DMSO</td>
</tr>
<tr>
<td>NS</td>
<td>8</td>
</tr>
<tr>
<td>DS</td>
<td>0</td>
</tr>
<tr>
<td>SNH</td>
<td>12376.337 Hz</td>
</tr>
<tr>
<td>FIDRES</td>
<td>0.188846 Hz</td>
</tr>
<tr>
<td>AQ</td>
<td>2.6477944 sec</td>
</tr>
<tr>
<td>RG</td>
<td>90.5</td>
</tr>
<tr>
<td>DW</td>
<td>40.400 usec</td>
</tr>
<tr>
<td>TE</td>
<td>298.0 K</td>
</tr>
<tr>
<td>D1</td>
<td>2.00000000 sec</td>
</tr>
</tbody>
</table>

**F2 - Processing parameters**

- **S1**: 65536
- **SF**: 600.1300071 MHz
- **WDW**: EM
- **SSB**: 0
- **LB**: 0 Hz
- **GB**: 0
- **FC**: 1.00

---

![NMR Spectrogram](chart.png)

ppm
### Current Data Parameters

| NAME     | KL-4-103-9-1_KLEXPNO                 | PROCNO                | 3 |

### Acquisition Parameters

| Date_          | 20120203                          | Time              | 11.17 |
| INSTRUM           | av600PROBHD   | 5 mm TBI5PULPROG      | cosygpmfphTD                 | 4096 |
| SOLVENT            | DMSONS                    | 2DS                    | 4 |
| DS                  | 4 |
| SWH            | 5387.931 Hz |
| FIDRES         | 1.315413 Hz |
| AQ                 | 0.38015888 sec |
| BG                  | 181 |
| DK                 | 92.800 usec |
| DE                 | 6.50 usec |
| TE                 | 194.5 K |
| D0                  | 0.00000845 sec |
| D1                 | 2.00000000 sec |
| D13                | 0.00000400 sec |
| D16                | 0.00002000 sec |
| IND                | 0.0000185400 sec |

#### CHANNEL f1 ####

| NUC1        | 1H |
| P1                 | 9.70 usec |
| P2                | 19.40 usec |
| P16               | 0.144 usec |
| P1w               | 39.81071854 |
| SFO1           | 600.1327006 MHz |

#### GRADIENT CHANNEL ####

| GPNAM1      | SINE.100 |
| GPNAM2      | SINE.100 |
| GPZ1              | 10.00 % |
| GPZ2              | 20.00 % |
| GPZ1W            | 1000.00 usec |
| F1 - Acquisition parameters |
| TD                  | 512 |
| SFO1           | 600.1327 MHz |
| FIDRES         | 10.523297 Hz |
| DK                 | 8.978 ppm |
| F2 - Processing parameters |
| SF                  | 4096 |
| SFM                | 600.1300099 MHz |
| WDM               | QSINE |
| LB                 | 0 Hz |
| GB                  | 0 |
| FC                  | 1.00 |

#### CHANNEL f2 ####

| NUC1        | 1H |
| P1                 | 9.70 usec |
| P2                | 19.40 usec |
| P16               | 0.144 usec |
| P1w               | 39.81071854 |
| SFO1           | 600.1327006 MHz |

#### GRADIENT CHANNEL ####

| GPNAM1      | SINE.100 |
| GPNAM2      | SINE.100 |
| GPZ1              | 10.00 % |
| GPZ2              | 20.00 % |
| GPZ1W            | 1000.00 usec |

### Processing Parameters

<p>| SI                        | 4096 |
| SFM                | 600.1300099 MHz |
| WDM               | 2 |
| LB                 | 0 Hz |
| GB                  | 0 |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current Data Parameters</strong></td>
<td></td>
</tr>
<tr>
<td><strong>NAME</strong></td>
<td>KL-4-103-9-1_KLEXPNO</td>
</tr>
<tr>
<td><strong>PROCNO</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Date</strong></td>
<td>20120203</td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td>11.59</td>
</tr>
<tr>
<td><strong>INSTRUM</strong></td>
<td>av600</td>
</tr>
<tr>
<td><strong>PROBHD</strong></td>
<td>5 mm TBI5</td>
</tr>
<tr>
<td><strong>PULPROG</strong></td>
<td>mlevetgp.js</td>
</tr>
<tr>
<td><strong>NS</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>DS</strong></td>
<td>16</td>
</tr>
<tr>
<td><strong>FIDRES</strong></td>
<td>1.350335 Hz</td>
</tr>
<tr>
<td><strong>A</strong></td>
<td>0.3703284 s</td>
</tr>
<tr>
<td><strong>RG</strong></td>
<td>128</td>
</tr>
<tr>
<td><strong>DW</strong></td>
<td>50.400 us</td>
</tr>
<tr>
<td><strong>D0</strong></td>
<td>0.00003000 ms</td>
</tr>
<tr>
<td><strong>D1</strong></td>
<td>1.20000005 ms</td>
</tr>
<tr>
<td><strong>D9</strong></td>
<td>0.0000000000 ms</td>
</tr>
<tr>
<td><strong>D11</strong></td>
<td>0.0000000000 ms</td>
</tr>
<tr>
<td><strong>D12</strong></td>
<td>0.0000000000 ms</td>
</tr>
<tr>
<td><strong>D16</strong></td>
<td>0.0000000000 ms</td>
</tr>
<tr>
<td><strong>L1</strong></td>
<td>24</td>
</tr>
</tbody>
</table>

--- CHANNEL f1 ---

<table>
<thead>
<tr>
<th>NUC1</th>
<th>LH</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>9.70 us</td>
</tr>
<tr>
<td>F2</td>
<td>19.40 us</td>
</tr>
<tr>
<td>F5</td>
<td>26.48 us</td>
</tr>
<tr>
<td>F6</td>
<td>40.00 us</td>
</tr>
<tr>
<td>F7</td>
<td>80.00 us</td>
</tr>
<tr>
<td>F17</td>
<td>2500.00 us</td>
</tr>
<tr>
<td>LL1</td>
<td>-2.00 dB</td>
</tr>
<tr>
<td>LL10</td>
<td>9.54 dB</td>
</tr>
</tbody>
</table>

--- GRADIENT CHANNEL ---

| GNAM1 | SINE.100 |
| GNAM2 | SINE.100 |
| GPE1  | 36.00 h |
| GPE2  | 48.00 h |
| P16   | 1000.00 us |

--- CHANNEL f2 ---

<table>
<thead>
<tr>
<th>F1</th>
<th>Acquisition parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD</td>
<td>600</td>
</tr>
<tr>
<td>SF01</td>
<td>600.1327 MHz</td>
</tr>
<tr>
<td>TD</td>
<td>10.6002 Hz</td>
</tr>
<tr>
<td>SF</td>
<td>10.6000 ppm</td>
</tr>
<tr>
<td>PC</td>
<td>Echo-Antiecho</td>
</tr>
</tbody>
</table>

--- Processing parameters ---

| SI | 40.00 |
| SF | 600.1300667 MHz |
| LB | 0 Hz          |
| GB | 1.00         |

--- CHANNEL f9 ---

<table>
<thead>
<tr>
<th>F1</th>
<th>Acquisition parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD</td>
<td>600</td>
</tr>
<tr>
<td>SF01</td>
<td>600.1327 MHz</td>
</tr>
<tr>
<td>TD</td>
<td>10.6002 Hz</td>
</tr>
<tr>
<td>SF</td>
<td>10.6000 ppm</td>
</tr>
<tr>
<td>PC</td>
<td>Echo-Antiecho</td>
</tr>
</tbody>
</table>
Compound 12

Current Data Parameters
NAME          DL5-103-9-1
EXPNO          39
PROCNO          1

F2 - Acquisition Parameters
Date_          20130222
Time            21:13
INSTRUM          av600
PROBHD         5 mm TBI5
PULPROG      roesyesgpphTD
TD            2048
SOLVENT        DMSO
NS               8
DS              16
GEW           7788.162 Hz
FIDRES      3.802814 Hz
AQ            0.1315316 sec
KG                2896.3
DM            64.200 usec
DE             6.50 usec
TE            296.0 K
D0            0.00003512 sec
D1          1.50000000 sec
D12          0.00000000 sec
D16          0.00000000 sec
IN0          0.00012840 sec

======== CHANNEL f1 ========
NUC1          1H
P1            11.12 usec
P2            32.24 usec
P15          20000.00 usec
P40            200.00 usec
PL0           120.00 dB
PL1           -2.00 dB
PL11           -17.28 dB
PL1W          0.00 W
PL1WW         39.81071854 W
PL11W         0.49203953 W
SP01          600.1336008 MHz
SP10          177.08 dB
SPNAM10       Squa100.100
SPAL10         0.500
SPOFFS10      -1546.00 Hz

======== GRADIENT CHANNEL ======
GPNAM1        SINE.100
GPNAM2        SINE.100
GPX1          0 %
GPX2          0 %
GPY1          0 %
GPY2          0 %
GPZ1          31.00 %
GPZ2          11.00 %
P16         1000.00 usec

F1 - Acquisition parameters
TD            512
SP01          600.1336 MHz
FIDRES      15.211274 Hz
SW            12.977 ppm
FNCODE States-TPPI

F2 - Processing parameters
SI            4096
SF          600.1336006 MHz
MDQ           QSINE
AMR            2.5
LB            0 Hz
QB            0
FC            1.00
Compound 12

Current Data Parameters
NAME        KL5-103-9-1
EXPNO       48
PROCNO      1

F2 - Acquisition Parameters
Date:       20130223
Time:       18.19
INSTRUM      av600
FIDRES   8.888882 Hz
AQ                0.1315316 sec
DS                   16
SWH            7788.162 Hz
FIDRES         3.802814 Hz
RS      0.00005287 sec
RG               2896.312000 usec
DE                 6.50 usec
TE                298.0 KD0           0.00005287 sec
D1           1.50000000 sec
D12          0.00002000 sec
D16          0.00001244 usec

--------- CHANNEL f1  ---------
NUC1                 1H
P1                11.52 usec
P2                23.04 usec
P15           200000.00 usec
P40             2000.00 usec
P50             120.00 dB
P11             7.20 dB
PL0              1.67 dB
PL0W        0 W
PL1W       39.817158 W
PL1MW      0.0564518 W
SP10           600.1336008 MHz
SP10W     0.550 MHz
SP10W     0.500 MHz
SP10W     0.0012845 W

--------- GRADIENT CHANNEL ---------
GPX1     0 %
GPX2     0 %
GPY1     0 %
GPY2     0 %
GPZ1              31.00 %
GPZ2              11.00 %
P16             1000.00 usec

F1 - Acquisition parameters
TD                  264
SFO1           600.1336 MHz
FIDRES        29.500652 Hz
FS                  12.977 ppm
F1 - Processing parameters
SF                  264
SFO1           600.1336 MHz
SFO1           29.500652 Hz
SW                12.977 ppm
Compound 12

Current Data Parameters
NAME       KL-4-103-9-1_KLEXPNO
PROCNO      1

F2 - Acquisition Parameters
Date        20120204
Time         15.46
INSTRUM      av600
PROBHD   5 mm TBI5
PULPROG    hmbcgpl2ndqf
TD          256
SFO1        600.1330006 MHz

F1 - Acquisition parameters
TD          256
SFO1        150.9164 MHz
FIDRES       117.903427 Hz
SW              200.000 ppm
FnMODE               QF

F2 - Processing parameters
SI                 4096
SF          150.9029037 MHz
WDW               QSINESSB                   2
LB       0 Hz
GB       0
PC               1.00

F1 - Processing parameters
SI                 4096
SF          150.9164 MHz
WDW               QSINESSB                   2
LB       0 Hz
GB       0
PC               1.00
Compound 4

Current Data Parameters
NAME  KL-4-100
EXPRO  2
PROCNO  1

F2 - Acquisition Parameters
Data  203103429
Time  10.25
INSTRUM  US-500
PROCBD  5 mm DCM 13C-1
PULPROG  zg10
TD  65386
SOLVENT  DMSO
NS  4
DS  0
SMH  10000.000 Hz
FIDRES  0.152384 Hz
AQ  3.2767999 sec
PG  11
DM  50.000 usec
dE  10.00 usec
tE  298.0 K
DI  2.0000000 sec
TD0  1

----- CHANNEL f1 ----- 
SFQ1  500.133000 MHz
MVCl  1N
F1  10.00 usec
PLMR  13.5000000 W

F2 - Processing parameters
ST  65386
SS  500.1300146 MHz
WCM  EM
SSB  0
LB  0.30 Hz
GB  0
PC  1.00
Compound 4

Current Data Parameters
NAME        XL-e-100
EXPO        0
PROCRO      1

F2 - Acquisition Parameters
Data_       20130429
Time        10.36
INSTBMD     ax550.0
F2RMBD      5 mm DCHA 12C-1
PULPROG     zgpl10
T2          65.536
SOLVENT     DMSO
NS          76
DS          2
SNM         31250.000 Hz
F1RES       0.578337 Hz
Acq         1.045760 sec
RG          202.91
DM          16000 usec
EX          18.00 usec
TE          298.0 K
D1          200000000 sec
D1I         600000000 sec
TD0         1

------- CHANNEL f1 -------
SFO1        125.777511 MHz
N0C1        13C
F1          9.63 usec
PLW1        23.00000000 W

------- CHANNEL f2 -------
SFO2        500.133000 MHz
N0C2        1H
CP2PRG[2]   walsr1k
PFC2        90.00 usec
PLW2        13.50000000 W
PLW42       3.2196000 W
PLW413      0.13500001 W

F1 - Processing parameters
SI          132.072
SF          125.7577892 MHz
WDM         EM
S2B         0
LB          1.00 Hz
GB          0
PC          1.40
Compound 5
Current Data Parameters
NAME MWY-Cy_AV500
EXPNO 8
PROCNO 1

F2 - Acquisition Parameters
Date 20130426
Time 11:11
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 11
DW 50000 usec
DE 10.00 usec
TE 298.0 K
DI 2.0000000 sec
TD0 1

------- CHANNEL f1 -------
SF01 500.1330008 MHz
NUC1 1H
PI 10.00 usec
PLW1 13.5000000 W

F2 - Processing parameters
SI 65536
SF 500.1300146 MHz
WDW EM
SSB 0
LB 0.30 Hz
GH 0
PC 1.00
Compound 5

Current Data Parameters
NAME  MTR-Cy_AH500
EXPO  9
PROCRO  1

F2 - Acquisition Parameters
Data  20132922
Time  11:15
INSTRUM  500000
PROBRD  5 mm DCM 13C-1
PULPROG  zgpi10
TD  65536
SOLVENT  DMSO
NS  77
DS  2
SNM  3250.000 Hz
FRES  3.479800 Hz
AQ  1.084500 sec
PG  202.93
DM  16.000 usec
DE  18.000 usec
t  298.0 K
D1  2.0000000 sec
D1  0.0000000 sec
TD0  1

------- CHANNEL f1 -------
SF01  125.772551 MHz
MC1  13C
F1  9.63 usec
PLM1  23.0000000 W

------- CHANNEL f2 -------
SF02  500.133000 MHz
MC2  1H
CPFFAG  2
PCEG  89.09 usec
PLM2  13.5000000 W
PLM12  12.219985 W
PLM13  0.1350001 W

F2 - Processing parameters
SF  132.072
SF  125.7577892 MHz
WDM  EM
SBB  0
LH  1.00 Hz
GB  0
PC  1.40
Current Data Parameters
NAME       Kl-4-296_F69
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20120802
Time              18.27
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                   13
DS                    0
SWH           10000.000 Hz
FIDRES            0.152588 Hz
AQ               3.2767999 sec
RG               202.91
DW               50.000 usec
DE                10.00 usec
TE                296.0 K
D1           2.00000000 sec
T00                   1

-------- CHANNEL f1 --------
NUC1                 1H
P1                10.00 usec
PLW1        13.50000000 W
SFO1      500.1330008 MHz

F2 - Processing parameters
SI                65536
SF           500.1300146 MHz
WDW                  EM
SSB                 0
LB                 0.30 Hz
GB                 0
PC                1.00
Current Data Parameters
NAME        F1-4-301_F36
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_       20120802
Time          18.23
INSTRUM       av500
PROBHD      5 mm DCH 13C-1
PULPROG     zg30
TD              65536
SOLVENT     DMSO
NS               24
DS                0
SWH         10000.000 Hz
FIDRES    0.152588 Hz
AQ           3.2767999 sec
RG             202.91
DW                50.000 usec
DE           10.00 usec
TE             296.0 K
D1           2.00000000 sec
TD0                  1

----- CHANNEL f1 -------
NUC1           1H
P1           10.00 usec
PLW1       13.50000000 W
SFU1          500.1330008 MHz

F2 - Processing parameters
SI                65536
SF          500.1300146 MHz
WDW                 EM
SSB                0
LB         0.30 Hz
GB                0
PC               1.00
Current Data Parameters
NAME        KL-4-300_F7
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20120802
Time              18.31
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                   22
DS                    0
SWH           10000.000 Hz
FIDRES     0.152588 Hz
AQ                3.2767999 sec
RG               202.91
DW               50.000 usec
DE                10.00 usec
TE               296.0 K
D1           2.00000000 sec
TDD                 1

---------- CHANNEL f1 ----------
NUC1                 1H
P1                10.00 usec
PLW1        13.50000000 W
SFU1          500.1330008 MHz

F2 - Processing parameters
SI                65536
SF          500.1330146 MHz
WDW                  EM
SSB                 0
LB                 0.30 Hz
PC                 1.00
Current Data Parameters
NAME             F1-4-295_F38
EXPNO                1
PROCNO                1

F2 - Acquisition Parameters
Date_          20120802
Time              18.18
INSTRUM           av500
PROBHDL  5 mm DCH 13C-1
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                   26
DS                    0
SWH           10000.000 Hz
FIDRES     0.152588 Hz
AQ               3.2767999 sec
RG               202.91
DW               50.000 usec
DE                10.00 usec
TE                296.0 K
D1           2.00000000 sec
TDO                1

== CHANNEL f1 ==
NUC1                 1H
P1                10.00 usec
PLW1        13.50000000 W
SP01          500.133008 MHz

F2 - Processing parameters
SI                65536
SF 500.1300146 MHz
WDW                  EM
SSB                  0
LB                   0
GB                   0
PC                1.00
Current Data Parameters
NAME        K1-4-295_F38
EXPN0       4
PROCNO      1

F1 - Acquisition parameters
TD            256
SF01         500.1324 MHz
FIDRES     20.121468 Hz
SW              10.299 ppm
F2 - Processing parameters
SI            2048
SF         500.1300135 MHz
WDW        QSINE
SSB            2
LB          0 Hz
GB          0
PC           1.00

F1 - Processing parameters
SI           2048
MC2       echo-antiecho
SF      500.1300135 MHz
WDW        TRAP
SSB         2
LB          0 Hz
GB          0
Current Data Parameters
NAME       Kl-4-295_F38
EXPNO                 5
PROCNO                1

F1 - Acquisition parameters
TD                  181
SP01           125.7678 MHz
FIDRES       138.969650 Hz
SW              200.000 ppm
FreqMODE   Echo-Antiecho

F2 - Processing parameters
SI                 2048
SF          500.1300135 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2       echo-antiecho
SF         125.7578472 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
References


The detailed preparation of 2 will be reported elsewhere. Lawson, K. V.; Rose, T. E.; Harran, P. G.; *Submitted*.


Large ring-forming Friedel-Crafts alkylations have been used on occasion to prepare paracyclopahnes and pillararenes: (a) Gribble, G.W.; Nutaitis, C.F., *Tetrahedron Lett.*, **1985**, *26*(49), 6023-6026. (b) Holler, M.; Allenbach, N.; Sonet, J.; Nuerengarten, F.,...


H-Trp(d5)-OH subjected to MeSO3H (15 eq) in MeNO2 showed considerable 2H/H exchange at 16 hours. Early time points (10 mins) did not show exchange, indicating the rate of macrocyclization would outcompete deuterium scrambling. When H-Trp(d5)-OH was exposed to Sc(OTf)3 in MeNO2, no 2H/H exchange was observed even at extended...
reaction times (16h). The anomalous loss of two mass units [M-2] from acidolysis of 13 to form labeled 9 could not be observed with Sc(OTf)₃ as 9 is formed in only trace quantities under these conditions.


Chapter 5 - Macrocycle shape diversity through large-ring forming Friedel-Crafts alkylations

5.1. Introduction

Small molecules are powerful tools to interrogate biological processes. As drugs discovery efforts expand to increasingly challenging targets, including expanded, shallow ligand binding surfaces and protein-protein interfaces, identifying potent and selective small molecule ligands has become an increasingly difficult challenge.\textsuperscript{1-5} Natural products have been a rich source of biologically active compounds.\textsuperscript{6-8} These frequently feature complex molecular architectures beyond the structural space occupied by traditional screening libraries and are often uniquely capable of modulating challenging biological targets.\textsuperscript{9} So-called diversity oriented synthesis (DOS) of natural product-like libraries has become an area of considerable interest.\textsuperscript{10-13} A structural motif often observed in medicinally valuable natural products is the macrocycle.\textsuperscript{7,9,14-17} Despite renewed enthusiasm for this structural class serving as therapeutic leads, general methods to generate macrocycle diversity are lacking.\textsuperscript{17}

We are interested in methods to prepare diverse composite macrocyclic peptidomimetics in short reaction sequences beginning with unprotected peptides.\textsuperscript{18} In this regard, nature produces extraordinary structural diversity via modification of tryptophan.\textsuperscript{19,20} In fact, tryptophan is a unique amino acid in this regard; there are multiple, potentially competing nucleophilic sites on the indole nucleus (Figure 1). We have exploited this promiscuity in the context of large-ring forming reactions.\textsuperscript{21}
We have recently described an electrophilic reagent able to directly engage electron rich aromatic amino acids via large-ring forming Friedel-Crafts alkylations.\textsuperscript{22} Reactions proceeded rapidly and efficiently to form macrocyclic composites of 1 and peptides containing tyrosine and 4-aryloxyprolines (Figure 2A). Additionally, reaction of 1 with Trp-Trp-Tyr provided a mixture of diverse macrocycles via promiscuous alkylation of indole (Figure 2B).\textsuperscript{23} Here we examine the scope and functional group tolerance of this method and identify numerous novel macrocyclic substructures. A pilot macrocycle library has been prepared and fully characterized. Statistical measures were utilized to assess diversity with respect to commercial screening libraries and to evaluate shape diversity amongst isomeric macrocycles.\textsuperscript{24-26}

Figure 1. Natural products derived from modification of tryptophan
5.2. Results and Discussion

Initial experiments were designed to investigate the scope of Friedel-Crafts macrocyclization employing template 1. The efficiency of peptide macrocyclization methodologies are notoriously susceptible to changes in peptide composition, length, and stereochemistry.\(^{27-29}\) Importantly, our method is largely insensitive to these parameters. In spite of employing reactive carbocationic intermediates, basic, acidic, and nucleophilic residues were well tolerated. Turn-inducing residues were not required and peptides containing 3-5 amino acids cyclized efficiently, an outcome difficult to achieve via direct lactamization.\(^{27}\) Tryptophan 5-substitution had notable effect on product distribution and macrocycle diversity in these systems.

5.2.1. Preparation, Isolation and Characterization of Isomeric Macrocycles

From the onset we chose to incorporate 5-substituted tryptophan derivatives. In preliminary studies alkylation of this position was dominant.\(^{23}\) We hypothesized blocking this position would temper indole reactivity and provide a more uniform distribution of isomeric
macrocycles. We employed SIW(5-Br)A as a model tetrapeptide to investigate the effect of 5-bromo substitution. N-terminal acylation of SIW(5-Br)A with template 1 provided seco-composite 2 (Figure 3A). Exposure of 2 to 75 mM methansulfonic acid in nitromethane at room temperature provided a mixture of five isomeric macrocycles. These could be readily resolved by HPLC (Figure 3B). Together these products accounted for ~90 % total peak area indicating this reaction proceeded efficiently. Also, these reactions were remarkably fast; complete conversion was observed within 15 minutes.

Individual acidolysis products were resolved by preparative HPLC and their structures determined by 2D homo- and heteronuclear correlation NMR spectroscopy. Products 3 - 7 were identified as five novel macrocyclic substructures with 19, 20, 21, 23-membered rings. The major product 6 (51%) is derived from alkylation of indole-C6 with minor constituents arising from substitution at N1 (13%), C2 (13%), C3 (19%), and C4 (4%). Alkylation of C3 induced pyrroloindoline formation by trapping of the intermediate indolium ion with the proximal amine. This product was isolated as a single diastereomer which was assigned as the endo-pyrroloindoline by diastereotopic proton assignment of the Trp-β-CH₂ and syn NOE to the cinnamyl methylene as previously described.23 Natural occurring indole alkaloids commonly possess the pyrroloindoline motif. However this all carbon quaternary macrocyclic ring juncture appears to be unique to this chemistry.
5.2.2. Investigation of function group compatibility.

Cyclization of SIW(5-Br)A demonstrated the compatibility of this method with alcohols. No alkylation or elimination of Ser(β-OH) was observed. There remained potential that the carbocationic intermediates generated in this chemistry would not be compatible with basic or strongly nucleophilic functional groups present in natural amino acids due to competing heteroatom alkylation. To evaluate this possibility we processed pentapeptide AQHW(5-F)R with template 1. Cyclization proceeded efficiently to provide composite macrocycles 8 - 12.
arising solely from tryptophan alkylation (Table 1). No arginine or histidine alkylation was observed. Analogous to previous examples, Indole C3 alkylation exclusively formed the endo-pyrroloindoline (8) suggesting a general mechanism of stereoinduction may be operative.
Phosphorylated peptides play a central role in many biological processes and numerous phosphorylation dependent binding epitopes have been exploited for therapeutic applications.\textsuperscript{30} This functionality has been scarcely reported in macrocyclic peptidomimetics, partly due to incompatibility with many cyclization strategies. We prepared Ala-D-pThr-Pip-Trp(5-Br) featuring an isostere for pSer/Thr-Pro motif commonly recognized by phosphorylation dependent peptidylprolyl isomerasers.\textsuperscript{31-34} The phosphate ester was well tolerated. Following acylation with 1, acidolysis with MeSO$_3$H cleanly afforded macrocycles 13 - 16 derived from alkylation at indole N1, C4, C6, and C7. No elimination or alteration of the phosphothreonine residue was observed. Interestingly, products derived from C2 and C3 alkylation were not isolated. This was again observed from acidolysis of Orn-Ile-Pro-Trp(5-F) acylated with 1 on the side-chain amino group of ornithine. Product 17 comprised 86\% of the reaction mixture and only a single additional indole N-alkylated regioisomer was isolated (18).

The perturbed product distribution may be due to geometric constraint imparted from the pipecolate and proline residues. The above data suggest the relative rates of indole alkylation are not governed solely by the electronics of the indole nucleus, which would presumably favor C3 alkylation. Rather, strain associated with the macrocyclic transition states leading to discrete regioisomeric products plays an important role and will likely be dependent on peptide composition.

5.2.3. Effect of Trp C5-substitution on Product Distribution

Product mixtures generated in these processes would ideally be composed of an evenly-distributed collection of composite macrocycles. This would maximize chemical space coverage and alleviate common issues associated with biological screening of compound mixtures. Conversely, the ability to enhance the abundance of specific isomers may become valuable as specific components are identified by screening exercises. It appeared likely this could be achieved by electronic perturbation of indole moiety. To investigate this possibility we compared
the relative alkylation rates of Phe-Trp-Thr congeners 19 and 20, possessing moderately electron-donating and withdrawing groups respectively.

Acylation of 19 with template 1 followed by treatment with MeSO₃H afforded a mixture of three isomeric macrocycles (Figure 3). Alkylation of C4 (49%) was favored, with minor products derived from substitution of C2 (31%) and C3 (20%). Conversely, products derived from acidolysis of 5-fluorotryptophan containing peptide 20 were more evenly distributed. Alkylation of every available indole position was observed, though C4-alkylation remained dominant (Figure 4B). Full spectral assignment of compounds derived from these sequences is ongoing. Assignment of the putative C6-alkylated macrocycle derived from 20 is complicated by slow interconversion of conformations on the NMR time scale at temperatures up to 70°C.

<table>
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<td>10 18 12 49</td>
</tr>
<tr>
<td>20</td>
<td>10 18 12 33 16 11</td>
</tr>
</tbody>
</table>

**Figure 4.** Comparison of product distribution from acidolysis of homologous peptides 19 and 20. A. Ligation of 19 and 20 with 1 followed by acidolysis affords sets of isomeric macrocycles. Alkylation at C3 affords pyrroloindoline products shown. Conditions: a) peptide (1 eq.), 1 (1 eq.), iPr₃NEt (4 eq.), DMF (50 mM), rt; b) MeSO₃H (15 eq.), MeNO₂ (5 mM in 2), rt, 2h. B. Comparison of product distribution. Table and Indole heat map proportional to percentage of substitution determined by HPLC (UV 254 nm).

This initial data demonstrate that subtle electronic perturbation of the indole nucleus can effect product distribution within homologous sequences. Although a more even distribution of composite macrocycles was observed from Trp(5-F) containing peptide 20, the major product remained constant. This is further evidence that peptide composition has a considerable effect of product distribution in these systems, rather than the electronic predisposition of the indole
moiety. This bias for C4-alkylation was not observed in sequences described above featuring either electron withdrawing Trp(5-F), Trp(5-Br) or electron releasing Trp(5-Me).

5.2.4. Additional Nucleophiles

We next sought to explore the reactivity of additional nucleophilic aromatic amino acids. Thiophenylalanine is a commonly employed isostere for phenylalanine and the electronic character of thiophene is well-suited to react with 1. As such, we prepared tripeptide Thr-Gln-Thi and investigated its propensity to engage 1 in large-ring forming reactions. Acylation of Thr-Gln-Thi with 1 followed by treatment with MeSO$_3$H afforded two isomeric macrocycles as observed by HPLC-MS. The major isomer resulted from alkylation of the thiophene 4-position (22, 71%). Surprisingly, NMR analysis of the minor isomer indicated the thiophene moiety was also 2,4-di-substituted. Despite what appeared to be similar structures the minor isomer exhibited a stark difference in polarity on hydrophobic stationary phase as well as distinct $^1$H NMR spectroscopic characteristics, specifically with respect to the threonine residue. Full spectral assignment revealed an unambiguous HMBC correlation from Thr-H$^\beta$ to the carbonyl carbon of the reagent. The anticipated analogous ThrH$^\alpha$ HMBC correlation was absent, suggesting and N-O acyl migration had occurred to form macrolactone 21. Furthermore, The ThrH$^N$ resonance integrated to 3H, presumably isolated as the TFA ammonium salt following preparative HPLC.

Although thiophene did not react with 1 precisely as anticipated, a new mechanism resulting in added structural diversity was identified. This atypical N- to O- migration is mechanistically intriguing. Presumably protonation of the carbonyl oxygen precedes nucleophilic attack of the $\beta$-hydroxyl group. The resulting macrolactone is likely not thermodynamically favored. However, protonation of the $\alpha$-amine may render the reaction irreversible under these conditions. Alternatively, macrolactone 21 may occupy a conformation which precludes the reverse O- to N- migration.
Following the successful macrocyclization of thiophene containing oligopeptides, we explored the reactivity of benzothiophene in these systems. Analogous to indole, electrophilic substitution of benzothiophene typically occur on the heterocyclic ring, but are generally less regioselective. As such we anticipated a broad, diverse product distribution. Surprisingly HPLC-MS analysis of the product mixture derived from the acidolysis of Arg-Glu-Val-BnThi (23), revealed predominantly a single isomeric macrocycle. A combination of homo- and heteronuclear correlation spectroscopy identified this product to be 24, derived from alkylation of arginine. This macrocycle showed an unique HMBC correlation from the cinnamyl methylene the guanidyl carbon at δ ~155 ppm. Also distinctive to this linkage was an extended $^1$H-$^1$H...
TOCSY correlation of the cinnamyl protons to the guanidyl H\textsuperscript{N} (Figure 6). Alkylation of arginine was not anticipated. Arginine was unreactive in previous examples (Table 1). Also sequences containing arginine (e.g. Gly-Ser-Pro-Arg) without an aromatic nucleophile resulted in a complex mixture of non-isomeric products, indicative of sequences which lack a competent nucleophile. Additional studies are necessary elucidate the factors leading to 24. Potentially, intermediate alkylation of neighboring residues within Arg-Glu-Val-BnThi followed by cinnamyl transposition may aid in the formation of 24. Also the proximity of Arg to the electrophilic center may play a role, though overall reaction efficiency has not correlated with the distance of the nucleophile to the cinnamyl moiety thus far.

![Diagram](image_url)

**Figure 6.** A. Acid treatment of 23 afford arginine alkylation macrocycle 24. Conditions: MeSO\textsubscript{3}H (15 eq.), MeNO\textsubscript{2} (5 mM), rt, 2h. B. Key TOCSY and HMBC indicating presence of cinnamyl guanidine.

**5.2.5. Assessing molecular and shape diversity of macrocyclic peptidomimetics**
Macrocycles are uniquely capable of recapitulating the larger interaction surfaces which often define challenging biological targets. Macrocycles occupy chemical space outside of typical descriptors of 'drug-likeness' while retaining favorable pharmacokinetic properties.\textsuperscript{9,15} Macrocycle diversity can be divided into two measures; 1. Chemical diversity displayed on the scaffold, and 2. Topological diversity of the macrocyclic core, including three-dimensional shape and volume. To evaluate the chemical space coverage of the composite peptide macrocycles generated from this method, we performed principle component analysis (PCA) on a set of 27 macrocycles, derived from the seven sequences described above. For comparison a set of 40 top-selling drugs, 60 diverse natural products and 20 molecules available from commercial vendors were similarly evaluated. According to protocols described by Tan and co-workers, an established set of 20 calculated and physicochemical descriptors was utilized.\textsuperscript{12,25} Linear combination of these descriptors reduced the data set to three principle components (presented as unitless axes) which represent 69% of original data set. This treatment allows variation across the 20 original descriptors to be readily visualized with minimal loss of information.

The composite macrocycle library occupied distinct chemical space relative to commercial libraries and top-selling drugs, but was largely encompassed by the diverse set of natural products (Figure 7A). The descriptors which differentiate the macrocycle library from the reference set can be elucidated from analysis of the PCA component loadings (see supplemental information). The increased molecular weight, number hydrogen bond donors and acceptors, and total polar surface area shift the macrocycle library left along the $x$-axis relative to the drug and commercial reference set. Considerably more overlap was observed along the $y$-axis, likely due to similarities in calculated measures of hydrophobicity, such as water solubility and membrane permeability.

The macrocycle library exhibited only a moderate shift from the N-terminal acetates of the peptides from which they were derived. This is likely due to homology across empirical measures of stereochemical diversity and heteroatom content. Also, the lipophilic template
imparts little additional polar surface area. The shift up along the y-axis of the macrocycles was likely due to a predicted decrease in aqueous solubility and a considerable reduction in rotatable bonds from macrocyclization.

The clustering of isomeric macrocycles within these PCA data sets is noteworthy. Considerable homology was observed amongst the physicochemical descriptors chosen, with only slight component shifts arising from variation in macrocyclic ring size as well as additional stereochemistry and hydrophobicity arising from pyrroloindoline formation. This highlights the deficiency of PCA to evaluate chemical space of conformationally complex peptidomimetics where minor modification can manifest substantial conformational perturbation (and thereby structural diversity). We anticipate variation in macrocycle shape will correlate with conformational change of the peptide, which will in turn allow unique interactions with molecular targets. We utilized three-dimensional descriptors of molecular shape to better evaluate diversity amongst isomeric macrocycles.

We chose to evaluate shape variation within macrocycles 3 - 7 derived from Ser-Ile-Trp(5-Br)-Ala. Low energy conformations were calculated using a macrocycle specific meta-sampling protocol consisting of a large scale low-mode conformation search followed by a stochastic dynamics simulated annealing and minimization. Conformations were generated from 5000 simulation cycles using the OPLS2005 force-field using an aqueous solvation model. Three principle moments of inertia (PMI) were calculated for unique conformations (1.0 rmsd) within 3.0 kcal/mol of the lowest energy conformation. Normalized ratios \( \frac{l_1}{l_3}, \frac{l_2}{l_3} \) were plotted with vertices (0,1), (0.5, 0.5), and (1,1) representing a rod, disc, and sphere respectively (Figure 7B). Macrocycles derived from Ser-Ile-Trp(5-Br)-Ala exhibit broad shape diversity. In general these macrocycles lie away from the rod-disc axis where established drugs and commercial libraries have been shown to occupy.\textsuperscript{24,37} Although there is partial overlap across isomeric macrocycles, three of the five isomers occupy largely unique regions of the chart. The
macrocyclic pyrroloindoline 5 lies primarily on the disc-sphere axis and occupies a relatively narrow area of the chart, likely due to reduced conformational mobility within 3.0 kcal/mol.

Interestingly the indole N-alkylated macrocycle 7 occupied two distinct molecular shape regions of the chart. One conformation lies largely along the rod-sphere axis and the second

Figure 6. A. Principle component analysis identified unique chemical space of macrocycle library. B. Graphical analysis of molecule shape from normalized principle moments of inertia. Conformations were plotted within 3.0 kcal/mol of the lowest energy conformer obtained from macrocycle-specific conformation search. C. Analysis of lowest-energy conformation show unique orientations of peptide domain.
nearer the disc vertex. This illustrates the propensity of peptidic macrocycles to occupy multiple, distinct low-energy conformations. Analysis of their structures revealed that they differ by inversion of the phenyl group around the metacyclophane. These conformations exhibit distinct orientations of the peptide (highlighted), suggesting shape analysis may be a good surrogate to indentify conformational changes within the peptide. Analysis of the low-energy conformations of the remaining macrocycles 3 - 7 shown in Figure 7C provides additional empirical evidence that the isomeric macrocycles display the peptide domain in unique conformations.

5.3. Conclusion

Lead optimization in medicinal chemistry generally follows multiple stages of synthetic divergence to access chemical diversity around lead structures. This strategy is difficult to recapitulate in macrocycle space due to a lack of broadly applicable, divergent methods to prepare macrocycles. In this study, we have demonstrated a method to rapidly access diverse macrocyclic peptidomimetics. Our method utilizes an electrophilic reagent to engage substituted tryptophan residues present in oligopeptides via large-ring forming Friedel-Crafts alkylations. These reactions proceed rapidly at room temperature and exploit the divergent reactivity of indole to provide mixtures of isomeric composite macrocycles. A broad range of functional groups present in native or modified amino acids were tolerated, including guanidines, alcohols, amides, and phosphates.

The distribution of isomeric macrocycles from these processes appear to be highly sequence dependent. Turn-inducing residues strongly favored specific isomeric outcomes in certain sequences. Furthermore, we have demonstrated the ability to enhance the formation of specific isomers within homologous sequences by subtle modification of the tryptophan residues. This macrocyclization method is unique in its ability to generate diversity in a single divergent reaction. We anticipate this will allow rapid access to chemical space around macrocyclic scaffolds. From seven sequences we prepared 30 compounds with 19 novel
macrocyclic substructures ranging from 16 to 27 membered rings (*see supporting information*). Principle component analysis identified unique chemical space coverage of the macrocycle library relative to commercial libraries and currently marketed drugs. Calculated principle moments of inertia revealed substantial shape diversity amongst macrocycles derived from a common oligopeptide. This method has the unique potential to prepare isomeric macrocycles displaying defined peptide conformation which we anticipate will be valuable in screening efforts targeting exposed protein surfaces involved in protein-protein interactions.
Chapter 5 - Supporting Information

General
Reactions were performed under ambient atmosphere, unless otherwise noted. Dichloromethane was deoxygenated and dried by passing through an activated alumina solvent drying system. Anhydrous N,N-dimethylformamide (EMD DriSolv®) was used without further purification. Nitromethane was dried over 4Å molecular sieves for at least 24 hr before use. Methanesulfonic acid (≥99.5%, Sigma Aldrich) was used without further purification. Column chromatography was performed on silica gel 60 (SiliCycle, 240-400 mesh). Thin layer chromatography (TLC) utilized pre-coated plates (Sorbent Technologies, silica gel 60 PF254, 0.25 mm) visualized with UV 245 nm, iodine, or basic potassium permanganate stain.

Purification of acidolysis products employed an Agilent 1100/1200 HPLC system equipped with G1361A preparative pumps, a G1314A autosampler, a G1314A VWD, and a G1364B automated fraction collector. Analytical HPLC was performed using the same system, but with a G1312A binary pump. Mass spectra were recorded using an Agilent 6130 LC/MS system equipped with an ESI source.

NMR methods:
NMR spectra were recorded on Bruker Avance (300, 500 or 600 MHz), DRX (500 MHz) and ARX (400 MHz) spectrometers. Data for 1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration), and are referenced to a residual protonated solvent peak.1 13C resonances are reported in terms of chemical shift (δ ppm) as referenced to the residual DMSO peak. For mass-limited samples, solvent magnetic susceptibility matched Shigemi tubes were used with a sample volume of ~300 µL. Optimization of on-axis shims was accomplished using the TopShim automated tool within Bruker Topspin™ 2.1. Optimization of off-axis shims was performed manually.2 1H 90º transmitter pulse lengths were calibrated by back calculation from the 360º or 180º null.3 The pulse width or power level for soft pulses and shaped pulses were calculated using the Shape Tool within TopSpin™ 2.1. 1H-1H COSY spectra were recorded using a phase sensitive, gradient enhanced double-

quantum-filtered experiment, using States-TPPI acquisition.\textsuperscript{4} TOCSY spectra were recorded using a sensitivity improved, phase sensitive experiment using a 60ms DIPSI-2 pulse train for homonuclear Hartman-Hahn transfer.\textsuperscript{5} NOESY spectra were recorded using a phase sensitive experiment with selection gradients during the mixing time.\textsuperscript{6} ROESY spectra were recorded using a phase sensitive experiment with selection gradients and water suppression with excitation sculpting.\textsuperscript{7} Carbon chemical shifts were measured from 2D plots of either HSQC spectra for protonated carbons or HMBC spectra for non-protonated carbons. $^1$H-$^{13}$C HSQC spectra were recorded using a sensitivity improved phase sensitive experiment using an adiabatic shape pulse for $^{13}$C inversion, and $^{13}$C decoupling during acquisition.\textsuperscript{8} Experimental parameters were optimized for $^1J_{CH} = 145$Hz. $^1$H-$^{13}$C HMBC spectra were recorded using a gradient selected experiment with a two-fold J-filter optimized for $^1J_{CH} = 125-165$Hz. Experimental parameters were optimized for long range $^aJ_{CH} = 8$Hz.

**Peptide Synthesis:**

C-terminal carboxamide peptides were synthesized manually using standard Fmoc solid phase synthesis protocols on Rink Amide MBHA resin (200-400 mesh, 0.70 mmol/g, 1% DVB) on 0.25-0.50 mmol scale using a fritted glass reaction vessel. Fmoc-deprotection was achieved with 20% piperidine in DMF (2 x 30 min). The reaction vessel was washed with DMF (3x) and CH$_2$Cl$_2$ (2x). The vessel was then charged with the appropriate Fmoc-amino acid (4 equiv) and TBTU (4 equiv) followed by DMF (10-20 ml) and iPr$_2$NEt (10 eq). The resin was agitated for 2 hours, drained, and washed with DMF (3X). After all coupling were completed the resin was cleaved with TFA/thioanisole/water/TIPS (90:2.5:5:2.5) for 2 hours. The cleaved resin was removed by filtration and the filtrate was concentrated under vacuum. The peptide was precipitated with ether and isolated by centrifugation. The peptide pellet was repeated washed with Et$_2$O to ensure complete removal of cleavage reagents. Fmoc-D-Thr(PO(OBzl)OH)-OH was used to prepare phosphothreonine containing peptides.


Summary of novel macrocyclic core structures:

Ser-Ile-Trp(5-Br)-Ala

Thr-Gln-Thi

Orn-Ile-Pro-Trp(5-F)

His-Gln-Ala-Trp(5-F)-Arg

Ala-D-Thr-Pip-Trp(5-Me)
Principle Component Analysis

Principle component analysis was performed according to procedures described by Tan and co-workers.¹

Importance of Components:

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List of Drugs (PCA):

- Abilify
- Aciphex
- Actos
- Adderall
- Ambien
- Avandia
- Benazepril
- Celebrex
- Concerta
- Coreg
- Crestor
- Cymbalta
- Diovax
- Effexor
- Flonase
- Fosamax
- Imitrex
- Lexapro
- Levaquins
- Lamictal
- Lipothor
- Lipitor
- Nexium
- Norvasc
- Plavix
- Prevacid
- Protonix
- Serquel
- Singulair
- Topamx
- Tricor
- Valtrex
- Wellbutrin
- Zelisa
- Zocor
- Zoloft
- Zyprexa

List of Natural Products (PCA):

- Actinonin
- Adriamycin
- Amphotericin B
- Apoptolidin
- Arglabin
- Artemisinin
- Avermectin B1a
- Bestatin
- Bleomycin
- Brefeldin A
- Brefeldin A
- Calicheamicin G1
- Calyculin
- Compactin
- Cyclosporin A
- Cytochalasin B
- Daptomycin
- Discodermolide
- Duocarmycin A
- Echinocandin B
- Epothilone A
- Erythromycin A
- FK506
- Fumagillin
- Geldanamycin
- Ginkgolide B
- Lactacystin
- Lipstatin
- Midecamycin A1
- Mizoribine
- Monensin
- Mycobactin S
- Penicillin G
- Phorbol MA
- Plaunotol
- Pseudomonac Acid A
- Quinine
- Radicicol
- Rapamycin
- Rifamycin B
- Salicylhalamide A
- Spergualin
- Sparganum A
- Spongistatin
- Streptomyacin
- Talaromyacin B
- Taxol
- Telomestatin
- Thienamycin
- Trapoxin B
- Trichostatin
- Validamycin
- Vancomycin
- Vincristine
- Zaragozic Acid A
General Procedure A - Acylation of unprotected peptides with 1.
An oven-dried, screw-capped scintillation vial was charged with unprotected peptide (0.5 mmol) and N-hydroxysuccinimidyl ester \( \mathbf{2} \) (0.5 mmol, 1 eq.) followed by addition of anhydrous DMF (10 ml) and \( \text{iPr}_2\text{NEt} \) (2.0 mmol). The reaction was allowed to stir at room temperature for 3 hours. The DMF was removed by rotary evaporation and the residue was dissolved in DMSO (1 ml) and purified by reverse-phase HPLC (C18, MeCN/H\(_2\)O, 0.1%TFA) to give the acyclic carbonate as a white solid.

General Procedure B - Acidolysis of cinnamyl carbonates.
The acyclic cinnamyl carbonate (0.25 mmol) was suspended in dry nitromethane (50 ml, 5 mM) under argon atmosphere, and treated with methane sulfonic acid (250 \( \mu \)l, 3.75 mmol, 15 eq.) at room temperature, which caused complete dissolution of the starting material. After 2 hours the reaction was partitioned between quenched by addition of \( \text{iPr}_2\text{NEt} \) (18 equiv). The solvent was
removed under reduced pressure and product mixture was reconstituted in N,N-DMF and purified by semi-preparative RP-HPLC (Sunfire C18, 5.0 μ, 10.0x250 mm, MeCN/H2O, 0.1% TFA). Fractions were pooled and evaporated under reduced pressure.

**Tabulated data for acyclic peptides:**

![Image of a molecule](image)

**Acyclic - Ser-Ile-Trp(5-Br)-Ala (2):** Following the general procedure A with 125 mg SIW(5-Br)-A. Isolation by preparative HPLC afforded 2 (118 mg, 62%).

$^1$H NMR (DMSO-$d_6$, 500 MHz): δ 11.00 (d, J = 2.5 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.74 (d, J = 1.8 Hz, 1H), 7.26-7.30 (m, 1H), 7.26 (br. s, 1H), 7.23-7.24 (m, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 2.3 Hz, 1H), 7.14 (d, J = 2 Hz, 1H), 7.13 (d, J = 2 Hz, 1H), 7.10 (br. d, J = 7.5 Hz, 1H), 7.07 (br. s, 1H), 6.99 (br. s, 1H), 6.61 (d, J = 15.9 Hz, 1H), 6.32 (dt, J = 15.6, 6.2 Hz, 1H), 4.65 (dd, J = 6.3, 6.2 Hz, 2H), 4.50 (ddd, J = 9.2, 8.2, 5.0 Hz, 1H), 4.41 (app q, J = 6.7 Hz, 1H), 4.15 (dddd, J = 7.2, 7.2, 7.2 Hz, 1H), 4.07 (dd, J = 7.8, 6.2 Hz, 1H), 3.56 (dd, J = 10.4, 6.0 Hz, 1H), 3.51 (dd, J = 10.4, 6.3 Hz, 1H), 3.11 (dd, J = 14.9, 4.8 Hz, 1H), 2.85 (dd, J = 14.7, 9.4 Hz, 1H), 2.78 (app t, J = 7.9 Hz, 2H), 2.43-2.49 (m, 3H), 1.60-2.49 (m, 1H), 1.41 (s, 9H), 1.19 (d, J = 7.0 Hz, 3H), 1.08-1.16 (m, 1H), 0.90-1.00 (m, 1H), 0.65 (d, J = 6.7 Hz, 3H). $^{13}$C NMR (DMSO-$d_6$, 125 MHz): δ 174.4, 172.1, 171.3, 171.3, 171.2, 153.3, 142.2, 136.3, 135.2, 133.9, 129.5, 129.1, 128.5, 126.9, 126.0, 124.7, 123.8, 121.2, 113.7, 111.5, 110.3, 82.0, 67.4, 62.2, 58.0, 55.0, 53.6, 48.7, 37.1, 36.7, 31.4, 27.85, 27.78, 27.6, 24.3, 18.6, 15.7, 11.7.

MS (ESI) Calculated for C$_{40}$H$_{50}$BrN$_{6}$O$_{9}$ [M+H]$^+$: 841.1, found 841.4.
Acyclic - Ala-Gln-His-Trp(5-F)-Arg (S1): Following the general procedure A with 115 mg AQHW95-F)R. Isolation by preparative HPLC afforded S1 (122 mg, 81%).

$^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 10.98 (d, $J = 2.3$ Hz, 1H), 8.96 (d, $J = 1.2$ Hz, 1H), 8.24 (d, $J = 7.9$ Hz, 1H), 8.06-8.16 (m, 4H), 7.74 (t, $J = 5.7$ Hz, 1H), 7.39 (dd, $J = 16.0$, 2.5 Hz, 1H), 7.36 (br. s, 1H), 7.23-7.34 (m, 7H), 7.09-7.14 (m, 2H), 6.87-6.93 (m, 2H), 6.65 (d, $J = 15.9$ Hz, 1H), 6.35 (dt, $J = 16.0$, 6.2 Hz, 1H), 4.68 (dd, $J = 6.5$, 1.0 Hz, 2H), 4.52-4.60 (m, 2H), 4.18-4.28 (m, 2H), 4.16 (ddd, $J = 7.9$, 5.6 Hz, 1H), 3.03-3.17 (m, 4H), 2.94 (dd, $J = 15.9$, 15.9, 9 Hz, 2H), 2.75-2.84 (m, 2H), 2.39-4.29 (m, 2H), 2.60-2.17 (m, 2H), 1.80-1.91 (m, 1H), 1.65-1.79 (m, 2H), 1.45-1.55 (m, 2H), 1.43 (s, 9H), 1.15 (d, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 174.1, 173.1, 172.7, 171.6, 171.4, 171.3, 169.8, 157.6, 156.8, 155.8, 152.8, 141.7, 135.8, 133.7, 133.4, 132.7, 129.3, 129.1, 128.6, 128.0, 127.5, 127.4, 126.4, 125.9, 124.2, 123.3, 117.7, 116.8, 115.3, 115.2, 112.2, 112.1, 109.9, 109.9, 81.5, 66.9, 55.0, 53.4, 52.4, 52.2, 51.5, 48.3, 36.6, 31.3, 30.8, 29.1, 27.3, 25.0, 17.9.

MS (ESI) Calculated for $C_{48}H_{64}FN_{13}O_{10}$ [M+H]$^+$: 1002.5, found 1002.7.

Acyclic - Orn-Ile-Pro-Trp(5-F) (S2): Following the general procedure A with 86 mg OIPW(5-F). Isolation by preparative HPLC afforded S2 (78 mg, 60%).

$^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 10.93 (d, $J = 2.5$ Hz, 1H), 7.97 (d, $J = 8.3$ Hz, 1H), 7.89 (d, $J = 8.4$ Hz, 1H), 7.83 (t, $J = 5.6$ Hz, 1H), 7.28-7.37 (m, 5H), 7.22-7.27 (m, 3H), 7.11 (br. d, $J = 7.3$ Hz, 1H), 7.04 (br. s, 1H), 6.89 (ddd, $J = 9.1$, 9.1, 2.5 Hz, 1H), 6.64 (d, $J = 16.0$ Hz, 1H), 6.34 (dt, $J = 16.0$, 6.2 Hz, 1H), 4.68 (dd, $J = 6.2$, 1.1 Hz, 2H), 4.38 (ddd, $J = 7.0$, 7.0, 7.0 Hz, 1H), 4.26-
4.35 (m, 3H), 3.74 (ddd, J = 9.6, 6.6, 6.6 Hz, 1H), 3.53 (ddd, J = 9.6, 5.7, 6.0 Hz, 1H), 2.96-3.10 (m, 4H), 2.80 (app t, J = 7.8 Hz, 2H), 2.37 (app t, J = 7.8 Hz, 2H), 1.93-2.03 (m, 1H), 1.70-1.91 (m, 6H), 1.47-1.60 (m, 2H), 1.44 (s, 9H), 1.27-2.39 (m, 2H), 1.00-1.08 (m, 1H), 0.84 (d, J = 6.8 Hz, 3H), 0.81 (t, J = 7.4 Hz, 1H). 13C NMR (DMSO-d6, 125 MHz): δ 173.0, 171.7, 171.2, 171.1, 170.2, 169.2, 155.7, 152.8, 141.8, 135.8, 133.4, 132.7, 128.6, 128.0, 127.7, 127.7, 126.4, 125.8, 124.2, 123.3, 112.1, 112.0, 110.32, 110.28, 108.9, 108.7, 103.3, 103.1, 81.5, 67.0, 66.9, 59.5, 54.5, 31.9, 47.2, 38.1, 36.9, 36.1, 31.0, 29.6, 28.9, 27.3, 25.8, 24.4, 24.1, 22.5, 14.9, 10.8. MS (ESI) Calculated for C46H62FN7O9 [M+H]+: 876.5, found 876.5.

Acyclic - Phe-Trp(5-F)-Thr (S3): Following the general procedure A with 91 mg FW(5-F)T. Isolation by preparative HPLC afforded S3 (72 mg, 63%).

1H NMR (DMSO-d6, 500 MHz): δ 10.97 (d, J = 2.2 Hz, 1H), 8.29 (d, J = 7.8 Hz, 1H), 8.08 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.41 (dd, J = 10.2, 2.4 Hz, 1H), 7.32 (dd, J = 8.8, 4.5 Hz, 1H), 7.29 (d, J = 2.2 Hz, 1H), 7.26 (br. d, J = 7.8 Hz, 1H), 7.23 (br. s, 1H), 7.21 (br. s, 1H), 7.2 (br. s, 1H), 7.14-7.18 (m, 4H), 7.09 (br. s, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.9 (ddd, J = 9.0, 9.0, 2.3 Hz, 1H), 6.63 (d, J = 15.7 Hz, 1H), 6.33 (dt, J = 15.9, 6.2 Hz, 1H), 4.67 (dd, J = 6.3, 1.1 Hz, 2H), 4.63 (ddd, J = 8.6, 8.0, 4.9 Hz, 1H), 4.54 (ddd, J = 9.9, 8.4, 4.0 Hz, 1H), 4.16 (dd, J = 8.7, 3.2 Hz, 1H), 4.08 (ddddd, J = 6.2, 6.2, 6.2, 3.4 Hz, 1H), 3.17 (dd, J = 15.0, 4.6 Hz, 1H), 3.02 (dd, J = 15.3, 9.3 Hz, 1H), 2.97 (dd, J = 13.7, 4.0 Hz, 1H), 2.71 (dd, J = 13.9, 16.0 Hz, 1H), 2.65 (app t, J = 7.9 Hz, 2H), 2.23-2.38 (m, 2H), 1.4 (s, 9H), 1.02 (d, J = 6.4 Hz, 3H). 13C NMR (DMSO-d6, 125 MHz): δ 172.0, 171.5, 171.4, 171.3, 157.6, 155.8, 152.8, 141.7, 137.9, 135.8, 133.4, 132.7, 129.1, 128.6, 127.9, 127.6, 127.5, 126.4, 126.1, 125.9, 124.1, 123.2, 112.14, 112.06, 110.2, 110.2, 109.0, 108.8, 103.3, 103.1, 81.5, 66.9, 66.3, 58.0, 53.7, 53.5, 37.4, 36.7, 30.9, 27.3, 19.9. MS (ESI) Calculated for C41H48FN5O9 [M+H]+: 758.4, found 758.8.
Acyclic - Thr-Gln-Thi (S4): Following the general procedure A with 300 mg Thr-Gln-Thi. Isolation by preparative HPLC afforded S4 (257 mg, 50%).

$^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 8.09 (d, J = 7.0 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.28 (br. s, 1H), 7.25 (d, J = 5.1 Hz, 1H), 7.13-7.25 (m, 4H), 7.07-7.12 (m, 2H), 6.87 (d, J = 4.7, 3.8 Hz, 1H), 6.82-6.86 (m, 1H), 6.68 (br. s, 1H), 6.61 (d, J = 15.9 Hz, 1H), 6.30 (dt, J = 16.0, 6.2 Hz, 1H), 4.04 (d, J = 5.9 Hz, 2H), 4.32 (ddd, J = 8.6, 8.6, 4.7 Hz, 1H), 4.2 (dd, J = 7.7, 4.1 Hz, 1H), 4.17 (ddd, J = 7.7, 7.7, 5.2 Hz, 1H), 3.96 (ddd, J = 10.6, 6.1, 6.1 Hz, 1H), 3.24 (dd, J = 14.9, 4.2 Hz, 1H), 3.04 (dd, J = 14.9, 9.1 Hz, 1H), 2.76-2.84 (m, 2H), 2.45-2.60 (m, 3H), 1.99-2.12 (m, 2H), 1.81-1.90 (m, 1H), 1.67-1.76 (m, 1H), 1.4 (s, 9H), 0.97 (d, J = 6.1 Hz, 3H).

$^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ 174.3, 172.5, 172.5, 171.4, 170.9, 153.1, 142.0, 140.0, 136.2, 133.8, 128.9, 128.4, 127.0, 126.7, 126.3, 124.6, 124.5, 123.7, 81.8, 67.2, 66.8, 58.8, 54.4, 53.2, 36.9, 31.8, 31.6, 31.3, 27.7, 27.6, 19.8.

MS (ESI) Calculated for C$_{33}$H$_{45}$N$_{5}$O$_{9}$S [M+H]$^+$: 688.4, found 688.2.

Acyclic - Arg-Glu-Val-BnThi (S5): Following the general procedure A with 344 mg Arg-Gly-Val-BnThi. Isolation by preparative HPLC afforded S4 (257 mg, 46%).

$^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ 8.12 (d, J = 8.3 Hz, 1H), 8.06 (d, J = 7.9 Hz, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.91 (br. d, J = 7.6 Hz, 1H), 7.88 (br. d, J = 7.5 Hz, 1H), 7.74 (br. d, J = 8.7 Hz, 1H), 7.31-7.44 (d, J = 7 Hz, 5H), 7.24-7.30 (m, 3H), 7.22 (m, 1H), 7.07-7.11 (t, J = 7 Hz, 2H), 6.62 (m, 1H), 6.32 (d, J = 15.9, 6.2 Hz, 1H), 4.65 (dt, J = 6.3, 1.2 Hz, 2H), 4.6 (dd, J = 8.4, 8.4, 5.6 Hz, 1H), 4.24-4.30 (dd, J = 7 Hz, 2H), 4.1 (m, 1H), 3.21 (dd, J = 15.0, 5.0 Hz, 1H), 2.97-3.09 (dd, J = 7 Hz, 3H), 2.69 (m, 2H), 2.44 (dd, J = 14.5, 12.6, 6.7 Hz, 1H), 2.15-2.29 (m, 2H), 1.82-1.94 (m, 2H), 1.68-1.79 (m, 1H), 1.55-1.65 (m, 1H), 1.32-1.48 (m, 13H), 0.76 (d, J = 6.7 Hz, 3H), 0.75 (d,
J = 6.7 Hz, 3H). $^{13}$C NMR (DMSO-d$_6$, 125 MHz): δ 174.5, 173.1, 172.1, 172.0, 171.5, 171.2, 157.1, 153.3, 142.1, 139.9, 139.2, 136.3, 133.9, 132.5, 129.1, 128.5, 126.9, 124.74, 124.69, 124.5, 123.83, 123.78, 123.2, 122.3, 82.0, 67.4, 58.2, 52.44, 52.40, 37.1, 31.5, 31.0, 30.7, 27.8, 27.7, 25.4, 19.6, 18.4.

MS (ESI) Calculated for C$_{44}$H$_{60}$N$_8$O$_{10}$S [M+H]$^+$: 893.4, found 893.1.

Spectral assignments for macrocycles:

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<td>6.53-6.60 (m, 1H) overlap</td>
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<td>123.6</td>
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![Chemical Structure Diagram](image-url)
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<th>6.99 (br d, J = 7.5 Hz, 1H) overlap</th>
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HMBC 9→3
HMBC 10→7,8,9,12
HMBC 11→9,12
HMBC 13→12, COSY 13→14
HMBC 14→15,16
HMBC 15→16
HMBC 17→14,15
HMBC 18→16, COSY 18→19
COSY 19→20, HMBC 19→24
HMBC 20→21,23
HMBC 25→24, COSY 25→26
HMBC 26→28, COSY 26→27
HMBC 27→28
HMBC 29→28,31,36
HMBC 32→31,34,36
HMBC 33→31
HMBC 38→37
HMBC 42→41
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**Diagram:**

![Chemical Structure Diagram]

**Atom Table:**

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### Peptide 19 - C2

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**VGW(5-Br)-C2**

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<td>1.83-1.90 (m, 1H)</td>
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**VGW(5-Br)-C4**
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<td>6.76 (br. s, 1H), 7.28 (br. s, 1H)</td>
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<td>25</td>
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<td>8.38 (d, J = 8.7 Hz, 1H)</td>
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<td>53.42</td>
<td>4.44 (dd, J = 11.1, 8.7, 2.4 Hz, 1H)</td>
<td>28, 26</td>
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<td>32.24</td>
<td>3.10 (d, J = 13.1 Hz, 1H), 2.91 (dd, J = 15.1, 11.2 Hz, 1H)</td>
<td>27, 26</td>
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<td>29</td>
<td>137.70</td>
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Tabulated $^1$H NMR for macrocycles:
The following products have been assigned by key HMBC/HSQC/TOCY/COSY. Full spectral assignment, analogous to those above is ongoing.

Cyclic Ala-(D-pThr)-Pip-Trp(5-Me) (15):

\[ \text{Cyclic Ala-(D-pThr)-Pip-Trp(5-Me) (15):} \]

$^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 10.51 (d, $J = 1.8$ Hz, 1H), 7.76 (d, $J = 7.6$ Hz, 1H), 7.75-7.61 (m, 2H), 7.28 (d, $J = 7$ Hz, 1H), 7.20-7.25 (m, 4H), 7.05-7.11 (m, 2H), 7.01 (s, 1H), 8.88 (d, $J = 8.9$ Hz, 1H), 6.5 (d, $J = 16$ Hz, 1H), 6.16 (dt, $J = 16.0$, $5.7$ Hz, 1H), 4.90-5.01 (m, 1H), 4.89-4.92 (m, 2H), 4.84 (dd, $J = 7.2$, 4.0 Hz, 1H), 4.37-4.44 (m, 1H), 4.34 (ddd, $J = 11.9$, 7.6, $3.0$ Hz, 1H), 4.23 (dq, $J = 7.6$, 7.6 Hz, 1H), 3.88 (d, $J = 12.5$ Hz, 1H), 3.15-3.25 (m, 1H), 3.03 (dd, $J = 14.4$, 2.6 Hz, 1H), 2.9 (dd, $J = 14.2$, 12.5 Hz, 1H), 2.68-2.81 (m, 3H), 2.36 (s, 3H), 2.26 (ddd, $J = 12.9$, 11.8, 6.4 Hz, 1H), 2.17 (ddd, $J = 13.0$, 11.5, 4.7 Hz, 1H), 1.40-1.58 (m, 4H), 1.18-1.30 (m, 1H), 1.09 (d, $J = 7.4$ Hz, 3H), 0.99 (d, $J = 6.4$ Hz, 3H).

Cyclic Ala-(D-pThr)-Pip-Trp(5-Me) (16):

$^1$H NMR (DMSO-d$_6$, 500 MHz): $\delta$ 8.38 (d, $J = 8.3$ Hz, 1H), 7.76 (d, $J = 7.6$ Hz, 1H), 7.55-7.61 (m, 2H), 7.28 (d, $J = 7$ Hz, 1H), 7.20-7.25 (m, 4H), 7.05-7.11 (m, 2H), 7.01 (s, 1H), 8.88 (d, $J = 8.9$ Hz, 1H), 6.5 (d, $J = 16$ Hz, 1H), 6.16 (dt, $J = 16.0$, $5.7$ Hz, 1H), 4.90-5.01 (m, 1H), 4.89-4.92 (m, 2H), 4.84 (dd, $J = 7.2$, 4.0 Hz, 1H), 4.37-4.44 (m, 1H), 4.34 (ddd, $J = 11.9$, 7.6, $3.0$ Hz, 1H), 4.23 (dq, $J = 7.6$, 7.6 Hz, 1H), 3.88 (d, $J = 12.5$ Hz, 1H), 3.15-3.25 (m, 1H), 3.03 (dd, $J = 14.4$, 2.6 Hz, 1H), 2.9 (dd, $J = 14.2$, 12.5 Hz, 1H), 2.68-2.81 (m, 3H), 2.36 (s, 3H), 2.26 (ddd, $J = 12.9$, 11.8, 6.4 Hz, 1H), 2.17 (ddd, $J = 13.0$, 11.5, 4.7 Hz, 1H), 1.40-1.58 (m, 4H), 1.18-1.30 (m, 1H), 1.09 (d, $J = 7.4$ Hz, 3H), 0.99 (d, $J = 6.4$ Hz, 3H).
Cyclic Orn-Ile-Pro-Trp(5-F) (17):

\begin{align*}
    &^1\text{H NMR (DMSO-d}_6\text{, 500 MHz): 10.82 (d, J = 1.9 Hz, H), 7.91} \\
    &\quad (d, J = 7.7 Hz, H), 7.81 (d, J = 8.4 Hz, H), 7.79 (d, J = 5.7 Hz, H), \\
    &\quad 7.44-7.52 (m, H), 7.79 (br. s, H), 7.21 (d, J = 6.4 Hz, H), \\
    &\quad 7.12-7.18 (m, H), 6.96-7.003 (m, H), 6.31 (dt, J = 15.8, 5.8 Hz, H), \\
    &\quad 6.3 (d, J = 15.9 Hz, H), 4.46 (ddd, J = 9.7, 8.0, 3.6 Hz, H), \\
    &\quad 4.22-4.29 (m, H), 4.17 (t, J = 8.2 Hz, H), 4.12 (dd, J = 8.3, 5.0 Hz, H), 3.69 (ddd, J = 9.5, 6.7, 6.7 Hz, H), 3.56 (d, J = 5.5 Hz, H), 3.44 (ddd, J = 9.4, 6.7, 6.4 Hz, H), 2.98-3.10 (m, H), 2.94 (dd, J = 14.9, 10.0 Hz, H), \\
    &\quad 2.75-2.85 (m, H), 2.69 (t, J = 15.6 Hz, H), 2.25 (t, J = 15.6 Hz, H), 1.88-1.99 (m, H), 1.78 (s, H), \\
    &\quad 1.61-1.76 (m, H), 1.42-1.55 (m, H), 1.19-1.33 (m, H), 0.96-1.08 (m, H), 0.85 (d, J = 6.8 Hz, H), \\
    &\quad 0.77 (t, J = 7.4 Hz, H).
\end{align*}

Cyclic Orn-Ile-Pro-Trp(5-F) (18):

\begin{align*}
    &^1\text{H NMR (DMSO-d}_6\text{, 500 MHz): 8.06-8.11 (m, H), 7.99 (d, J = 8.6} \\
    &\quad Hz, H), 7.89 (d, J = 8 Hz, H), 7.69 (d, J = 5.7 Hz, H), 7.44 (t, J = \\
    &\quad 8.9, 4.5 Hz, H), 7.37 (dd, J = 10.1, 2.4 Hz, H), 7.34 (dd, J = Hz, H), \\
    &\quad 7.27 (s, H), 7.14-7.21 (br. s, H), 7.11 (m, H), 7.03-7.07 (br. s, H), \\
    &\quad 6.90-6.96 (m, H), 6.48 (m, H), 6.33 (d, J = 15.8, 6.0 Hz, H), \\
    &\quad 4.96 (dt, J = 16.6, 5.6 Hz, H), 4.87 (dd, J = 16.3, 5.6 Hz, H), 4.39 \\
    &\quad (dd, J = 10.8, 8.0, 3.1 Hz, H), 4.22-4.30 (ddd, J = Hz, H), 4.16 \\
    &\quad (dd, J = 8.2, 5.0 Hz, H), 3.50-3.64 (m, H), 3.44-3.52 (m, H), 3.28 \\
    &\quad (t, J = 7.1 Hz, H), 2.96-3.03 (m, H), 2.86 (dddd, J = 12.6, 12.6, 6.7, 6.7 Hz, H), 2.72 (t, J = 7.5 Hz, H), \\
    &\quad 2.52 (s, H), 2.20-2.31 (m, H), 1.81-1.93 (m, H), 1.65-1.75 (m, H), 1.55-1.64 (m, H), 1.38- \\
    &\quad 1.53 (m, H), 1.26-1.35 (m, H), 1.13-1.25 (m, H), 0.93-1.05 (m, H), 0.81 (d, J = 6.7 Hz, H), 0.76 \\
    &\quad (d, J = 7.4 Hz, H).
\end{align*}

Current Data Parameters
NAME           KL-5-104
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20121218
Time              10.45
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                    8
DS                    0
SWW            100000.000 Hz
FIDRES         0.152588 Hz
AQ            3.2767999 sec
RG                   11
DW               50.000 usec
DE                10.00 usec
TE                298.0 K
D1           2.00000000 sec
TDD0                   1

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SFO1        500.1330008 MHz
NUC1                1H
P1            10.00 usec
PLW1        13.50000000 W

F2 - Processing parameters
SI                65536
SF            500.1300146 MHz
WDW                  EM
SSB      0
LB                 0.30 Hz
GB                 1.40
Current Data Parameters
NAME           KL-5-104
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20121218
Time              10.48
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG          zgpg30
TD                65536
SOLVENT            DMSO
NS                   39
DS                    2
SWH           31250.000 Hz
FIDRES         0.476837 Hz
AQ               1.0485760 sec
RG                 202.91
DW               16.000 usec
DE               18.00 usec
TE             298.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TDD                   1

======== CHANNEL f1 ========
SFO1        125.7722511 MHz
NUC1                13C
P1                 9.63 usec
PLW1        23.00000000 W

======== CHANNEL f2 ========
SFO2        500.1330008 MHz
NUC2                 1H
CPDP@[2        waltz16
CPD2           80.00 usec
PLW2           13.50000000 W
PLW12       0.21094000 W
PLW13        0.13500001 W

F2 - Processing parameters
SI               131072
SF          125.7577892 MHz
WDM                   EM
SSB                  0
LB                1.00 Hz

Current Data Parameters
NAME ICON-W-B1
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121013
Time 13.06
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 11
DW 50.000 usec
DE 10.00 usec
TE 298.0 K
D1 2.0000000 sec
TDD 1

== CHANNEL f1 ==
NUC1 1H
P1 10.00 usec
PLW1 13.50000000 W
SFU1 500.1330008 MHz

F2 - Processing parameters
SI 65536
SF 500.133000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 1.00
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EXPNO 2
PROCNO 1

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WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
Current Data Parameters
NAME           KL-5-226
EXPNO                 2
PROCNO                1
F2 - Processing parameters
SI                65536
SF                  150.9028319 MHz
WDW                 EM
SSB                 0
LB                 1.00 Hz
GB                 0
PC                1.00
Current Data Parameters
NAME           KL-5-228
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20131013
Time              12.42
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                    8
DS                    0
SWH           10000.000 Hz
FIDRES       0.152588 Hz
AQ                3.2767999 sec
RG                12.14
DW               50.000 usec
DE                10.00 usec
TE                298.0 K
D1           2.00000000 sec
TDO                   1

------- CHANNEL f1 -------
SFO1        500.1330008 MHz
NUC1                 1H
P1                10.00 usec
PLM1        13.50000000 W

F2 - Processing parameters
SI                65536
SF      500.1300146 MHz
WDM            EM
SSB                0
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NAME        KL5-106-2-1
EXPNO                 3
PROCNO                1

F1 - Acquisition parameters
TD                  512
SFO1           600.1327 MHz
FIDRES        10.523297 Hz
SW                8.978 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                 2048
SF          600.1300067 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2         States-TPPI
SF          600.1300058 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME        KL5-106-2-1
EXPNO                 4
PROCNO                1
F1 - Acquisition parameters
TD                  128
SFO1           600.1327 MHz
FIDRES        42.093212 Hz
SW                8.978 ppm
FnMODE    Echo-Antiecho
F2 - Processing parameters
SI                 4096
SF          600.1300273 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
PC                 1.00
F1 - Processing parameters
SI                 4096
MC2       echo-antiecho
SF          600.1300273 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME        KL5-106-2-1
EXPNO                 5
PROCNO                1
F1 - Acquisition parameters
TD                  512
SFO1           150.9134 MHz
FIDRES        47.160427 Hz
SW              160.000 ppm
FnMODE    Echo-Antiecho
F1 - Processing parameters
SI                 4096
SF          600.1300450 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
PC       1.00 Hz
F2 - Processing parameters
SI                4096
MC2 echo-antiecho
SF             150.9028800 MHz
WDW           QSINE
SSB      0 Hz
LB      0 Hz
GB      0
Current Data Parameters
NAME        KL5-106-2-1
EXPNO                 6
PROCNO                1
F1 - Acquisition parameters
TD                  256
SFO1           150.9156 MHz
FIDRES       112.007698 Hz
SW              190.000 ppm
FnMODE               QF
F2 - Processing parameters
SI                 4096
SF          600.1300273 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
PC                 1.40
F1 - Processing parameters
SI         2048
MC2                  QF
SF          150.9028090 MHz
WDW             USER
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME          KL5-106-3
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20121219
Time              17.27
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG              zg
TD                65536
SOLVENT            DMSO
NS                    8
DS                    0
SWH           12376.237 Hz
FIDRES         0.188646 Hz
AQ                   2.6476543 sec
RG                   64
DW               40.400 usec
DE                6.50 usec
TE                298.0 K
D1           2.00000000 sec
TDO                   1

-------- CHANNEL f1 --------
NUC1                 1H
P1                 9.35 usec
PL1               -2.00 dB
PL1W       39.81071854 W
SFO1        600.1336008 MHz

F2 - Processing parameters
SI                65536
SF            600.1300070 MHz
WDW                  EM
SSB                    0
LB                     0 Hz
GB                     0
PC                   1.00
Current Data Parameters
NAME          KL5-106-3
EXPNO                 3
PROCNO                1

F1 - Acquisition parameters
TD                  512
SFO1           600.1327 MHz
FIDRES        10.523297 Hz
SW                8.978 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                 2048
SF          600.1300273 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2         States-TPPI
SF          600.1300273 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME          KL5-106-3
EXPNO                 4
PROCNO                1

F1 - Acquisition parameters
TD                  128
SFO1           600.1327 MHz
FIDRES        42.093212 Hz
SW                8.978 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 4096
SF          600.1300273 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 4096
MC2       echo-antiecho
SF          600.1300273 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME          KL5-106-3
EXPNO                 6
PROCNO                1

F1 - Acquisition parameters
TD                  256
SFO1           150.9156 MHz
FIDRES       112.007698 Hz
SW              190.000 ppm
FnMODE               QF

F2 - Processing parameters
SI                 4096
SF          600.1300273 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
PC                 1.40

F1 - Processing parameters
SI                 2048
MC2                  QF
SF          150.9028090 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
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![Chemical Structure](image)

Diagram showing a 2D NMR spectrum with peaks at various ppm values.
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PROCNO                1

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TD                  200
SFO1           600.1328 MHz
FIDRES        30.637295 Hz
SW               10.210 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                 2048
SF          600.1300070 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI        4096
MC2         States-TPPI
SF          600.1300070 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME     KL5-106-4_AV600
EXPNO                22
PROCNO                1

F2 - Acquisition Parameters
Date_          20130104
Time              18.26
INSTRUM           av600
PROBHD   5 mm BB5
PULPROG              zg
TD                65536
SOLVENT            DMSO
NS                    8
DS                    0
SWH           12376.237 Hz
FIDRES       0.188846 Hz
AQ                  2.6476543 sec
RG                  114
DW               40.400 usec
DE                6.50 usec
TE               340.0 K
D1             2.00000000 sec
TDO                   1

--- CHANNEL f1 ---
NUC1                 1H
P1                15.25 usec
PL1               -1.00 dB
PL1W       31.62277603 W
SFO1      600.1336008 MHz

F2 - Processing parameters
SI                65536
SF       600.1300069 MHz
WDW  EM
SSB                   0
LB                   0 Hz
GB                   0
PC                1.00
Current Data Parameters
NAME       KL5-106-4_AV600
EXPNO                 25
PROCNO                1

F1 - Acquisition parameters
TD                  512
SFO1           600.1327 MHz
FIDRES        10.523297 Hz
SW                8.978 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                 2048
SF          600.1300102 MHz
WDW                SINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2         States-TPPI
SF          600.1299991 MHz
WDW                SINE
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME: KL5-106-4_AV600
EXPNO: 27
PROCNO: 1

F1 - Acquisition parameters
TD: 175
SFO1: 150.9134 MHz
FIDRES: 137.977936 Hz
SW: 160.000 ppm
FnMODE: Echo-Antiecho

F2 - Processing parameters
SI: 4096
SF: 600.1300059 MHz
WDW: EM
SSB: 0
LB: 1.00 Hz
GB: 0
PC: 1.40

F1 - Processing parameters
SI: 4096
MC2: echo-antiecho
SF: 150.9027571 MHz
WDW: Q1INE
SSB: 0
LB: 0 Hz
GB: 0
Current Data Parameters
NAME     KL5-106-4_AV600
EXPNO                28
PROCNO                1

F1 - Acquisition parameters
TD                  210
SFO1           150.9156 MHz
FIDRES       136.542725 Hz
SW              190.000 ppm
FnmODE               QF

F2 - Processing parameters
SI                 4096
SF          600.1300273 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
PC                 1.40

F1 - Processing parameters
SI                2048
MC2                  QF
SF           150.9028090 MHz
WDW                  USER
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME KL5-106-5-1
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date 20121221
Time 17.32
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG zg
TD 65536
SOLVENT DMSO
NS 8
DS 0
SWH 12376.237 Hz
FIDRES 0.188846 Hz
AQ 2.6476543 sec
RG 114
DW 40.400 usec
DE 6.50 usec
TE 298.0 K
DL 2.0000000 sec
TDD 1

---- CHANNEL f1 ----
NUC1 1H
P1 9.23 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1336008 MHz

F2 - Processing parameters
SI 65536
SF 600.1300070 MHz
WDM EM
SUB 0
LB 0 Hz
GB 0
PC 1.00
Current Data Parameters
NAME        KL5-106-5-1
EXPNO                 3
PROCNO                1

F1 - Acquisition parameters
TD                  512
SFO1           600.1327 MHz
FIDRES        10.523297 Hz
SW                8.978 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                 2048
SF          600.1300067 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2         States-TPPI
SF          600.1300058 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME        KL5-106-5-1
EXPNO                 4
PROCNO                1
F1 - Acquisition parameters
TD                  128
SFO1           600.1327 MHz
FIDRES        42.093212 Hz
SW                8.978 ppm
FnMODE    Echo-Antiecho
F2 - Processing parameters
SI                 4096
SF          600.1300072 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
PC                 1.00
F1 - Processing parameters
SI                  4096
MC2       echo-antiecho
SF          600.1300081 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME        KL5-106-5-1
EXPNO            6
PROCNO           1

F1 - Acquisition parameters
TD                  256
SFO1           150.9156 MHz
FIDRES       112.007698 Hz
SW              190.000 ppm
FnMODE               QF

F2 - Processing parameters
SI                 4096
SF          600.1300061 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.40

F1 - Processing parameters
SI                2048
MC2                  QF
SF          150.9030067 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters

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**F2 - Acquisition Parameters**

- **Date:** 20121217
- **Time:** 16.32
- **INSTRUM:** av600
- **PROBHD:** 5 mm TBI5
- **PULPROG:** zg
- **TD:** 65536
- **SOLVENT:** DMSO
- **NS:** 64
- **DS:** 0
- **SWH:** 12376.237 Hz
- **FIDRES:** 0.188846 Hz
- **AQ:** 2.6476543 sec
- **RG:** 181
- **DW:** 40.400 usec
- **DE:** 6.50 usec
- **TE:** 294.0 K
- **D1:** 2,000,000,000 sec

**F2 - Processing parameters**

- **SI:** 65536
- **SF:** 600.1300273 MHz
- **WDW:** EM
- **LB:** 0.30 Hz
- **GB:** 0
- **PC:** 1.00

---

**SHIRLEY PEAK LIST**

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**Chemical Shifts:**

- 8.5 ppm: 8.0 ppm
- 7.5 ppm: 7.0 ppm
- 6.5 ppm: 6.0 ppm
- 5.5 ppm: 5.0 ppm
- 4.5 ppm: 4.0 ppm
- 3.5 ppm: 3.0 ppm
- 2.5 ppm: 2.0 ppm
- 1.5 ppm: 1.0 ppm
Current Data Parameters

NAME           W-A4-1-1
EXPNO                 3
PROCNO                1

F1 - Acquisition parameters
TD                  256
SFO1            600.133 MHz
FIDRES        23.442696 Hz
SW               10.000 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                 2048
SF          600.1300273 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2         States-TPPI
SF          600.1300273 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters

NAME W-A4-1-1
EXPNO 4
PROCNO 1

F1 - Acquisition parameters
TD 408
SFO1 600.133 MHz
FIDRES 14.709142 Hz
SW 10.000 ppm
FnMODE Echo-Antiecho

F2 - Processing parameters
SI 1024
SF 600.1300273 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00

F1 - Processing parameters
SI 1024
MC2 echo-antiecho
SF 600.1300273 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
Current Data Parameters
NAME w-a4-1-1_AV500
EXPN0 2
PROCNO 1

F2 - Acquisition Parameters
Date 20121219
Time 17.14
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hsqcedetgp
TD 2048
SOLVENT DMso
NS 6
DS 16
SWM 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 202.91
DW 100.000 usec
DE 10.00 usec
TR 338.0 K
CNST2 145.0000000
D0 0.0000000 sec
D1 1.5000000 sec
D4 0.00172414 sec
D11 0.00000400 sec
D16 0.0001990 sec
D21 0.00000000 sec
D28 0 usec
P1 10.00 usec
P2 20.00 usec
PLW1 13.5000000 W

====== GRADIENT CHANNEL ======
GPNAM SMSQ10 100

====== CHANNEL f1 ======
SFO1 500.1325007 MHz
NUC1 1H
P1 10.00 usec
P2 20.00 usec
PLW1 13.5000000 W

====== CHANNEL f2 ======
SFO2 125.7678496 MHz
NUC2 13C
CPDPRG garp
P3 9.63 usec
P4 19.26 usec
PLW2 23.0139999 W
PLW12 0.43557000 W

====== GRADIENT CHANNEL ======
Current Data Parameters
NAME             W-A4-2
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20121020
Time              15.18
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG              zg
TD                65536
SOLVENT            DMSO
NS                    8
DE                   0
SWH           10000.000 Hz
FIDRES        0.152568 Hz
AQ                3.2767999 sec
RG                 9.65
DW               50.000 usec
DE                10.00 usec
TE               298.0 K
D1            2.00000000 sec
TDD                   1

==== CHANNEL f1 ======
NUC1                 1H
P1                10.00 usec
PLW1            13,5000000 W
SFO1        500.1330008 MHz

F2 - Processing parameters
SI                65536
SF          500.1300146 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                   1.00
Current Data Parameters

NAME             W-A4-2
EXPNO             3
PROCNO             1

F1 - Acquisition parameters
TD                  256
SFO1           500.1328 MHz
FIDRES        19.536423 Hz
SW              10.000 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                 2048
SF          500.1300135 MHz
WDW                SINE
SSB                   1
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2      States-TPPI
SF          500.1303720 MHz
WDW                GM
SSB                   1
LB       0 Hz
GB       0
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Current Data Parameters

NAME: W-A4-2
EXPNO: 6
PROCNO: 1

F1 - Acquisition parameters
- TD: 256
- SFO1: 125.7678 MHz
- FIDRES: 98.255890 Hz
- SW: 200.000 ppm
- FnMODE: Echo-Antiecho

F2 - Processing parameters
- SI: 2048
- SF: 500.1300135 MHz
- WDN: QUINE
- SSB: 2
- LB: 0 Hz
- GB: 0
- PC: 1.00

F1 - Processing parameters
- SI: 2048
- MC2: echo-antiecho
- SF: 125.7578472 MHz
- WDN: USER
- SSB: 2
- LB: 0 Hz
- GB: 0
Current Data Parameters
NAME             W-A4-2
EXPN0             7
PROCNO                1

F1 - Acquisition parameters
TD                  256
SP01           125.7704 MHz
FIDRES         98.257607 Hz
SW             199.999 ppm
F1nMODE     QF

F2 - Processing parameters
SI                 2048
SF            500.1300135 MHz
WDW               QF
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2               QF
SF       125.7578472 MHz
WDW             USER
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME           W-A4-3-1
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20121110
Time              12.10
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG              zg
TD                65536
SOLVENT            DMSO
NS                   32
DE                 0
SWH           10000.000 Hz
FIDRES        0.152568 Hz
AQ                 3.2767999 sec
RG                   7
DW               50.000 usec
DE                10.00 usec
TE                298.0 K
D1           2.00000000 sec
TDD                 1

======== CHANNEL f1 ========
NUC1                 1H
P1                10.00 usec
PLW1        13.50000000 W
SFO1        500.1330008 MHz

F2 - Processing parameters
SI                65536
SF          500.1300146 MHz
WDW                  EM
SSB                 0
LB                 0.30 Hz
GB                 0
PC                 1.00
Current Data Parameters
NAME           W-A4-3-1
EXPNO                 3
PROCNO                1

F1 - Acquisition parameters
TD                  256
SFO1           500.1328 MHz
FIDRES        21.490080 Hz
SW               11.000 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                 2048
SF          500.1303720 MHz
WDW                  GM
SSB                   1
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2         States-TPPI
SF          500.1303720 MHz
WDW                  GM
SSB                   1
LB       0 Hz
GB       0
Current Data Parameters
NAME           W-A4-3-1
EXPNO          4
PROCNO          1

F1 - Acquisition parameters
TD                  256
SFO1           500.1325 MHz
FIDRES        19.536406 Hz
SW               10.000 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 2048
SF          500.1300135 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2    echo-antiecho
SF          500.1300135 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME          W-A4-3-1
EXPNO           5
PROCNO           1

F1 - Acquisition parameters
TD                  256
SFO1           125.7678 MHz
FIDRES        98.255890 Hz
SW              200.000 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 2048
SF          500.1300135 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2       echo-antiecho
SF          125.7578472 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME          W-A4-3-1
EXPNO         6
PROCNO        1

F1 - Acquisition parameters
TD           256
SFO1        125.7704 MHz
FIDRES    98.257607 Hz
SW         199.999 ppm
FnMODE      QF

F2 - Processing parameters
SI          2048
SF       500.1300135 MHz
WDW        TRAP
SSB             2
LB       0 Hz
GB       0
PC        1.00
Current Data Parameters
NAME       W-A4-4-17(2)
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date       20121023
Time              18.51
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG              zg
TD    65536
SOLVENT            DMSO
NS                    8
DS                    0
SWH           10000.000 Hz
FIDRES        0.152588 Hz
AQ                3.2767999 sec
RG                20.17
DW               50.000 usec
DE                10.00 usec
TE                298.0 K
D1              2.00000000 sec
TD0               1

======== CHANNEL f1 ========
NUC1                 1H
P1              10.00 usec
PLW1      13.50000000 W
SFO1    500.1330008 MHz

F2 - Processing parameters
SI                65536
SF      500.1300146 MHz
WDW                  EM
SSB             0
LB              0.30 Hz
GB             0.00
PC             1.00
NAME       W-A4-4-17(2)
EXPN0                 3
PROCNO                1

F1 - Acquisition parameters
TD                  256
SF01           500.1328 MHz
FIDRES        19.536423 Hz
SW               10.000 ppm
FnMODE States-TPPI

F2 - Processing parameters
SI                 2048
SF          500.1300137 MHz
WDW                  GM
SSB                   1
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2         States-TPPI
SF          500.1300137 MHz
WDW                  GM
SSB                   1
LB       0 Hz
GB       0
Current Data Parameters
NAME       W-A4-4-17(2)
EXPNO       4
PROCNO       1

F1 - Acquisition parameters
TD                  256
SFO1           500.1325 MHz
FIDRES        19.536406 Hz
SW               10,000 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 2048
SF          500.1300135 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2       echo-antiecho
SF          500.1300135 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME W-A4-4-17(2) EXPNO 5
PROCNO 1
F1 - Acquisition parameters
TD 256
SFO1 125.7678 MHz
FIDRES 98.255890 Hz
SW 200.000 ppm
FnMODE Echo-Antiecho
F2 - Processing parameters
SI 2048
SF 500.1300135 MHz
WDW TRAP
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 2048
MC2 echo-antiecho
SF 125.7578472 MHz
WDW TRAP
SSB 2
LB 0 Hz
GB 0
Current Data Parameters

NAME       W-A4-4-17(2)
EXPNO       6
PROCNO      1

F1 - Acquisition parameters
TD           256
SFO1         125.7704 MHz
FIDRES       98.257607 Hz
SW           199.999 ppm
FnMODE       QF

F2 - Processing parameters
SI           2048
SF           500.1300135 MHz
WDW          QSINE
SSB          2
LB           0 Hz
GB           0
PC           1.00

F1 - Processing parameters
SI           2048
MC2          QF
SF           125.7578472 MHz
WDW          USER
SSB          2
LB           0 Hz
GB           0
Current Data Parameters
NAME           W-A4-5-1
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20121027
Time              17.23
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG              zg
TD                65536
SOLVENT            DMSO
NS                    8
DS                    0
SWH           10000.000 Hz
FIDRES        0.152588 Hz
AQ                  3.2767999 sec
RG                    7
DW               50.000 usec
DE                10.00 usec
TE                298.0 K
D1           2.00000000 sec
TD0                   1

-------- CHANNEL f1 --------
NUC1                 1H
P1                10.00 usec
PLW1         13.50000000 W
SFO1      500.1330008 MHz

F2 - Processing parameters
SI                65536
SF          500.1300146 MHz
WDW                  EM
SSB                 0
LB          0.30 Hz
GB                 0
PC                 1.00
Current Data Parameters
NAME       W-A4-5-1
EXPNO      4
PROCNO     1

F1 - Acquisition parameters
TD          256
SFO1        500.1325 MHz
FIDRES      19.536406 Hz
SW          10.000 ppm
FnMODE      Echo-Antiecho

F2 - Processing parameters
SI          2048
SF          500.1300135 MHz
WDW         TRAP
SSB         2
LB          0 Hz
GB          0
PC          1.00

F1 - Processing parameters
SI          2048
MC2         echo-antiecho
SF          500.1300135 MHz
WDW         TRAP
SSB         2
LB          0 Hz
GB          0
Current Data Parameters
NAME           W-A4-5-1
EXPNO                5
PROCNO                1
F1 - Acquisition parameters
TD                  256
SFO1           125.7678 MHz
FIDRES        98.255890 Hz
SW              200.000 ppm
FnMODE    Echo-Antiecho
F2 - Processing parameters
SI                 2048
SF          500.1300135 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.00
F1 - Processing parameters
SI                2048
MC2    echo-antiecho
SF         125.7578472 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME          W-A4-5-1
EXPNO         6
PROCNO        1

F1 - Acquisition parameters
TD             256
SFO1           125.7704 MHz
FIDRES         98.257607 Hz
SW             199.999 ppm
FnMODE         QF

F2 - Processing parameters
SI             2048
SF             500.1300135 MHz
WDW            QSINE
SSB            2
LB             0 Hz
GB             0
PC             1.00

F1 - Processing parameters
SI             2048
MC2            QF
SF             125.7578472 MHz
WDW            QSINE
SSB            2
LB             0 Hz
GB             0
Current Data Parameters
NAME      KL-5-225-1m-1
EXPNO                 4
PROCNO                1
F1 - Acquisition parameters
TD                  256
SFO1           600.1336 MHz
FIDRES        28.131262 Hz
SW               12.000 ppm
FnMODE      States-TPPI
F2 - Processing parameters
SI                 2048
SF          600.1300273 MHz
WDW               QSINE
SSB                   1
LB       0 Hz
GB       0
PC                 1.00
F1 - Processing parameters
SI                 2048
MC2         States-TPPI
SF          600.1300273 MHz
WDW               QSINE
SSB                   1
LB       0 Hz
GB       0
Current Data Parameters

NAME: KL-5-225-1m-1
EXPNO: 3
PROCNO: 1

F1 - Acquisition parameters
TD: 600
SFO1: 600.1336 MHz
FIDRES: 12.002672 Hz
SW: 12.000 ppm
FnMODE: Echo-Antiecho

F2 - Processing parameters
SI: 1024
SF: 600.1300273 MHz
WDW: QSINE
SSB: 2
LB: 0 Hz
GB: 0
PC: 1.00

F1 - Processing parameters
SI: 1024
MC2: Echo-Antiecho
SF: 600.1300273 MHz
WDW: QSINE
SSB: 2
LB: 0 Hz
GB: 0
F1 - Acquisition parameters
TD 512
SFO1 150.9134 MHz
FIDRES 47.160427 Hz
SW 160.000 ppm
FnMODE Echo-Antiecho

F2 - Processing parameters
SI 4096
SF 600.1300051 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

F1 - Processing parameters
SI 4096
MC2 echo-antiecho
SF 150.9029331 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
### Current Data Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>NAME</td>
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<tr>
<td>EXPNO</td>
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<td>PROCNO</td>
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**F1 - Acquisition parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>TD</td>
<td>512</td>
</tr>
<tr>
<td>SFO1</td>
<td>150.9156 MHz</td>
</tr>
<tr>
<td>FIDRES</td>
<td>56.003849 Hz</td>
</tr>
<tr>
<td>SW</td>
<td>190.000 ppm</td>
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<tr>
<td>FnMODE</td>
<td>QF</td>
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**F2 - Processing parameters**

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<tr>
<th>Parameter</th>
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<tbody>
<tr>
<td>SI</td>
<td>4096</td>
</tr>
<tr>
<td>SF</td>
<td>600.1300066 MHz</td>
</tr>
<tr>
<td>WDW</td>
<td>QSINE</td>
</tr>
<tr>
<td>SSB</td>
<td>0</td>
</tr>
<tr>
<td>LB</td>
<td>0 Hz</td>
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<tr>
<td>GB</td>
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</tr>
<tr>
<td>PC</td>
<td>1.40</td>
</tr>
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**F1 - Processing parameters**

<table>
<thead>
<tr>
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<th>Value</th>
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</thead>
<tbody>
<tr>
<td>SI</td>
<td>4096</td>
</tr>
<tr>
<td>SF</td>
<td>150.9029181 MHz</td>
</tr>
<tr>
<td>WDW</td>
<td>QSINE</td>
</tr>
<tr>
<td>SSB</td>
<td>3</td>
</tr>
<tr>
<td>LB</td>
<td>0 Hz</td>
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<tr>
<td>GB</td>
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### Current Data Parameters

<table>
<thead>
<tr>
<th>Name</th>
<th>KL-5-225-3-1</th>
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<tbody>
<tr>
<td>Expno</td>
<td>2</td>
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<tr>
<td>Procno</td>
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</table>

#### F2 - Acquisition Parameters

- **Date**: 20131029
- **Time**: 20.40
- **Instrum**: av600
- **Probhd**: 5 mm TBI5
- **Pulprog**: zg
- **TD**: 65536
- **Solvent**: DMSO
- **NS**: 1
- **DS**: 0
- **SWH**: 12376.237 Hz
- **Fidres**: 0.188846 Hz
- **AQ**: 2.6476543 sec
- **RG**: 812.7
- **DW**: 40.400 usec
- **DE**: 6.50 usec
- **TE**: 295.0 K
- **D1**: 2.0000000 sec

#### CHANNEL f1

- **NUC1**: 1H
- **P1**: 9.75 usec
- **PLL**: -2.00 dB
- **PLLW**: 39.81071854 W
- **SP01**: 600.1336008 MHz

#### F2 - Processing parameters

- **SI**: 65536
- **SP**: 600.1300273 MHz
- **WDW**: 0
- **SSB**: 0
- **LB**: 0.30 Hz
- **GB**: 0
- **PC**: 1.00
Current Data Parameters
NAME: KL-5-225-3-1
EXPNO: 3
PROCNO: 1

F1 - Acquisition parameters
TD: 600
SF01: 600.1336 MHz
FIDRES: 12.002672 Hz
SW: 12.000 ppm
FnMODE: Echo-Antiecho

F2 - Processing parameters
SI: 1024
SF: 600.1300273 MHz
WDW: QSINE
SSB: 2
LB: 0 Hz
GB: 0
PC: 1.00

F1 - Processing parameters
SI: 1024
MC2: echo-antiecho
SF: 600.1300273 MHz
WDW: TRAP
SSB: 2
LB: 0 Hz
GB: 0
Current Data Parameters
NAME      KL-5-225-3-1
EXPN0     4
PROCNO    1

F1 - Acquisition parameters
TD       256
SP01      600.1336 MHz
FIDRES    28.131262 Hz
SW          12.000 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI       2048
SF       600.1300273 MHz
WDW      QSINE
SSB       1
LB       0 Hz
GB       0
PC       1.00

F1 - Processing parameters
SI       2048
MC2      States-TPPI
SF       600.1300273 MHz
WDW      QSINE
SSB       1
LB       0 Hz
GB       0
Current Data Parameters
NAME       KL=5-225-3-1
EXPNO                 5
PROCNO                1

F1 - Acquisition parameters
TD                  512
SFO1           150.9134 MHz
FIDRES        47.160427 Hz
SW              160.000 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 4096
SF          150.9029231 MHz
WDW                TRAP
SSB                   2
LB       1.00 Hz
GB       1.40
PC                 echo-antiecho

F1 - Processing parameters
SI                 4096
MC2       echo-antiecho
SF          150.9029231 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME       KL-5-225-3-1
EXPN0                6
PROCNO                1
F1 - Acquisition parameters
TD                  512
SFO1           150.9156 MHz
FIDRES      56.003849 Hz
SW              190.000 ppm
FnMODE               QF
F2 - Processing parameters
SI                 4096
SF          600.1300066 MHz
WDW                TRAP
SSB         0
LB       0 Hz
GB       0
PC                   1.40
F1 - Processing parameters
SI                 4096
M2                  QF
SF          150.9029181 MHz
WDW                TRAP
SSB         0
LB       0 Hz
GB       0
Current Data Parameters
NAME Kl-5-225-4-1
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date 20131014
Time 18.31
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG zg
TD 65536
SOLVENT DMSO
NS 64
DS 0
SNH 12376.237 Hz
FIDRES 0.188846 Hz
AQ 2.6476543 sec
RG 574.7
DW 40.400 usec
DE 6.50 usec
TE 294.9 K
D1 2.0000000 sec
TDO 1

-------- CHANNEL f1 --------
NUC1 1H
P1 9.60 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SF01 600.1336008 MHz

F2 - Processing parameters
SI 65536
SF 600.1300273 MHz
WDM EM
SNR 0
LB 0.30 Hz
GB 0
PC 1.00
Current Data Parameters
NAME       Kl-5-225-4-1
EXPNO        4
PROCNO        1
F1 - Acquisition parameters
TD            256
SFO1        600.1336 MHz
FIDRES      28.131262 Hz
SW            12.000 ppm
FnMODE     States-TPPI
F2 - Processing parameters
SI            2048
SF        600.1300273 MHz
WDW       TRAP
SSB           1
LB       0 Hz
GB          0
PC          1.00
F1 - Processing parameters
SI            2048
MC2       States-TPPI
SF        600.1300273 MHz
WDW       TRAP
SSB           1
LB       0 Hz
GB          0
Current Data Parameters
NAME       Kl-5-225-4-1
EXPNO                3
PROCNO                1

F1 - Acquisition parameters
TD                  600
SP01           600.1336 MHz
FIDRES        12.002672 Hz
SW               12.000 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 1024
SF          600.1300273 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                1024
MC2       echo-antiecho
SF          600.1300273 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME        K1-5-225-4-1
EXPNO                5
PROCNO                1

F1 - Acquisition parameters
TD                  512
SFO1           150.9134 MHz
FIDRES        47.160427 Hz
SW              160.000 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 4096
SF          150.9029231 MHz
WDW                SINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.40

F1 - Processing parameters
SI                 4096
MC2       echo-antiecho
SF          150.9029231 MHz
WDW                SINE
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME    KL-5-225-4-2
EXPN0   4
PROCNO  1

F1 - Acquisition parameters
TD      256
SFO1  600.1336 MHz
FIDRES  28.131262 Hz
SW      12.000 ppm
FnMODE  States-TPPI

F2 - Processing parameters
SI      2048
SF      600.1300273 MHz
WDW     SINE
SSB     1
LB      0 Hz
GB      0
PC      1.00

F1 - Processing parameters
SI      2048
MC2     States-TPPI
SF      600.1300273 MHz
WDW     QSINE
SSB     1
LB      0 Hz
GB      0
NAME       KL-5-225-4-2
EXPN0                3
PROCNO                1

F1 - Acquisition parameters
TD                  600
SFO1           600.1336 MHz
FIDRES        12.002672 Hz
SW               12.000 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 1024
SF          600.1300273 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 1024
MC2       echo-antiecho
SF          600.1300273 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME      KL-5-225-4-2  
EXPN0     5
PROCNO    1

F1 - Acquisition parameters
TD        512
SFO1              150.9134 MHz
FIDRES        47.160427 Hz
SW             160.000 ppm
FnMODE     Echo-Antiecho

F2 - Processing parameters
SI         4096
SF          600.1300051 MHz
WDW          EM
SSB         0
LB           1.00 Hz
GB           0
PC           1.40

F1 - Processing parameters
SI         4096
MC2     echo-antiecho
SF          150.9029231 MHz
WDW          TRAP
SSB         0
LB           0 Hz
GB           0
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<th>Parameter</th>
<th>Value</th>
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<td>EXPNO</td>
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<td>PROCNO</td>
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</table>

### F1 - Acquisition parameters
- TD: 512
- SFO1: 150.9156 MHz
- FIDRES: 56.003849 Hz
- SW: 190.00 ppm
- FnMODE: QF

### F2 - Processing parameters
- SI: 4096
- SF: 600.1300066 MHz
- WDW: TRAP
- SSB: 3
- LB: 0 Hz
- GB: 0
- PC: 1.40

### F1 - Processing parameters
- SI: 4096
- MC2: QF
- SF: 150.9029181 MHz
- WDW: TRAP
- SSB: 3
- LB: 0 Hz
- GB: 0
Current Data Parameters
NAME          W-B1-1a-4
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date          20121023
Time              17.17
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG              zg
TD                65536
SOLVENT            DMSO
NS                    8
DS                   0
SWH           10000.000 Hz
FIDRES       0.152568 Hz
AQ                     3.2767999 sec
RG                    7
DW               50.000 usec
DE                 10.00 usec
TE                298.0 K
D1           2.00000000 sec
TDO                   1

-------- CHANNEL f1 --------
NUC1                 1H
P1                10.00 usec
PLW1        13.50000000 W
SFO1         500.1330008 MHz

F2 - Processing parameters
SI                65536
SF         500.1300146 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                   0
PC                     1.00
Current Data Parameters
NAME         W-B1-1a-4
EXPNO                3
PROCNO                1

F1 - Acquisition parameters
TD                  256
SFO1           500.1328 MHz
FIDRES        19.536423 Hz
SW               10.000 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                 2048
SF          500.1300135 MHz
WDW                  SINE
SSB                   1
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                2048
MC2         States-TPPI
SF          500.1303720 MHz
WDW                  GM
SSB                   1
LB       0 Hz
GB       0
Current Data Parameters
NAME          W-B1-1a-4
EXPN0         4
PROCNO        1

F1 - Acquisition parameters
TD                  256
SF01           500.1325 MHz
FIDRES       19.536406 Hz
SW               10.000 ppm
FnMODE   Echo-Antiecho

F2 - Processing parameters
SI                 2048
SF          500.1300135 MHz
WDW            QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2       echo-antiecho
SF          500.1300135 MHz
WDW            QSINE
SSB                   2
LB       0 Hz
GB       0

ppm
Current Data Parameters
NAME W-B1-1a-4
EXPNO 5
PROCNO 1

F1 - Acquisition parameters
TD 256
SFO1 125.7678 MHz
FIDRES 98.255890 Hz
SW 200.000 ppm
FnMODE Echo-Antiecho

F2 - Processing parameters
SI 2048
SF 500.1300135 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00

F1 - Processing parameters
SI 2048
MC2 echo-antiecho
SF 125.7578472 MHz
WDW USER
SSB 2
LB 0 Hz
GB 0
Current Data Parameters
NAME          W-B1-1a-4
EXPNO                  6
PROCNO                1

F1 - Acquisition parameters
TD                  256
SFO1           125.7704 MHz
FIDRES        98.257607 Hz
SW              199.999 ppm
FnMODE               QF

F2 - Processing parameters
SI                 2048
SF          500.1300135 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2                  QF
SF          125.7578472 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME W-B1-2
EXPN0 1
PROCNO 1

F2 - Acquisition Parameters
Date 20121020
Time 13.37
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 0
SWM 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 15.53
DW 50.000 usec
DE 10.000 usec
TE 298.0 K
D1 2.00000000 sec
TDO 1

------ CHANNEL f1 ------
NUC1 1H
P1 10.000 usec
PLW1 13.50000000 W
SF01 500.1330008 MHz

F2 - Processing parameters
SI 65536
SF 500.1300146 MHz
WDM EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
Current Data Parameters

NAME             W-B1-2
EXPNO            3
PROCNO            1

F1 - Acquisition parameters
TD                  256
SFO1           500.1328 MHz
FIDRES        19.936423 Hz
SW               10.000 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                 2048
SF          500.1300135 MHz
WDW                  SINE
SSB                   1
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2         States-TPPI
SF          500.1303720 MHz
WDW                  GM
SSB                   1
LB       0 Hz
GB       0
Current Data Parameters
NAME             W-B1-2
EXPN0            4
PROCNO           1
F1 - Acquisition parameters
TD                  256
SP01           125.7678 MHz
FIDRES         98.255890 Hz
SW              200.000 ppm
FnMODE       Echo-Antiecho
F2 - Processing parameters
SI                 2048
SF            500.1300135 MHz
WDW           QSINE
SSB                2
LB       0 Hz
GB       0
PC             1.00
F1 - Processing parameters
SI                 2048
MC:2       echo-antiecho
SF          125.7578472 MHz
WDW           QSINE
SSB                2
LB       0 Hz
GB       0
Current Data Parameters

NAME             W-B1-2
EXPNO             5
PROCNO             1

F1 - Acquisition parameters
TD                  256
SFO1           125.7704 MHz
FIDRES        98.257607 Hz
SW              199.999 ppm
FnMODE               QF

F2 - Processing parameters
SI                 2048
SF          500.1300135 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2                  QF
SF          125.7578472 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME KL-5-108-2_TROSE
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20130110
Time 18.39
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG zg
TD 65536
SOLVENT DMSO
NS 8
DS 0
SWH 12376.237 Hz
FIDRES 0.188846 Hz
AQ 2.6476543 sec
RG 114
DW 40.400 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
DDO 1

-------- CHANNEL f1 --------
NUC1 1H
P1 9.55 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1336008 MHz

F2 - Processing parameters
SI 65536
SF 600.1300070 MHz
WDW EMSSB 0
LB 0.20 Hz
GB 0
PC 1.00
Current Data Parameters

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<tr>
<th>NAME</th>
<th>KL-5-108-2_TROSEEXPNO</th>
<th>PROCNO</th>
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</table>

**F1 - Acquisition parameters**
- TD: 512
- SFO1: 600.1335 MHz
- FIDRES: 13.451290 Hz
- SW: 11.476 ppm
- FnMODE: States-TPPI

**F2 - Processing parameters**
- SI: 4096
- SF: 600.1300014 MHz
- WDW: QSINE
- SSB: 2
- LB: 0 Hz
- GB: 0
- PC: 1.00

**F1 - Processing parameters**
- SI: 4096
- MC2: States-TPPI
- SF: 600.1300177 MHz
- WDW: QSINE
- SSB: 2
- LB: 0 Hz
- GB: 0
Current Data Parameters

NAME	KL-5-108-2_TROSE
EXPNO	8
PROCNO	1

F1 - Acquisition parameters
TD	128
SFO1	600.1335 MHz
FIDRES	53.805161 Hz
SW	11.476 ppm
FnMODE	Echo-Antiecho

F2 - Processing parameters
SI	4096
SF	600.1300273 MHz
WDW	TRAP
SSB	2
LB	0 Hz
GB	0
PC	1.00

F1 - Processing parameters
SI	4096
MC2	echo-antiecho
SF	600.1300273 MHz
WDW	TRAP
SSB	2
LB	0 Hz
GB	0
Current Data Parameters
NAME     KL-5-108-2_TROSE
EXPNO     6
PROCNO    1

F1 - Acquisition parameters
TD                  253
SFO1           150.9134 MHz
FIDRES        95.439285 Hz
SW              160.000 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 4096
SF          600.1300051 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
PC                 1.40

F1 - Processing parameters
SI                 4096
MC2       echo-antiecho
SF          150.9029231 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME: KL-5-108-2_TROSE
EXPNO: 7
PROCNO: 1

F1 - Acquisition parameters
TD: 256
SFO1: 150.9156 MHz
FIDRES: 112.007698 Hz
SW: 190.000 ppm
FnMODE: QF

F2 - Processing parameters
SI: 4096
SF: 600.1300273 MHz
WDW: QSINE
SSB: 2
LB: 0 Hz
GB: 0
PC: 1.40

F1 - Processing parameters
SI: 2048
MC2: QF
SF: 150.9028090 MHz
WDW: USER
SSB: 2
LB: 0 Hz
GB: 0
Current Data Parameters
NAME       KL-5-108-3-1_TROSE
EXPNO      4
PROCNO     1

F2 - Acquisition Parameters
Date       20130113
Time        17.25
INSTRUM      av600
PROBHD      5 mm TBI5
PULPROG      zg
TD          65536
SOLVENT     DMSO
NS          8
DS          0
SNR         12376.237 Hz
FIDRES      0.188846 Hz
AQ          2.6476543 sec
RG          128
DW         40.400 usec
DE           6.50 usec
TE         320.0 K
D1      2.00000000 sec
TDD         1

----- CHANNEL f1 -----
NUC1       1H
P1         9.73 usec
PL1       -2.00 dB
PL1W    39.81071854 W
SFO1   600.1336008 MHz

F2 - Processing parameters
SI          65536
SF       600.1300070 MHz

PC          1.00
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<thead>
<tr>
<th></th>
<th>NAME</th>
<th>EXPNO</th>
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</table>

**F1 - Acquisition parameters**
- TD: 512
- SF01: 600.1335 MHz
- FIDRES: 13.451290 Hz
- SW: 11.476 ppm
- FnMODE: States-TPPI

**F2 - Processing parameters**
- SI: 4096
- SF: 600.130014 MHz
- WDW: QSINE
- SSB: 2
- LB: 0 Hz
- GB: 0
- PC: 1.00

**F1 - Processing parameters**
- SI: 4096
- MC2: States-TPPI
- SF: 600.1300177 MHz
- WDW: TRAP
- SSB: 2
- LB: 0 Hz
- GB: 0
Current Data Parameters
NAME: KL-5-108-3-1_TROSE
EXPNO: 1
PROCNO: 1

F1 - Acquisition parameters
TD: 533
SP1: 150.9134 MHz
FIDRES: 45.3023 Hz
SW: 160.00 ppm
F1MODE: Echo-Antiecho

F1 - Processing parameters
SI: 4096
SF: 600.1300 MHz
WDW: TRAP
SSB: 2
LB: 0 Hz
GB: 0
PC: 1.40

F2 - Processing parameters
SI: 4096
SF: 150.9029 MHz
WDW: TRAP
SSB: 2
LB: 0 Hz
GB: 0
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>NAME</td>
<td>KL-5-108-3-1_TROSE</td>
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<tr>
<td>EXPNO</td>
<td>14</td>
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<tr>
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<tr>
<td>TD</td>
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<tr>
<td>SFO1</td>
<td>150.9156 MHz</td>
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<tr>
<td>FIDRES</td>
<td>112.007698 Hz</td>
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<td>SW</td>
<td>190.000 ppm</td>
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<td>F1MODE</td>
<td>QF</td>
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<tr>
<td>SI</td>
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<tr>
<td>LB</td>
<td>0 Hz</td>
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<td>GB</td>
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<td>F1 MODE</td>
<td>QF</td>
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<tr>
<td>SI</td>
<td>4096</td>
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<tr>
<td>MC2</td>
<td>QF</td>
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<td>SF</td>
<td>150.9029322 MHz</td>
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<td>WDW</td>
<td>USER</td>
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<tr>
<td>LB</td>
<td>0 Hz</td>
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<tr>
<td>GB</td>
<td>0</td>
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</table>
Current Data Parameters
NAME: KL-5-108-5-1_AV500
PROCNO: 1

F2 - Acquisition Parameters
Date: 20130110
Time: 19.43
INSTRUM: av500
PROBHD: 5 mm DCH 13C-1
PULPROG: cosygpmfph
TD: 4096
SOLVENT: DMSO
DS: 4
DSW: 5498.534 Hz
FIDRES: 1.342415 Hz
AQ: 0.3734439 sec
RG: 202.81
DW: 90.333 usc
DE: 10.00 usec
TE: 298.0 K
D0: 0.00003740 sec
D1: 2.00000000 sec
D13: 0.00000400 sec
D16: 0.00020000 sec
IN0: 0.00018180 sec

====== CHANNEL f1 ======
SFO1: 500.1327507 MHz
NUC1: 1H
P1: 9.50 usec
PLW1: 13.50000000 W

F1 - Acquisition parameters
TD: 256
SFO1: 500.1328 MHz
FIDRES: 21.486525 Hz
SW: 10.998 ppm
FnMODE: States-TPPI

F2 - Processing parameters
SI: 2048
SF: 500.1300135 MHz
WDW: SINESSB
LB: 0 Hz
PC: 1.00

F1 - Processing parameters
SI: 2048
MC2: States-TPPI
SF: 500.1303720 MHz
WDW: SIN
LB: 0 Hz
GR: 0
Current Data Parameters
NAME     KL-5-108-5-1_AV500
EXPNO                 4
PROCNO                1

F2 - Acquisition Parameters
Date_          20130110
Time              20.24
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG     mlevetgp.js
TD                 2048
SOLVENT            DMSO
NS                    4
DS                    8
SWH            5000.000 Hz
FIDRES         2.441406 Hz
AQ            0.2048000 sec
RG                37.94
DW              100.000 usec
DE                10.00 usec
TE                298.0 K
D0           0.00000300 sec
D1           2.00000000 sec
D9           0.06000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
IN0          0.00020000 sec
L1                   24

========= CHANNEL f1 ========
SFO1        500.1325007 MHz
NUC1                 1H
P1                 9.50 usec
P2                19.00 usec
P5                26.68 usec
P6                40.00 usec
P7                80.00 usec
P17             2500.00 usec
PLW1        13.50000000 W
PLW10        0.84375000 W

====== GRADIENT CHANNEL =====
GPNAM[1]       SINE.100
GPNAM[2]       SINE.100
GPZ1              30.00 %
GPZ2              30.00 %
P16             1000.00 usec
F1 - Acquisition parameters
TD                  256
SFO1           500.1325 MHz
SW                9.997 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 2048
SF          500.1300135 MHz
WDW               QS
TRAPSSB                   2
LB       0 Hz
GB       0 Hz
PC       1.00

F1 - Processing parameters
G2       1000 Hz
G3       500.130015 MHz
G4       1000 Hz
GB       0 Hz
GC       0 Hz
Current Data Parameters
NAME             W-B2-3
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20121110
Time              14.34
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG              zg
TD                65536
SOLVENT            DMSO
NS                    8
DS                    0

SWH           10000.000 Hz
FIDRES        0.152588 Hz
AQ                3.2767999 sec
RG                    7
DW               50.000 usec
DE                10.00 usec
TE                298.0 K
D1           2.00000000 sec
TDO                   1

------- CHANNEL f1 -------
NUC1                 1H
P1                10.00 usec
PLW1         13.50000000 W
SF01    500.1330008 MHz

F2 - Processing parameters
SI                65536
SF          500.1300146 MHz
WDW                  EM
SSB                 0
LB                 0.30 Hz
GB                    0
PC                    1.00
Current Data Parameters
NAME             W-B2-3
EXPNO            3
PROCNO           1

F1 - Acquisition parameters
TD                  256
SFO1           500.1328 MHz
FIDRES        21.490080 Hz
SW             11.000 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                 2048
SF          500.1300135 MHz
WDW                  SINE
SSB                   1
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2         States-TPPI
SF          500.1300135 MHz
WDW                  GM
SSB                   1
LB       0 Hz
GB       0
Current Data Parameters

NAME               W-B2-3EXPNO      4
PROCNO             1

F1 - Acquisition parameters
TD                  256
SF01                500.1325 MHz
FIDRES         19.536406 Hz
SW               10.000 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 2048
SF          500.1300135 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2       echo-antiecho
SF          500.1300135 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
PC                 1.00
Current Data Parameters
NAME             W-B2-3
EXPN0               5
PROCNO               1

F1 - Acquisition parameters
TD                  256
SF01           125.7678 MHz
FIDRES        98.255890 Hz
SW              200.000 ppm
FnMODE   Echo-Antiecho

F2 - Processing parameters
SI                 2048
SF        500.1300135 MHz
WDW               TRAP
SSB                   2
LB       0 Hz
GB       0
PC                1.00

F1 - Processing parameters
SI                 2048
MC2       echo-antiecho
SF        125.7578472 MHz
WDW               TRAP
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME             W-B2-3
EXPNO            6
PROCNO            1

F1 - Acquisition parameters
TD                  256
SFO1           125.7704 MHz
FIDRES        98.257607 Hz
SW              199.999 ppm
FnMODE               QF

F2 - Processing parameters
SI                 2048
SF             500.1300135 MHz
WDW                QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2                QF
SF            125.7578472 MHz
WDW                QSINE
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME             W-B2-4
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20121110
Time              15.59
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                    8
DS                    0
SNH          10000.000 Hz
FIDRES 0.152588 Hz
AQ            3.2767999 sec
RG                   11
DW               50.000 usec
DE                10.00 usec
TE                298.0 K
D1           2.00000000 sec
TDD0                   1

-------- CHANNEL f1 --------
NUC1                 1H
P1                10.00 usec
PLW1        13.50000000 W
SFU1     500.1330008 MHz

F2 - Processing parameters
SI                65536
SF                      500.1300146 MHz
WDW            EM
SSB             0
LB                   0
GB                   0
PC                   1.00

--- Chart ---
Current Data Parameters
NAME            W-B2-4
EXPNO           3
PROCNO          1

F1 - Acquisition parameters
TD              256
SPD1            500.1328 MHz
FIDRES          21.490080 Hz
SW              11.000 ppm
FnMODE          States-TPPI

F1 - Processing parameters
SI              2048
SF              500.1300135 MHz
WDW             SINE
SSB             1
LB              0 Hz
GB              0
PC              1.00

F2 - Processing parameters
SI              2048
SF              500.1300135 MHz
WDW             GM
SSB             1
LB              0 Hz
GB              0
Current Data Parameters
NAME
W-B2-4
EXPNO 4
PROCNO 1

F1 - Acquisition parameters
TD 256
SFO1 500.1325 MHz
FIDRES 19.536406 Hz
SW 10.000 ppm
FnMODE Echo-Antiecho

F2 - Processing parameters
SI 2048
SF 500.1300135 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00

F1 - Processing parameters
SI 2048
MC2 echo-antiecho
SF 500.1300135 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
Current Data Parameters
NAME             W-B2-4EXPNO                 5PROCNO                1
F1 - Acquisition parameters
TD                  256SFO1           125.7678 MHz
FIDRES        98.255890 Hz
SW              200.000 ppm
FnMODE    Echo-Antiecho
F2 - Processing parameters
SI                 2048SF          500.1300135 MHzWDW               QSINE
SSB                   2LB       0 Hz
GB       0
PC                 1.00
F1 - Processing parameters
SI                 2048SF          500.1300135 MHzWDW               QSINE
SSB                   2LB       0 Hz
GB       0
F1 - Processing parameters
SI                 2048MC2       echo-antiecho
SF          125.7578472 MHz
WDW               QSINE
SSB                   2LB       0 Hz
GB       0
Current Data Parameters
NAME             W-B2-4
EXPNO             6
PROCNO             1

F1 - Acquisition parameters
TD 256
SFO1 125.7704 MHz
FIDRES 98.257607 Hz
SW 199.966 ppm
FnMODE QF

F1 - Processing parameters
SI 2048
SF 125.7578472 MHz
WDW USER
SSB 2
LB 0 Hz
GB 0
PC 1.00

F2 - Processing parameters
SI 2048
MC2 QF
SF 125.7578472 MHz
WDW USER
SSB 2
LB 0 Hz
GB 0
Current Data Parameters
NAME     W-B2-5(09-2013)
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date          20130911
Time              19.37
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                   32
DS                    0
SWH           12376.237 Hz
FIDRES    0.188846 Hz
AQ            2.6476543 sec
RG                  181
DW               40.400 usec
DE                6.50 usec
TE                294.5 K
D1           2.00000000 sec
TDO                   1

---------- CHANNEL f1 ----------
NUC1                 1H
P1                11.00 usec
PL1               -2.00 dB
PL1W         39.81071854 W
SFO1          600.1336008 MHz

F2 - Processing parameters
SI                65536
SF      600.1300273 MHz
WDW      0
LB                 0.30 Hz
GB                    0
PC                   1.00
Current Data Parameters
NAME     W-B2-5(09-2013) EXPNO                 4
PROCNO                1
F1 - Acquisition parameters
TD                  256
SF01           600.1336 MHz
FIDRES        28.131262 Hz
SW               12.000 ppm
FnMODE      States-TPPI
F2 - Processing parameters
SI                 2048
SF          600.1300273 MHz
WDW                TRAP
SSB                   1
LB       0 Hz
GB       0
PC                 1.00
F1 - Processing parameters
SI                 2048
MC2   States-TPPI
SF          600.1300273 MHz
WDW
SSB                   1
LB       0 Hz
GB       0
Current Data Parameters
NAME     W-B2-5 (09-2013)
EXPNO     5
PROCNO    1

F1 - Acquisition parameters
TD       512
SFO1      150.9134 MHz
FIDRES   47.160427 Hz
SW       160.000 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI       4096
SF       600.1300200 MHz
WDW      QSINE
SSB      2
LB       0 Hz
GB       0
PC       1.40

F1 - Processing parameters
SI       4096
MC2      echo-antiecho
SF       150.9029231 MHz
WDW      QPINE
SSB      2
LB       0 Hz
GB       0
Current Data Parameters

NAME     W-B2-5(09-2013)
EXPNO                 6
PROCNO                1

F2 - Acquisition Parameters
Date_          20130911
Time              22.18
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG    hmbcgplpndqf
TD                 2048
SOLVENT            DMSONS                   16
DS                   64
SWH            7183.908 Hz
FIDRES         3.507768 Hz
AQ            0.1425408 sec
RG                26008
DW               69.600 usec
DE                 6.00 usec
TE                296.6 K
CNST2       145.0000000
CNST13        7.0000000
d0           0.00000300 sec
D1           1.20000005 sec
d2           0.00344828 sec
D6           0.07142857 sec
D16          0.00020000 sec
in0      0 sec
ST1CNT              512
d0orig       0.00000300 sec
ph1loop               0		
t1loop                0
SFO1        600.1336008 MHz
NUC1                 1H
P1                10.10 usec
P2                20.20 usec
PLW1        -1.00000000 W
SFO2        150.9156357 MHz
NUC2                13C
P3                18.50 usec
PLW2        -1.00000000 W
GPNAM[1]       SINE.100
GPNAM[2]       SINE.100
GPNAM[3]       SINE.100
GPZ1              50.00 %
GPZ2              30.00 %
GPZ3              40.10 %
P16             1000.00 usec
F1 - Acquisition parameters
TD                  512
SFO1           150.9156 MHz
FIDRES        56.003849 Hz
SW              190.000 ppm
FnMODE               QF

F2 - Processing parameters
SI                 4096
SF          600.1300066 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.40

F1 - Processing parameters
SI                 4096
MC2                  QF
SF          150.9029181 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters

NAME           W-B2-7-2EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters

Date_          20121124
Time              15.10
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG      cosygpmfph
TD                 4096
SOLVENT            DMSO
NS                    2
DS                    8
SWH            5498.534 Hz
FIDRES         1.342415 Hz
AQ            0.3724629 sec
RG               202.91
DW               90.933 usec
DE                10.00 usec
TE                298.0 KD
D0           0.000007817 sec
D1           2.00000000 sec
D13          0.00000400 sec
D16          0.00020000 sec
IN0          0.00018180 sec

======== CHANNEL f1 ========

SFO1        500.1327507 MHz
NUC1                 1H
P1                10.00 usec
P2                20.00 usec
PLW1        13.50000000 W

====== GRADIENT CHANNEL =====

GPNAM[1]     SMSQ10.100
GPNAM[2]     SMSQ10.100
GPZ1              10.00 %
GPZ2              20.00 %
P16             1000.00 usec

F1 - Acquisition parameters

TD                  256
SFO1           500.1328 MHz
FIDRES        21.486525 Hz
SW               10.998 ppm
FnMODE      States-TPPI

F2 - Processing parameters

SI                 2048
SF          500.1300135 MHz
WDW                SINESSB                   1
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters

SI                 2048
MC2         States-TPPI
SF          500.1303720 MHz
WDW                SINSSB                   1
LB       0 Hz
GB       0
Current Data Parameters

NAME           W-B2-7-2
EXPNO                4
PROCNO                1

F2 - Acquisition Parameters
Date_       20121124
Time             15.31
INSTRUM      av500
PROBHD     5 mm DCH 13C-1
PULPROG   mlevetgp.js
TD                  2048
SOLVENT      DMSO
NS                   2
DS                   8
SWH           5000.000 Hz
FIDRES        2.441406 Hz
AQ                0.2048000 sec
RG                37.94
DW              100.000 usec
DE               10.00 usec
TE                298.0 K
D0           0.00000300 sec
D1           2.00000000 sec
D9           0.06000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
IN0          0.00020000 sec

======== CHANNEL f1 ========
SFO1        500.1325007 MHz
NUC1                 1H
P1                10.00 usec
P2                20.00 usec
P5                26.68 usec
P6                40.00 usec
P7                80.00 usec
P17             2500.00 usec
PLW1        13.50000000 W
PLW10       0.84375000 W

====== GRADIENT CHANNEL ======
GPNAM[1]       SINE.100
GPNAM[2]       SINE.100
GPZ1              30.00 %
GPZ2              30.00 %
P16             1000.00 usec

F1 - Acquisition parameters
TD                  256
SFO1           500.1325 MHz
FIDRES        19.531250 Hz
SW                9.997 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 2048
MC2       echo-antiecho
SF          500.1300135 MHz
WDW            QS
TRAPSS     2
LB       0 Hz
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2       echo-antiecho
SF          500.1300135 MHz
WDW            QS
TRAPSS     2
LB       0 Hz
PC                 1.00
Current Data Parameters
NAME W-BZ-7-3
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date 20121124
Time 16.44
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG zg
TD 65536
SOLVENT DMSO
NS 16
DS 0
SWM 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
KG 7
DW 50.000 usec
DE 10.00 usec
TE 298.0 K
DL 2.00000000 sec
TDO 1

-------- CHANNEL f1 --------
SP01 500.1330008 MHz
NUC1 1H
P1 10.00 usec
PLW1 13.50000000 W

F2 - Processing parameters
SI 65536
SF 500.1330008 MHz
WDW EM
SSB 0
LB 0.30 Hz
PC 1.00
Current Data Parameters
NAME     W-B2-7-3_AV600
EXPN0                2
PROCNO                1

F1 - Acquisition parameters
TD                  256
SP01           150.9134 MHz
FIDRES       106.110962 Hz
SW              180.000 ppm
FmMODE     Echo-Antiecho

F2 - Processing parameters
SI                 2048
SF          600.1300273 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
PC                 1.40

F1 - Processing parameters
SI                 2048
MC2     echo-antiecho
SF         150.9028800 MHz
WDW                TRAP
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME     W-B2-7-3_AV600
EXPN0            3
PROCNO           1

F1 - Acquisition parameters
TD                  256
SFO1           150.9164 MHz
FIDRES       117.903427 Hz
SW              200.000 ppm
FtMODE                QF

F2 - Processing parameters
SI                 1024
SF          600.1300273 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 1024
MC2                  QF
SF          150.9028090 MHz
WDW               QSINE
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME: KL-5-227-1-F37
EXPN0: 1
PROCNO: 1

F2 - Acquisition Parameters
Date: 20131012
Time: 17.47
INSTRUM: av600
PROBHD: 5 mm TBI5
PULPROG: zg30
TD: 65536
SOLVENT: DMSO
NS: 14
DS: 0
SWH: 12376.237 Hz
FIDRES: 0.188846 Hz
AQ: 2.6476543 sec
RG: 161.3
DW: 40.400 usec
DE: 6.500 usec
TE: 294.7 K
DI: 2.00000000 sec
T0: 1

-------- CHANNEL f1 --------
NUC1: 1H
P1: 1.000 usec
PL1: -2.00 dB
PL1W: 39.81071854 W
SFO1: 600.133600 MHz

F2 - Processing parameters
SI: 65536
SF: 600.1300273 MHz
WDW: EM
LB: 0.30 Hz
GB: 0.00
PC: 1.00
Current Data Parameters

NAME     KL-5-227-1-F37
EXPN0                 4
PROCNO                1
F1 - Acquisition parameters
TD                  256
SFO1           600.1336 MHz
FIDRES        28.131262 Hz
SW               12.000 ppm
FMODE      States-TPPI
F1 - Processing parameters
SI                 2048
SF          600.1300273 MHz
WDW                SINE
SSB                   1
LB       0 Hz
GB       0
PC                 1.00
F2 - Processing parameters
SI                 2048
SF          600.1300273 MHz
WDW                SINE
SSB                   1
LB       0 Hz
GB       0
MC2         States-TPPI
Current Data Parameters
NAME  KL-5-227-1-F37EXPNO                 5
       PROCNO                1
F1 - Acquisition parameters
   TD                  512
   SFO1           150.9134 MHz
   FIDRES        47.160427 Hz
   SW              160,000 ppm
   FnMODE    Echo-Antiecho
F2 - Processing parameters
   SI                 4096
   SF          600.1300051 MHz
   WDW               EM
   SSB                   2
   LB       0 Hz
   GB             1.00 Hz
   PC             1.40
F1 - Processing parameters
   SI                 4096
   MC2       echo-antiecho
   SF          150.9029231 MHz
   WDW              QSINE
   SSB                   2
   LB       0 Hz
   GB             0
Current Data Parameters
NAME KL-5-227-1-F37
EXPNO 6
PROCNO 1

F1 - Acquisition parameters
TD 512
SFO1 150.9156 MHz
FIDRES 56.003849 Hz
SW 190.000 ppm
FnMODE QF

F2 - Processing parameters
SI 4096
SF 600.1300066 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.40

F1 - Processing parameters
SI 4096
MC2 QF
SF 150.9029181 MHz
WDW USER
SSB 2
LB 0 Hz
GB 0
Current Data Parameters

NAME       KL-5-227-2-1
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20131012
Time              14.18
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG              zg
TD                65536
SOLVENT            DMSO
NS                    8
DS                    0
SWH           12376.237 Hz
FIDRES         0.188846 Hz
AQ            2.6476543 sec
RG                   18
DW               40.400 usec
DE                 6.50 usec
TE                294.7 K
D1           2.00000000 sec
D2                  0
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                10.60 usec
PL1               -2.00 dB
PL1W        39.81071854 W
SFO1        600.1336008 MHz

F2 - Processing parameters
SI                65536
SF          600.1300273 MHz
WDW                  EMSSB      0
LB                 0.30 Hz
GB       0.00000000 sec
Current Data Parameters
NAME       KL-5-227-2-1
EXPNO                 4
PROCNO                1

F1 - Acquisition parameters
TD                  256
SFO1           600.1336 MHz
FIDRES        28.131262 Hz
SW               12.000 ppm
FmMODE      States-TPPI

F2 - Processing parameters
SI                 2048
SF          600.1300273 MHz
WDW               QSINE
SSB                   1
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2         States-TPPI
SF          600.1300273 MHz
WDW               QSINE
SSB                   1
LB       0 Hz
GB       0
Current Data Parameters

NAME       KL-5-227-2-1
EXPNO                 5
PROCNO                1

F1 - Acquisition parameters
TD                  512
SFO1           150.9134 MHz
FIDRES        47.160427 Hz
SW              160.000 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 4096
SF          600.1300051 MHz
WDW                SINE
SSB                   2
LB       1.00 Hz
GB       0
PC       1.40

F1 - Processing parameters
SI                 4096
MC2       echo-antiecho
SF      150.9029231 MHz
WDW                SINE
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME         KL-5-229-1
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date          20131109
Time           19.17
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG            zg30
TD                65536
SOLVENT            DMSO
NS                    8
DS                    0
SWH           12376.237 Hz
FIDRES    0.188846 Hz
AQ                2.6476543 sec
RG                 35.9
DW               40.400 usec
DE                6.50 usec
TE                295.3 K
D1           2.00000000 sec
TDD                   1

--------- CHANNEL f1 ---------
NUC1                 1H
P1                 9.50 usec
PL1                -2.00 dB
PL1W        39.81071854 W
SF01        600.1336008 MHz

F2 - Processing parameters
SI                65536
SF     600.1300273 MHz
WDW                  EM
SBR               0
LB                0.30 Hz
GB               0.100
PC                 1
Current Data Parameters
NAME         KL-5-229-1
EXPN0                 4
PROCNO                1

F1 - Acquisition parameters
TD                  256
SFO1           600.1336 MHz
FIDRES        28.131262 Hz
SW               12.000 ppm
FnMODE      States-TPPI

F2 - Processing parameters
SI                 2048
SF          600.1300273 MHz
WDW       SINE
SSB                   1
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 2048
MC2         States-TPPI
SF          600.1300273 MHz
WDW
SSB                   1
LB       0 Hz
GB       0
Current Data Parameters
NAME         KL-5-229-1
EXPNO                3
PROCNO                1

F1 - Acquisition parameters
TD                  400
SFO1           600.1336 MHz
FIDRES        18.004007 Hz
SW               12.000 ppm
FMODE    Echo-Antiecho

F2 - Processing parameters
SI                 1024
SF          600.1300273 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 1024
MC2       echo-antiecho
SF          600.1300273 MHz
WDW                USER
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME         KL-5-229-1
EXPNO                 5
PROCNO                1

F1 - Acquisition parameters
TD                  512
SFO1           150.9134 MHz
FIDRES        47.160427 Hz
SW              160.000 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 4096
SF          600.1300282 MHz
WDW               QSINE
SSB                   2
LB       1.00 Hz
GB       0
PC                 1.40

F1 - Processing parameters
SI                 4096
MC2       echo-antiecho
SF          150.9029231 MHz
WDW               QZINE
SSB                   2
LB       0 Hz
GB       0
Current Data Parameters
NAME        KL-5-229-1
EXPNO       6
PROCNO      1

F1 - Acquisition parameters
TD          512
SFO1        150.9156 MHz
FIDRES      56.003849 Hz
SW          190.000 ppm
FnMODE      QF

F1 - Processing parameters
SI          4096
SF          150.9029181 MHz
WDW         SINE
SSB         3
LB          0 Hz
GB          0
PC          1.40

F2 - Processing parameters
SI          4096
MC2         QF
SF          600.1300231 MHz
WDW         Q8INE
SSB         0
LB          0 Hz
GB          0

References


