

Solution Structure and Constrained Molecular Dynamics Study of Vitamin B₁₂ Conjugates of the Anorectic Peptide PYY(3–36)

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Vitamin B₁₂-peptide conjugates have considerable therapeutic potential through improved pharmacokinetic and/or pharmacodynamic properties imparted on the peptide upon covalent attachment to vitamin B₁₂ (B₁₂). There remains a lack of structural studies investigating the effects of B₁₂ conjugation on peptide secondary structure. Determining the solution structure of a B₁₂-peptide conjugate or conjugates and measuring functions of the conjugate(s) at the target peptide receptor may offer considerable insight concerning the future design of fully optimized conjugates. This methodology is especially useful in tandem with constrained molecular dynamics (MD)

studies, such that predictions may be made about conjugates not yet synthesized. Focusing on two B₁₂ conjugates of the anorectic peptide PYY(3–36), one of which was previously demonstrated to have improved food intake reduction compared with PYY(3–36), we performed NMR structural analyses and used the information to conduct MD simulations. The study provides rare structural insight into vitamin B₁₂ conjugates and validates the fact that B₁₂ can be conjugated to a peptide without markedly affecting peptide secondary structure.

Introduction

Peptide YY (PYY), a member of the pancreatic polypeptide family,^[1–8] was first isolated from porcine intestinal tissue extracts in 1980^[9] and was later shown to be a critical enteroendocrine hormone involved in appetite regulation.^[10–12] PYY has two main circulating forms: PYY(1–36) and a truncated form, PYY(3–36).^[13] PYY(1–36) is released in concert with caloric intake or exercise and is cleaved by dipeptidyl peptidase IV (DPP-IV)^[14] in the gut to produce PYY(3–36). PYY(1–36) has an appetite-stimulating effect through activation of the orexigenic Y1 receptor (Y1-R) located in the intestines, blood vessels, and brain.^[15] The two-amino-acid N-terminal (Tyr-Pro) truncation to PYY(3–36) results in an approximate 100-fold decrease in activity at the Y1-R,^[5,16] and generates an agonist of the anorexigen-

ic Y2 receptor (Y2-R) located in the intestines (vagal afferent sensory neuron signaling)^[17,18] and brain,^[19,20] which exerts a G-protein-coupled receptor (GPCR) G_i-mediated anorectic effect.

We recently reported a B₁₂-PYY(3–36) conjugate that demonstrated similar activity to native PYY(3–36) at the Y2-R in vitro, but improved function over PYY(3–36) upon subcutaneous (s.c.) administration in vivo in a lean rat model (conjugate **3** as described herein below).^[21] In earlier work, we focused on conjugating to B₁₂ through the ribose hydroxy group, as it is well established in the field that this is an optimal site for such conjugation, as it does not hinder recognition of B₁₂ by its carrier proteins.^[22–25] Likewise, we focused on an N-terminal region of PYY(3–36) for conjugation (specifically the K₄ residue), because again it has been well documented that modifications at (or indeed complete loss of) this area do not significantly affect Y2-R agonism.^[26–28] These assumptions bore out, as the EC₅₀ values at the Y2-R obtained for the conjugate produced (and noted as conjugate **3** herein) were similar to that of unconjugated PYY(3–36) used for comparison. These were established using a Fura-2 assay that monitors intracellular Ca²⁺ mobilization under conditions in which the Y2-R signals through a promiscuous G_q GTP binding protein.^[21] Questions that remained from this work, however, were what affect, if any, does B₁₂ conjugation actually have on the PYY(3–36) secondary structure and whether MD simulations could be used to better understand, and possibly predict, any structural modifications observed. To investigate these questions, two conjugates located at the same coupling sites (ribose on B₁₂ and K₄ on PYY(3–36)

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but with a slightly varying spacer length (one methylene unit difference) were assayed for agonism of the Y2-R using a new fluorescence resonance energy transfer (FRET)-based assay that faithfully reports the normal signal transduction process by which the Y2-R signals through G_i proteins to lower levels of intracellular cyclic adenosine monophosphate (cAMP).^[29] NMR structures were solved for these conjugates, and their in-solution NMR structures were compared with those previously reported by Keire et al.^[30] and Nygaard et al.^[7] Subsequent unconstrained and NMR constrained MD simulations were then also performed.

Results and Discussion

In vitro evaluation of conjugates 3 and 4

All assays were performed *at least* in triplicate. Conjugates 3 and 4 were tested for their abilities to lower cAMP levels. Figure 1 shows the dose–response relationships for 3 and 4 relative to K_4 PYY, showing both conjugates are less active than K_4 PYY and that 4 is more active than 3. Both conjugates are, however, within one-half log order of K_4 PYY.

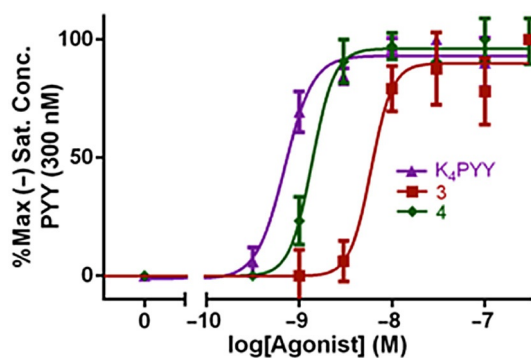


Figure 1. Dose–response curves monitored as percent inhibition of Ex-4 action at AKAR3 by K_4 PYY and conjugates 3 and 4 at the Y2-R. EC_{50} values: K_4 PYY: 1 ± 0.2 nM, 3: 6 ± 2 nM, 4: 2 ± 0.2 nM. EC_{50} values are the average \pm SEM.

This difference in EC_{50} values in comparing conjugates with K_4 PYY was initially presumed to be a compromise between steric hindrance and/or unfavorable flexibility resulting in modifications/interactions that negatively affect the peptide structure–activity profile. At this point we decided to pursue NMR and molecular dynamics (MD) studies to further explore these in vitro observations.

NMR analysis of 3 and 4

Proton chemical shifts for 3 were assigned by analyzing TOCSY, DQF-COSY, and 2D NOE spectra at 25 °C. The experiments were also performed at 20 and 30 °C, at which slight shifts of some proton signals resolved overlapping peaks. The NMR spectra of 3 have some similarity to those of PYY(3–36), such as line broadening of many signals,^[7] indicating increased dynamics,

and a decrease in the chemical shift range of the backbone amide protons relative to full-length PYY. All backbone amide protons were assigned with the exception of Leu24, which could not be definitely determined due to overlap. Figure S17 (Supporting Information) shows the proton chemical shift difference between 3 and PYY(3–36). There are chemical shift differences for residue Lys4, which is not surprising, as this is the attachment site for B_{12} . Figure 2 shows an overlay of 3 after

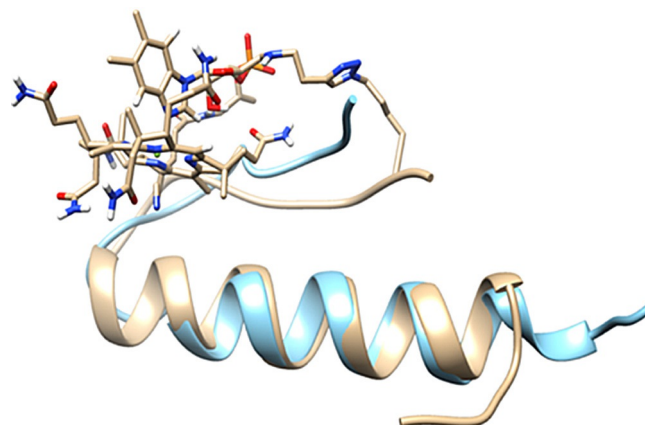


Figure 2. Overlay of PYY(3–36) (blue) versus 3 (tan). The structure of PYY(3–36) was obtained from the RCSB Protein Data Bank (www.pdb.org); PDB ID: 2DF0. The program Chimera (UCSF; www.cgl.ucsf.edu/chimera/)^[31] was used to display the image.

MD calculations and PYY(3–36). The first chemical shift difference to consider is that for the methyl and α protons of Ala7. In PYY(3–36), the methyl group of residue Ala7 is pointing toward the α helix, whereas in conjugate 3 the methyl group is oriented away from the α helix. A 2D NOE cross-peak between the Ala7 methyl group and the ring protons of Tyr20 was observed in PYY(3–36),^[7] but in 3 only a very weak cross-peak was observed in the longest mixing time 2D NOE experiment. This difference in orientation would also put the Ala7 α proton in distinct environments. The backbone amide protons have different chemical shifts for the β turn residues and residues in the N-terminal side of the α helix, specifically residues Gly9, Ala12, Ser13, Glu15, Leu17, and Arg19. This can be explained by the unraveling of the α helix and increased dynamics at the N-terminal side in the PYY(3–36) structure. Conjugate 3 maintains an α -helical structure similar to that of full-length PYY, and the residue with the largest chemical shift difference for the amide proton, Leu17, has a chemical shift value closer to that of the full-length peptide: PYY Leu17 NH 8.40 ppm,^[7] 3 Leu17 NH 8.36 ppm, PYY(3–36) 7.95 ppm.^[7] Nygaard et al. suggest that the Pro2–Tyr27 interaction is important for the stability of the PP fold, and that loss of this interaction in PYY(3–36) creates both conformational and dynamic changes in the structure, especially around the turn region.^[7] Close inspection of 3 indicates possible hydrogen bonds from Glu6 to Tyr27 and Ser23, which may stabilize the PP fold in the conjugate.^[7]

To elaborate on the structural studies, we decided to also investigate the solution structure of **4** to allow a direct comparison with **3**. Based on the NMR spectra, the conjugate structures appear very similar with only minor differences in the proton chemical shift assignments (Supporting Information Figure S18) and greater than 95% similarity in the 2D NOE spectra (Supporting Information Figure S19).

The major difference observed between **3** and **4** is the proton chemical shift change at B7 and B2 on the dimethylbenzimidazole (DMB) ligand (see Supporting Information Figure S12 for B₁₂ atom numbering scheme). The C20 methyl protons are closer to the B4 and B2 protons in **4** based on the presence of a weak cross-peak between the C20 methyl protons and B2, which is only seen in the longest mixing time 2D NOE spectra of **3**, and a cross-peak between the methyl protons and B4, which is stronger for **4**. Weak cross-peaks are observed in **4** between a propionamide proton of the *g* side chain of B₁₂ (Supporting Information Figure S12) and the H α of D11 as well as the methyl protons of A12. The α helix motif as a whole is critical for association and subsequent agonism.^[26] This is consistent with reported Y2-R interactions, as the C-terminal pentapeptide region is well established as the critical region, or “address”, of the main interactions with Y2-R, while the α helix is considered the “message”, indicating that both areas are critical in Y2-R agonism.^[26]

NMR constrained MD studies of **3** and **4**

Molecular dynamics simulations of **3** and **4** were performed both with and without the NMR constraints defined for **3** to consider differences in behavior and potential alternative structures in the simulations. The observed structural changes

across the simulations identified intra-PYY(3–36) interactions that might, through their stabilization in the isolated conjugate, promote the decreased activity of **3** relative to **4**. The unconstrained MD simulation data then provide an additional set of structures for considering accessible geometries beyond the restrained set. The average structures from representative MD time ranges for **3** and **4** are shown in Figures 3 (front/side view) and 4 (top view). Apparent from these views, and the full simulations in general, are the persistence of 1) much of the α helical structure and 2) localization of the B₁₂ fragment itself to the unstructured region approaching the loop into the α helix (in the images, this loop is at the base of all structures, including residues Glu10, Asp11, and Ala12). Across all of the simulations, several hydrogen bonding motifs are found to persist at the onset of the simulations and over the time evolution of the structure dynamics that serve to effectively anchor the B₁₂ at this loop region. Those which specifically anchor the B₁₂ to this region in all simulations are shown in Figure 5, visualizing the two most persistent motifs for these structures: a pair of hydrogen bonds from a single B₁₂ amide side chain to Pro8 and Glu16 (left, Motif 1) and an amide side chain to Pro8 hydrogen bond and coordination of a hydroxy group H atom on Ser13 to the B₁₂ cyano nitrogen atom (right, Motif 2). The structural basis for preservation of the loop region itself across all simulations is evident in Figure 6, which shows that (left) Glu16 is engaged in several persistent hydrogen bonding interactions with Gly9, Glu10, and Asp11, whereas at the far end of the loop (right), Glu6 is in close proximity to hydrogen bond acceptors on Tyr27 and Ser23. The NMR distance lists, ranges, and time-averaged MD structures for **3** and **4** are provided in the Supporting Information.

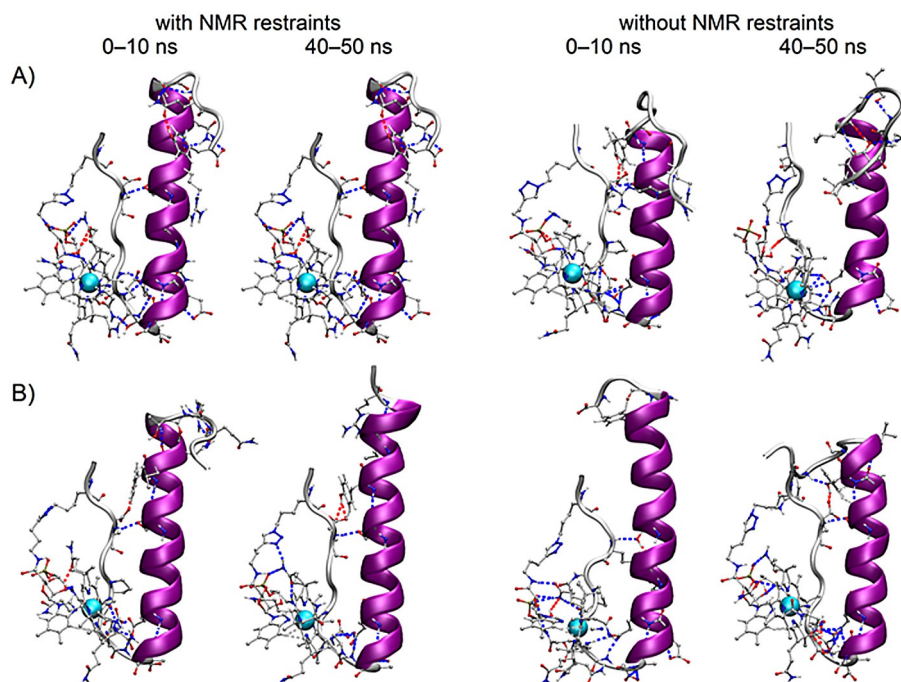


Figure 3. Side-on views (aligned along the α helix) of RMSD average structures (across 10 ns sampling increments) for restrained (left) and unrestrained (right) MD simulations of A) **3** and B) **4**.

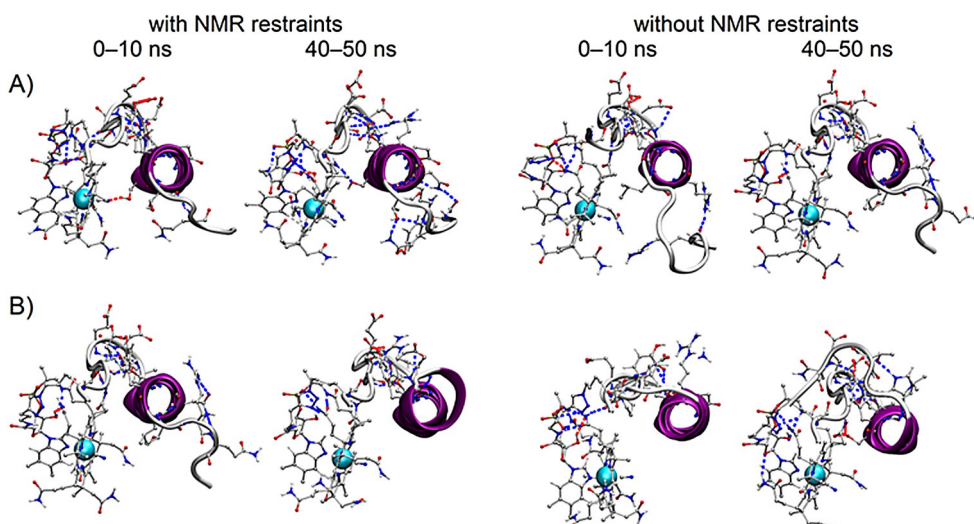


Figure 4. Top-down views (aligned along the α helix) of RMSD average structures (across 10 ns sampling increments) for restrained (left) and unrestrained (right) MD simulations of A) **3** and B) **4**.

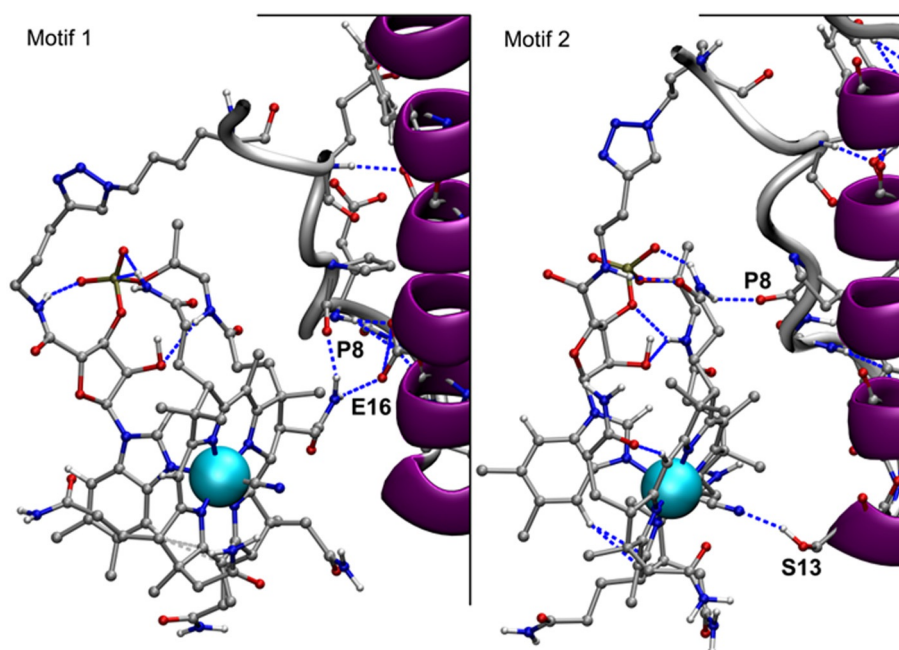


Figure 5. Two persistent hydrogen bonding interaction motifs between the B_{12} and PYY(3–36) unstructured region (residues 3–10) across all simulations.

The differences between structures **3** and **4**, both with and without NMR constraints, are largely localized to the C-terminal side of the α helix and occur to varying degrees in all of the simulations. With the B_{12} largely predicted to be confined to the PYY(3–36) loop due to several strong hydrogen bonding interactions, and with the well-known attenuation of PYY(3–36) activity with modifications to or removal of the C-terminal region, the most logical explanation for any change in behavior to come from these single conjugate simulations is some structural change at the C-terminal region of PYY(3–36). This may occur from B_{12} binding-induced conformational changes at the PYY N terminus, causing changes in activity, meaning

any observed interactions between the B_{12} binding-constrained N terminus and concomitantly proximal C-terminal regions are of great interest. Despite the small change in tether length for these two cases, RMSD analyses and average structure generation produced two distinct structures that, for each case, revealed binding interactions deemed consistent with the trends in activity.

MD simulations of **3** and **4** highlight hydrogen bonding interactions that may govern the differences observed in Y2-R agonism and subsequent calcium mobilization and inhibitory cAMP effects. PYY(3–36) does not tolerate any interaction at the C terminus with respect to Y2-R stimulation.^[32] If the

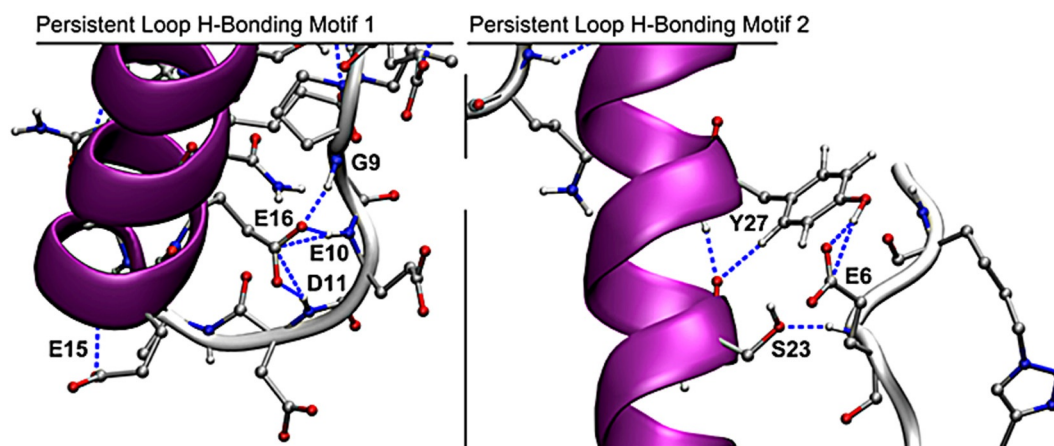


Figure 6. Two persistent hydrogen bonding motifs that define the PYY(3–36) loop region (left) and stabilizing interactions between the unstructured N-terminal region and the α helix.

answer to the decreased activity of **3** lies solely on some response internal to the conjugate, one might argue from the MD simulations that the shortened tether length enhances the stiffness of the unstructured region (residues 3–9) by decreasing its conformational flexibility upon hydrogen bonding between the B_{12} and the near-loop region. This result would provide a less flexible N-terminal region and a more persistent hydrogen bonding pocket for the C-terminal region with which to interact. By the loss of flexibility, necessary at the C-terminal region for biological activity, reduced activity would be predicted (and is observed). Kaiser et al. recently reported data showing that unwinding of C-terminal residues of neuropeptide Y (NPY) is critical for Y2 receptor binding and activation.^[32] Solution NMR experiments showed that the ligand is tethered to the second extracellular loop by hydrophobic contacts and revealed NPY to undergo remarkable structural changes within the C terminus. The C-terminal pentapeptide plays a role in extensive and susceptible interactions in NPY; a network that is also relevant for PYY(3–36) in regards to Y2-R agonism. Changes in the C-terminal amino acids can easily disturb receptor binding or switch receptor selectivity for both NPY and PYY(3–36) as observed in numerous earlier structure-activity studies.^[33] The ultimate conclusion from Kaiser et al. directly relates to our work, as the binding mode of NPY [and in our case, B_{12} conjugates of PYY(3–36)] might have more general implications for peptide binding GPCR systems.

The MD simulations from this study do indicate that if the origin of the decreased activity of **3** is entirely due to factors internal to the B_{12} -PYY(3–36) conjugate itself, then constraint of the C-terminal region by hydrogen bonding interactions with the N-terminal region could explain it—and that this kind of internal mechanism may have its origin in the reduction of tether length.

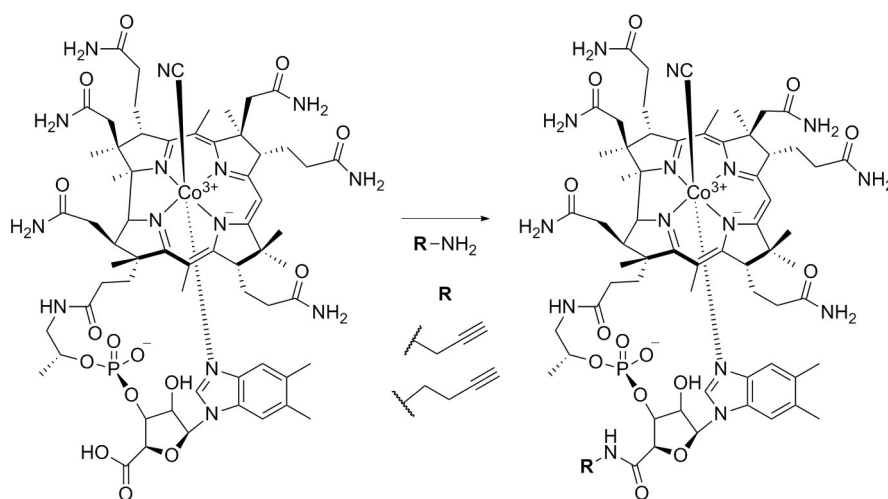
Conclusions

B_{12} -PYY(3–36) conjugates **3** and **4** with various methylene spacer lengths between the B_{12} and PYY(3–36) show similar

Y2-R agonism to that of PYY(3–36). Both intra- and intermolecular interactions between B_{12} and the peptide and small changes in the secondary structure of the peptide brought on by conjugation were observed. Based on the information collected from the NMR constrained MD studies, it would have been possible to offer a detailed assessment of the potential function of both conjugates. These observations suggest that MD could be used a priori to guide conjugate rational design and minimize the number of conjugates that would need to be screened—information of considerable benefit in development terms. Conjugates and modifications of B_{12} have garnered much interest in recent years for their clinical and medicinal applicability.^[34] Based on the studies described herein, an ideal B_{12} -peptide conjugate would be one with an appropriate linker length to allow optimal function of both the peptide and B_{12} , which could be predicted by MD via inter- and intramolecular interactions that are known to be useful and/or harmful to the overall function of each component.

Experimental Section

Synthesis of alkyne precursors (1 and 2) and conjugates (3 and 4): Two B_{12} -alkyne precursors were prepared by activation of a B_{12} -carboxylic acid (B_{12} -CA) derivative^[35] with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and hydroxybenzotriazole (HOBT) in anhydrous DMSO under argon (Scheme 1). Full characterization of the alkyne precursor **1** and **2**, including RP-HPLC, MALDI-ToF MS, and NMR can be found in the Supporting Information (Figure S1–11, Table S1). For conjugate synthesis, click chemistry^[36] was implemented using a copper iodide (CuI) and tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) method, adapted from Gryko et al.^[37,38] Copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) synthesis of conjugates **3** and **4** via the alkyne precursors **1** and **2** and a K_4 -azido PYY(3–36) (K_4 PYY) is described in Scheme 2 (spacer length $n=2, 3$ for precursors **1** and **2**). K_4 PYY was initially tested against PYY(3–36) amide (Sigma-Aldrich), and there was no observed difference in Y2-R agonism. Subsequently, K_4 PYY was used as the control for all assays. Characterization of the B_{12} -PYY(3–36) conjugates **3** and **4**, including HPLC and MALDI-ToF MS, can be found in the Supporting Information (Figure S13–16).



Scheme 1. Synthesis of B₁₂-alkyne precursors **1** and **2**. *Reagents and conditions:* EDC, HOBT, anhydrous DMSO; reactions carried out under argon for 16 h at RT.

In vitro assay of 3 and 4 at the Y2 receptor coupled to G_i: Conjugates **3** and **4** were tested for their abilities to lower levels of cAMP in an in vitro assay using HEK293 cell monolayers (Figure 7).^[29] These cells were engineered so that they stably express the human GLP-1 receptor (GLP-1R), while also transiently expressing the human Y2-R. Furthermore, these cells were virally transduced with the genetically encoded FRET reporter AKAR3, which is used to monitor cAMP-dependent protein kinase (PKA) activation intracellularly. This assay is unique in that it allows FRET-based detection of the ability of PYY(3–36) to counteract the action of a GLP-1R agonist (Exendin-4; Ex-4) to raise levels of cAMP. When the cells are first treated with Ex-4 (33 pM; injection 1) so that levels of cAMP are elevated, AKAR3 exhibits increased FRET, measured as a decrease in the 485/535 nm emission ratio (Figure 7). This change of FRET occurs after an approximate lag time of 50 s. If PYY(3–36) is then applied at the 180 s time point (injection 2), a functional antagonism of the action of Ex-4 is measured so that the change of FRET is decreased. Note that no

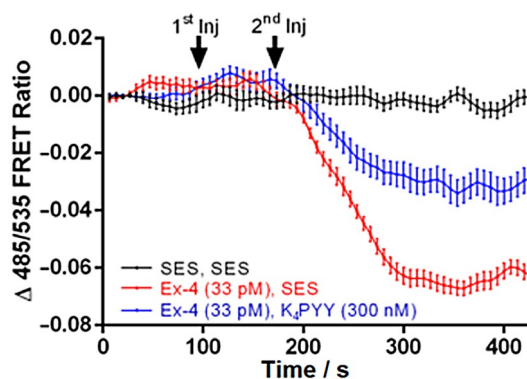
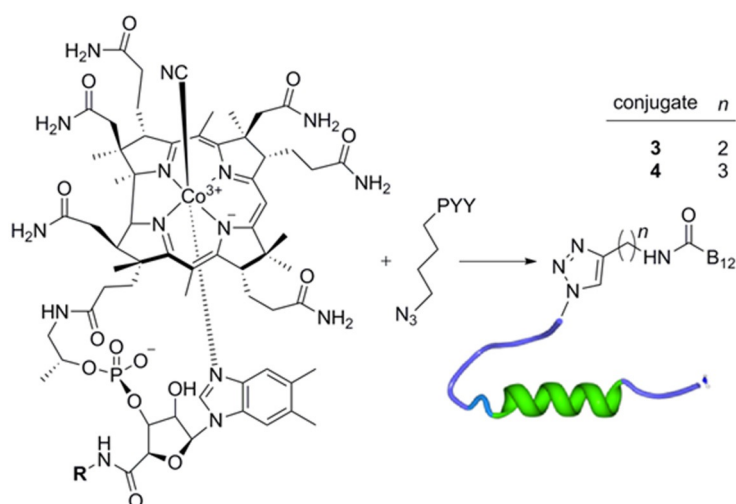


Figure 7. $\Delta 485/535$ FRET ratio through the course of a run. The first injection occurs at 100 s followed by a second injection at 180 s.



Scheme 2. Copper(I) alkyne-azide cycloaddition synthesis of B₁₂-PYY(3–36) conjugates **3** and **4** via alkyne precursors **1** and **2** with a two- or three-methylene-unit spacer between the 5'-amide on B₁₂ and the triazole linkage to K₄PYY. *Reagents and conditions:* Cu^I, TBTA; reactions were carried out for 16 h at RT. PYY(3–36) adapted from PDB ID: 2DF0.

change of FRET is measured in response to the administration of a negative control standard extracellular saline (SES; Figure 7). By varying the concentration of added conjugate, it is possible to determine dose–response relationships, and to also determine EC₅₀ values describing inhibitory actions of PYY(3–36) conjugates versus 33 pM Ex-4 in this assay. Figure 7 illustrates these responses to the first injection of either Ex-4 or SES, and the second injection of K₄PYY or SES. To normalize these raw data for subsequent dose–response analysis, “end-point” values of FRET were measured during the last 10 sample intervals (Figure 7). As illustrated in Figure 1, the dose-dependent inhibitory actions of PYY(3–36) conjugates are then quantified relative to a value of 100% that corresponds to the maximal inhibitory effect measured when testing 300 nM PYY(3–36) in this assay.

NMR studies of 3 and 4: NMR studies were executed initially to observe any structural differences between the conjugates and free peptide in solution. Because in vivo studies had previously established in vivo function for **3**, extensive structural studies were first performed with **3** and a direct comparison made to published PYY(3–36).^[7] Full NMR studies of **4** were then completed to serve as

a comparison with **3**. Full descriptions of methods and conditions are provided in the Supporting Information.

MD studies of 3 and 4: To complement the NMR studies, MD simulations of **3** and **4** were completed in attempts to explain the minor differences of Y2-R agonism between the two conjugates. These MD studies took the form of 50 ns simulations to probe the potential variation in simulation geometries and time-averaged structures that arise from different tether lengths. MD simulations were performed using the GROMACS (ver. 5.0.4)^[39] software package. The NMR distance lists, ranges, and tabulated distances from the time-averaged MD structure for **3** are provided in the Supporting Information.

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Keywords: GPCR · molecular dynamics · NMR spectroscopy · PYY(3–36) · vitamin B₁₂

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1. Synthesis of B₁₂-Alkyne Precursors (1-2)

1.1 B₁₂-Amino Butyne (1)

B₁₂-CA (10 mg, 0.007 mmol), EDC (14 mg, 0.07 mmol), and HOBt (19.7 mg, 0.15 mmol) were mixed in 5 mL anhydrous DMSO for 30 min under argon. To this activated mixture, 1-amino-3-butyne (5.99 μ L, 0.07 mmol) was added, and the reaction mixture was stirred for 16 h at rt. The crude product was precipitated out of DMSO using diethyl ether and centrifuged at 4000g for 5 min. The pellet was redissolved in ddH₂O for purification by RP-HPLC. The crude reaction was purified via RP-HPLC with a C₁₈ analytical column using a gradient of 10% MeCN, 90% H₂O/0.1% TFA, increased to 27% MeCN over 17 min, with a flow rate of 1.0 mL/min and UV detection at 360 nm; t_R of **1** = 12.1 min. Yield was 79-80%. Compound **1** was analyzed via MALDI-ToF MS using a CHCA matrix with a 1:1 sample/matrix ratio. MALDI-ToF MS: [M-CN]⁺ expected 1395 m/z , found 1395.004 m/z . ¹H NMR was used to confirm the purity of the final product. ¹H NMR (400 MHz, D₂O): δ 7.219 (s, 1H), δ 7.002 (s, 1H), δ 6.920 (s, 2H), δ 5.998 (s, 1H). 2D NMR (HSQC/HMBC) was used to confirm the methylene and alkyne protons: ¹H NMR (500 MHz, D₂O): δ 3.482 (t, 1H_{a1}), δ 3.406 (t, 1H_{a2}), δ 2.489 (t, 2H_b), δ 2.406 (s, 1H_c). ¹³C NMR (500 MHz, D₂O): δ 41.1 (C_a), δ 21.6 (C_b), δ 73.8 (C_c). See Table S1 for labeling schematic.

1.2 B₁₂-Amino Pentyne (2)

B₁₂-CA (10 mg, 0.007 mmol), EDC (14 mg, 0.07 mmol), and HOBt (19.7 mg, 0.1462 mmol) were mixed in 5 mL anhydrous DMSO for 30 min under argon. To this activated mixture, 1-amino-4-pentyne (7.1 μ L, 0.07 mmol) was added, and the reaction mixture was stirred for 16 h at rt. The crude product was precipitated out of DMSO using diethyl ether and centrifuged at 4000g for 5 min. The pellet was redissolved in ddH₂O for purification by RP-

HPLC. The crude reaction was purified via RP-HPLC with a C₁₈ analytical column using a gradient of 10% MeCN and 90% H₂O/0.1% TFA, increased to 27% MeCN over 17 min with flow rate of 1.0 mL/min and UV detection at 360 nm; t_R of **2** = 13.1 min. Yield was 77-81%. Compound **2** was analyzed via MALDI-ToF MS with a 1:1 sample/matrix ratio using a CHCA matrix. MALDI-ToF MS: [M-CN]⁺ expected 1409 *m/z*, found 1408.949 *m/z*. ¹H NMR was used to confirm the purity of the final product. ¹H NMR (400 MHz, D₂O): δ 7.281 (s, 1H), δ 7.040 (s, 1H), δ 6.480 (s, 2H), δ 6.058 (s, 1H). 2D NMR (HSQC/HMBC) was used to confirm the methylene and alkyne protons: ¹H NMR (500 MHz, D₂O): δ 3.407 (t, 1H_a), δ 1.809 (m, 2H_b), δ 2.315 (t, 2H_c), δ 2.340 (s, 1H_d). ¹³C NMR (500 MHz, D₂O): δ 41.7 (C_a), δ 30.1 (C_b), δ 18.2 (C_c), δ 72.7 (C_d). See Table S1 for labeling schematic.

2. Synthesis and Characterization of B₁₂-PYY₃₋₃₆ Conjugates (3-4)

2.1 Synthesis of **3**

CuI (1 mg, 0.005 mmol) and tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine (TBTA) (2.2 mg, 0.004 mmol) were mixed DMF and H₂O (4:1 v/v, 0.5 mL) for 20 min at rt or until a yellow color change occurred. K₄PYY (1 mg, 0.25 μmol) and **2** (3 mg, 0.002 mmol) were added to the mixture and stirred for 16 h. The crude reaction was centrifuged at 4000g for 10 min to remove the catalyst/TBTA. Crude product was purified via RP-HPLC with a C₁₈ analytical column using a gradient of 20% MeCN, 80% H₂O/0.1% TFA, increased to 35% MeCN over 4 min then increased to 37 % MeCN over 10 min; t_R of **3** = 6.12 min. Yield for **3** was 95-98%. Compound **3** was characterized via MALDI-ToF MS using a CHCA matrix plated in a 1:1 sample/matrix ratio. MALDI-ToF MS: [M-CN]⁺ expected 5470 *m/z*, found 5469.603 *m/z*.

2.2 Synthesis of **4**

CuI (1 mg, 0.005 mmol) and TBTA (2.2 mg, 0.004 mmol) were mixed DMF and H₂O (4:1 v/v, 0.5 mL) for 20 min at rt or until a yellow color change occurred. K₄PYY (1 mg, 0.25 μ mol) and **3** (3 mg, 0.002 mmol) were added to the mixture and stirred for 16 h. The crude reaction was centrifuged at 4000g for 10 min to remove the catalyst/TBTA. Crude product was purified via RP-HPLC with a C₁₈ analytical column using a gradient of 20% MeCN, 80% H₂O/0.1% TFA, increased to 35% MeCN over 4 min then increased to 37 % MeCN over 10 min; t_R of **4** = 6.15 min. Yield for **4** was 90-95%. Compound **4** was characterized via MALDI-ToF MS using a CHCA matrix plated in a 1:1 sample/matrix ratio. MALDI-ToF MS: [M-CN]⁺ expected 5484 m/z , found 5484.821 m/z .

3. Characterization of B₁₂-Alkyne Precursors 1-2

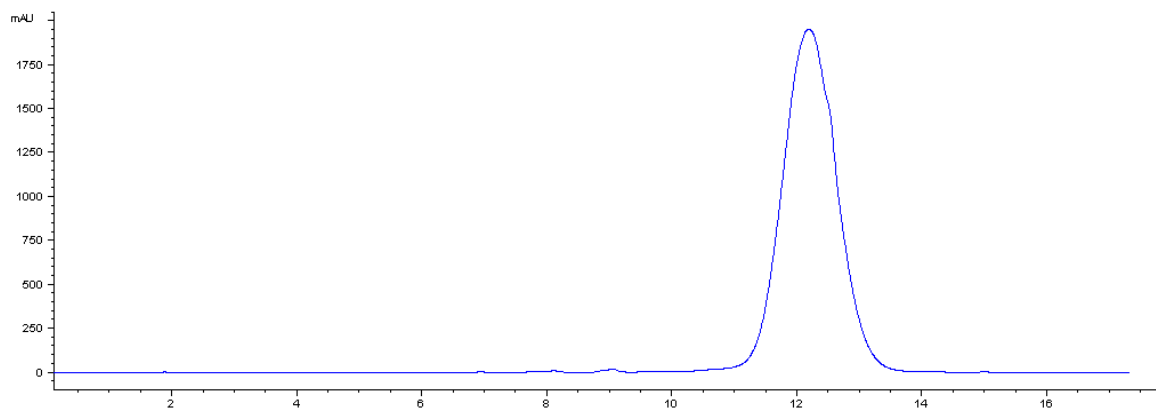


Figure S1. RP-HPLC of **1**; t_R = 12.1 min. UV detection is at 360 nm on a C₁₈ column.

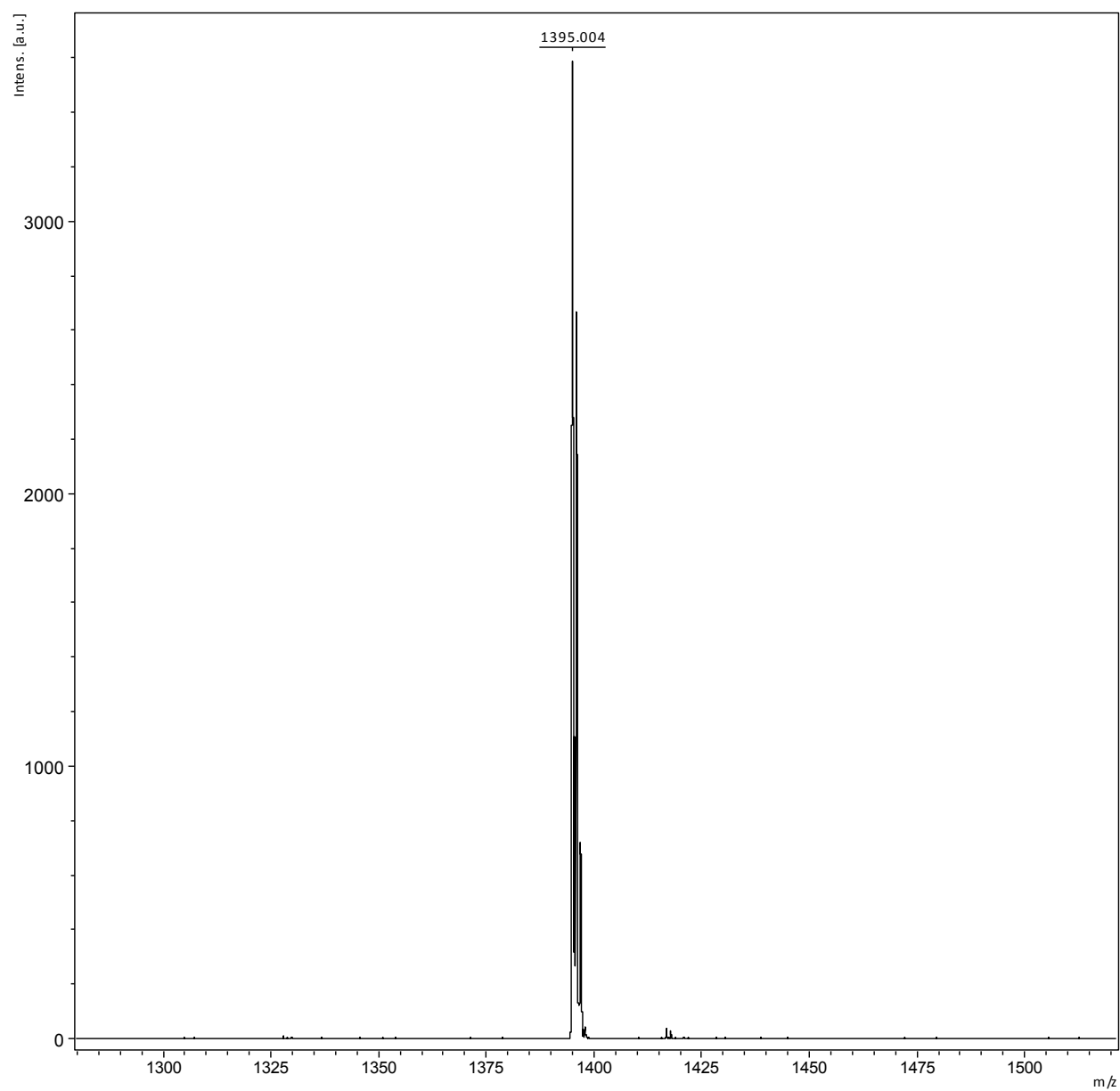


Figure S2. MALDI-ToF mass spectrum of **1**. Expected peak highlighted as $[M-CN]^+ = 1395.004$ m/z .

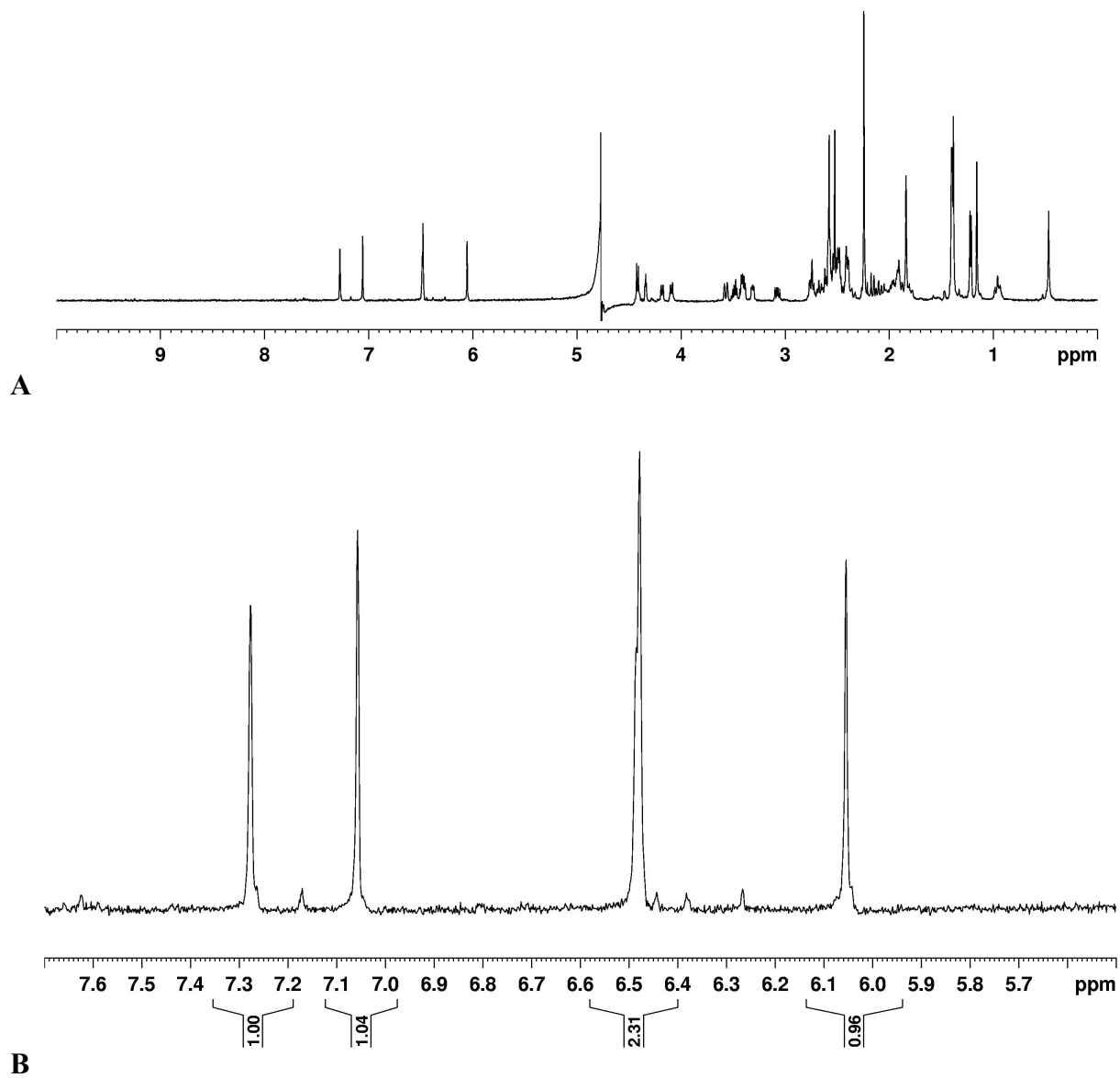


Figure S3. ^1H NMR of spectrum **1** in D_2O on a 400 MHz spectrometer. The five peaks from 6.0-7.3 ppm are characteristic of protons on the ribose ring, corrin ring, and DMB ligand of B_{12} (**A**). Key diagnostic protons between 6-8 ppm with appropriate integration highlighted (**B**).

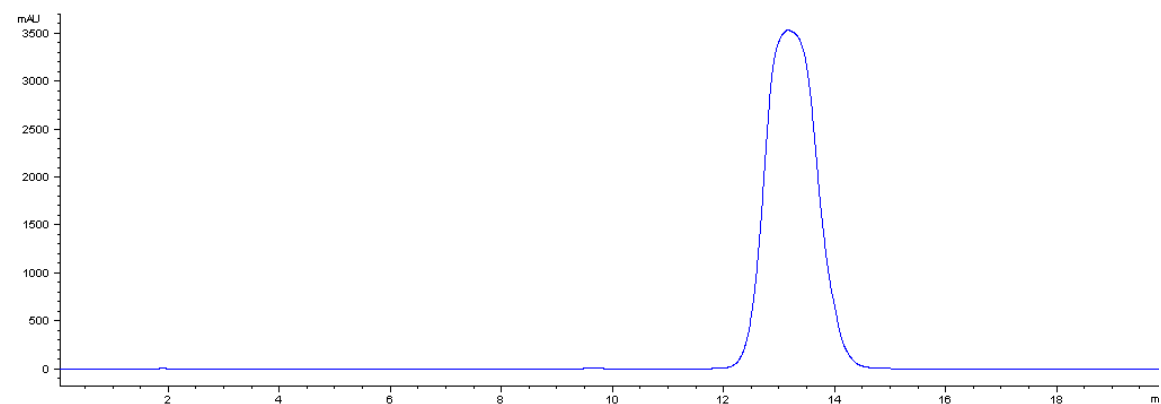


Figure S4. RP-HPLC of **2**; $t_R = 13.1$ min. UV detection is at 360 nm on a C_{18} column.

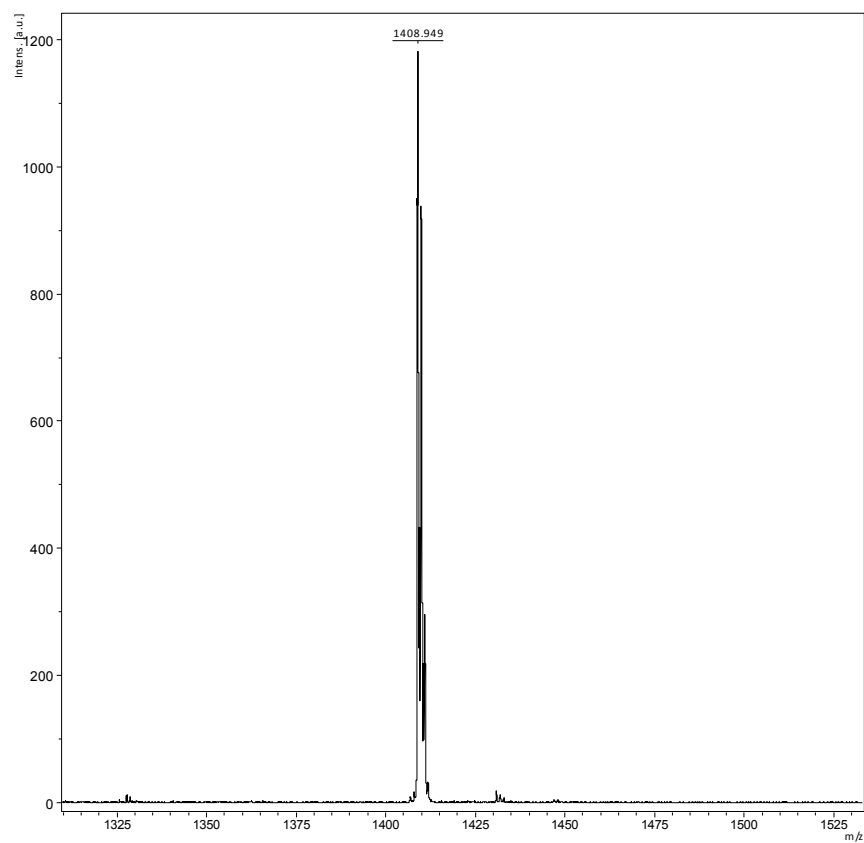


Figure S5. MALDI-ToF mass spectrum of **2**. Expected peak highlighted as $[M-CN]^+ = 1408.949$ m/z .

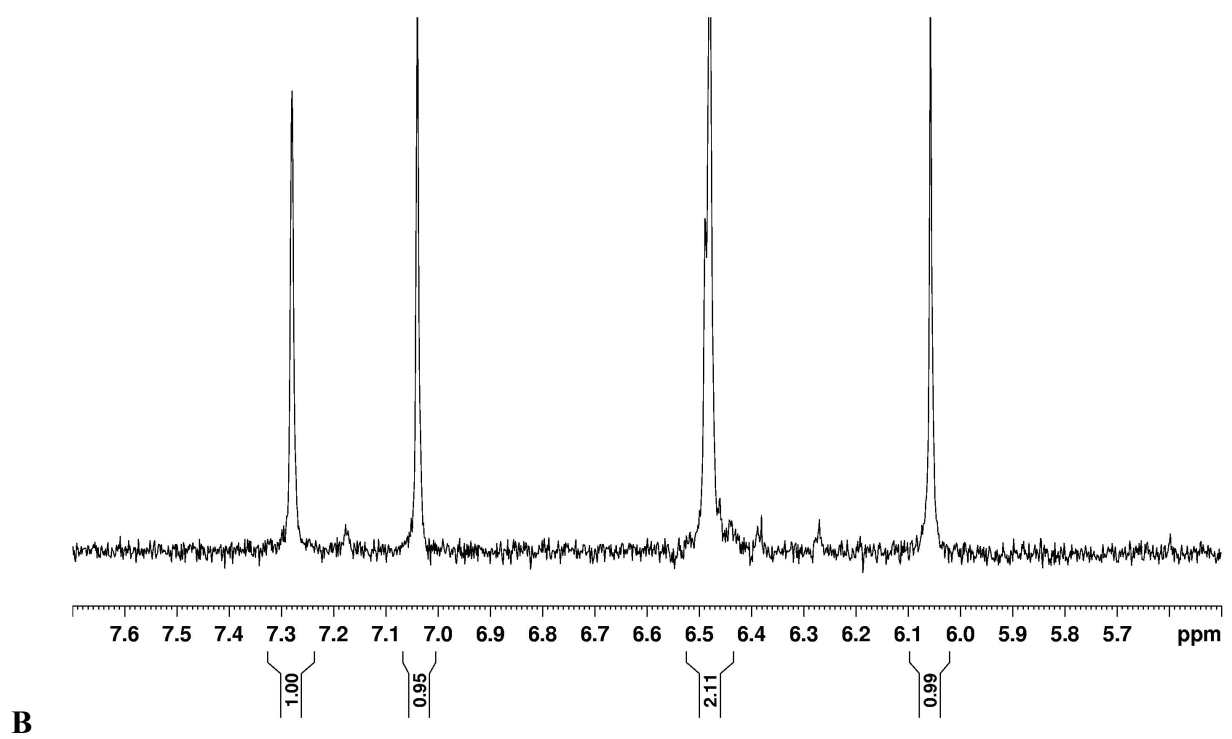
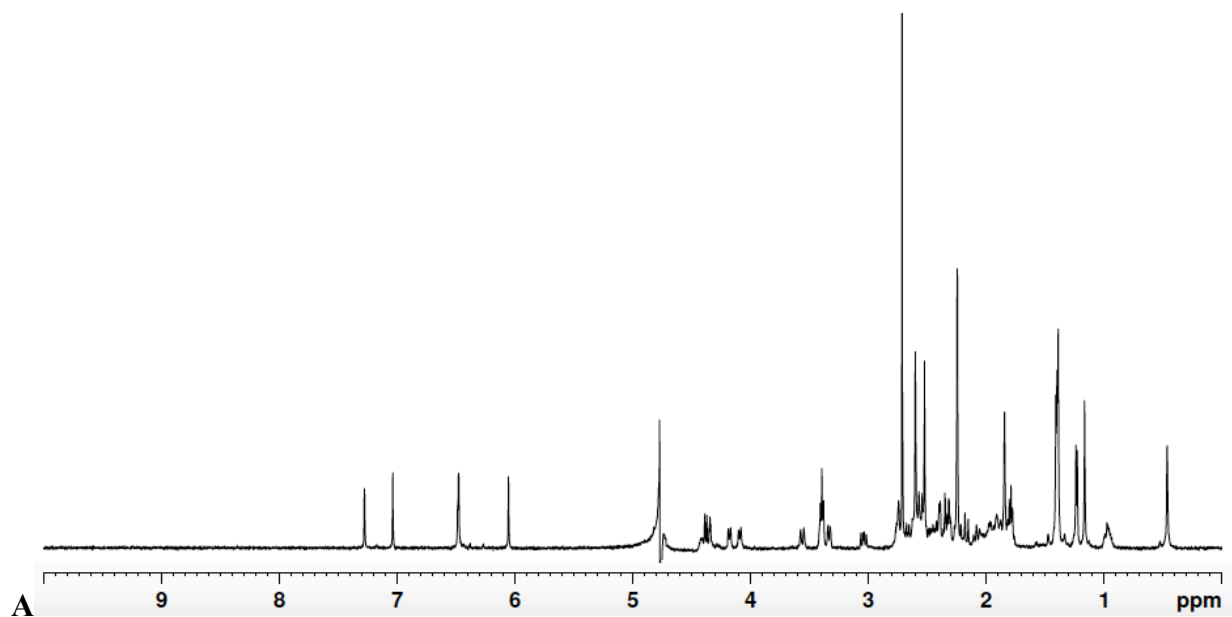


Figure S6. ^1H NMR spectrum of **2** in D_2O on a 500 MHz spectrometer. The five peaks from 6.0-7.3 ppm are characteristic of protons on the ribose ring, corrin ring, and DMB ligand of B_{12} (**A**). Key diagnostic protons between 6-8 ppm with appropriate integration highlighted (**B**).

4. 2D NMR Spectra of 1-2 and B₁₂ NMR Numbering Scheme

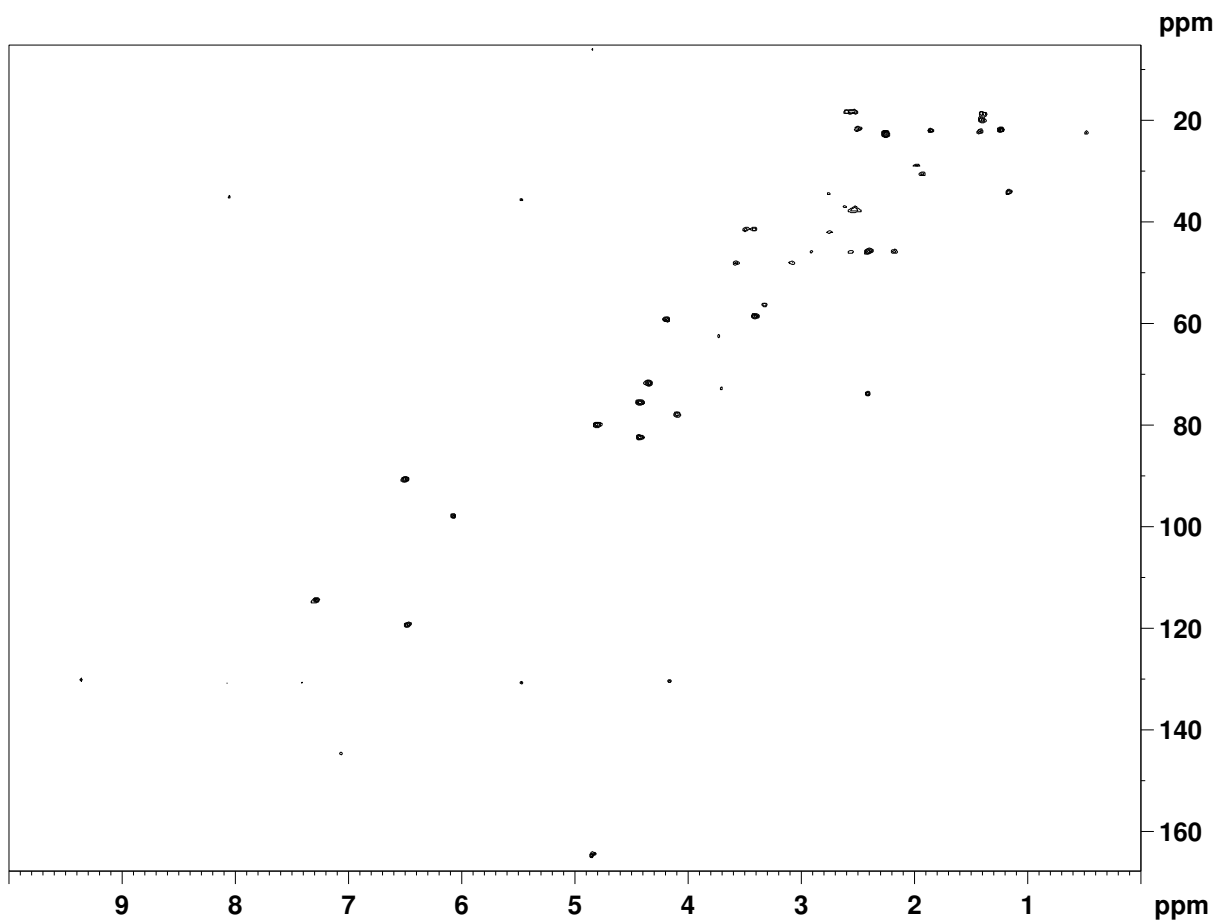


Figure S7. HSQC of **1** in D₂O on a 500 MHz spectrometer.

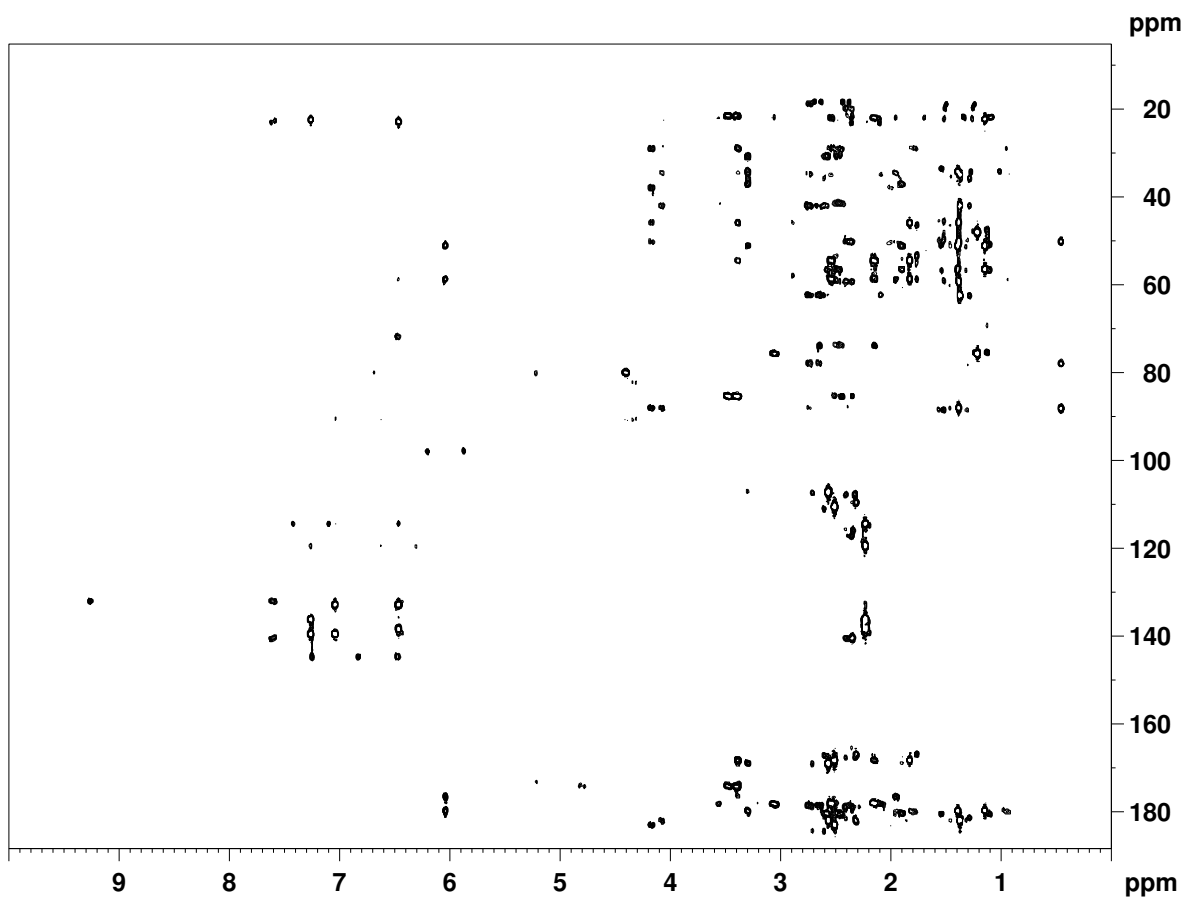


Figure S8. HMBC of **1** in D₂O on a 500 MHz spectrometer.

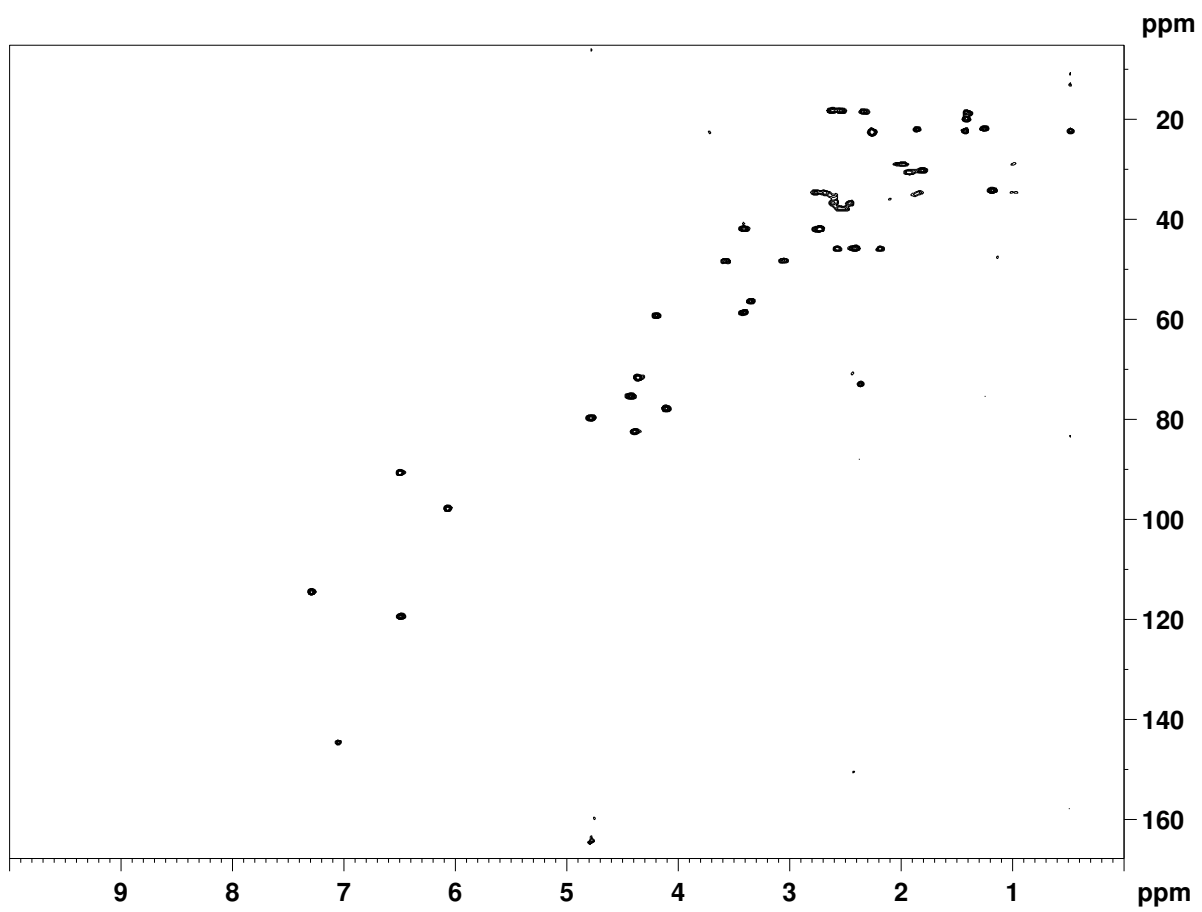


Figure S9. HSQC of **2** in D_2O on a 500 MHz spectrometer.

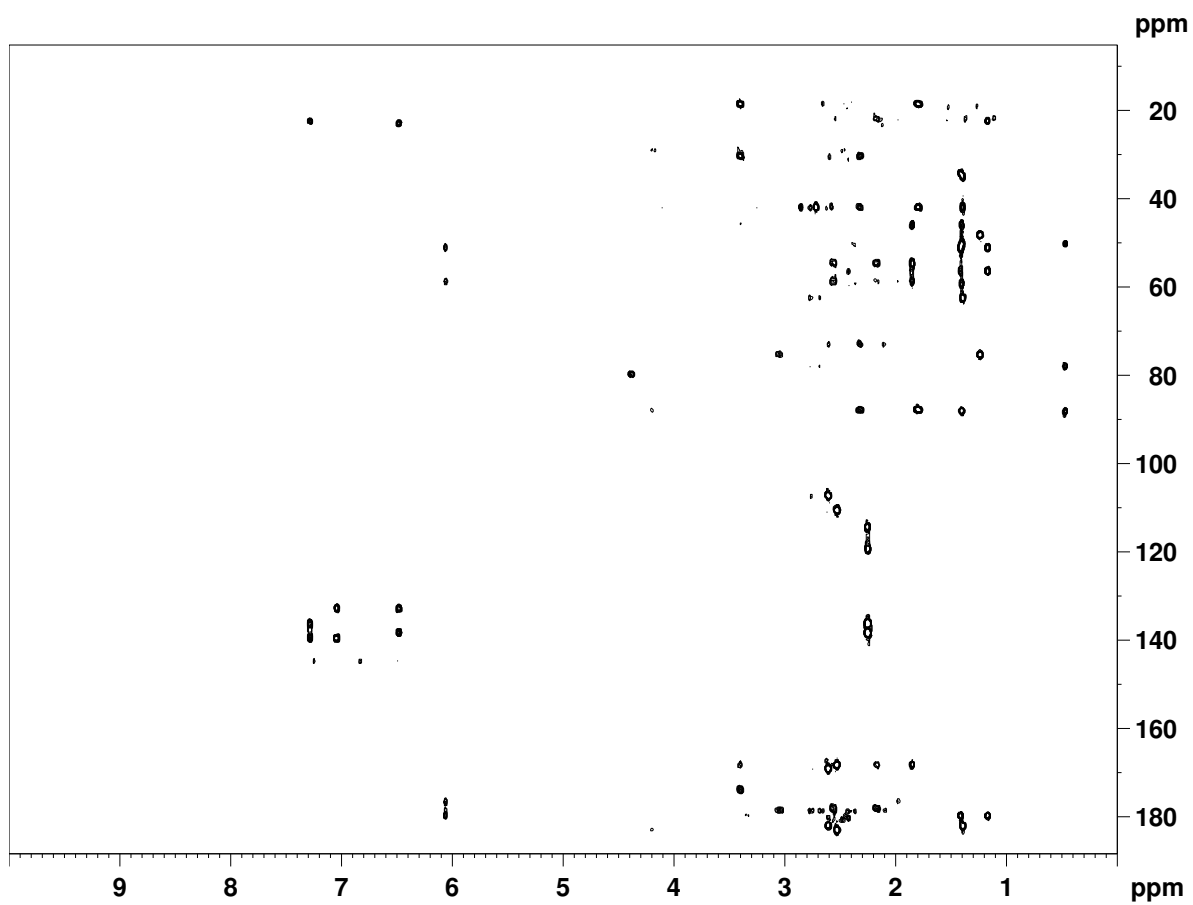


Figure S10. HMBC of **2** in D₂O on a 500 MHz spectrometer.

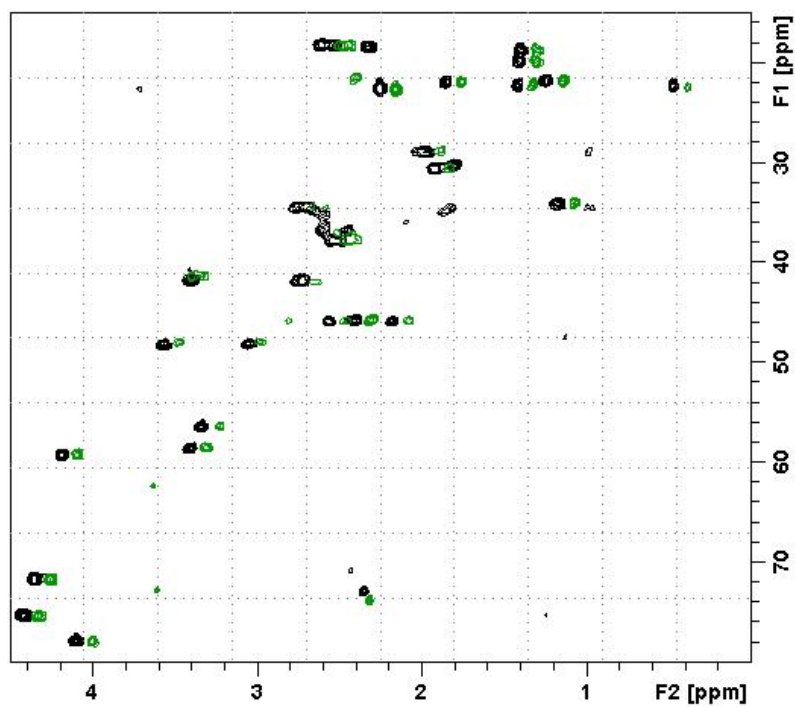


Figure S11. HSQC Overlay of **1** and **2** to display shifts on a 500 MHz spectrometer. The black represents conjugate **2** and the green is conjugate **1**, shifted right to show differences in ppm.

Table S1 outlines the assignments of key protons and carbons to of **1** and **2**.

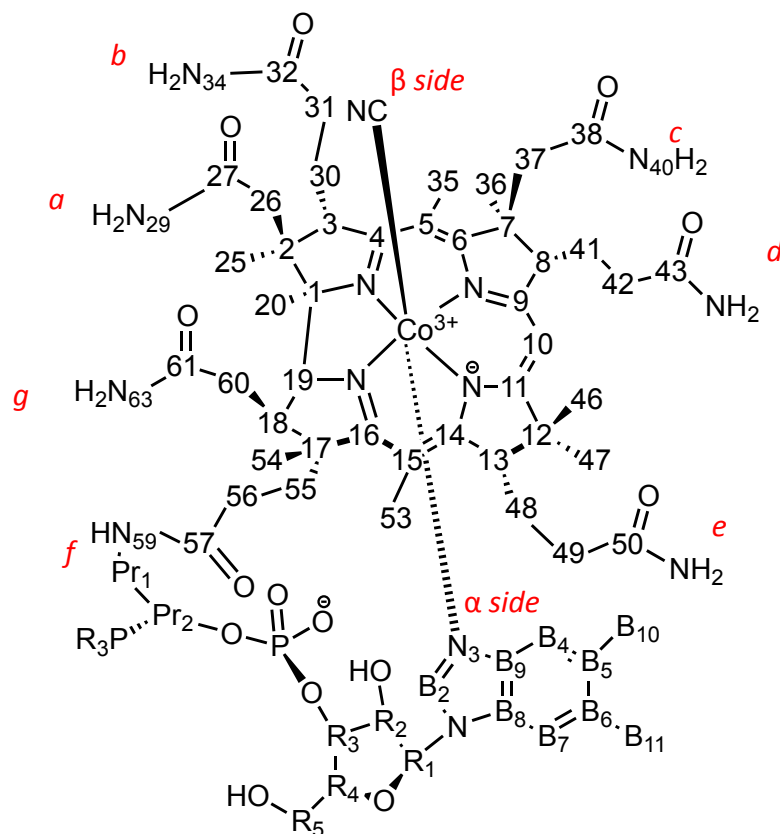


Figure S12. Numbering Scheme for B₁₂ NMR.

Table S1. ¹H-¹³C Correlations of New Protons on Derivatives **1-2** as Determined via HSQC/HMBC.

Alkyne Derivative					
1			2		
Proton	¹ H (ppm)	¹³ C (ppm)	Proton	¹ H (ppm)	¹³ C (ppm)
a ₁	3.482	41.1	a	3.407	41.7
a ₂	3.406	41.1	b	1.809	30.1
b	2.489	21.6	c	2.315	18.2
c	2.406	73.8	d	2.345	72.7

5. Characterization of B₁₂-PYY₃₋₃₆ Conjugates 3-4

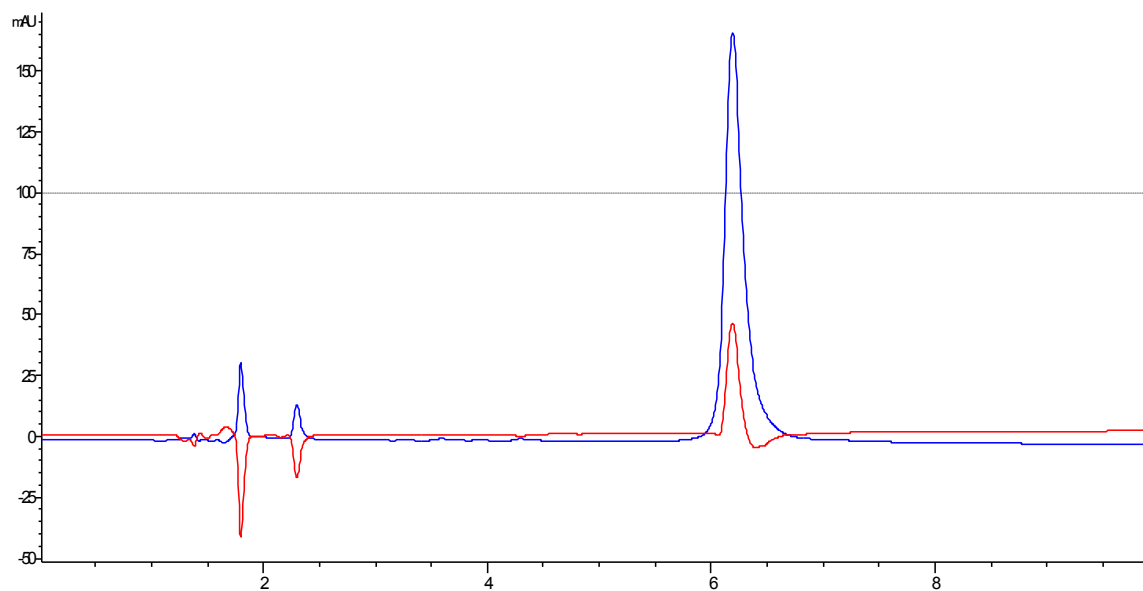


Figure S13. RP-HPLC of **3** at > 98% purity; $t_R = 6.12$ min. UV detection is at 280 (blue) and 360 (red) nm on a C₁₈ column.

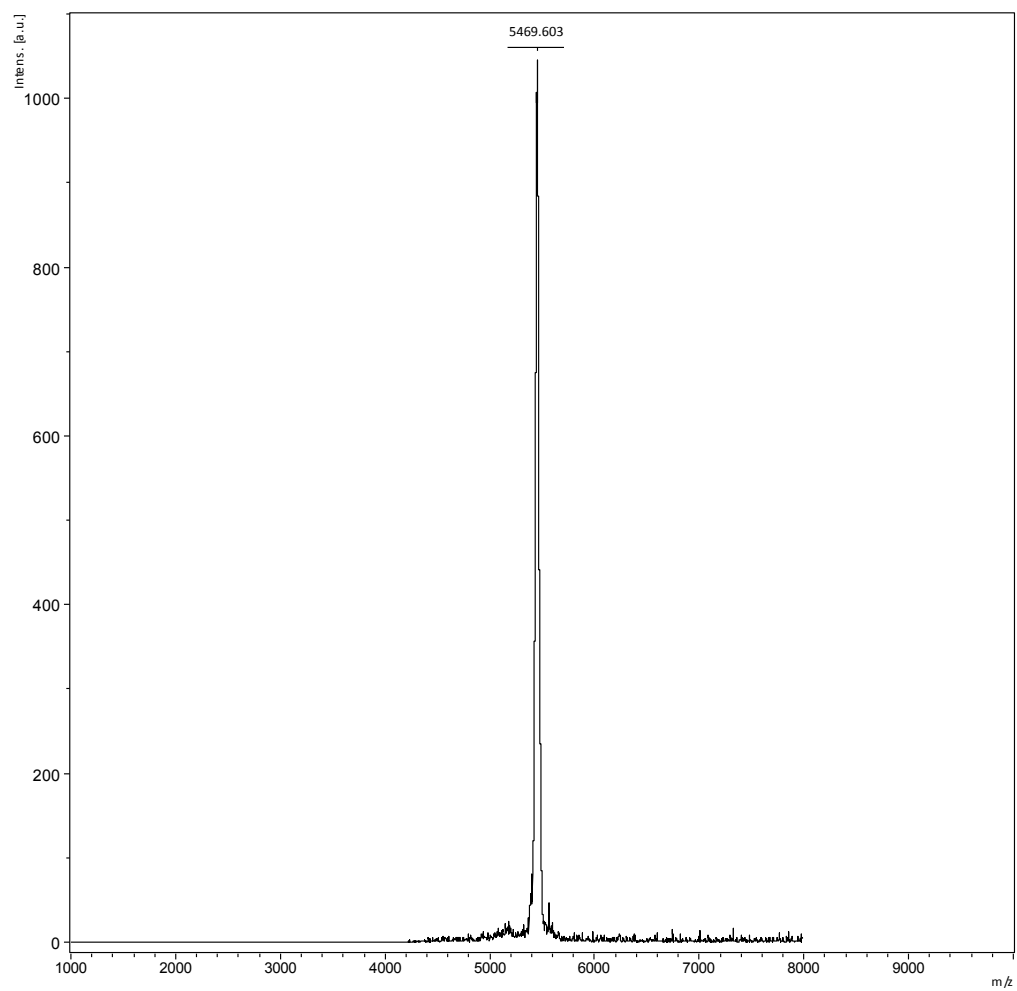


Figure S14. MALDI ToF mass spectrum of **3**. Expected peak highlighted as $[M-CN]^+ = 5469.603$ *m/z*.

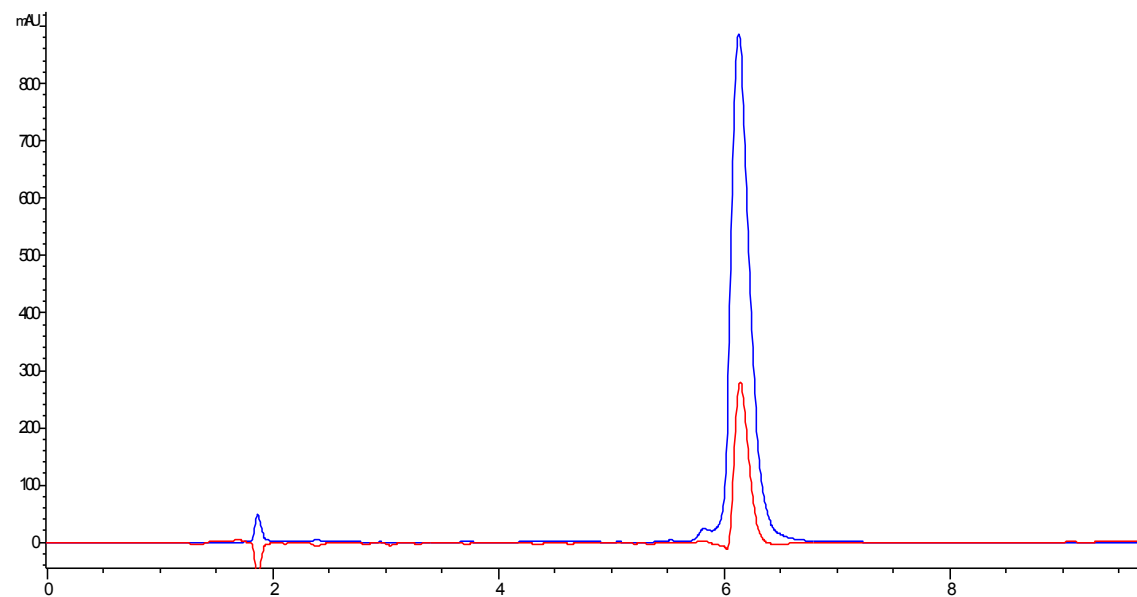


Figure S15. RP-HPLC of **4** at > 98% purity; $t_R = 6.15$ min. UV detection is at 280 (blue) and 360 (red) nm on a C_{18} column.

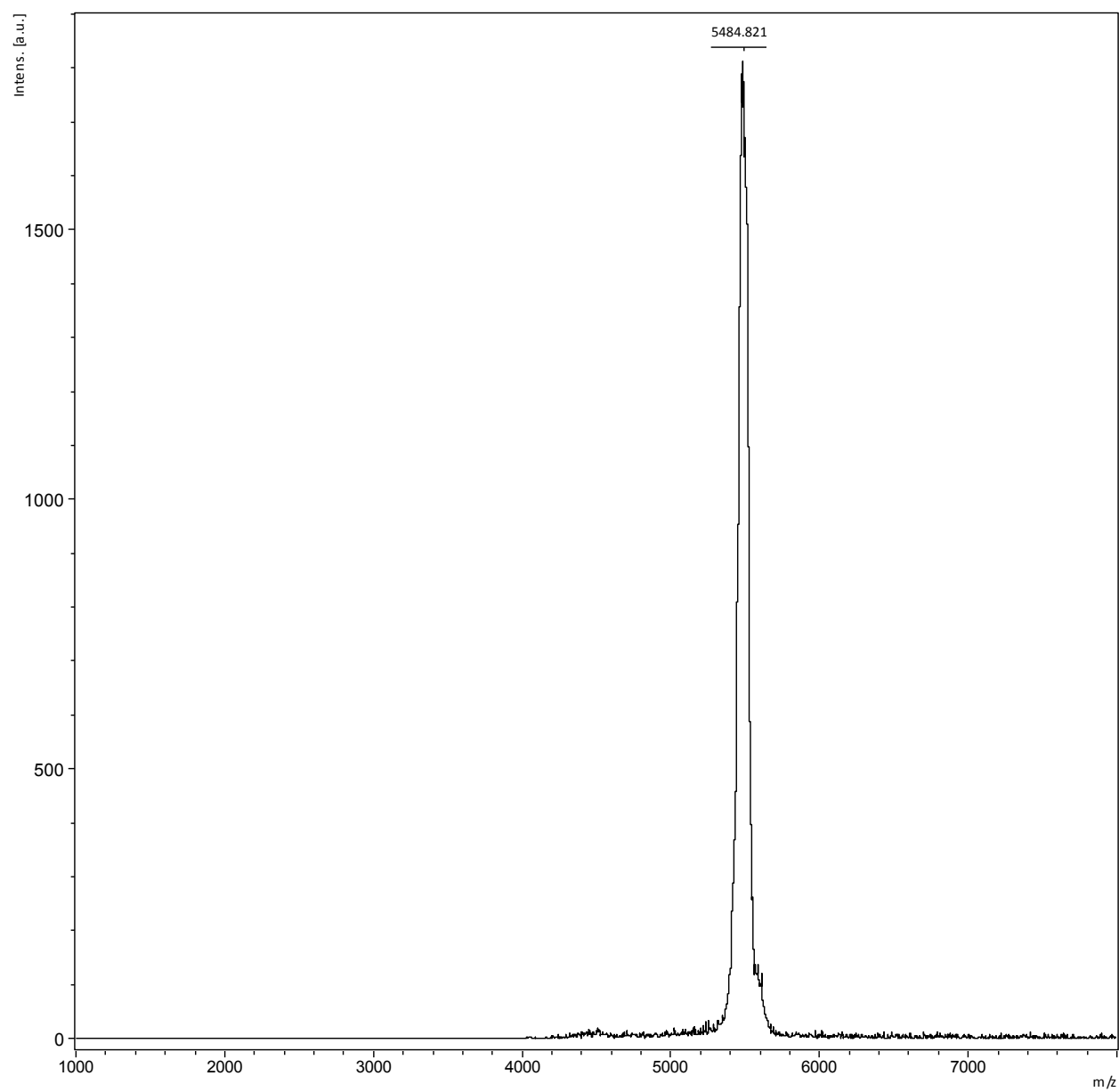


Figure S16. MALDI ToF-MS of **4**. Expected peak highlighted as $[M-CN]^+ = 5484.821$ m/z .

6. NMR Methods and Conditions

NMR experiments were performed on a Bruker DRX500 Advance spectrometer equipped with a 5 mm inverse detection probe. The NMR samples were prepared at a concentration of 1 mM in 90% H₂O/10% D₂O, pH adjusted to 5.5. Both 1- and 2D NMR were acquired with a spectral width of 5518 Hz using excitation sculpting³³ for water suppression. Proton chemical shifts were referenced based on the HDO signal. For chemical shift assignment of conjugate **3** and **4**, TOCSY (total correlation spectroscopy) and DQFCOSY (double-quantum-filtered correlation spectroscopy) experiments were performed at temperature of 20, 25, and 30 °C. TOCSY experiments were run with mixing times of 60 or 90 ms and a relaxation delay of 2 s. 2D nuclear Overhauser effect (NOE) spectra were acquired at the three different temperatures with mixing times of 100, 200 and 300 ms and a relaxation delay of 5 s. For all 2D experiments, 2k points were collected in t₂ and 512 points in t₁ with 96 scans per t₁ increment. The data was processed using a cosine squared function along both dimensions and zero filled to give a final dimension of 1k X 1K. The 2D NOE cross peaks were categorized as strong, medium or weak and proton distance ranges were set to 1.8 – 3.5, 1.8 – 4.5, 1.8 – 6 Å, respectively.

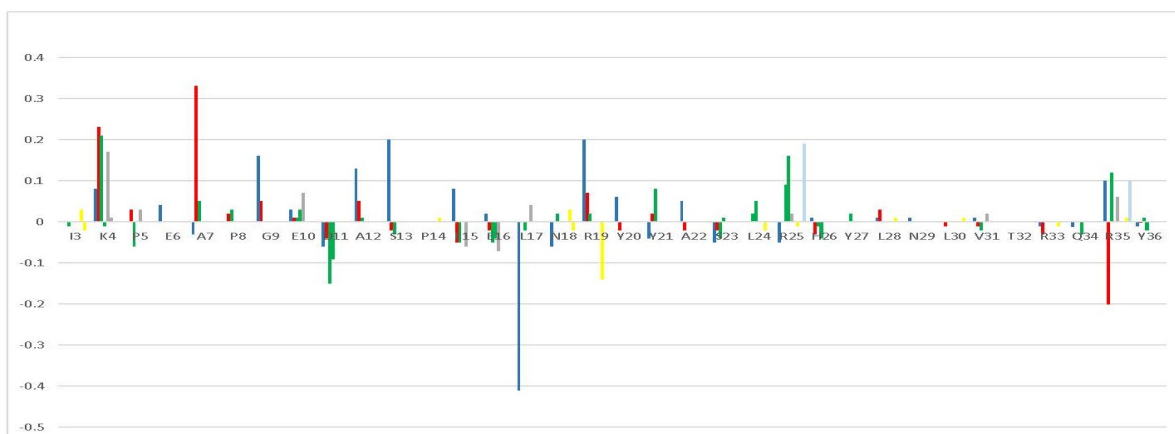


Figure S17. Highlighted differences (ppm) in the assigned proton chemical shift between PYY(3-36) and the **3**. The chemical shifts for the PYY(3-36) were obtained from the Biological Magnetic Resonance Bank (www.bmr.b.wisc.edu). The backbone amide protons are represented by blue lines, α protons by red, β protons by green, γ protons by gray, δ by yellow and ϵ by light blue.

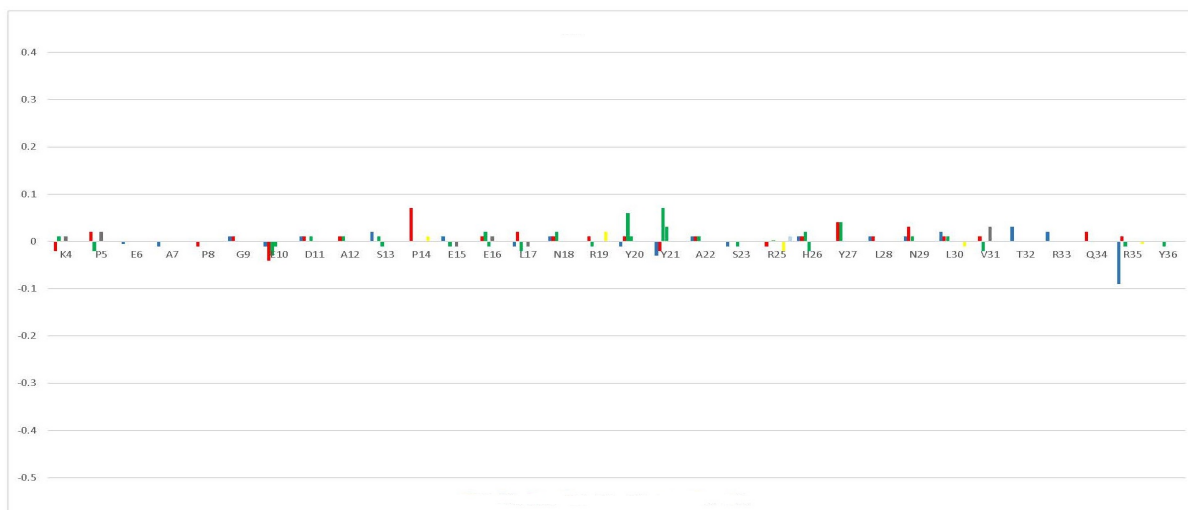


Figure S18. Highlighted differences (ppm) in the assigned proton chemical shift between conjugate **3** and **4**. The backbone amide protons are represented by blue lines, α protons by red, β protons by green, γ protons by gray, δ by yellow, and ϵ by light blue.

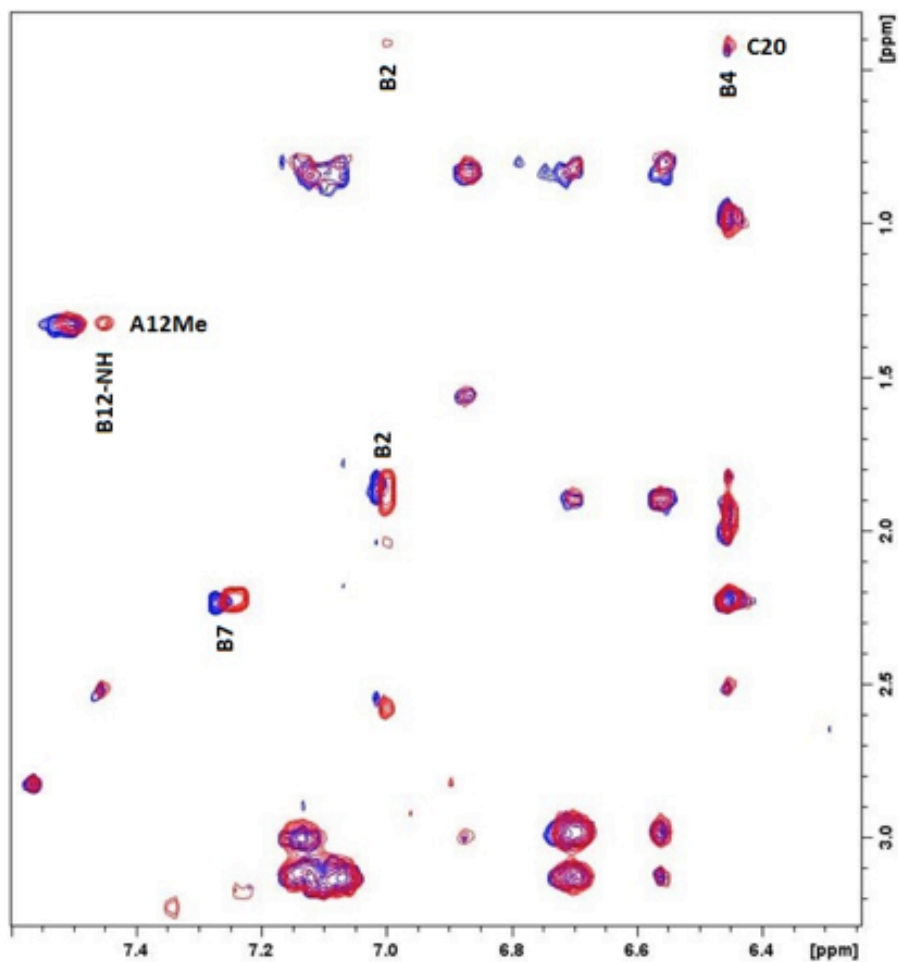


Figure S19. Overlay of 2D NOE spectra for **3** in blue and **4** in red. The spectra were acquired at 25 °C with conjugate concentration of 1 mM concentration and pH of 5.5.

7. Average Structures For 3-4 From MD Simulations

Geometry For 3

ATOM	1	N	ILE	1	3.910	8.456	6.261	1.00	0.00
ATOM	2	H1	ILE	1	3.198	9.227	6.363	1.00	0.00
ATOM	3	H2	ILE	1	3.390	7.702	6.716	1.00	0.00
ATOM	4	H3	ILE	1	4.779	8.752	6.745	1.00	0.00
ATOM	5	CA	ILE	1	4.060	8.165	4.826	1.00	0.00
ATOM	6	CB	ILE	1	5.120	7.111	4.517	1.00	0.00
ATOM	7	CG1	ILE	1	6.427	7.532	5.176	1.00	0.00
ATOM	8	CG2	ILE	1	5.479	7.005	3.069	1.00	0.00
ATOM	9	CD	ILE	1	7.425	6.455	5.478	1.00	0.00
ATOM	10	C	ILE	1	2.693	7.679	4.284	1.00	0.00
ATOM	11	O	ILE	1	2.384	6.555	4.687	1.00	0.00
ATOM	12	C27	LP2	2	-9.013	-9.596	2.385	1.00	0.00
ATOM	13	O28	LP2	2	-9.978	-10.047	1.771	1.00	0.00
ATOM	14	N29	LP2	2	-8.032	-10.333	2.958	1.00	0.00
ATOM	15	HAE	LP2	2	-7.299	-9.859	3.433	1.00	0.00
ATOM	16	HAD	LP2	2	-8.075	-11.293	3.006	1.00	0.00

ATOM	17	C32 LP2	2	-11.875	-9.769	7.734	1.00	0.00
ATOM	18	O34 LP2	2	-11.541	-9.397	8.826	1.00	0.00
ATOM	19	N33 LP2	2	-12.969	-10.527	7.667	1.00	0.00
ATOM	20	HAG LP2	2	-13.266	-11.099	6.885	1.00	0.00
ATOM	21	HAF LP2	2	-13.398	-10.841	8.480	1.00	0.00
ATOM	22	C38 LP2	2	-4.352	-9.102	7.820	1.00	0.00
ATOM	23	O39 LP2	2	-4.144	-8.745	6.665	1.00	0.00
ATOM	24	N40 LP2	2	-4.085	-10.337	8.182	1.00	0.00
ATOM	25	HAI LP2	2	-4.341	-10.716	9.081	1.00	0.00
ATOM	26	HAH LP2	2	-3.591	-10.863	7.511	1.00	0.00
ATOM	27	C43 LP2	2	-5.568	-2.592	10.094	1.00	0.00
ATOM	28	O44 LP2	2	-5.046	-2.096	9.100	1.00	0.00
ATOM	29	N45 LP2	2	-6.574	-1.987	10.595	1.00	0.00
ATOM	30	HAK LP2	2	-7.164	-2.310	11.336	1.00	0.00
ATOM	31	HAJ LP2	2	-6.820	-1.095	10.111	1.00	0.00
ATOM	32	C50 LP2	2	-4.884	1.958	3.343	1.00	0.00
ATOM	33	O51 LP2	2	-6.019	2.012	2.901	1.00	0.00
ATOM	34	N52 LP2	2	-4.214	3.028	3.670	1.00	0.00
ATOM	35	HAM LP2	2	-3.330	2.792	4.101	1.00	0.00
ATOM	36	HAL LP2	2	-4.652	3.917	3.495	1.00	0.00
ATOM	37	C61 LP2	2	-11.516	-4.876	0.823	1.00	0.00
ATOM	38	O63 LP2	2	-12.238	-5.003	1.866	1.00	0.00
ATOM	39	N62 LP2	2	-12.122	-4.864	-0.377	1.00	0.00
ATOM	40	HAO LP2	2	-11.688	-4.665	-1.229	1.00	0.00
ATOM	41	HAN LP2	2	-13.091	-4.945	-0.478	1.00	0.00
ATOM	42	C20 LP2	2	-10.343	-5.036	4.615	1.00	0.00
ATOM	43	C25 LP2	2	-11.235	-7.535	3.225	1.00	0.00
ATOM	44	C36 LP2	2	-7.033	-7.210	9.772	1.00	0.00
ATOM	45	C46 LP2	2	-2.310	-3.378	5.141	1.00	0.00
ATOM	46	C47 LP2	2	-3.108	-1.352	6.512	1.00	0.00
ATOM	47	C54 LP2	2	-7.501	-4.298	0.047	1.00	0.00
ATOM	48	C26 LP2	2	-8.887	-8.107	2.728	1.00	0.00
ATOM	49	C30 LP2	2	-10.805	-8.183	6.077	1.00	0.00
ATOM	50	C31 LP2	2	-11.172	-9.597	6.390	1.00	0.00
ATOM	51	C37 LP2	2	-5.034	-8.314	8.982	1.00	0.00
ATOM	52	C41 LP2	2	-5.954	-5.050	10.035	1.00	0.00
ATOM	53	C42 LP2	2	-5.284	-3.922	10.711	1.00	0.00
ATOM	54	C48 LP2	2	-4.501	-0.332	4.543	1.00	0.00
ATOM	55	C49 LP2	2	-4.113	0.610	3.367	1.00	0.00
ATOM	56	C56 LP2	2	-9.515	-1.456	1.791	1.00	0.00
ATOM	57	C55 LP2	2	-8.577	-2.234	0.836	1.00	0.00
ATOM	58	C60 LP2	2	-9.981	-4.976	0.814	1.00	0.00
ATOM	59	C2R LP2	2	-8.922	0.497	5.257	1.00	0.00
ATOM	60	O7R LP2	2	-8.066	0.049	4.220	1.00	0.00
ATOM	61	HAA LP2	2	-7.567	0.952	4.022	1.00	0.00
ATOM	62	C1R LP2	2	-8.695	-0.213	6.628	1.00	0.00
ATOM	63	O6R LP2	2	-7.575	0.451	7.313	1.00	0.00
ATOM	64	C4R LP2	2	-7.469	1.759	6.649	1.00	0.00
ATOM	65	C3R LP2	2	-8.617	1.917	5.668	1.00	0.00
ATOM	66	C5R LP2	2	-7.069	3.070	7.326	1.00	0.00
ATOM	67	P LP2	2	-9.088	4.070	4.199	1.00	0.00
ATOM	68	O2P LP2	2	-8.328	2.656	4.483	1.00	0.00
ATOM	69	O4 LP2	2	-10.027	4.473	5.322	1.00	0.00
ATOM	70	O5 LP2	2	-8.047	5.105	3.938	1.00	0.00
ATOM	71	O3 LP2	2	-10.011	3.802	2.947	1.00	0.00
ATOM	72	C2P LP2	2	-9.152	3.465	1.845	1.00	0.00
ATOM	73	C3P LP2	2	-9.016	4.629	0.843	1.00	0.00
ATOM	74	C1P LP2	2	-9.424	2.192	1.049	1.00	0.00
ATOM	75	N59 LP2	2	-9.404	0.986	1.612	1.00	0.00
ATOM	76	HAC LP2	2	-8.947	0.904	2.479	1.00	0.00
ATOM	77	C57 LP2	2	-10.093	-0.104	1.224	1.00	0.00
ATOM	78	O58 LP2	2	-11.226	-0.081	0.726	1.00	0.00
ATOM	79	C5B LP2	2	-9.921	-4.671	9.102	1.00	0.00
ATOM	80	C5M LP2	2	-10.556	-6.002	9.549	1.00	0.00
ATOM	81	C6B LP2	2	-10.483	-3.436	9.446	1.00	0.00
ATOM	82	C6M LP2	2	-11.613	-3.370	10.465	1.00	0.00
ATOM	83	C4B LP2	2	-8.893	-4.742	8.124	1.00	0.00
ATOM	84	H4B LP2	2	-8.358	-5.620	8.034	1.00	0.00
ATOM	85	C7B LP2	2	-10.054	-2.309	8.745	1.00	0.00
ATOM	86	H7B LP2	2	-10.230	-1.303	9.127	1.00	0.00
ATOM	87	N3B LP2	2	-7.754	-3.525	6.277	1.00	0.00
ATOM	88	C9B LP2	2	-8.558	-3.661	7.333	1.00	0.00
ATOM	89	N1B LP2	2	-8.665	-1.644	6.811	1.00	0.00

ATOM	90	C8B	LP2	2	-9.148	-2.431	7.692	1.00	0.00
ATOM	91	C2B	LP2	2	-7.811	-2.260	5.988	1.00	0.00
ATOM	92	H2B	LP2	2	-7.112	-1.685	5.373	1.00	0.00
ATOM	93	C5	LP2	2	-7.594	-7.810	6.799	1.00	0.00
ATOM	94	C35	LP2	2	-7.661	-9.311	7.174	1.00	0.00
ATOM	95	C15	LP2	2	-5.876	-2.803	2.684	1.00	0.00
ATOM	96	C53	LP2	2	-5.219	-2.061	1.475	1.00	0.00
ATOM	97	FE	LP2	2	-6.851	-5.012	5.027	1.00	0.00
ATOM	98	N21	LP2	2	-8.235	-6.177	5.072	1.00	0.00
ATOM	99	N22	LP2	2	-6.148	-5.778	6.630	1.00	0.00
ATOM	100	N23	LP2	2	-5.525	-3.678	5.037	1.00	0.00
ATOM	101	N24	LP2	2	-7.362	-4.563	3.394	1.00	0.00
ATOM	102	C1	LP2	2	-9.271	-5.973	4.080	1.00	0.00
ATOM	103	C2	LP2	2	-9.791	-7.438	3.829	1.00	0.00
ATOM	104	C3	LP2	2	-9.596	-8.166	5.157	1.00	0.00
ATOM	105	C4	LP2	2	-8.415	-7.364	5.751	1.00	0.00
ATOM	106	C6	LP2	2	-6.530	-6.976	7.269	1.00	0.00
ATOM	107	C7	LP2	2	-5.924	-7.130	8.682	1.00	0.00
ATOM	108	C8	LP2	2	-5.121	-5.810	8.924	1.00	0.00
ATOM	109	C9	LP2	2	-5.149	-5.250	7.452	1.00	0.00
ATOM	110	C16	LP2	2	-7.009	-3.628	2.472	1.00	0.00
ATOM	111	C17	LP2	2	-8.031	-3.560	1.277	1.00	0.00
ATOM	112	C18	LP2	2	-9.170	-4.325	1.889	1.00	0.00
ATOM	113	C19	LP2	2	-8.530	-5.289	2.884	1.00	0.00
ATOM	114	C11	LP2	2	-4.567	-3.347	5.935	1.00	0.00
ATOM	115	C12	LP2	2	-3.425	-2.450	5.471	1.00	0.00
ATOM	116	C13	LP2	2	-4.041	-1.760	4.233	1.00	0.00
ATOM	117	C14	LP2	2	-5.151	-2.856	3.948	1.00	0.00
ATOM	118	C10	LP2	2	-4.391	-4.082	7.104	1.00	0.00
ATOM	119	H10	LP2	2	-3.721	-3.604	7.787	1.00	0.00
ATOM	120	N	LP2	2	1.900	8.473	3.531	1.00	0.00
ATOM	121	H	LP2	2	2.308	9.273	3.035	1.00	0.00
ATOM	122	CA	LP2	2	0.494	8.172	3.223	1.00	0.00
ATOM	123	CB	LP2	2	-0.182	9.554	3.396	1.00	0.00
ATOM	124	CG	LP2	2	-1.569	9.338	3.944	1.00	0.00
ATOM	125	CD	LP2	2	-1.581	8.659	5.352	1.00	0.00
ATOM	126	CE	LP2	2	-3.043	8.499	5.715	1.00	0.00
ATOM	127	C	LP2	2	0.340	7.502	1.851	1.00	0.00
ATOM	128	O	LP2	2	0.103	8.263	0.871	1.00	0.00
ATOM	129	OLB	LP2	2	-7.189	4.392	6.565	1.00	0.00
ATOM	130	C1N	LP2	2	-5.501	-6.030	4.469	1.00	0.00
ATOM	131	N1C	LP2	2	-4.628	-6.618	4.071	1.00	0.00
ATOM	132	CZ	LP2	2	-5.363	4.174	8.575	1.00	0.00
ATOM	133	CY	LP2	2	-4.182	3.998	7.633	1.00	0.00
ATOM	134	CT1	LP2	2	-3.498	5.323	7.469	1.00	0.00
ATOM	135	CT2	LP2	2	-3.676	6.128	6.397	1.00	0.00
ATOM	136	NT1	LP2	2	-3.329	7.339	6.721	1.00	0.00
ATOM	137	NT2	LP2	2	-2.944	7.352	8.022	1.00	0.00
ATOM	138	NT3	LP2	2	-3.037	6.098	8.419	1.00	0.00
ATOM	139	NZ2	LP2	2	-6.186	3.008	8.363	1.00	0.00
ATOM	140	HZ2	LP2	2	-5.785	2.121	8.685	1.00	0.00
ATOM	141	N	PRO	3	0.186	6.155	1.734	1.00	0.00
ATOM	142	CA	PRO	3	0.103	5.540	0.434	1.00	0.00
ATOM	143	CB	PRO	3	0.057	4.001	0.771	1.00	0.00
ATOM	144	CG	PRO	3	0.588	3.923	2.183	1.00	0.00
ATOM	145	CD	PRO	3	0.191	5.236	2.846	1.00	0.00
ATOM	146	C	PRO	3	-1.003	6.010	-0.500	1.00	0.00
ATOM	147	O	PRO	3	-1.954	6.502	0.007	1.00	0.00
ATOM	148	N	GLU	4	-0.825	5.858	-1.851	1.00	0.00
ATOM	149	H	GLU	4	-0.149	5.227	-2.301	1.00	0.00
ATOM	150	CA	GLU	4	-2.116	6.025	-2.593	1.00	0.00
ATOM	151	CB	GLU	4	-1.865	6.750	-3.932	1.00	0.00
ATOM	152	CG	GLU	4	-1.616	8.225	-3.711	1.00	0.00
ATOM	153	CD	GLU	4	-0.941	8.923	-4.895	1.00	0.00
ATOM	154	OE1	GLU	4	-1.673	9.539	-5.750	1.00	0.00
ATOM	155	OE2	GLU	4	0.217	8.572	-5.088	1.00	0.00
ATOM	156	C	GLU	4	-2.886	4.764	-2.759	1.00	0.00
ATOM	157	O	GLU	4	-2.679	3.900	-3.647	1.00	0.00
ATOM	158	N	ALA	5	-3.860	4.609	-1.891	1.00	0.00
ATOM	159	H	ALA	5	-4.143	5.364	-1.338	1.00	0.00
ATOM	160	CA	ALA	5	-4.496	3.283	-1.544	1.00	0.00
ATOM	161	CB	ALA	5	-4.920	3.301	-0.088	1.00	0.00
ATOM	162	C	ALA	5	-5.765	2.910	-2.333	1.00	0.00

ATOM	163	O	ALA	5	-6.654	3.771	-2.337	1.00	0.00
ATOM	164	N	PRO	6	-5.712	1.826	-3.148	1.00	0.00
ATOM	165	CA	PRO	6	-6.941	1.182	-3.770	1.00	0.00
ATOM	166	CB	PRO	6	-6.409	0.268	-4.828	1.00	0.00
ATOM	167	CG	PRO	6	-5.004	-0.058	-4.316	1.00	0.00
ATOM	168	CD	PRO	6	-4.529	1.322	-3.812	1.00	0.00
ATOM	169	C	PRO	6	-7.681	0.320	-2.737	1.00	0.00
ATOM	170	O	PRO	6	-7.310	0.256	-1.569	1.00	0.00
ATOM	171	N	GLY	7	-8.600	-0.477	-3.284	1.00	0.00
ATOM	172	H	GLY	7	-8.725	-0.567	-4.280	1.00	0.00
ATOM	173	CA	GLY	7	-9.523	-1.252	-2.416	1.00	0.00
ATOM	174	C	GLY	7	-10.953	-1.170	-2.829	1.00	0.00
ATOM	175	O	GLY	7	-11.736	-0.613	-2.077	1.00	0.00
ATOM	176	N	GLU	8	-11.348	-1.739	-3.958	1.00	0.00
ATOM	177	H	GLU	8	-10.698	-2.233	-4.602	1.00	0.00
ATOM	178	CA	GLU	8	-12.518	-1.285	-4.725	1.00	0.00
ATOM	179	CB	GLU	8	-12.465	0.169	-5.292	1.00	0.00
ATOM	180	CG	GLU	8	-11.398	0.508	-6.353	1.00	0.00
ATOM	181	CD	GLU	8	-11.660	1.884	-7.017	1.00	0.00
ATOM	182	OE1	GLU	8	-12.182	1.997	-8.138	1.00	0.00
ATOM	183	OE2	GLU	8	-11.285	2.863	-6.327	1.00	0.00
ATOM	184	C	GLU	8	-12.962	-2.272	-5.846	1.00	0.00
ATOM	185	O	GLU	8	-14.131	-2.212	-6.211	1.00	0.00
ATOM	186	N	ASP	9	-12.101	-3.160	-6.360	1.00	0.00
ATOM	187	H	ASP	9	-11.167	-3.123	-6.064	1.00	0.00
ATOM	188	CA	ASP	9	-12.346	-4.072	-7.510	1.00	0.00
ATOM	189	CB	ASP	9	-11.809	-3.567	-8.823	1.00	0.00
ATOM	190	CG	ASP	9	-12.256	-4.431	-9.944	1.00	0.00
ATOM	191	OD1	ASP	9	-11.451	-5.240	-10.342	1.00	0.00
ATOM	192	OD2	ASP	9	-13.395	-4.277	-10.500	1.00	0.00
ATOM	193	C	ASP	9	-11.779	-5.513	-7.185	1.00	0.00
ATOM	194	O	ASP	9	-12.665	-6.338	-7.016	1.00	0.00
ATOM	195	N	ALA	10	-10.454	-5.734	-6.918	1.00	0.00
ATOM	196	H	ALA	10	-9.774	-5.003	-6.901	1.00	0.00
ATOM	197	CA	ALA	10	-9.869	-7.079	-6.646	1.00	0.00
ATOM	198	CB	ALA	10	-9.145	-7.651	-7.858	1.00	0.00
ATOM	199	C	ALA	10	-8.929	-7.020	-5.424	1.00	0.00
ATOM	200	O	ALA	10	-7.759	-6.694	-5.616	1.00	0.00
ATOM	201	N	SER	11	-9.297	-7.743	-4.369	1.00	0.00
ATOM	202	H	SER	11	-10.122	-8.282	-4.401	1.00	0.00
ATOM	203	CA	SER	11	-8.612	-7.558	-3.079	1.00	0.00
ATOM	204	CB	SER	11	-9.377	-8.042	-1.887	1.00	0.00
ATOM	205	OG	SER	11	-9.455	-9.483	-1.923	1.00	0.00
ATOM	206	HG	SER	11	-10.087	-9.847	-2.659	1.00	0.00
ATOM	207	C	SER	11	-7.145	-8.087	-3.018	1.00	0.00
ATOM	208	O	SER	11	-6.321	-7.286	-2.614	1.00	0.00
ATOM	209	N	PRO	12	-6.753	-9.197	-3.703	1.00	0.00
ATOM	210	CA	PRO	12	-5.355	-9.590	-3.830	1.00	0.00
ATOM	211	CB	PRO	12	-5.351	-11.063	-4.299	1.00	0.00
ATOM	212	CG	PRO	12	-6.648	-11.588	-3.744	1.00	0.00
ATOM	213	CD	PRO	12	-7.608	-10.352	-3.969	1.00	0.00
ATOM	214	C	PRO	12	-4.467	-8.601	-4.666	1.00	0.00
ATOM	215	O	PRO	12	-3.437	-8.195	-4.142	1.00	0.00
ATOM	216	N	GLU	13	-5.035	-8.066	-5.705	1.00	0.00
ATOM	217	H	GLU	13	-5.996	-8.207	-5.977	1.00	0.00
ATOM	218	CA	GLU	13	-4.259	-7.248	-6.608	1.00	0.00
ATOM	219	CB	GLU	13	-4.567	-7.451	-8.122	1.00	0.00
ATOM	220	CG	GLU	13	-4.368	-8.892	-8.662	1.00	0.00
ATOM	221	CD	GLU	13	-5.201	-9.170	-9.913	1.00	0.00
ATOM	222	OE1	GLU	13	-6.414	-9.208	-9.712	1.00	0.00
ATOM	223	OE2	GLU	13	-4.623	-9.498	-10.980	1.00	0.00
ATOM	224	C	GLU	13	-4.215	-5.701	-6.309	1.00	0.00
ATOM	225	O	GLU	13	-3.213	-5.039	-6.481	1.00	0.00
ATOM	226	N	GLU	14	-5.276	-5.270	-5.643	1.00	0.00
ATOM	227	H	GLU	14	-6.176	-5.715	-5.702	1.00	0.00
ATOM	228	CA	GLU	14	-5.323	-3.980	-4.878	1.00	0.00
ATOM	229	CB	GLU	14	-6.789	-3.690	-4.621	1.00	0.00
ATOM	230	CG	GLU	14	-7.499	-3.289	-5.957	1.00	0.00
ATOM	231	CD	GLU	14	-8.970	-2.953	-5.786	1.00	0.00
ATOM	232	OE1	GLU	14	-9.319	-1.857	-6.287	1.00	0.00
ATOM	233	OE2	GLU	14	-9.620	-3.681	-5.059	1.00	0.00
ATOM	234	C	GLU	14	-4.482	-4.068	-3.554	1.00	0.00
ATOM	235	O	GLU	14	-3.786	-3.103	-3.328	1.00	0.00

ATOM	236	N	LEU	15	-4.403	-5.241	-2.903	1.00	0.00
ATOM	237	H	LEU	15	-5.161	-6.002	-2.895	1.00	0.00
ATOM	238	CA	LEU	15	-3.399	-5.487	-1.914	1.00	0.00
ATOM	239	CB	LEU	15	-3.686	-6.836	-1.260	1.00	0.00
ATOM	240	CG	LEU	15	-3.792	-6.753	0.281	1.00	0.00
ATOM	241	CD1	LEU	15	-4.138	-8.155	0.845	1.00	0.00
ATOM	242	CD2	LEU	15	-2.553	-6.283	1.065	1.00	0.00
ATOM	243	C	LEU	15	-1.981	-5.320	-2.470	1.00	0.00
ATOM	244	O	LEU	15	-1.351	-4.370	-1.920	1.00	0.00
ATOM	245	N	ASN	16	-1.661	-5.803	-3.662	1.00	0.00
ATOM	246	H	ASN	16	-2.121	-6.673	-3.931	1.00	0.00
ATOM	247	CA	ASN	16	-0.341	-5.567	-4.292	1.00	0.00
ATOM	248	CB	ASN	16	0.133	-6.628	-5.307	1.00	0.00
ATOM	249	CG	ASN	16	-0.122	-8.115	-4.991	1.00	0.00
ATOM	250	OD1	ASN	16	-0.242	-8.447	-3.819	1.00	0.00
ATOM	251	ND2	ASN	16	-0.146	-8.910	-6.036	1.00	0.00
ATOM	252	1HD2	ASN	16	0.027	-8.632	-7.055	1.00	0.00
ATOM	253	2HD2	ASN	16	-0.088	-9.915	-5.811	1.00	0.00
ATOM	254	C	ASN	16	-0.114	-4.175	-4.851	1.00	0.00
ATOM	255	O	ASN	16	1.019	-3.761	-5.157	1.00	0.00
ATOM	256	N	ARG	17	-1.198	-3.552	-5.265	1.00	0.00
ATOM	257	H	ARG	17	-2.018	-4.052	-5.433	1.00	0.00
ATOM	258	CA	ARG	17	-1.203	-2.109	-5.605	1.00	0.00
ATOM	259	CB	ARG	17	-2.455	-1.884	-6.407	1.00	0.00
ATOM	260	CG	ARG	17	-2.047	-0.841	-7.453	1.00	0.00
ATOM	261	CD	ARG	17	-2.973	-0.458	-8.603	1.00	0.00
ATOM	262	NE	ARG	17	-4.260	0.123	-8.120	1.00	0.00
ATOM	263	HE	ARG	17	-4.080	1.076	-7.777	1.00	0.00
ATOM	264	CZ	ARG	17	-5.495	-0.477	-8.205	1.00	0.00
ATOM	265	NH1	ARG	17	-5.648	-1.692	-8.668	1.00	0.00
ATOM	266	1HH1	ARG	17	-4.979	-2.309	-9.103	1.00	0.00
ATOM	267	2HH1	ARG	17	-6.478	-2.192	-8.422	1.00	0.00
ATOM	268	NH2	ARG	17	-6.602	0.172	-7.985	1.00	0.00
ATOM	269	1HH2	ARG	17	-6.491	1.127	-7.823	1.00	0.00
ATOM	270	2HH2	ARG	17	-7.548	-0.244	-8.229	1.00	0.00
ATOM	271	C	ARG	17	-0.875	-1.164	-4.477	1.00	0.00
ATOM	272	O	ARG	17	0.003	-0.307	-4.599	1.00	0.00
ATOM	273	N	TYR	18	-1.447	-1.567	-3.304	1.00	0.00
ATOM	274	H	TYR	18	-2.202	-2.224	-3.295	1.00	0.00
ATOM	275	CA	TYR	18	-1.023	-1.038	-1.959	1.00	0.00
ATOM	276	CB	TYR	18	-2.038	-1.474	-0.950	1.00	0.00
ATOM	277	CG	TYR	18	-1.699	-1.112	0.556	1.00	0.00
ATOM	278	CD1	TYR	18	-1.063	-2.179	1.291	1.00	0.00
ATOM	279	HD1	TYR	18	-1.076	-3.233	1.004	1.00	0.00
ATOM	280	CD2	TYR	18	-1.622	0.226	0.932	1.00	0.00
ATOM	281	HD2	TYR	18	-1.807	1.043	0.197	1.00	0.00
ATOM	282	CE1	TYR	18	-0.301	-1.751	2.317	1.00	0.00
ATOM	283	HE1	TYR	18	0.433	-2.429	2.746	1.00	0.00
ATOM	284	CE2	TYR	18	-0.884	0.578	2.064	1.00	0.00
ATOM	285	HE2	TYR	18	-1.083	1.476	2.587	1.00	0.00
ATOM	286	CZ	TYR	18	-0.238	-0.404	2.760	1.00	0.00
ATOM	287	OH	TYR	18	0.406	-0.190	3.945	1.00	0.00
ATOM	288	HH	TYR	18	0.411	-1.016	4.578	1.00	0.00
ATOM	289	C	TYR	18	0.396	-1.225	-1.582	1.00	0.00
ATOM	290	O	TYR	18	1.116	-0.217	-1.454	1.00	0.00
ATOM	291	N	TYR	19	0.866	-2.516	-1.580	1.00	0.00
ATOM	292	H	TYR	19	0.250	-3.284	-1.712	1.00	0.00
ATOM	293	CA	TYR	19	2.330	-2.798	-1.523	1.00	0.00
ATOM	294	CB	TYR	19	2.772	-4.255	-1.291	1.00	0.00
ATOM	295	CG	TYR	19	2.282	-4.788	0.017	1.00	0.00
ATOM	296	CD1	TYR	19	1.261	-5.699	0.201	1.00	0.00
ATOM	297	HD1	TYR	19	1.043	-6.282	-0.646	1.00	0.00
ATOM	298	CD2	TYR	19	2.846	-4.221	1.101	1.00	0.00
ATOM	299	HD2	TYR	19	3.776	-3.690	0.892	1.00	0.00
ATOM	300	CE1	TYR	19	0.888	-6.056	1.500	1.00	0.00
ATOM	301	HE1	TYR	19	0.145	-6.837	1.646	1.00	0.00
ATOM	302	CE2	TYR	19	2.458	-4.456	2.453	1.00	0.00
ATOM	303	HE2	TYR	19	2.747	-3.762	3.256	1.00	0.00
ATOM	304	CZ	TYR	19	1.483	-5.431	2.568	1.00	0.00
ATOM	305	OH	TYR	19	1.085	-6.015	3.720	1.00	0.00
ATOM	306	HH	TYR	19	0.091	-6.081	3.716	1.00	0.00
ATOM	307	C	TYR	19	3.199	-1.989	-2.542	1.00	0.00
ATOM	308	O	TYR	19	4.104	-1.333	-2.128	1.00	0.00

ATOM	309	N	ALA	20	2.943	-2.156	-3.818	1.00	0.00
ATOM	310	H	ALA	20	2.229	-2.750	-4.160	1.00	0.00
ATOM	311	CA	ALA	20	3.626	-1.393	-4.894	1.00	0.00
ATOM	312	CB	ALA	20	2.846	-1.586	-6.124	1.00	0.00
ATOM	313	C	ALA	20	3.656	0.133	-4.584	1.00	0.00
ATOM	314	O	ALA	20	4.756	0.697	-4.549	1.00	0.00
ATOM	315	N	SER	21	2.576	0.730	-4.093	1.00	0.00
ATOM	316	H	SER	21	1.842	0.132	-4.006	1.00	0.00
ATOM	317	CA	SER	21	2.452	2.172	-3.692	1.00	0.00
ATOM	318	CB	SER	21	1.004	2.642	-3.470	1.00	0.00
ATOM	319	OG	SER	21	0.980	3.986	-3.062	1.00	0.00
ATOM	320	HG	SER	21	1.135	4.516	-3.943	1.00	0.00
ATOM	321	C	SER	21	3.308	2.599	-2.473	1.00	0.00
ATOM	322	O	SER	21	4.190	3.411	-2.544	1.00	0.00
ATOM	323	N	LEU	22	3.169	1.753	-1.410	1.00	0.00
ATOM	324	H	LEU	22	2.740	0.852	-1.521	1.00	0.00
ATOM	325	CA	LEU	22	3.926	1.843	-0.139	1.00	0.00
ATOM	326	CB	LEU	22	3.449	0.693	0.694	1.00	0.00
ATOM	327	CG	LEU	22	4.088	0.485	2.015	1.00	0.00
ATOM	328	CD1	LEU	22	4.142	1.753	2.835	1.00	0.00
ATOM	329	CD2	LEU	22	3.347	-0.480	2.837	1.00	0.00
ATOM	330	C	LEU	22	5.447	1.766	-0.315	1.00	0.00
ATOM	331	O	LEU	22	6.177	2.650	0.145	1.00	0.00
ATOM	332	N	ARG	23	5.930	0.920	-1.235	1.00	0.00
ATOM	333	H	ARG	23	5.356	0.251	-1.674	1.00	0.00
ATOM	334	CA	ARG	23	7.378	0.799	-1.472	1.00	0.00
ATOM	335	CB	ARG	23	7.771	-0.545	-2.083	1.00	0.00
ATOM	336	CG	ARG	23	7.385	-1.706	-1.121	1.00	0.00
ATOM	337	CD	ARG	23	8.047	-3.048	-1.615	1.00	0.00
ATOM	338	NE	ARG	23	7.115	-4.158	-1.458	1.00	0.00
ATOM	339	HE	ARG	23	6.731	-4.311	-0.501	1.00	0.00
ATOM	340	CZ	ARG	23	6.897	-4.991	-2.481	1.00	0.00
ATOM	341	NH1	ARG	23	7.489	-4.995	-3.724	1.00	0.00
ATOM	342	1HH1	ARG	23	8.002	-4.177	-3.999	1.00	0.00
ATOM	343	2HH1	ARG	23	7.401	-5.749	-4.353	1.00	0.00
ATOM	344	NH2	ARG	23	6.042	-5.960	-2.186	1.00	0.00
ATOM	345	1HH2	ARG	23	5.695	-6.075	-1.207	1.00	0.00
ATOM	346	2HH2	ARG	23	5.900	-6.676	-2.876	1.00	0.00
ATOM	347	C	ARG	23	8.075	1.961	-2.253	1.00	0.00
ATOM	348	O	ARG	23	9.190	2.383	-1.925	1.00	0.00
ATOM	349	N	HIS	24	7.285	2.426	-3.211	1.00	0.00
ATOM	350	H	HIS	24	6.464	1.868	-3.468	1.00	0.00
ATOM	351	CA	HIS	24	7.392	3.703	-3.926	1.00	0.00
ATOM	352	CB	HIS	24	6.219	3.784	-4.934	1.00	0.00
ATOM	353	CG	HIS	24	6.061	5.154	-5.678	1.00	0.00
ATOM	354	ND1	HIS	24	6.732	5.490	-6.805	1.00	0.00
ATOM	355	CD2	HIS	24	5.185	6.115	-5.400	1.00	0.00
ATOM	356	HD2	HIS	24	4.537	6.235	-4.535	1.00	0.00
ATOM	357	CE1	HIS	24	6.221	6.621	-7.283	1.00	0.00
ATOM	358	HE1	HIS	24	6.495	7.100	-8.233	1.00	0.00
ATOM	359	NE2	HIS	24	5.261	7.043	-6.383	1.00	0.00
ATOM	360	HE2	HIS	24	4.508	7.689	-6.522	1.00	0.00
ATOM	361	C	HIS	24	7.360	4.900	-2.925	1.00	0.00
ATOM	362	O	HIS	24	8.392	5.544	-2.756	1.00	0.00
ATOM	363	N	TYR	25	6.307	5.031	-2.132	1.00	0.00
ATOM	364	H	TYR	25	5.625	4.231	-2.043	1.00	0.00
ATOM	365	CA	TYR	25	6.208	6.091	-1.080	1.00	0.00
ATOM	366	CB	TYR	25	4.828	5.904	-0.434	1.00	0.00
ATOM	367	CG	TYR	25	3.876	6.944	-1.048	1.00	0.00
ATOM	368	CD1	TYR	25	3.213	6.550	-2.231	1.00	0.00
ATOM	369	HD1	TYR	25	3.203	5.459	-2.464	1.00	0.00
ATOM	370	CD2	TYR	25	3.563	8.136	-0.445	1.00	0.00
ATOM	371	HD2	TYR	25	3.975	8.396	0.559	1.00	0.00
ATOM	372	CE1	TYR	25	2.281	7.405	-2.846	1.00	0.00
ATOM	373	HE1	TYR	25	1.832	7.114	-3.802	1.00	0.00
ATOM	374	CE2	TYR	25	2.630	9.006	-1.041	1.00	0.00
ATOM	375	HE2	TYR	25	2.391	9.918	-0.496	1.00	0.00
ATOM	376	CZ	TYR	25	1.925	8.645	-2.226	1.00	0.00
ATOM	377	OH	TYR	25	1.117	9.531	-2.824	1.00	0.00
ATOM	378	HH	TYR	25	0.764	9.259	-3.802	1.00	0.00
ATOM	379	C	TYR	25	7.460	6.004	-0.151	1.00	0.00
ATOM	380	O	TYR	25	8.010	7.063	0.095	1.00	0.00
ATOM	381	N	LEU	26	7.869	4.792	0.256	1.00	0.00

ATOM	382	H	LEU	26	7.206	4.024	0.225	1.00	0.00
ATOM	383	CA	LEU	26	9.172	4.569	1.002	1.00	0.00
ATOM	384	CB	LEU	26	9.459	3.065	1.403	1.00	0.00
ATOM	385	CG	LEU	26	8.875	2.539	2.689	1.00	0.00
ATOM	386	CD1	LEU	26	9.281	1.082	2.992	1.00	0.00
ATOM	387	CD2	LEU	26	9.073	3.486	3.902	1.00	0.00
ATOM	388	C	LEU	26	10.367	5.193	0.280	1.00	0.00
ATOM	389	O	LEU	26	10.861	6.184	0.823	1.00	0.00
ATOM	390	N	ASN	27	10.729	4.663	-0.920	1.00	0.00
ATOM	391	H	ASN	27	10.160	3.899	-1.328	1.00	0.00
ATOM	392	CA	ASN	27	11.869	5.184	-1.721	1.00	0.00
ATOM	393	CB	ASN	27	11.839	4.498	-3.084	1.00	0.00
ATOM	394	CG	ASN	27	13.282	4.280	-3.586	1.00	0.00
ATOM	395	OD1	ASN	27	14.148	5.108	-3.544	1.00	0.00
ATOM	396	ND2	ASN	27	13.463	3.117	-4.177	1.00	0.00
ATOM	397	1HD2	ASN	27	12.856	2.295	-4.231	1.00	0.00
ATOM	398	2HD2	ASN	27	14.285	3.160	-4.721	1.00	0.00
ATOM	399	C	ASN	27	11.810	6.690	-2.021	1.00	0.00
ATOM	400	O	ASN	27	12.874	7.319	-1.921	1.00	0.00
ATOM	401	N	LEU	28	10.614	7.222	-2.203	1.00	0.00
ATOM	402	H	LEU	28	9.838	6.592	-2.396	1.00	0.00
ATOM	403	CA	LEU	28	10.371	8.661	-2.358	1.00	0.00
ATOM	404	CB	LEU	28	8.915	8.899	-2.798	1.00	0.00
ATOM	405	CG	LEU	28	8.561	8.702	-4.270	1.00	0.00
ATOM	406	CD1	LEU	28	7.101	9.264	-4.591	1.00	0.00
ATOM	407	CD2	LEU	28	9.615	9.167	-5.276	1.00	0.00
ATOM	408	C	LEU	28	10.703	9.562	-1.123	1.00	0.00
ATOM	409	O	LEU	28	11.368	10.552	-1.393	1.00	0.00
ATOM	410	N	VAL	29	10.488	9.024	0.097	1.00	0.00
ATOM	411	H	VAL	29	10.101	8.113	0.208	1.00	0.00
ATOM	412	CA	VAL	29	10.813	9.850	1.278	1.00	0.00
ATOM	413	CB	VAL	29	9.532	9.786	2.109	1.00	0.00
ATOM	414	CG1	VAL	29	9.154	8.488	2.838	1.00	0.00
ATOM	415	CG2	VAL	29	9.501	10.994	3.075	1.00	0.00
ATOM	416	C	VAL	29	12.146	9.373	2.035	1.00	0.00
ATOM	417	O	VAL	29	12.844	10.254	2.515	1.00	0.00
ATOM	418	N	THR	30	12.345	8.029	2.050	1.00	0.00
ATOM	419	H	THR	30	11.732	7.305	1.695	1.00	0.00
ATOM	420	CA	THR	30	13.574	7.494	2.626	1.00	0.00
ATOM	421	CB	THR	30	13.163	6.653	3.881	1.00	0.00
ATOM	422	OG1	THR	30	12.366	7.461	4.657	1.00	0.00
ATOM	423	HG1	THR	30	11.739	6.882	5.178	1.00	0.00
ATOM	424	CG2	THR	30	14.440	6.319	4.645	1.00	0.00
ATOM	425	C	THR	30	14.302	6.576	1.649	1.00	0.00
ATOM	426	O	THR	30	13.826	5.515	1.305	1.00	0.00
ATOM	427	N	ARG	31	15.618	6.889	1.444	1.00	0.00
ATOM	428	H	ARG	31	16.132	7.348	2.167	1.00	0.00
ATOM	429	CA	ARG	31	16.356	6.342	0.270	1.00	0.00
ATOM	430	CB	ARG	31	17.622	7.150	0.192	1.00	0.00
ATOM	431	CG	ARG	31	18.439	6.795	-1.057	1.00	0.00
ATOM	432	CD	ARG	31	17.831	7.287	-2.377	1.00	0.00
ATOM	433	NE	ARG	31	18.626	6.906	-3.571	1.00	0.00
ATOM	434	HE	ARG	31	19.570	7.039	-3.485	1.00	0.00
ATOM	435	CZ	ARG	31	18.156	6.835	-4.843	1.00	0.00
ATOM	436	NH1	ARG	31	16.944	7.119	-5.223	1.00	0.00
ATOM	437	1HH1	ARG	31	16.227	7.438	-4.621	1.00	0.00
ATOM	438	2HH1	ARG	31	16.796	6.999	-6.156	1.00	0.00
ATOM	439	NH2	ARG	31	19.024	6.587	-5.807	1.00	0.00
ATOM	440	1HH2	ARG	31	19.992	6.425	-5.592	1.00	0.00
ATOM	441	2HH2	ARG	31	18.674	6.275	-6.642	1.00	0.00
ATOM	442	C	ARG	31	16.504	4.777	0.164	1.00	0.00
ATOM	443	O	ARG	31	17.313	4.103	0.818	1.00	0.00
ATOM	444	N	GLN	32	15.680	4.216	-0.745	1.00	0.00
ATOM	445	H	GLN	32	15.075	4.806	-1.274	1.00	0.00
ATOM	446	CA	GLN	32	15.658	2.800	-1.129	1.00	0.00
ATOM	447	CB	GLN	32	16.605	2.332	-2.266	1.00	0.00
ATOM	448	CG	GLN	32	18.007	3.013	-2.371	1.00	0.00
ATOM	449	CD	GLN	32	18.738	2.927	-3.719	1.00	0.00
ATOM	450	OE1	GLN	32	18.558	3.682	-4.677	1.00	0.00
ATOM	451	NE2	GLN	32	19.655	2.075	-3.896	1.00	0.00
ATOM	452	1HE2	GLN	32	19.919	1.425	-3.216	1.00	0.00
ATOM	453	2HE2	GLN	32	19.862	1.927	-4.870	1.00	0.00
ATOM	454	C	GLN	32	15.668	1.786	0.074	1.00	0.00

ATOM	455	O	GLN	32	16.392	0.846	0.145	1.00	0.00
ATOM	456	N	ARG	33	14.878	2.167	1.080	1.00	0.00
ATOM	457	H	ARG	33	14.489	3.137	1.078	1.00	0.00
ATOM	458	CA	ARG	33	14.591	1.357	2.273	1.00	0.00
ATOM	459	CB	ARG	33	14.503	2.278	3.491	1.00	0.00
ATOM	460	CG	ARG	33	15.839	2.750	4.001	1.00	0.00
ATOM	461	CD	ARG	33	16.499	1.549	4.836	1.00	0.00
ATOM	462	NE	ARG	33	15.597	1.265	5.978	1.00	0.00
ATOM	463	HE	ARG	33	15.182	0.320	5.914	1.00	0.00
ATOM	464	CZ	ARG	33	15.498	2.049	7.049	1.00	0.00
ATOM	465	NH1	ARG	33	16.289	3.047	7.383	1.00	0.00
ATOM	466	1HH1	ARG	33	17.072	3.377	6.831	1.00	0.00
ATOM	467	2HH1	ARG	33	16.233	3.486	8.254	1.00	0.00
ATOM	468	NH2	ARG	33	14.618	1.713	8.002	1.00	0.00
ATOM	469	1HH2	ARG	33	14.150	0.865	7.985	1.00	0.00
ATOM	470	2HH2	ARG	33	14.418	2.399	8.683	1.00	0.00
ATOM	471	C	ARG	33	13.359	0.466	2.131	1.00	0.00
ATOM	472	O	ARG	33	12.313	0.728	2.631	1.00	0.00
ATOM	473	N	TYR	34	13.605	-0.716	1.605	1.00	0.00
ATOM	474	H	TYR	34	14.403	-0.844	0.995	1.00	0.00
ATOM	475	CA	TYR	34	12.749	-1.946	1.566	1.00	0.00
ATOM	476	CB	TYR	34	11.631	-1.880	0.511	1.00	0.00
ATOM	477	CG	TYR	34	11.949	-1.226	-0.823	1.00	0.00
ATOM	478	CD1	TYR	34	11.712	0.137	-0.900	1.00	0.00
ATOM	479	HD1	TYR	34	11.325	0.677	-0.031	1.00	0.00
ATOM	480	CD2	TYR	34	12.280	-1.987	-1.945	1.00	0.00
ATOM	481	HD2	TYR	34	12.577	-3.016	-1.801	1.00	0.00
ATOM	482	CE1	TYR	34	11.889	0.744	-2.171	1.00	0.00
ATOM	483	HE1	TYR	34	11.395	1.661	-2.334	1.00	0.00
ATOM	484	CE2	TYR	34	12.404	-1.392	-3.203	1.00	0.00
ATOM	485	HE2	TYR	34	12.797	-2.002	-3.988	1.00	0.00
ATOM	486	CZ	TYR	34	12.233	0.035	-3.312	1.00	0.00
ATOM	487	OH	TYR	34	12.208	0.685	-4.464	1.00	0.00
ATOM	488	HH	TYR	34	12.730	0.140	-5.199	1.00	0.00
ATOM	489	C	TYR	34	13.559	-3.195	1.349	1.00	0.00
ATOM	490	O1	TYR	34	14.683	-3.093	0.903	1.00	0.00
ATOM	491	O2	TYR	34	13.029	-4.229	1.695	1.00	0.00

Geometry For 4

ATOM	1	N	ILE	1	8.017	10.417	4.295	1.00	0.00
ATOM	2	H1	ILE	1	8.453	11.259	3.837	1.00	0.00
ATOM	3	H2	ILE	1	7.751	10.662	5.217	1.00	0.00
ATOM	4	H3	ILE	1	8.693	9.703	4.341	1.00	0.00
ATOM	5	CA	ILE	1	6.843	9.843	3.603	1.00	0.00
ATOM	6	CB	ILE	1	6.856	10.040	2.105	1.00	0.00
ATOM	7	CG1	ILE	1	5.589	9.642	1.400	1.00	0.00
ATOM	8	CG2	ILE	1	8.042	9.479	1.377	1.00	0.00
ATOM	9	CD	ILE	1	4.333	10.040	2.098	1.00	0.00
ATOM	10	C	ILE	1	6.696	8.348	3.996	1.00	0.00
ATOM	11	O	ILE	1	7.698	7.641	4.023	1.00	0.00
ATOM	12	C27	LP3	2	-8.434	-10.538	6.420	1.00	0.00
ATOM	13	O28	LP3	2	-8.468	-11.685	6.789	1.00	0.00
ATOM	14	N29	LP3	2	-9.582	-9.955	6.077	1.00	0.00
ATOM	15	HAE	LP3	2	-9.771	-8.954	6.035	1.00	0.00
ATOM	16	HAD	LP3	2	-10.338	-10.635	5.941	1.00	0.00
ATOM	17	C32	LP3	2	-4.390	-14.367	4.184	1.00	0.00
ATOM	18	O34	LP3	2	-4.514	-14.786	3.073	1.00	0.00
ATOM	19	N33	LP3	2	-3.285	-14.650	4.868	1.00	0.00
ATOM	20	HAG	LP3	2	-3.347	-14.696	5.884	1.00	0.00
ATOM	21	HAF	LP3	2	-2.503	-14.937	4.314	1.00	0.00
ATOM	22	C38	LP3	2	-9.230	-9.155	-1.243	1.00	0.00
ATOM	23	O39	LP3	2	-9.027	-9.983	-2.148	1.00	0.00
ATOM	24	N40	LP3	2	-10.383	-8.463	-1.389	1.00	0.00
ATOM	25	HAI	LP3	2	-10.929	-8.162	-0.590	1.00	0.00
ATOM	26	HAH	LP3	2	-10.696	-8.409	-2.337	1.00	0.00
ATOM	27	C43	LP3	2	-5.101	-6.610	-3.448	1.00	0.00
ATOM	28	O44	LP3	2	-4.052	-6.341	-2.948	1.00	0.00
ATOM	29	N45	LP3	2	-5.231	-6.734	-4.781	1.00	0.00
ATOM	30	HAK	LP3	2	-6.090	-7.067	-5.280	1.00	0.00
ATOM	31	HAJ	LP3	2	-4.549	-6.313	-5.300	1.00	0.00
ATOM	32	C50	LP3	2	-2.143	-0.344	3.220	1.00	0.00
ATOM	33	O51	LP3	2	-1.455	0.107	2.312	1.00	0.00
ATOM	34	N52	LP3	2	-1.715	-0.364	4.473	1.00	0.00
ATOM	35	HAM	LP3	2	-2.386	-0.396	5.277	1.00	0.00
ATOM	36	HAL	LP3	2	-0.831	-0.285	4.680	1.00	0.00
ATOM	37	C61	LP3	2	-4.953	-7.831	10.175	1.00	0.00
ATOM	38	O63	LP3	2	-4.721	-8.995	10.082	1.00	0.00
ATOM	39	N62	LP3	2	-4.737	-7.145	11.216	1.00	0.00
ATOM	40	HAO	LP3	2	-5.006	-6.185	11.354	1.00	0.00
ATOM	41	HAN	LP3	2	-4.335	-7.712	11.962	1.00	0.00
ATOM	42	C20	LP3	2	-3.472	-8.998	5.785	1.00	0.00
ATOM	43	C25	LP3	2	-5.205	-10.811	7.410	1.00	0.00
ATOM	44	C36	LP3	2	-6.269	-10.171	-0.682	1.00	0.00
ATOM	45	C46	LP3	2	-7.376	-2.873	1.900	1.00	0.00
ATOM	46	C47	LP3	2	-5.436	-2.707	0.350	1.00	0.00
ATOM	47	C54	LP3	2	-5.868	-4.819	8.327	1.00	0.00
ATOM	48	C26	LP3	2	-7.246	-9.604	6.559	1.00	0.00
ATOM	49	C30	LP3	2	-4.808	-12.096	4.775	1.00	0.00
ATOM	50	C31	LP3	2	-5.378	-13.501	4.908	1.00	0.00
ATOM	51	C37	LP3	2	-8.618	-9.433	0.170	1.00	0.00
ATOM	52	C41	LP3	2	-5.734	-8.001	-1.469	1.00	0.00
ATOM	53	C42	LP3	2	-6.256	-7.257	-2.692	1.00	0.00
ATOM	54	C48	LP3	2	-3.732	-2.249	2.563	1.00	0.00
ATOM	55	C49	LP3	2	-3.602	-0.747	2.920	1.00	0.00
ATOM	56	C56	LP3	2	-3.410	-3.314	8.695	1.00	0.00
ATOM	57	C55	LP3	2	-3.355	-4.757	8.116	1.00	0.00
ATOM	58	C60	LP3	2	-5.597	-7.098	8.917	1.00	0.00
ATOM	59	C2R	LP3	2	-0.218	-4.839	4.688	1.00	0.00
ATOM	60	O7R	LP3	2	-1.454	-4.115	4.899	1.00	0.00
ATOM	61	HAA	LP3	2	-1.128	-3.180	4.653	1.00	0.00
ATOM	62	C1R	LP3	2	-0.167	-5.910	3.523	1.00	0.00
ATOM	63	O6R	LP3	2	0.369	-5.289	2.433	1.00	0.00
ATOM	64	C4R	LP3	2	0.323	-3.912	2.715	1.00	0.00
ATOM	65	C3R	LP3	2	0.698	-3.803	4.176	1.00	0.00
ATOM	66	C5R	LP3	2	1.283	-3.123	1.870	1.00	0.00
ATOM	67	P	LP3	2	1.510	-1.815	5.618	1.00	0.00
ATOM	68	O2P	LP3	2	0.363	-2.518	4.811	1.00	0.00
ATOM	69	O4	LP3	2	2.807	-2.292	5.036	1.00	0.00
ATOM	70	O5	LP3	2	1.136	-0.364	5.662	1.00	0.00

ATOM	71	O3	LP3	2	1.351	-2.409	7.099	1.00	0.00
ATOM	72	C2P	LP3	2	1.008	-1.422	8.050	1.00	0.00
ATOM	73	C3P	LP3	2	2.207	-1.082	8.950	1.00	0.00
ATOM	74	C1P	LP3	2	-0.056	-1.820	9.052	1.00	0.00
ATOM	75	N59	LP3	2	-1.293	-2.066	8.598	1.00	0.00
ATOM	76	HAC	LP3	2	-1.471	-1.851	7.651	1.00	0.00
ATOM	77	C57	LP3	2	-2.043	-2.979	9.267	1.00	0.00
ATOM	78	O58	LP3	2	-1.783	-3.402	10.429	1.00	0.00
ATOM	79	C5B	LP3	2	-2.488	-10.021	1.262	1.00	0.00
ATOM	80	C5M	LP3	2	-3.022	-11.331	0.657	1.00	0.00
ATOM	81	C6B	LP3	2	-1.115	-9.793	1.233	1.00	0.00
ATOM	82	C6M	LP3	2	-0.099	-10.771	0.669	1.00	0.00
ATOM	83	C4B	LP3	2	-3.358	-9.072	1.760	1.00	0.00
ATOM	84	H4B	LP3	2	-4.384	-9.299	1.858	1.00	0.00
ATOM	85	C7B	LP3	2	-0.713	-8.590	1.890	1.00	0.00
ATOM	86	H7B	LP3	2	0.412	-8.469	1.964	1.00	0.00
ATOM	87	N3B	LP3	2	-3.544	-7.032	3.157	1.00	0.00
ATOM	88	C9B	LP3	2	-2.987	-7.940	2.381	1.00	0.00
ATOM	89	N1B	LP3	2	-1.406	-6.612	3.185	1.00	0.00
ATOM	90	C8B	LP3	2	-1.608	-7.645	2.430	1.00	0.00
ATOM	91	C2B	LP3	2	-2.605	-6.197	3.623	1.00	0.00
ATOM	92	H2B	LP3	2	-2.787	-5.341	4.224	1.00	0.00
ATOM	93	C5	LP3	2	-6.482	-10.114	2.581	1.00	0.00
ATOM	94	C35	LP3	2	-7.133	-11.460	2.257	1.00	0.00
ATOM	95	C15	LP3	2	-4.867	-4.013	5.135	1.00	0.00
ATOM	96	C53	LP3	2	-4.834	-2.609	5.733	1.00	0.00
ATOM	97	FE	LP3	2	-5.448	-7.067	3.698	1.00	0.00
ATOM	98	N21	LP3	2	-5.476	-8.705	4.369	1.00	0.00
ATOM	99	N22	LP3	2	-6.049	-7.732	1.946	1.00	0.00
ATOM	100	N23	LP3	2	-5.386	-5.278	3.025	1.00	0.00
ATOM	101	N24	LP3	2	-5.168	-6.333	5.368	1.00	0.00
ATOM	102	C1	LP3	2	-5.017	-8.785	5.782	1.00	0.00
ATOM	103	C2	LP3	2	-5.828	-10.057	6.192	1.00	0.00
ATOM	104	C3	LP3	2	-5.862	-11.011	4.955	1.00	0.00
ATOM	105	C4	LP3	2	-5.930	-9.955	3.879	1.00	0.00
ATOM	106	C6	LP3	2	-6.533	-9.044	1.647	1.00	0.00
ATOM	107	C7	LP3	2	-7.087	-9.198	0.241	1.00	0.00
ATOM	108	C8	LP3	2	-6.807	-7.829	-0.395	1.00	0.00
ATOM	109	C9	LP3	2	-6.333	-7.006	0.797	1.00	0.00
ATOM	110	C16	LP3	2	-4.880	-5.154	5.997	1.00	0.00
ATOM	111	C17	LP3	2	-4.661	-5.352	7.542	1.00	0.00
ATOM	112	C18	LP3	2	-4.650	-6.869	7.737	1.00	0.00
ATOM	113	C19	LP3	2	-5.382	-7.380	6.428	1.00	0.00
ATOM	114	C11	LP3	2	-5.683	-4.777	1.720	1.00	0.00
ATOM	115	C12	LP3	2	-5.904	-3.267	1.664	1.00	0.00
ATOM	116	C13	LP3	2	-5.114	-2.829	2.937	1.00	0.00
ATOM	117	C14	LP3	2	-5.128	-4.109	3.736	1.00	0.00
ATOM	118	C10	LP3	2	-6.142	-5.598	0.681	1.00	0.00
ATOM	119	H10	LP3	2	-6.444	-5.088	-0.175	1.00	0.00
ATOM	120	N	LP3	2	5.555	8.039	4.655	1.00	0.00
ATOM	121	H	LP3	2	5.029	8.793	4.929	1.00	0.00
ATOM	122	CA	LP3	2	5.166	6.706	5.081	1.00	0.00
ATOM	123	CB	LP3	2	5.341	6.611	6.566	1.00	0.00
ATOM	124	CG	LP3	2	5.510	5.093	6.860	1.00	0.00
ATOM	125	CD	LP3	2	4.248	4.292	7.226	1.00	0.00
ATOM	126	CE	LP3	2	4.414	2.799	7.151	1.00	0.00
ATOM	127	C	LP3	2	3.708	6.360	4.626	1.00	0.00
ATOM	128	O	LP3	2	2.809	7.043	5.127	1.00	0.00
ATOM	129	OLB	LP3	2	2.609	-3.707	1.384	1.00	0.00
ATOM	130	C1N	LP3	2	-7.015	-6.361	3.927	1.00	0.00
ATOM	131	N1C	LP3	2	-8.006	-5.869	4.051	1.00	0.00
ATOM	132	CZ	LP3	2	1.910	-0.826	1.139	1.00	0.00
ATOM	133	CY	LP3	2	3.022	-0.384	2.082	1.00	0.00
ATOM	134	CX	LP3	2	2.409	0.580	3.073	1.00	0.00
ATOM	135	CT1	LP3	2	3.429	1.247	4.004	1.00	0.00
ATOM	136	CT2	LP3	2	3.403	1.356	5.360	1.00	0.00
ATOM	137	NT1	LP3	2	4.317	2.234	5.725	1.00	0.00
ATOM	138	NT2	LP3	2	5.005	2.621	4.685	1.00	0.00
ATOM	139	NT3	LP3	2	4.415	2.040	3.575	1.00	0.00
ATOM	140	NZ2	LP3	2	0.985	-1.839	1.785	1.00	0.00
ATOM	141	HZ2	LP3	2	0.209	-1.440	2.366	1.00	0.00
ATOM	142	N	PRO	3	3.650	5.749	3.461	1.00	0.00
ATOM	143	CA	PRO	3	2.297	5.348	2.911	1.00	0.00

ATOM	144	CB	PRO	3	2.624	4.491	1.689	1.00	0.00
ATOM	145	CG	PRO	3	3.815	5.211	1.206	1.00	0.00
ATOM	146	CD	PRO	3	4.649	5.466	2.477	1.00	0.00
ATOM	147	C	PRO	3	1.226	4.655	3.733	1.00	0.00
ATOM	148	O	PRO	3	1.325	3.507	4.179	1.00	0.00
ATOM	149	N	GLU	4	0.196	5.412	4.112	1.00	0.00
ATOM	150	H	GLU	4	0.126	6.369	3.790	1.00	0.00
ATOM	151	CA	GLU	4	-0.970	4.821	4.857	1.00	0.00
ATOM	152	CB	GLU	4	-1.145	5.608	6.125	1.00	0.00
ATOM	153	CG	GLU	4	0.089	5.579	7.034	1.00	0.00
ATOM	154	CD	GLU	4	-0.053	6.629	8.137	1.00	0.00
ATOM	155	OE1	GLU	4	0.544	7.730	7.851	1.00	0.00
ATOM	156	OE2	GLU	4	-0.405	6.296	9.271	1.00	0.00
ATOM	157	C	GLU	4	-2.275	4.902	4.009	1.00	0.00
ATOM	158	O	GLU	4	-2.807	5.964	3.764	1.00	0.00
ATOM	159	N	ALA	5	-2.689	3.784	3.449	1.00	0.00
ATOM	160	H	ALA	5	-2.098	2.978	3.391	1.00	0.00
ATOM	161	CA	ALA	5	-3.984	3.710	2.687	1.00	0.00
ATOM	162	CB	ALA	5	-3.612	3.749	1.193	1.00	0.00
ATOM	163	C	ALA	5	-5.006	2.587	3.007	1.00	0.00
ATOM	164	O	ALA	5	-5.185	1.680	2.164	1.00	0.00
ATOM	165	N	PRO	6	-5.793	2.823	4.119	1.00	0.00
ATOM	166	CA	PRO	6	-6.665	1.865	4.847	1.00	0.00
ATOM	167	CB	PRO	6	-7.707	2.675	5.490	1.00	0.00
ATOM	168	CG	PRO	6	-7.158	4.049	5.671	1.00	0.00
ATOM	169	CD	PRO	6	-6.186	4.162	4.540	1.00	0.00
ATOM	170	C	PRO	6	-7.458	0.790	3.985	1.00	0.00
ATOM	171	O	PRO	6	-7.374	-0.375	4.251	1.00	0.00
ATOM	172	N	GLY	7	-8.074	1.194	2.884	1.00	0.00
ATOM	173	H	GLY	7	-8.175	2.174	2.644	1.00	0.00
ATOM	174	CA	GLY	7	-9.025	0.316	2.078	1.00	0.00
ATOM	175	C	GLY	7	-10.249	-0.156	2.863	1.00	0.00
ATOM	176	O	GLY	7	-10.127	-1.081	3.663	1.00	0.00
ATOM	177	N	GLU	8	-11.335	0.622	2.819	1.00	0.00
ATOM	178	H	GLU	8	-11.469	1.076	1.916	1.00	0.00
ATOM	179	CA	GLU	8	-12.517	0.371	3.567	1.00	0.00
ATOM	180	CB	GLU	8	-12.675	1.493	4.612	1.00	0.00
ATOM	181	CG	GLU	8	-11.955	1.192	5.918	1.00	0.00
ATOM	182	CD	GLU	8	-12.319	2.054	7.085	1.00	0.00
ATOM	183	OE1	GLU	8	-12.942	1.565	8.030	1.00	0.00
ATOM	184	OE2	GLU	8	-12.020	3.282	6.965	1.00	0.00
ATOM	185	C	GLU	8	-13.815	0.160	2.827	1.00	0.00
ATOM	186	O	GLU	8	-14.660	-0.556	3.393	1.00	0.00
ATOM	187	N	ASP	9	-13.894	0.968	1.762	1.00	0.00
ATOM	188	H	ASP	9	-13.145	1.527	1.476	1.00	0.00
ATOM	189	CA	ASP	9	-15.077	0.983	0.919	1.00	0.00
ATOM	190	CB	ASP	9	-15.661	2.350	1.142	1.00	0.00
ATOM	191	CG	ASP	9	-17.094	2.630	0.900	1.00	0.00
ATOM	192	OD1	ASP	9	-17.518	3.380	-0.049	1.00	0.00
ATOM	193	OD2	ASP	9	-17.848	2.245	1.813	1.00	0.00
ATOM	194	C	ASP	9	-14.939	0.547	-0.526	1.00	0.00
ATOM	195	O	ASP	9	-15.003	-0.666	-0.835	1.00	0.00
ATOM	196	N	ALA	10	-14.689	1.562	-1.405	1.00	0.00
ATOM	197	H	ALA	10	-14.778	2.480	-1.185	1.00	0.00
ATOM	198	CA	ALA	10	-14.592	1.371	-2.865	1.00	0.00
ATOM	199	CB	ALA	10	-15.106	2.557	-3.588	1.00	0.00
ATOM	200	C	ALA	10	-13.205	0.899	-3.299	1.00	0.00
ATOM	201	O	ALA	10	-12.233	1.601	-3.522	1.00	0.00
ATOM	202	N	SER	11	-13.263	-0.374	-3.628	1.00	0.00
ATOM	203	H	SER	11	-14.073	-0.990	-3.449	1.00	0.00
ATOM	204	CA	SER	11	-12.065	-1.091	-4.084	1.00	0.00
ATOM	205	CB	SER	11	-12.237	-2.585	-4.110	1.00	0.00
ATOM	206	OG	SER	11	-12.923	-3.020	-2.930	1.00	0.00
ATOM	207	HG	SER	11	-13.955	-3.080	-3.134	1.00	0.00
ATOM	208	C	SER	11	-11.304	-0.682	-5.392	1.00	0.00
ATOM	209	O	SER	11	-10.055	-0.739	-5.306	1.00	0.00
ATOM	210	N	PRO	12	-11.957	-0.204	-6.479	1.00	0.00
ATOM	211	CA	PRO	12	-11.265	0.408	-7.603	1.00	0.00
ATOM	212	CB	PRO	12	-12.311	0.716	-8.574	1.00	0.00
ATOM	213	CG	PRO	12	-13.206	-0.451	-8.413	1.00	0.00
ATOM	214	CD	PRO	12	-13.273	-0.680	-6.922	1.00	0.00
ATOM	215	C	PRO	12	-10.473	1.648	-7.131	1.00	0.00
ATOM	216	O	PRO	12	-9.263	1.878	-7.421	1.00	0.00

ATOM	217	N	GLU	13	-11.191	2.495	-6.373	1.00	0.00
ATOM	218	H	GLU	13	-12.129	2.417	-6.303	1.00	0.00
ATOM	219	CA	GLU	13	-10.561	3.650	-5.731	1.00	0.00
ATOM	220	CB	GLU	13	-11.509	4.521	-4.965	1.00	0.00
ATOM	221	CG	GLU	13	-11.184	5.981	-4.913	1.00	0.00
ATOM	222	CD	GLU	13	-11.913	6.721	-3.771	1.00	0.00
ATOM	223	OE1	GLU	13	-11.970	6.206	-2.651	1.00	0.00
ATOM	224	OE2	GLU	13	-12.551	7.732	-4.163	1.00	0.00
ATOM	225	C	GLU	13	-9.311	3.420	-4.886	1.00	0.00
ATOM	226	O	GLU	13	-8.176	3.441	-5.399	1.00	0.00
ATOM	227	N	GLU	14	-9.471	2.835	-3.682	1.00	0.00
ATOM	228	H	GLU	14	-10.380	2.460	-3.354	1.00	0.00
ATOM	229	CA	GLU	14	-8.396	2.624	-2.623	1.00	0.00
ATOM	230	CB	GLU	14	-8.972	1.982	-1.347	1.00	0.00
ATOM	231	CG	GLU	14	-10.096	2.944	-0.904	1.00	0.00
ATOM	232	CD	GLU	14	-11.207	2.201	-0.110	1.00	0.00
ATOM	233	OE1	GLU	14	-11.821	2.957	0.707	1.00	0.00
ATOM	234	OE2	GLU	14	-11.530	0.993	-0.341	1.00	0.00
ATOM	235	C	GLU	14	-7.170	1.825	-3.109	1.00	0.00
ATOM	236	O	GLU	14	-5.993	2.234	-2.847	1.00	0.00
ATOM	237	N	LEU	15	-7.359	0.892	-4.015	1.00	0.00
ATOM	238	H	LEU	15	-8.320	0.641	-4.354	1.00	0.00
ATOM	239	CA	LEU	15	-6.184	0.134	-4.547	1.00	0.00
ATOM	240	CB	LEU	15	-6.794	-1.103	-5.221	1.00	0.00
ATOM	241	CG	LEU	15	-7.072	-2.321	-4.415	1.00	0.00
ATOM	242	CD1	LEU	15	-8.116	-3.215	-4.953	1.00	0.00
ATOM	243	CD2	LEU	15	-5.781	-3.141	-4.160	1.00	0.00
ATOM	244	C	LEU	15	-5.169	0.765	-5.460	1.00	0.00
ATOM	245	O	LEU	15	-4.001	0.352	-5.405	1.00	0.00
ATOM	246	N	ASN	16	-5.612	1.945	-5.987	1.00	0.00
ATOM	247	H	ASN	16	-6.549	2.324	-6.008	1.00	0.00
ATOM	248	CA	ASN	16	-4.660	2.733	-6.836	1.00	0.00
ATOM	249	CB	ASN	16	-5.440	3.824	-7.580	1.00	0.00
ATOM	250	CG	ASN	16	-6.094	3.306	-8.896	1.00	0.00
ATOM	251	OD1	ASN	16	-5.431	2.691	-9.769	1.00	0.00
ATOM	252	ND2	ASN	16	-7.304	3.755	-9.197	1.00	0.00
ATOM	253	1HD2	ASN	16	-7.699	4.617	-8.793	1.00	0.00
ATOM	254	2HD2	ASN	16	-7.968	3.091	-9.513	1.00	0.00
ATOM	255	C	ASN	16	-3.481	3.368	-6.088	1.00	0.00
ATOM	256	O	ASN	16	-2.312	3.356	-6.515	1.00	0.00
ATOM	257	N	ARG	17	-3.864	4.076	-4.991	1.00	0.00
ATOM	258	H	ARG	17	-4.832	4.411	-4.792	1.00	0.00
ATOM	259	CA	ARG	17	-2.897	4.643	-4.027	1.00	0.00
ATOM	260	CB	ARG	17	-3.537	5.503	-2.894	1.00	0.00
ATOM	261	CG	ARG	17	-2.527	6.439	-2.294	1.00	0.00
ATOM	262	CD	ARG	17	-3.318	7.433	-1.383	1.00	0.00
ATOM	263	NE	ARG	17	-4.317	8.214	-2.241	1.00	0.00
ATOM	264	HE	ARG	17	-4.974	7.577	-2.697	1.00	0.00
ATOM	265	CZ	ARG	17	-4.566	9.499	-2.294	1.00	0.00
ATOM	266	NH1	ARG	17	-3.831	10.228	-1.462	1.00	0.00
ATOM	267	1HH1	ARG	17	-3.081	9.852	-0.895	1.00	0.00
ATOM	268	2HH1	ARG	17	-4.028	11.202	-1.329	1.00	0.00
ATOM	269	NH2	ARG	17	-5.535	9.992	-2.992	1.00	0.00
ATOM	270	1HH2	ARG	17	-6.099	9.361	-3.604	1.00	0.00
ATOM	271	2HH2	ARG	17	-5.812	10.945	-2.925	1.00	0.00
ATOM	272	C	ARG	17	-1.993	3.562	-3.365	1.00	0.00
ATOM	273	O	ARG	17	-0.854	3.616	-3.618	1.00	0.00
ATOM	274	N	TYR	18	-2.598	2.413	-2.937	1.00	0.00
ATOM	275	H	TYR	18	-3.594	2.339	-2.889	1.00	0.00
ATOM	276	CA	TYR	18	-1.772	1.225	-2.551	1.00	0.00
ATOM	277	CB	TYR	18	-2.789	0.149	-2.433	1.00	0.00
ATOM	278	CG	TYR	18	-2.254	-1.243	-2.078	1.00	0.00
ATOM	279	CD1	TYR	18	-2.631	-2.166	-3.041	1.00	0.00
ATOM	280	HD1	TYR	18	-2.986	-1.773	-4.034	1.00	0.00
ATOM	281	CD2	TYR	18	-1.918	-1.590	-0.774	1.00	0.00
ATOM	282	HD2	TYR	18	-1.602	-0.872	-0.053	1.00	0.00
ATOM	283	CE1	TYR	18	-2.702	-3.525	-2.748	1.00	0.00
ATOM	284	HE1	TYR	18	-2.958	-4.244	-3.493	1.00	0.00
ATOM	285	CE2	TYR	18	-1.957	-2.935	-0.512	1.00	0.00
ATOM	286	HE2	TYR	18	-1.761	-3.138	0.465	1.00	0.00
ATOM	287	CZ	TYR	18	-2.359	-3.874	-1.432	1.00	0.00
ATOM	288	OH	TYR	18	-2.476	-5.175	-1.102	1.00	0.00
ATOM	289	HH	TYR	18	-2.980	-5.693	-1.844	1.00	0.00

ATOM	290	C	TYR	18	-0.717	0.833	-3.610	1.00	0.00
ATOM	291	O	TYR	18	0.500	0.881	-3.415	1.00	0.00
ATOM	292	N	TYR	19	-1.252	0.502	-4.796	1.00	0.00
ATOM	293	H	TYR	19	-2.257	0.461	-4.983	1.00	0.00
ATOM	294	CA	TYR	19	-0.487	0.115	-5.984	1.00	0.00
ATOM	295	CB	TYR	19	-1.347	-0.296	-7.114	1.00	0.00
ATOM	296	CG	TYR	19	-1.816	-1.717	-6.943	1.00	0.00
ATOM	297	CD1	TYR	19	-1.181	-2.668	-6.281	1.00	0.00
ATOM	298	HD1	TYR	19	-0.213	-2.509	-5.828	1.00	0.00
ATOM	299	CD2	TYR	19	-3.026	-2.087	-7.592	1.00	0.00
ATOM	300	HD2	TYR	19	-3.679	-1.330	-7.909	1.00	0.00
ATOM	301	CE1	TYR	19	-1.697	-3.940	-6.087	1.00	0.00
ATOM	302	HE1	TYR	19	-1.165	-4.626	-5.393	1.00	0.00
ATOM	303	CE2	TYR	19	-3.515	-3.381	-7.477	1.00	0.00
ATOM	304	HE2	TYR	19	-4.418	-3.597	-8.057	1.00	0.00
ATOM	305	CZ	TYR	19	-2.888	-4.303	-6.654	1.00	0.00
ATOM	306	OH	TYR	19	-3.311	-5.540	-6.377	1.00	0.00
ATOM	307	HH	TYR	19	-2.690	-5.990	-5.768	1.00	0.00
ATOM	308	C	TYR	19	0.587	1.111	-6.368	1.00	0.00
ATOM	309	O	TYR	19	1.770	0.698	-6.409	1.00	0.00
ATOM	310	N	ALA	20	0.243	2.378	-6.422	1.00	0.00
ATOM	311	H	ALA	20	-0.718	2.637	-6.219	1.00	0.00
ATOM	312	CA	ALA	20	1.263	3.428	-6.772	1.00	0.00
ATOM	313	CB	ALA	20	0.408	4.682	-6.855	1.00	0.00
ATOM	314	C	ALA	20	2.347	3.474	-5.755	1.00	0.00
ATOM	315	O	ALA	20	3.520	3.332	-6.209	1.00	0.00
ATOM	316	N	SER	21	2.029	3.574	-4.491	1.00	0.00
ATOM	317	H	SER	21	1.079	3.728	-4.203	1.00	0.00
ATOM	318	CA	SER	21	2.988	3.470	-3.408	1.00	0.00
ATOM	319	CB	SER	21	2.260	3.403	-2.110	1.00	0.00
ATOM	320	OG	SER	21	1.631	4.647	-1.930	1.00	0.00
ATOM	321	HG	SER	21	0.982	4.618	-1.153	1.00	0.00
ATOM	322	C	SER	21	3.944	2.293	-3.434	1.00	0.00
ATOM	323	O	SER	21	5.178	2.460	-3.187	1.00	0.00
ATOM	324	N	LEU	22	3.433	1.106	-3.699	1.00	0.00
ATOM	325	H	LEU	22	2.379	1.017	-3.683	1.00	0.00
ATOM	326	CA	LEU	22	4.209	-0.118	-4.125	1.00	0.00
ATOM	327	CB	LEU	22	3.176	-1.220	-4.406	1.00	0.00
ATOM	328	CG	LEU	22	2.515	-1.892	-3.175	1.00	0.00
ATOM	329	CD1	LEU	22	1.313	-2.715	-3.588	1.00	0.00
ATOM	330	CD2	LEU	22	3.504	-2.761	-2.377	1.00	0.00
ATOM	331	C	LEU	22	5.173	0.189	-5.297	1.00	0.00
ATOM	332	O	LEU	22	6.369	0.413	-5.060	1.00	0.00
ATOM	333	N	ARG	23	4.615	0.424	-6.472	1.00	0.00
ATOM	334	H	ARG	23	3.626	0.298	-6.487	1.00	0.00
ATOM	335	CA	ARG	23	5.338	0.685	-7.705	1.00	0.00
ATOM	336	CB	ARG	23	4.357	1.078	-8.837	1.00	0.00
ATOM	337	CG	ARG	23	3.499	-0.091	-9.290	1.00	0.00
ATOM	338	CD	ARG	23	2.276	0.411	-10.171	1.00	0.00
ATOM	339	NE	ARG	23	1.711	-0.793	-10.824	1.00	0.00
ATOM	340	HE	ARG	23	1.077	-1.360	-10.309	1.00	0.00
ATOM	341	CZ	ARG	23	2.141	-1.212	-12.013	1.00	0.00
ATOM	342	NH1	ARG	23	3.110	-0.598	-12.713	1.00	0.00
ATOM	343	1HH1	ARG	23	3.655	0.185	-12.360	1.00	0.00
ATOM	344	2HH1	ARG	23	3.374	-0.903	-13.631	1.00	0.00
ATOM	345	NH2	ARG	23	1.686	-2.372	-12.473	1.00	0.00
ATOM	346	1HH2	ARG	23	1.120	-2.882	-11.839	1.00	0.00
ATOM	347	2HH2	ARG	23	1.883	-2.605	-13.445	1.00	0.00
ATOM	348	C	ARG	23	6.390	1.809	-7.576	1.00	0.00
ATOM	349	O	ARG	23	7.501	1.619	-8.151	1.00	0.00
ATOM	350	N	HIS	24	6.083	2.819	-6.825	1.00	0.00
ATOM	351	H	HIS	24	5.141	2.795	-6.430	1.00	0.00
ATOM	352	CA	HIS	24	6.797	4.095	-6.673	1.00	0.00
ATOM	353	CB	HIS	24	5.835	5.312	-6.855	1.00	0.00
ATOM	354	CG	HIS	24	6.692	6.656	-6.744	1.00	0.00
ATOM	355	ND1	HIS	24	7.333	7.278	-7.784	1.00	0.00
ATOM	356	CD2	HIS	24	6.981	7.349	-5.645	1.00	0.00
ATOM	357	HD2	HIS	24	6.405	7.286	-4.688	1.00	0.00
ATOM	358	CE1	HIS	24	7.981	8.330	-7.241	1.00	0.00
ATOM	359	HE1	HIS	24	8.696	9.004	-7.764	1.00	0.00
ATOM	360	NE2	HIS	24	7.808	8.361	-5.929	1.00	0.00
ATOM	361	HE2	HIS	24	8.481	8.735	-5.305	1.00	0.00
ATOM	362	C	HIS	24	7.780	4.084	-5.472	1.00	0.00

ATOM	363	O	HIS	24	8.974	3.823	-5.616	1.00	0.00
ATOM	364	N	TYR	25	7.177	4.184	-4.253	1.00	0.00
ATOM	365	H	TYR	25	6.296	3.801	-4.110	1.00	0.00
ATOM	366	CA	TYR	25	7.993	4.330	-3.014	1.00	0.00
ATOM	367	CB	TYR	25	7.113	4.690	-1.832	1.00	0.00
ATOM	368	CG	TYR	25	6.656	6.132	-1.921	1.00	0.00
ATOM	369	CD1	TYR	25	5.333	6.352	-2.001	1.00	0.00
ATOM	370	HD1	TYR	25	4.685	5.469	-2.169	1.00	0.00
ATOM	371	CD2	TYR	25	7.552	7.168	-1.999	1.00	0.00
ATOM	372	HD2	TYR	25	8.604	7.018	-1.718	1.00	0.00
ATOM	373	CE1	TYR	25	4.861	7.626	-2.316	1.00	0.00
ATOM	374	HE1	TYR	25	3.817	7.710	-2.475	1.00	0.00
ATOM	375	CE2	TYR	25	7.091	8.460	-2.331	1.00	0.00
ATOM	376	HE2	TYR	25	7.781	9.344	-2.396	1.00	0.00
ATOM	377	CZ	TYR	25	5.699	8.728	-2.494	1.00	0.00
ATOM	378	OH	TYR	25	5.319	9.944	-2.749	1.00	0.00
ATOM	379	HH	TYR	25	6.084	10.478	-3.037	1.00	0.00
ATOM	380	C	TYR	25	8.761	3.071	-2.603	1.00	0.00
ATOM	381	O	TYR	25	9.989	3.106	-2.696	1.00	0.00
ATOM	382	N	LEU	26	7.999	1.967	-2.320	1.00	0.00
ATOM	383	H	LEU	26	7.057	2.026	-1.977	1.00	0.00
ATOM	384	CA	LEU	26	8.592	0.658	-1.983	1.00	0.00
ATOM	385	CB	LEU	26	7.507	-0.329	-1.567	1.00	0.00
ATOM	386	CG	LEU	26	6.957	0.082	-0.188	1.00	0.00
ATOM	387	CD1	LEU	26	5.655	-0.705	-0.023	1.00	0.00
ATOM	388	CD2	LEU	26	7.807	-0.301	0.997	1.00	0.00
ATOM	389	C	LEU	26	9.467	0.019	-3.112	1.00	0.00
ATOM	390	O	LEU	26	10.399	-0.654	-2.695	1.00	0.00
ATOM	391	N	ASN	27	8.992	-0.094	-4.345	1.00	0.00
ATOM	392	H	ASN	27	8.023	-0.068	-4.522	1.00	0.00
ATOM	393	CA	ASN	27	9.769	-0.638	-5.458	1.00	0.00
ATOM	394	CB	ASN	27	8.833	-0.860	-6.653	1.00	0.00
ATOM	395	CG	ASN	27	7.907	-2.081	-6.426	1.00	0.00
ATOM	396	OD1	ASN	27	7.083	-2.134	-5.511	1.00	0.00
ATOM	397	ND2	ASN	27	7.908	-2.948	-7.450	1.00	0.00
ATOM	398	1HD2	ASN	27	8.615	-2.688	-8.239	1.00	0.00
ATOM	399	2HD2	ASN	27	7.093	-3.546	-7.740	1.00	0.00
ATOM	400	C	ASN	27	11.122	0.141	-5.824	1.00	0.00
ATOM	401	O	ASN	27	12.121	-0.522	-6.141	1.00	0.00
ATOM	402	N	LEU	28	10.928	1.422	-6.017	1.00	0.00
ATOM	403	H	LEU	28	9.962	1.721	-6.128	1.00	0.00
ATOM	404	CA	LEU	28	12.084	2.275	-6.401	1.00	0.00
ATOM	405	CB	LEU	28	11.741	3.178	-7.577	1.00	0.00
ATOM	406	CG	LEU	28	11.899	2.610	-8.946	1.00	0.00
ATOM	407	CD1	LEU	28	10.936	1.395	-9.210	1.00	0.00
ATOM	408	CD2	LEU	28	11.751	3.716	-10.060	1.00	0.00
ATOM	409	C	LEU	28	12.674	3.171	-5.370	1.00	0.00
ATOM	410	O	LEU	28	13.831	2.922	-5.007	1.00	0.00
ATOM	411	N	VAL	29	11.897	4.218	-4.943	1.00	0.00
ATOM	412	H	VAL	29	11.035	4.482	-5.408	1.00	0.00
ATOM	413	CA	VAL	29	12.496	5.278	-4.097	1.00	0.00
ATOM	414	CB	VAL	29	11.400	6.356	-3.929	1.00	0.00
ATOM	415	CG1	VAL	29	12.002	7.509	-3.035	1.00	0.00
ATOM	416	CG2	VAL	29	10.976	6.903	-5.251	1.00	0.00
ATOM	417	C	VAL	29	13.121	4.906	-2.702	1.00	0.00
ATOM	418	O	VAL	29	14.244	5.320	-2.432	1.00	0.00
ATOM	419	N	THR	30	12.246	4.441	-1.771	1.00	0.00
ATOM	420	H	THR	30	11.286	4.204	-2.083	1.00	0.00
ATOM	421	CA	THR	30	12.442	4.078	-0.312	1.00	0.00
ATOM	422	CB	THR	30	11.679	4.851	0.807	1.00	0.00
ATOM	423	OG1	THR	30	10.682	5.572	0.106	1.00	0.00
ATOM	424	HG1	THR	30	9.932	5.701	0.867	1.00	0.00
ATOM	425	CG2	THR	30	12.657	5.638	1.727	1.00	0.00
ATOM	426	C	THR	30	11.986	2.605	0.009	1.00	0.00
ATOM	427	O	THR	30	10.919	2.247	0.421	1.00	0.00
ATOM	428	N	ARG	31	12.971	1.778	-0.058	1.00	0.00
ATOM	429	H	ARG	31	13.901	2.164	-0.078	1.00	0.00
ATOM	430	CA	ARG	31	12.871	0.345	-0.008	1.00	0.00
ATOM	431	CB	ARG	31	14.103	-0.207	-0.784	1.00	0.00
ATOM	432	CG	ARG	31	13.944	-0.188	-2.301	1.00	0.00
ATOM	433	CD	ARG	31	15.216	-0.732	-3.008	1.00	0.00
ATOM	434	NE	ARG	31	14.933	-0.722	-4.444	1.00	0.00
ATOM	435	HE	ARG	31	14.228	-1.399	-4.779	1.00	0.00

ATOM	436	CZ	ARG	31	15.574	-0.128	-5.423	1.00	0.00
ATOM	437	NH1	ARG	31	16.654	0.593	-5.206	1.00	0.00
ATOM	438	1HH1	ARG	31	16.956	0.788	-4.201	1.00	0.00
ATOM	439	2HH1	ARG	31	17.334	0.795	-6.030	1.00	0.00
ATOM	440	NH2	ARG	31	15.071	-0.110	-6.647	1.00	0.00
ATOM	441	1HH2	ARG	31	14.168	-0.529	-6.952	1.00	0.00
ATOM	442	2HH2	ARG	31	15.589	0.272	-7.379	1.00	0.00
ATOM	443	C	ARG	31	12.804	-0.226	1.479	1.00	0.00
ATOM	444	O	ARG	31	13.787	-0.053	2.245	1.00	0.00
ATOM	445	N	GLN	32	11.695	-0.854	1.799	1.00	0.00
ATOM	446	H	GLN	32	11.003	-0.831	1.096	1.00	0.00
ATOM	447	CA	GLN	32	11.372	-1.546	3.101	1.00	0.00
ATOM	448	CB	GLN	32	11.367	-3.069	2.975	1.00	0.00
ATOM	449	CG	GLN	32	10.620	-3.595	4.213	1.00	0.00
ATOM	450	CD	GLN	32	9.097	-3.512	3.914	1.00	0.00
ATOM	451	OE1	GLN	32	8.583	-3.979	2.906	1.00	0.00
ATOM	452	NE2	GLN	32	8.390	-2.876	4.772	1.00	0.00
ATOM	453	1HE2	GLN	32	8.841	-2.710	5.614	1.00	0.00
ATOM	454	2HE2	GLN	32	7.498	-2.492	4.470	1.00	0.00
ATOM	455	C	GLN	32	12.121	-0.985	4.352	1.00	0.00
ATOM	456	O	GLN	32	13.140	-1.597	4.727	1.00	0.00
ATOM	457	N	ARG	33	11.730	0.218	4.704	1.00	0.00
ATOM	458	H	ARG	33	11.076	0.702	4.113	1.00	0.00
ATOM	459	CA	ARG	33	12.257	0.921	5.875	1.00	0.00
ATOM	460	CB	ARG	33	12.550	2.407	5.553	1.00	0.00
ATOM	461	CG	ARG	33	13.684	2.588	4.541	1.00	0.00
ATOM	462	CD	ARG	33	14.948	1.790	4.946	1.00	0.00
ATOM	463	NE	ARG	33	16.029	1.979	3.876	1.00	0.00
ATOM	464	HE	ARG	33	15.892	1.853	2.906	1.00	0.00
ATOM	465	CZ	ARG	33	17.244	2.312	4.201	1.00	0.00
ATOM	466	NH1	ARG	33	17.581	2.441	5.465	1.00	0.00
ATOM	467	1HH1	ARG	33	16.900	2.328	6.258	1.00	0.00
ATOM	468	2HH1	ARG	33	18.555	2.565	5.705	1.00	0.00
ATOM	469	NH2	ARG	33	18.274	2.391	3.287	1.00	0.00
ATOM	470	1HH2	ARG	33	18.140	2.153	2.350	1.00	0.00
ATOM	471	2HH2	ARG	33	19.211	2.753	3.544	1.00	0.00
ATOM	472	C	ARG	33	11.248	0.770	7.122	1.00	0.00
ATOM	473	O	ARG	33	11.074	1.734	7.830	1.00	0.00
ATOM	474	N	TYR	34	10.681	-0.407	7.349	1.00	0.00
ATOM	475	H	TYR	34	10.817	-1.177	6.709	1.00	0.00
ATOM	476	CA	TYR	34	9.665	-0.704	8.380	1.00	0.00
ATOM	477	CB	TYR	34	8.329	0.063	8.204	1.00	0.00
ATOM	478	CG	TYR	34	7.326	-0.353	7.095	1.00	0.00
ATOM	479	CD1	TYR	34	7.571	0.075	5.771	1.00	0.00
ATOM	480	HD1	TYR	34	8.427	0.679	5.601	1.00	0.00
ATOM	481	CD2	TYR	34	6.222	-1.112	7.406	1.00	0.00
ATOM	482	HD2	TYR	34	5.965	-1.274	8.471	1.00	0.00
ATOM	483	CE1	TYR	34	6.707	-0.282	4.736	1.00	0.00
ATOM	484	HE1	TYR	34	6.919	-0.022	3.740	1.00	0.00
ATOM	485	CE2	TYR	34	5.354	-1.521	6.385	1.00	0.00
ATOM	486	HE2	TYR	34	4.437	-1.966	6.745	1.00	0.00
ATOM	487	CZ	TYR	34	5.649	-1.163	5.039	1.00	0.00
ATOM	488	OH	TYR	34	5.084	-1.863	4.015	1.00	0.00
ATOM	489	HH	TYR	34	4.206	-2.028	4.442	1.00	0.00
ATOM	490	C	TYR	34	9.412	-2.231	8.434	1.00	0.00
ATOM	491	O1	TYR	34	9.192	-2.876	9.471	1.00	0.00
ATOM	492	O2	TYR	34	9.663	-2.839	7.407	1.00	0.00

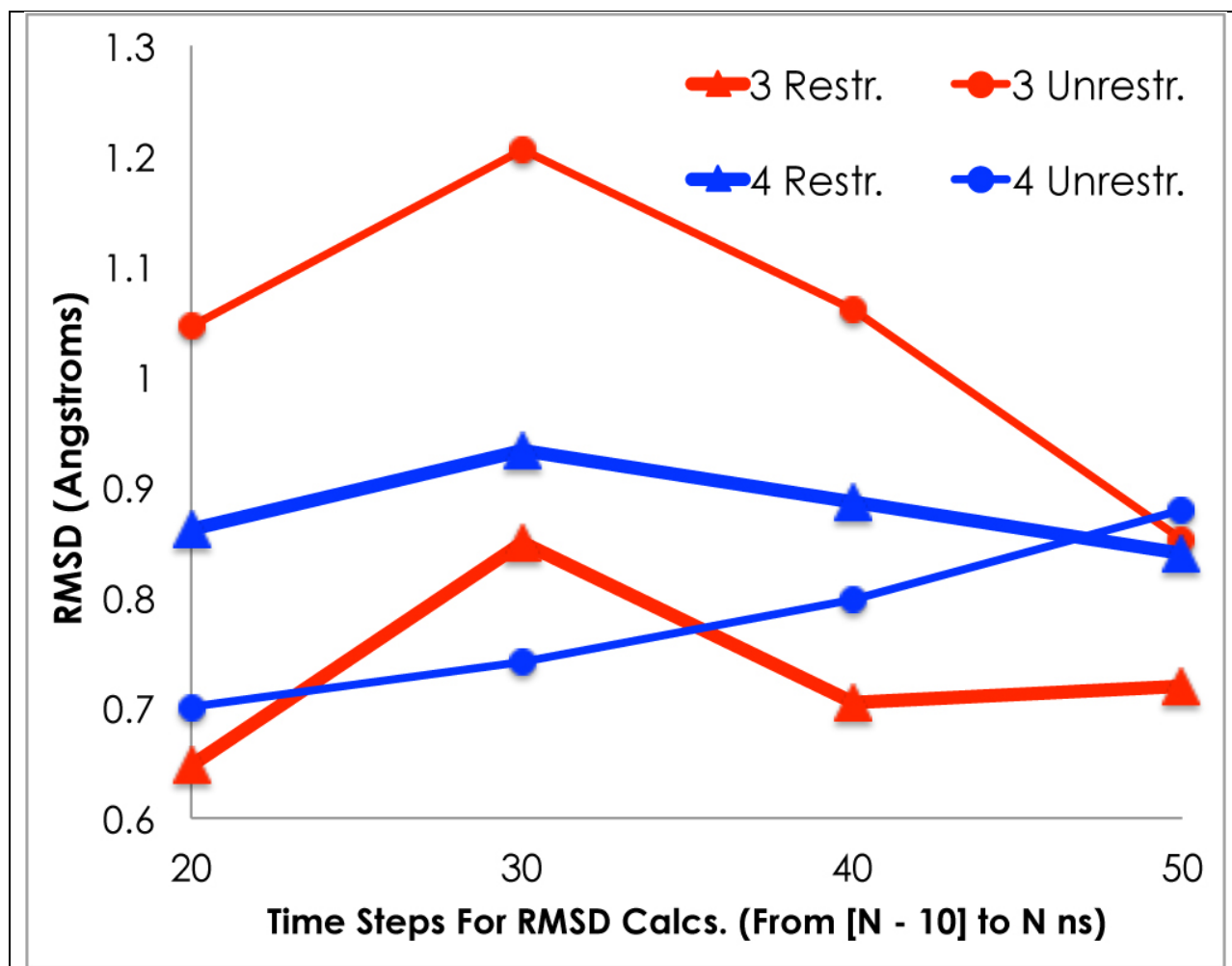


Figure S20. RMSD values for the four simulations, sampling geometries across 10 ns intervals (the 20 ns RMSD values generated from RMSD calculations of structures from 10 to 20 ns, etc.).

8. Molecular Dynamics Simulations: Experimental Details

The GROMOS96² (53a6) united-atom force field was used both as the force field set for the defined amino acids and as the basis force field for B₁₂-tether-lysine residues. All simulations were performed as NPT ensembles (X,Y,Z) under periodic boundary conditions. Simulation temperatures were kept constant at 300 K using program option v-rescale thermostat³ with 0.1 ps coupling time constants for solvent (flexible Simple Point Charge (SPC) water model + neutralizing counter-ions) and solute separately. Simulation pressures were kept constant using

program-option Parrinello-Rahman barostats of 1.0 bar with isotropic coupling (scaling of the cell vectors) and a time coupling constant of 2.0 ps.⁴ Electrostatic interactions were evaluated by the particle mesh Ewald (PME) method order 4 with a grid spacing of 0.2 nm in the X,Y,Z-directions.⁵ The real-space and neighbor-search cut-off were set to 1.0 nm, with non-bonded pair lists updated every 10 steps. MD simulations for all systems were performed with 1.0 fs timesteps for 100 ns.

Parameter generation, topology definitions, and structural data for B₁₂-[tether]-(LYS) residues are an amalgam of quantum chemical, crystallographic, and pre-existing G53a6 force field data, with the majority of the B₁₂ terms coming from two previous studies.^{6,7} The base structure and heavy atom labeling scheme for the B₁₂ topology definition are taken from the human Cbl/TCII crystal structure (PDB 2BB5)⁸ as reported in a previous study outlining the parameter generation approach.⁷ The geometries and derived charges for the B₁₂-tether structures were generated at a B3LYP^{9,10} level of theory with the 6-31G(d) basis set¹¹ using the program Gaussian09.¹² Averaged geometries for all of the B₁₂-tether-LYS structures are provided as Supplemental Material. All images were rendered with VMD.¹³

9. Tables of NMR Constraints And Distances From The Time-Averaged Simulation of 3

Table S2. Intra-residue NMR Distance Constraints and the Corresponding Simulation Distances

		NMR constraints			MD Simulation Distances For 3			
H1	H2	lower	upper					methyl ave
A12NH	A12me	1.8	3.5		3.23	2.78	3.85	3.29
A12NH	A12Ha	1.8	6		2.78	3.23	3.85	3.29
A22NH	A22Ha	1.8	4.5		2.74			
A22NH	A22me	1.8	3.5		2.43	2.27	3.44	2.71
A7NH	A7Ha	1.8	6		2.92			
A7NH	A7me	1.8	4.5		2.48	3.6	2.6	2.89
D11NH	D11Ha	1.8	3.5		2.94			
D11NH	D11Hb1	1.8	4.5		3.14			
D11NH	D11Hb2	1.8	4.5		2.79			
E10NH	E10Ha	1.8	4.5		2.87			
E15NH	E15Ha	1.8	3.5		2.87			
E15NH	E15Hg	1.8	4.5		2.72	4.01		
E15NH	E15Hb1	1.8	3.5		2.57			
E15NH	E16NH	1.8	3.5		2.51			
E16NH	E16Ha	1.8	3.5		2.83			
E16NH	E16Hg	1.8	4.5		3.46			
E16NH	E16Hb	1.8	4.5		3.44			
G9NH	G9Ha2	1.8	3.5		2.99			
G9NH	G9Ha1	1.8	3.5		2.57			
H26NH	H26Ha	1.8	3.5		2.82			
H26NH	H26Hb	1.8	4.5		2.5	2.27		
K4NH	K4Hb	1.8	6		2.74			
K4NH	K4H	1.8	6		2.36			
L17NH	L17Hb1	1.8	3.5		1.81	3.07		
L17NH	L17Hb2	1.8	3.5		1.81	3.07		
L28NH	L28Hb1	1.8	4.5		2.51	3.72		
L30NH	L30Ha	1.8	4.5		2.79			
L30NH	N29Hb	1.8	4.5		2.5	3.46		
L30NH	L30Hg	1.8	4.5		2.6			
L30NH	L30Hb	1.8	4.5		2.25	3.54		
L30NH	L30me	1.8	6		3.51	4.76	4.36	4.21
N18NH	N18Ha	1.8	3.5		2.73			
N18NH	N18Hb	1.8	4.5		2.95	3.65		
N18NH	L17Hb1	1.8	4.5		2.67	3.43		
N18NH	L17Hb2	1.8	4.5		2.67	3.43		
N18NH	L17me	1.8	6		4.85	4.86	6.11	5.27
N18NH	R19NH	1.8	3.5		3.02			
N29NH	N29Ha	1.8	3.5		2.85			
N29NH	N29Hb	1.8	3.5		2.07	2.98		
Q34NH	Q34Hb	1.8	4.5		3.18	4.03		
R19NH	R19Ha	1.8	3.5		2.78			
R35NH	R35Hb	1.8	4.5		2.22	3.54		
S13NH	S13Hb2	1.8	4.5		3.69			
S13NH	S13Ha	1.8	3.5		2.81			
S23NH	S23Ha	1.8	4.5		2.85			
S23NH	S23Hb2	1.8	4.5		2.64			
S23NH	S23Hb1	1.8	4.5		2.81			
T32NH	T32me	1.8	6		4.57	4.38	4.82	4.59
V31NH	V31Ha	1.8	3.5		2.99			
V31NH	V31Hb	1.8	3.5		2.6			
V31NH	V31me	1.8	4.5		2.18	3.45	3.64	3.09

Y20NH	Y20Ha	1.8	3.5		2.8			
Y20NH	Y20Hb1	1.8	3.5		2.54			
Y20NH	Y20Hb2	1.8	3.5		2.3			
Y21NH	Y21Ha	1.8	4.5		2.78			

Y21NH	Y21Hb1	1.8	4.5	3.77			
Y21NH	Y21Hb2	1.8	3.5	2.68			
Y27NH	Y27Ha	1.8	4.5	2.9			
Y27NH	Y27Hb	1.8	3.5	1.95	3.33		
Y36NH	Y36Ha	1.8	4.5	2.89			
Y36NH	R35Ha	1.8	3.5	2.35			
Y36NH	Y36Hb1	1.8	4.5	3.66			
Y36NH	Y36Hb2	1.8	4.5	3.77			
N29Hd1	N29Hb	1.8	6	2.32	3.44		
N18Hd1	N18Hb	1.8	6	3.67	2.93		
Y21Hd	Y21Hb1	1.8	3.5	2.29			
N18Hd2	N18Hb	1.8	6	2.93	2.39		
N29Hd2	N29Hb	1.8	6	2.32	3.26		
Y21He	Y21Hb2	1.8	6	4.7			
Y21He	Y21Hb1	1.8	6	5.48			
Y21Hd	Y21Ha	1.8	3.5	2.32			
Y21He	Y21Ha	1.8	6	4.1			
Y27he	Y27Ha	1.8	6	4.9			
Y20Hd	Y20Ha	1.8	3.5	2.53			
Y20He	Y20Ha	1.8	6	5.61	4.84		
Y20He	Y21Ha	1.8	6	3.97			
Y20Hd	Y20Hb1	1.8	3.5	2.42			
Y20Hd	Y20Hb2	1.8	3.5	2.77			
Y20He	Y20Hb2	1.8	6	4.7			
Y20He	Y20Hb1	1.8	6	4.78			
I3Ha	I3me	1.8	4.5	3.01	2.46	3.69	3.05
I3Ha	I3Hb	1.8	3.5	3.04			
L17Ha	L17Hg	1.8	3.5	2.41			
A22Ha	A22me	1.8	3.5	2.37	2.51	3.01	
P5Hd	P5Hd	1.8	3.5	1.79			
H26Ha	H26Hb	1.8	3.5	2.42	3.05		
Y36Ha	Y36Hb	1.8	3.5	2.58	2.28		
Y20Ha	Y20Hb1	1.8	3.5	2.96			
Y27Ha	Y27Hb	1.8	3.5	2.77	2.95		
Y20Ha	Y20Hb2	1.8	3.5	2.28			
Y21Ha	Y21Hb	1.8	3.5	2.91			
Y21Ha	Y21Hb	1.8	3.5	2.45			
N29Ha	N29Hb	1.8	3.5	2.71	2.99		
N18Ha	N18Hb	1.8	3.5	2.29	2.98		
E15Ha	E15Hg	1.8	3.5	2.84	2.82		
D11Ha	D11Hb	1.8	3.5	2.46	3.01		
E6Ha	E6Hg	1.8	3.5	2.55	2.53		
P5Ha	P5Hb	1.8	3.5	2.32	3.02		
P14Hg	P14Hd	1.8	3.5	2.43	2.46		
P14Hg	P14Ha	1.8	4.5	2.77	3.82		
P5Hd	P5Hg	1.8	3.5	2.72	2.35		
P5Hd	P5Hg	1.8	3.5	2.35	3.03		
P5Ha	P5Hg	1.8	3.5	3.01			
E15Ha	E15Hb	1.8	3.5	2.46	3.02		
V31Ha	V31Hb	1.8	3.5	2.46			
L30Ha	L30Hb	1.8	3.5	2.62	2.99		
A12Ha	A12me	1.8	3.5	2.46	2.43	3.03	2.64
A7Ha	A7me	1.8	3.5	2.43	3.03	2.48	2.65
I3me	I3Hb	1.8	3.5	3.03	2.47	2.44	2.65
V31me	V31Hb	1.8	3.5	2.38	3.02	2.47	2.62
L24Hb	L24me	1.8	4.5	3.18	2.52	3.7	3.13
L24Hg	L28Hg	1.8	4.5	3.66			
L30Ha	L30me	1.8	4.5	2.32	2.31	3.61	2.75

Table S3. Inter-residue NMR Distance Constraints and the Corresponding Simulation Distance

		NMR constraints		MD Simulation Distances For 3			
H1	H2	lower	upper				methyl ave
A12NH	D11Ha	1.8	4.5		3.82		
A22NH	Y21Ha	1.8	4.5		3.63		
A7NH	E6Hg	1.8	4.5		4.2		
A7NH	E6Hb	1.8	4.5		3.75		
D11NH	E10Ha	1.8	4.5		3.51		
D11NH	E10Hb	1.8	6		4.18		
D11NH	A12NH	1.8	3.5		2.49		
D11NH	E10NH	1.8	3.5		1.79		
E10NH	G9Ha2	1.8	4.5		2.41		
E15NH	P14Hd	1.8	4.5		3.06	4.25	
E15NH	A12me	1.8	6		3.23	4.73	3.35
E16NH	E15Hb1	1.8	6		3.89		
E16NH	E15Hb2	1.8	4.5		3.03		
E16NH	L17NH	1.8	3.5		3		
E16NH	E15Ha	1.8	4.5		3.58		
E6NH	P5Ha	1.8	3.5		2.59		
G9NH	P8Ha	1.8	3.5		2.74		
H26NH	R25Ha	1.8	3.5		3.45		
H26NH	R25Hb	1.8	4.5		2.7	3.61	
H26NH	Y27NH	1.8	3.5		2.89		
K4NH	I3Ha	1.8	3.5		2.4		
K4NH	I3Hb	1.8	6		4.42		
L17NH	S13Ha	1.8	6		3.41		
L17NH	E16Hb	1.8	4.5		2.86	3.71	
L28NH	Y27Hb	1.8	4.5		3.11	3.01	
L30NH	N29Ha	1.8	4.5		3.59		
N29NH	L28Hb	1.8	3.5		2.64		
N29NH	L28Hb	1.8	4.5		2.98		
N29NH	L28NH	1.8	4.5		3.34		
Q34NH	R33Hd	1.8	4.5		2.96		
R19NH	N18Ha	1.8	4.5		3.48		
R19NH	N18Hb	1.8	4.5		3.01	4.05	
S13NH	E16Hb	1.8	6		4.68		
S13NH	A12me	1.8	4.5		3.51	4.4	4.31
S23NH	A22me	1.8	4.5		3.36	2.45	3.86
T32NH	L28Hb	1.8	6		4.52	5.65	
V31NH	L30Hb	1.8	4.5				
V31NH	L30H	1.8	6				
Y21NH	N18Ha	1.8	6		2.94		
Y21NH	Y20NH	1.8	3.5		3.11		

Y27NH	H26Ha	1.8	6		3.68			
Y27NH	H26Hb	1.8	4.5		2.47	3.91		
Y36NH	R35Ha	1.8	3.5		2.35			
A12me	E15Hb	1.8	4.5		2.7	3.59	4.27	3.52
A7me	Y20Hb2	1.8	4.5		4.29	5.02	5.88	5.06
E15Ha	N18Hb	1.8	4.5		3.14			
E15Ha	N18Hb	1.8	3.5		3.14			
G9Ha	B12-56	1.8	4.5		4.14			
H26Hb	S23Hb1	1.8	6		4.95			
H26Hb	S23Hb2	1.8	6		5.28			
L17Ha	Y20Hb2	1.8	4.5		2.58			
L17Ha	Y20Hb1	1.8	4.5		3.75			
L17Ha	Y20Hb1	1.8	4.5		3.75			
L17Ha	Y20Hb2	1.8	4.5		2.58			
P14Ha	L17me	1.8	4.5		3.32	3.96	5	4.09
P8Hd	A7Ha	1.8	3.5		1.92			
P8Hg	Y20Hb	1.8	3.5		3.08			
P8Hg	Y20Hb2	1.8	3.5		3.01			
S23Ha	H26Hb	1.8	6		3.73	2.6		
Y20Hd	L17me	1.8	4.5		3.39	3.81	3.64	3.61
Y20Hd	P5Hg	1.8	4.5		3.78			
Y20Hd	Y21Ha	1.8	6		4.11			
Y20Hd	S23Hb2	1.8	6		3.86	5.34		
Y20He	P5Hg	1.8	4.5		2.02			
Y20He	A7me	1.8	6		4.9	4.17		
Y20He	L17me	1.8	6		4.42	5.37	5.03	4.94
Y20He	Y21He	1.8	6		2.72			
Y21Hd	N18Hb	1.8	6		4.79			
Y21Hd	N18Ha	1.8	4.5		3			
Y21HE	L17me	1.8	3.5		3	2.03	3.04	2.69
Y21He	L17me	1.8	6		4.95			
Y21He	N18Ha	1.8	6		5.26			
Y27Hd	H26Hb	1.8	6		3.42			
Y27He	S23Hb1	1.8	6		4.82			

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