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# Peptidomimetic Antagonists Designed to Inhibit the Binding of CD4 To HIV GP120

Savithri Ramurthy,[‡§] Min S. Lee,[†‡] Hiroshi Nakanishi,[†‡] Richard Shen[‡] and Michael Kahn[†‡*]

[†]*Department of Pathobiology, University of Washington, Seattle, WA 98195, U.S.A.*
[‡]*Molecumetics Institute, 2023 120th Avenue N. E., Suite 400, Bellevue, WA 98005, U.S.A.*

**Abstract**—Attempts to enhance the efficacy of our previously reported CD4 CDR2-like (residues 40–45) mimetic **1** by incorporation of the critical guanidine residue Arg-59 of CD4 are described.

## Introduction

CD4 is a cell-surface glycoprotein that is found principally on T lymphocytes,[1] which associates with class II major histocompatibility molecules on antigen-presenting cells.[2,3] CD4, via high-affinity binding ($K_d \approx 10^{-9}$ M) to the human immunodeficiency virus (HIV) viral envelope glycoprotein gp120 is utilized as the principle cellular attachment site for HIV,[4,5] although other binding sites may also be important.[6] Several recombinant CD4-derived candidates have been developed as anti-HIV therapeutics. However, their clinical efficacy was rather limited.[7] In general, poor bioavailability, rapid degradation and antigenicity affect the utility of proteinaceous pharmaceuticals.[8,9] The dissection of complex proteins into small synthetic conformationally restricted functional subunits may overcome these problems. Mimetics of important functional domains might possess beneficial properties in comparison to the intact proteinaceous species with regard to specificity and therapeutic potential. Additionally, peptidomimetics can serve as valuable probes for the study of molecular recognition events.

Arguably, the most extensive set of publically available mutagenesis,[10,11] antibody[12,13] and peptide[14,15] mapping experiments have been utilized to characterize the interaction between CD4 and gp120. The exact limits of the contact surface have not been delineated; however, the V1 second complementarity-determining region (residues 40–55) of CD4 has been implicated as being essential. The X-ray structure of an N-terminal 182-residue fragment of CD4 has been determined.[16,17] Inspection of the structure localizes residues Gln-40–Phe-43 to a highly surface-exposed β-turn connecting the C′ and C″ β-strands. In addition, based on mutagenesis experiments, a significant role for binding to gp120 has been attributed to Phe-43. However, peptides derived from this loop region have failed to exhibit significant inhibitory activity.[15,18] This is presumably due to a loss of critical secondary structure elements in the peptides and highlights the necessity for developing conformationally constrained mimetics.[19]

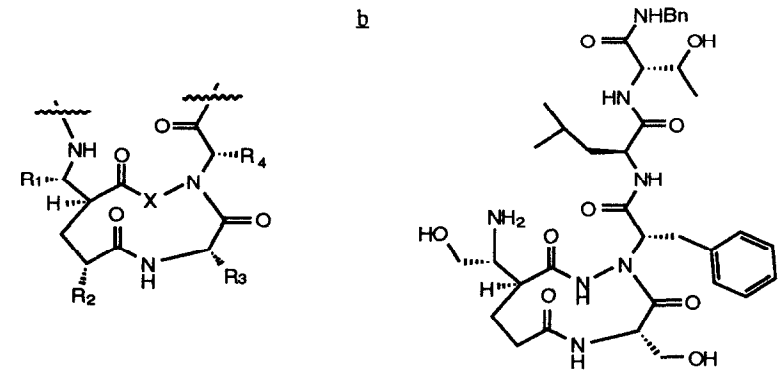
Peptides are characteristically highly flexible molecules whose structure is strongly influenced by their environment,[20] and their random conformation in solution may preclude their practical application for the study of molecular recognition processes.[21] We have developed a method to construct conformationally restricted mimetics of peptide-chain reversals (β-turns, γ-turns, Ω-loops, etc.).[22,23,24a,25a,b] The surface localization of turns in proteins, and the predominance of residues containing potentially critical pharmacophoric information, has led to the belief that turns play important roles in a myriad of molecular recognition events.[26] The family of turn mimetics (Figure 1a) possesses considerable potential for delineating structure–function relationships.[22,23,24a,25a] The generic system allows for the facile introduction of any natural or unnatural amino acid side-chain functionality through a modular component approach which is fully compatible with solid phase peptide synthesis. The ability to alter the X-group linker provides reliable control and variation of side-chain orientations, backbone distances, and φψ dihedral angles.

We have previously demonstrated that the 10-membered ring mimetic framework (X=NH) (Figure 1a) closely mimics the β-turn at Gln-40–Phe-43. Importantly, the conformationally restricted peptidomimetic **1** (Figure 1b), which incorporates CD4 residues 40–45, inhibited the binding of HIV IIIB gp120 to CD4$^+$ cells (4–20 μM) and reduced synctium formation by 50 % at 250 μg/mL.[24a,b]

The reduction of this complex protein to a low molecular weight species was a critical and significant step along the pathway to generate nonpeptidic molecules which antagonize the CD4/gp120 interaction and inhibit HIV infection. We anticipated that we could enhance the activity of our first generation mimetic **1**, in that the CD4/gp120 contact surface undoubtedly incorporates a greater surface area than our mimetic.

Mutational analyses concur in identifying the side chain of CD4 residue Arg-59 (at the beginning of the DE loop) as an additional key determinant for binding to gp120. Scanning alanine mutagenesis showed that replacement of this residue decreased the affinity of CD4 for gp120 by

[§]Present address: Department of Chemistry, University of Notre Dame, Notre Dame, IN 46556, U.S.A.



1

**Figure 1.** (a) Generic structure of the mimetic ring system. X = 1–5 atoms. (b) CDR-2 like peptidomimetic **1**.

approximately one order of magnitude.[11] Inspection of the X-ray structure of CD4 highlights the close spatial juxtaposition of the guanidinium moiety of Arg-59 and the side chain of Leu-44.[16,17] Analysis of this relationship utilizing interactive molecular graphics, led us to design the homoarginine analog **2** (Figures 2 and 3).

The synthesis of **2** (Scheme I) is analogous to that previously reported for the synthesis of **1**. Coupling of the Z-protected hydrazinophenylalanine **3**[27] to *N*-ε-Boc ornithine methyl ester (**4**) using an aqueous carbodiimide protocol provided 70 % of the dipeptide **5**. Acylation using the silver cyanide procedure,[28] subsequent removal of the Fmoc protecting group and coupling to azetidinone **6**[24a] afforded the key cyclization precursor **7** in 40 % overall yield. Removal of the Boc group and subsequent guanylation using the di Z-pyrazole **8**[29] proceeded smoothly to provide **9**. Cyclization was effected via catalytic hydrogenolysis to provide the desired mimetic **2**.

The mimetic was purified to homogeneity by high performance liquid chromatography (HPLC) on a C-18 reverse phase column with a gradient of $H_2O$ and $CH_3CN$ with 0.1 % (v/v) TFA prior to use in biological assays and spectroscopic analysis. All spectroscopic studies performed [1D and 2D NMR (Figure 4), MS] are fully consistent with the assigned structure.

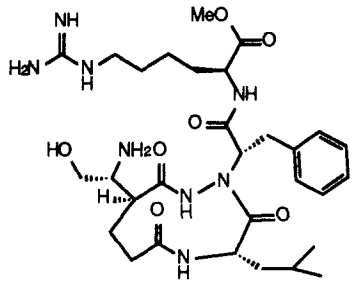


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**Figure 2.** Peptidomimetic incorporating the homoarginine side chain.

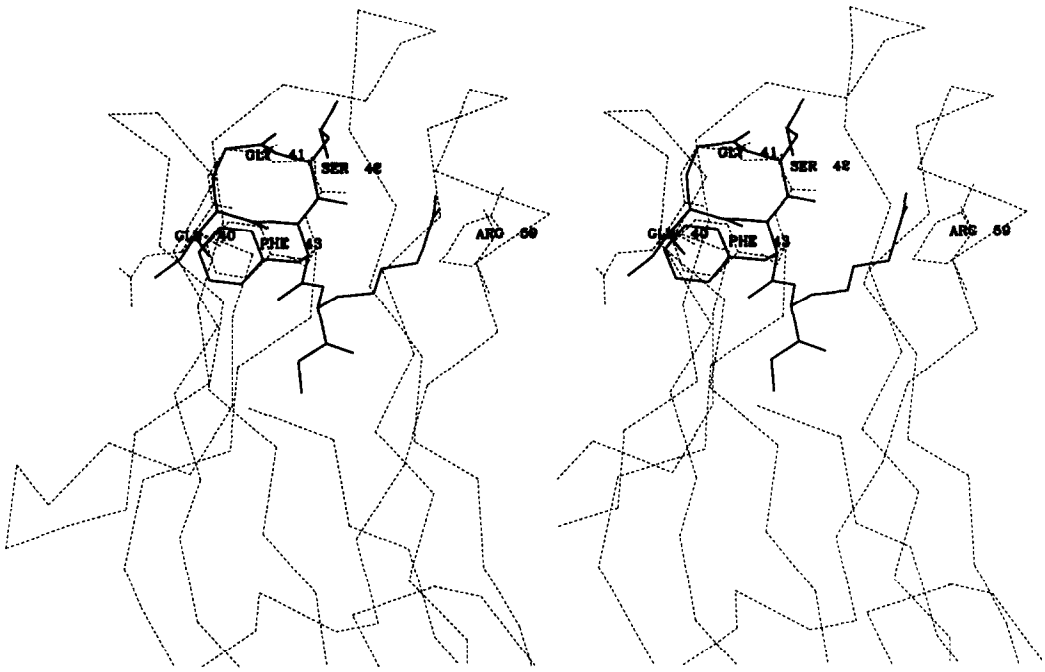
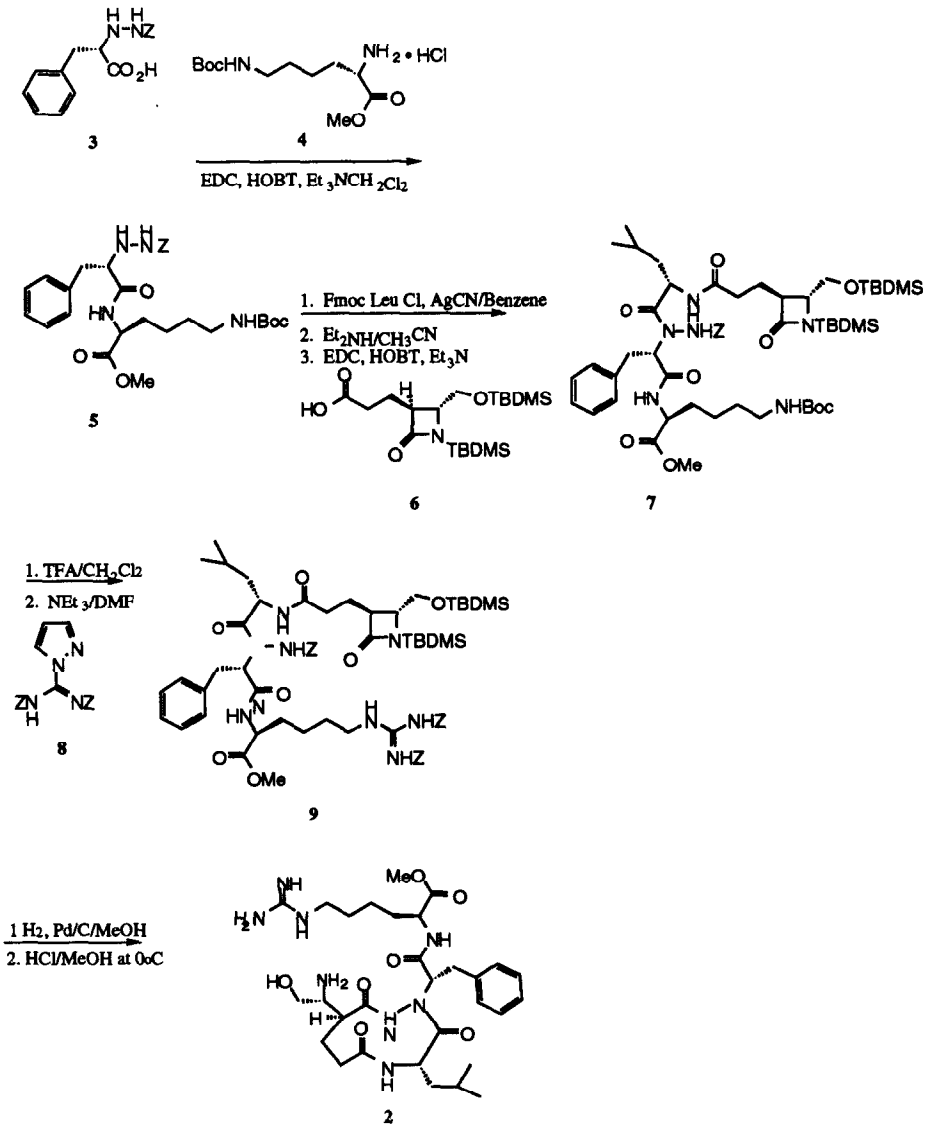


**Figure 3.** Stereoview of CD4 mimetic **2** matched to CD4. CD4 mimetic **2** in solid line, CD4 $V_1$ domain in dashed line.



Scheme I.

Furthermore, with the exception of the conformationally mobile homoarginine side chain, the remainder of the mimetic framework adopts essentially one low energy conformation in $H_2O$.[32]

The biological evaluation of this analog has been somewhat perplexing. Despite showing significant inhibition of viral infectivity in cell culture $IC_{50} \cong 100$ μM,[30] a slight enhancement compared to mimetic **1**, surprisingly, it displayed no ability to block the binding of biotinylated sCD4 to antibody immobilized gp120.[31] Further investigations into this compound's mechanism of antiviral activity are underway and will be reported in due course.

## Conclusions

The design of mimetic **2** was based on the previous success we had with CD4 mimetic **1**. The major modification which we have incorporated into mimetic **2** is the substitution of a homoarginine side chain for Leu-44. This was done in an attempt to mimic the CD4 side chain guanidine moiety of Arg-59, which is strongly implicated in the binding of CD4 to gp120. From molecular modeling (Figure 3) and NMR (Figure 4) it appears that mimetic **2** reasonably, although perhaps not optimally, accomplishes this goal. The fact that mimetic **2** inhibits infectivity slightly more efficiently than mimetic **1** was encouraging. However, rather surprisingly and disappointingly, this could not be correlated with binding to gp120. Several possible explanations arise. In mimetic **2**, we have additionally modified the side chain of Ser-42 to Leu, although in earlier analogs this led to a slight apparent increase in binding.[32] We have also truncated the C-terminus by removing the *N*-benzyl threonineamide. The effect of this modification is not known; however, it could conceivably reduce binding. Finally, these results have been obtained from a variety of assay formats and may reflect certain idiosyncracies, although alternative mechanisms for antiviral activity are certainly plausible.[33] Nevertheless, the study outlines what we believe to be a conceptually useful approach to incorporate functionality, from residues remote in primary sequence yet topologically close, into small molecule peptidomimetics.

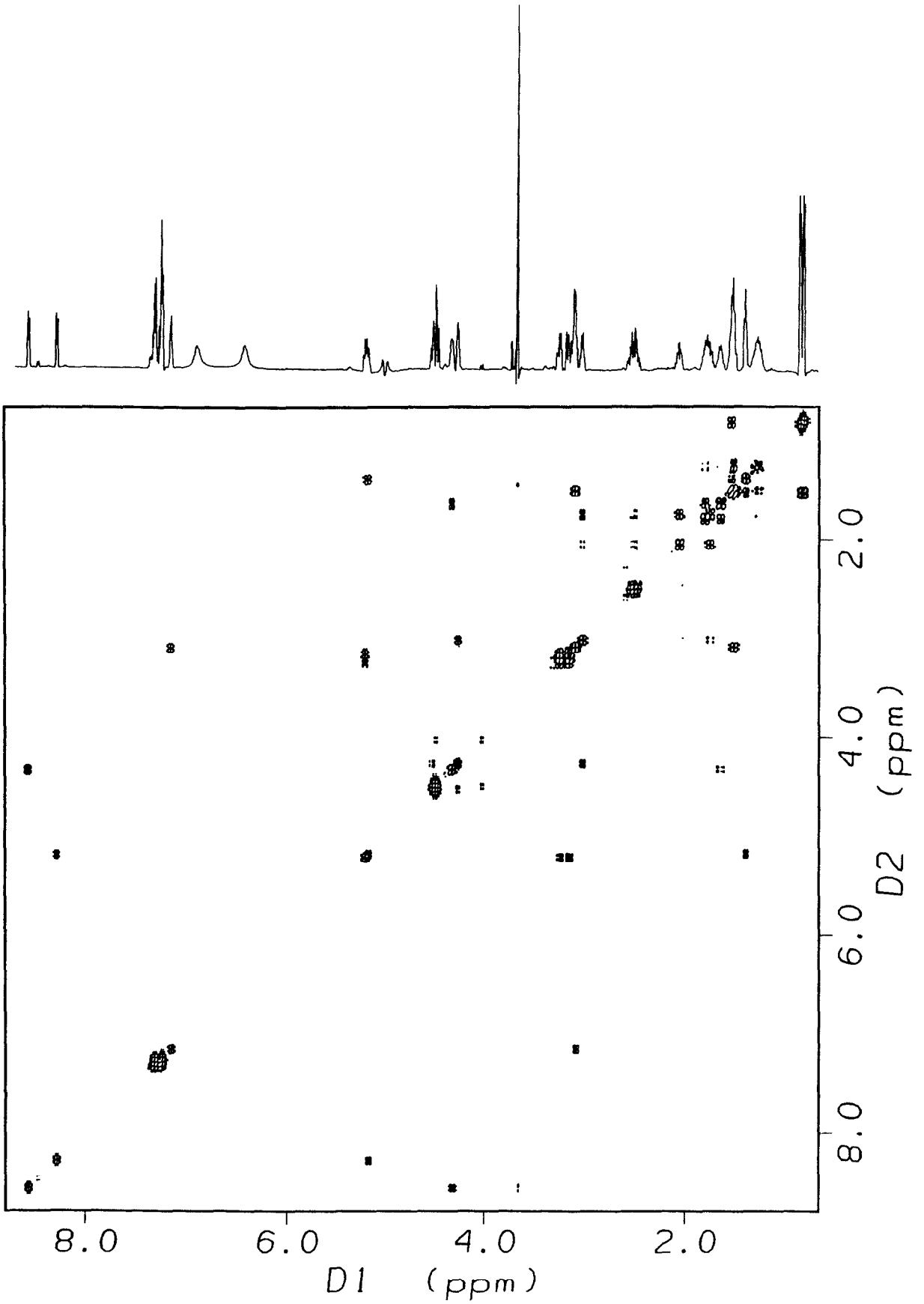



**Figure 4.** The $^{1}H$ NMR spectra of 500 MHz 1D and 2D phase-sensitive 2QF-COSY of the CD4 β-turn mimetic in 90 % $^{1}H_2O$/10 % $^{2}H_2O$ at 0 °C and pH 4.2. The two most downfield protons at 8.47 and 8.28 ppm represent amide protons of homoArg-5 and Leu-3, respectively. The cross-peaks of the NH and C$^{\alpha}$H protons for homoArg-5 and Leu-3 residues are clearly observed in the 2QF-COSY.

## Experimental

*Sample preparation*

The sample in water for NMR spectroscopy was prepared by dissolving the mimetic in 90 % $^1H_2O$/10 % $^2H_2O$ to provide a final concentration of ~20 mM. The pH was adjusted using 1.0 N $NaHCO_3$ and 0.1 N $NaHCO_3$ to pH 4.2. The pH was measured with a glass electrode and was not corrected for isotope effects.

*Acquisition of NMR spectra*

The NMR experiments were performed using a Varian Unity 500-MHz spectrometer. Spectra were recorded at 273 K in water with the carrier set on the $^1H_2O$ at 5.01 ppm and in $CDCl_3$ at ambient temperature. Standard pulse sequences and phase cycling schemes were used for the DQF-COSY,[34] TOCSY[35] and ROESY[36] experiments with 8–40 scans per $t_1$ value and 512–800 $t_1$ values. Low-power irradiation of the solvent resonance during the relaxation delay of 1.4–1.5 s was used for all experiments. TOCSY experiment was performed with a spin-lock period of 80 ms with a 2 kHz field strength. ROESY spectrum was recorded with mixing time of 200 ms. All 2D spectra were acquired with 2048 complex data points and a spectral width of 6250 Hz in $F_2$. Spectra were recorded in the phase-sensitive mode with quadrature detection in the $F_1$ dimension using the methods of States and Haberkorn.[37]

*Data processing*

All 2D NMR data were transferred to a Silicon Graphics Iris Indigo 2/XZ and processed using the program FELIX (Biosym Technologies, Inc.). 1D NMR data was processed using VNMR (Varian NMR Instruments). TOCSY and ROESY spectra were Fourier transformed using a Lorentzian-to-Gaussian weighting function in the $F_2$ dimension and a shifted sine bell weighting function in the $F_1$ dimension. For DQF-COSY data, unshifted sine bell and shifted sine bell weighting functions for $F_2$ and $F_1$ dimensions were used, respectively. For spectra recorded in 90 % $^1H_2O$/10 % $^2H_2O$, a low frequency-deconvolution was applied to the time domain data prior to Fourier transformation in order to improve the size of the residual $H_2O$.[38] The transformed spectra contained 2048 real points in both dimensions.

*Preparation of* N*-benzyloxycarbonyl hydrazino-(*s*)-phenylalanyl-*Nε*-t-butyloxy carbonyl lysine methyl ester* **5**

To a solution of *Z*-protected phenylalanyl hydrazide (**3**) (610 mg, 1.9 mmol) in methylene chloride (15 mL) were added $N^{\varepsilon}$-*t*-butyloxycarbonyl-(*s*)-lysine methyl ester hydrochloride **4** (634 mg, 2.1 mmol) and HOBT (262 mg, 1.9 mmol). The mixture was cooled to 0 °C and EDC (559 mg, 2.9 mmol) and triethylamine (0.3 mL, 2.1 mmol) were added. The reaction was stirred overnight at rt and diluted to 100 mL with methylene chloride. The mixture was washed with water (5 mL), sat. sodium bicarbonate (10 mL), 1 N hydrochloric acid (10 mL), and brine (10 mL). The separated organic layer was dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography of the crude product on silica gel with 3:2 ethyl acetate:hexanes provided 850 mg (80 %) of **5** as a glassine solid. IR (KBr): 3500, 1267, 1452, 1512 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.7 (b, 1H), 7.2–7.0 (m, 10H), 5.0 (s, 2H), 4.4 (m, 1H), 4.05 (m, 1H), 3.8 (b, 1H), 3.7 (s, 3H), 3.15 (m, 1H), 3.0 (m, 1H), 2.8 (m, 2H), 1.8–1.6 (m, 4H), 1.4 (s, 9H), 1.2 (s, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 171.8, 171.6, 156.6, 155.2, 135.6, 135.1, 128.3, 127.9, 127.6, 127.4, 127.3, 127.2, 126.9, 126.2, 78.0, 66.2, 64.8, 51.3, 51.0, 50.8, 40.6, 37.4, 30.5, 28.4, 27.3, 27.1, 22.0, 21.9.

*Preparation of precursor* **7**

To a solution of Fmoc–leucine (545 mg, 1.5 mmol) in 60 mL methylene chloride were added oxalyl chloride (0.49 mL, 4.5 mmol) and DMF (catalytic). The reaction was stirred for 1 h at rt, diluted with 10 mL of benzene and filtered through a pad of Celite. The volatiles were removed *in vacuo*. Flash chromatography of the residue on silica gel with 1:1 ethyl acetate:hexanes ($R_f$ = 0.28) provided 500 mg (54 %) of the Fmoc protected tertiary amide as a colorless oil.

To a solution of the tertiary amide in acetonitrile (5 mL) was added 1 mL of diethylamine and the reaction was stirred for 1 h at rt. The volatiles were removed *in vacuo* and the resulting amine was purified on silica gel using 19:1 methylene chloride:methanol (saturated with ammonia) to yield 250 mg (66 %) of the tertiary amide as a clear oil. IR (neat) 3500, 1720, 1454 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.4–7.2 (m, 5H), 6.75 (b, 1H), 5.3–5.05 (m, 3H), 4.4 (m, 1H), 3.79 (m, 1H), 3.68 (s, 3H), 3.4 (m, 2H), 3.2–3.0 (m, 2H), 1.8–1.6 (m, 5H), 1.4 (s, 9H), 1.4–1.2 (m, 2H), 0.95 (d, $J$ = 6.5 Hz, 3H), 0.79 (d, $J$ = 6.5 Hz, 3H). To a solution of β-lactam acid (**6**) (149 mg, 0.37 mmol) in methylene chloride (3 mL) were added the tertiary amide (250 mg, 0.373) and HOBT (50 mg, 0.37 mmol). The mixture was cooled to 0 °C and EDC (106 mg, 0.55 mmol) was added. The reaction was stirred overnight at rt and diluted to 15 mL with methylene chloride. The mixture was washed with water (2 mL), sat. sodium bicarbonate (4 mL), 1 N hydrochloric acid (4 mL), and brine (2 mL). The separated organic layer was dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography of the crude material on silica gel with 1:1 ethyl acetate:hexanes ($R_f$ = 0.26) provided 325 mg (83 %) of **7** as a mixture (approximately 3:1) of diastereomers at the leucyl position. IR (neat): 3500, 1745 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.3–8.1 (b, 1H), 7.4–7.1 (m, 10H), 6.3–6.2 (b, 1H), 5.27–5.15 (m, 2H), 4.8–4.6 (m, 3H), 3.8 (s, 3H), 3.7 (m, 1H), 3.6 (m, 1H), 3.44–3.4 (m, 1H), 3.28–2.23 (m, 1H), 3.09 (b, 1H), 2.9–2.82 (m, 3H), 2.3–2.1 (m, 2H), 2.0–1.8 (m, 2H), 1.8–1.6 (m, 5H), 1.432 (s, 11H), 1.06 (s, 9H), 0.938 (s, 9H), 0.851–0.827 (d, $J$ = 12.0 Hz, 3H), 0.793–0.769 (d, $J$ = 12.0 Hz, 3H), 0.223 (s, 3H), 0.198 (s, 3H), 0.047 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 175.3, 175.0, 172.2, 172.1, 169.5, 157.2, 155.8, 136.7, 135.0, 129.1, 128.7, 128.5, 128.4, 128.1, 127.8, 127.0, 126.6, 78.7, 68.7, 68.1, 64.7, 61.8, 57.2, 53.2, 52.0, 51.8, 47.3, 46.9, 40.1, 34.0, 33.5, 32.9, 31.6, 31.1, 29.0, 28.7, 28.6, 28.0, 26.6, 26.4, 25.9, 25.6, 25.4, 24.8, 24.6, 24.4, 22.6, 22.4, 22.2, 22.0, 18.0.

*Preparation of the cyclization precursor* **9**

To a solution of **7** (325 mg, 0.30 mmol) in 4 mL of methylene chloride at 0 °C was added 2 mL of TFA. The mixture was stirred for 1.5 h at 0 °C, and the volatiles were removed *in vacuo*. The residue (319 mg, 0.3032 mmol) was dissolved in DMF (2 mL) to which was added *N,N'*-bis-Cbz-1-guanyl pyrazole (**8**) (114 mg, 0.3032 mmol) and triethylamine (42 μL). The reaction mixture was stirred overnight at rt and concentrated *in vacuo*. The residue was taken up in ethyl acetate, and washed with sat. ammonium chloride. The aqueous layer was re-extracted with ethyl acetate (2 × 20 mL) and the combined organic layers were washed with brine and water. The volatiles were removed *in vacuo*, and the residue was chromatographed on silica gel with 20:1 methylene chloride:methanol ($R_f$ = 0.25) to provide **9** as a glassine solid. IR(KBr) 1729.3, 1673.6 $cm^{-1}$, $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.7 (b, 1H), 8.38 (b, 1H), 7.4–7.09 (m, 15H), 5.26–5.14 (m, 2H), 5.12 (s, 4H), 5.0 (m, 1H), 4.68 (m, 1H), 4.5 (m, 1H), 3.8 (s, 3H), 3.7 (m, 1H), 3.6 (m, 1H), 3.44–3.34 (m, 1H), 3.28–3.23 (m, 1H), 3.09 (b, 1H), 2.9–2.82 (m, 3H), 2.3–2.1 (m, 2H), 2.0–1.8 (m, 2H), 1.8–1.6 (m, 5H), 1.432 (s, 2H), 0.827 (d, $J$ = 12.0 Hz, 3H), 0.793–0.769 (d, $J$ = 12.0 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 176.3, 173.2, 172.2, 163.6, 157.5, 155.8, 153.7, 136.5, 134.9, 134.4, 129.1, 128.7, 128.6, 128.3, 128.2, 128.0, 127.8, 126.8, 68.4, 68.0, 67.0, 63.7, 63.3, 55.2, 52.5, 51.9, 47.6, 40.8, 39.7, 34.4, 33.0, 31.5, 28.4, 28.3, 24.6, 24.1, 23.2, 22.8, 21.3, 21.0, m/z = 1034.

*Synthesis of the 10-membered ring mimetic* **2**

To a solution of **9** (125 mg, 0.917 mmol) in methanol (2 mL) was added a catalytic amount of 5 % Pd/C. The reaction was stirred overnight at rt under one atmosphere of hydrogen. The reaction was filtered through a pad of Celite and the volatiles were removed *in vacuo*. A solution of the residue in methanol (1 mL) was cooled to 0 °C and sat. HCl in methanol (0.5 mL) was added dropwise. After stirring the reaction for 10 min at 0 °C, the volatiles were removed *in vacuo*. Flash chromatography of the residue on silica gel with 20:1 methylene chloride:methanol (saturated with ammonia) provided 45 mg (79 %) of **2** as a glassine solid. IR (KBr): 3500, 1684.2, 1431.6 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3OD$): δ 7.3–7.1 (m, 5H), 5.25 (m, 1H), 5.18 (m, 1H), 4.26–4.23 (dd, $J_a$ = 3.5 Hz, $J_b$ = 8.5 Hz, 1H), 4.15–4.08 (m, 1H), 3.66 (s, 3H), 3.60 (m, 1H), 3.574–3.540 (dd, $J_a$ = 6.0 Hz, $J_b$ = 11.0 Hz, 1H), 3.34 (m, 1H), 3.2 (m, 1H), 3.14–3.0 (m, 1H), 2.84–2.8 (m, 1H), 2.3–2.2 (m, 2H), 2.02–1.9 (m, 1H), 1.82–1.74 (m, 1H), 1.68–1.44 (m, 3H), 1.4–1.22 (m, 2H), 0.932–0.920 (d, $J$ = 6.0 Hz, 3H), 0.860–0.848 (d, $J$ = 6.0 Hz, 3H); $^{13}C$ NMR (125 MHz, $CD_3OD$): δ 177.9, 175.0, 173.8, 163.9, 158.7, 138.4, 130.4, 130.1, 130.0, 128.2, 127.9, 71.0, 65.8, 64.6, 56.8, 53.8, 53.4, 52.6, 50.2, 41.8, 40.8, 40.2, 35.8, 34.4, 34.0, 30.6, 28.6, 26.2, 25.8, 22.8, 23.0, 21.8, m/z = 633.9.

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