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Design and Synthesis of Broad-Based Mono- and Bi- Cyclic Inhibitors of FIV and HIV Proteases

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Abstract—Based on the substrate transition state and our strategy to tackle the problem of drug resistance, a series of HIV/FIV protease (HIV /FIV PR) monocyclic inhibitors incorporating a 15- or 17-membered macrocycle with an equivalent P3 or P3' group and a unique unnatural amino acid, (2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyric acid, have been designed and synthesized. In addition, based on the structure of TL3 with small P3/P3' group, we have synthesized two conformationally restricted bicyclic inhibitors containing the macrocycle, which mimic the P1/P1'-P3/P3' tripeptide [Phe-Val-Ala] of TL3. We have found that the contribution of the macrocycle in our monocyclic inhibitors is important to the overall activity, but the ring size does not affect the activity to a significant extent. Several inhibitors that were developed in this work, exhibit low nanomolar inhibitory activity against the wild-type HIV/FIV PR and found to be highly effective against some drug-resistant as well as TL3-resistant mutants of HIV PRs. Compound **15**, in particular, is the most effective cyclic inhibitor in hand to inhibit FIV replication in tissue culture at a concentration of 1.0 µg/mL (1.2 µM).

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Introduction

Since human immunodeficiency virus (HIV-1) was identified as the causative agent of acquired immunodeficiency syndrome (AIDS), and the virally encoded aspartic protease (PR) was proven essential for the proliferation of HIV, intensive research has been devoted to the development of potent inhibitors of HIV PR. Despite six competitive inhibitors of this protease have been approved and several others are in clinical trials,¹ many drug-resistant variants of HIV have been identified,² rendering AIDS with no definitive cure. Feline immunodeficiency virus (FIV) causes an immunodeficiency syndrome in cats comparable to AIDS in humans.³ Although their active site structures are superimposable and have an identical mechanism of catalysis,⁴ binding of inhibitors to these proteases is remarkably different. All the approved inhibitors with *K_i* values in the low nanomolar range for HIV PR, only bind to FIV PR in micromolar range. In addition, many

HIV PR mutants have a shrunken P3 binding site, which is a structural characteristic of FIV PR, and good inhibitors of FIV PR are usually better inhibitors of the wild type and drug-resistant HIV proteases.⁵ Therefore, FIV PR may behave like the drug-resistant phenotype of HIV protease and could be used as a model for the development of new broad-based inhibitors to slow down the development of drug resistance.

It has been known that the inhibitors of aspartic PRs commonly bind in an extended β -strand conformation.⁶ Restriction of an inhibitor's conformation to one recognized by the enzyme may increase the potency by lowering the entropic barrier to complex formation. As a result, conformational restriction of inhibitors through the introduction of macrocycles into such extended conformation has been shown to be an effective way of increasing affinity toward HIV PR.^{6,7} The introduction of cyclic structures in PR inhibitors have also been demonstrated to have comparable or better antiviral activity compared to the acyclic analogues,^{7b,d} suggesting improved cell penetration properties and resistance to cellular enzymes for the macrocyclic inhibitors.

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Recently, HIV PR inhibitors containing allophenylnorstatine [(2*S*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyric acid] have been reported by several research groups.⁸ In particular, Kiso et al.^{8d} have demonstrated that inhibitor **1** (JE-2147) (Fig. 1) has very potent antiviral activities in vitro and exhibits good oral bioavailability and plasma pharmacokinetic profiles. Earlier we disclosed our approach⁹ for the design, synthesis and in vitro evaluation of a series of phenylnorstatine (Pns), [(2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyric acid], containing macrocyclic HIV/FIV PR inhibitors. The macrocycle was designed to mimic the conformationally constrained Phe-Val-Ala motif, which has been used in the development of FIV PR and drug-resistant HIV PR inhibitors such as **2** (TL3) (Fig. 1).⁵ All these results provided the foundations of the work described in this paper. Reported herein are additional findings and examples for our monocyclic PR inhibitors as well as the bicyclic PR inhibitors (Fig. 2). To the best of our knowledge, there is only one example reported so far for the preparation of bicyclic inhibitor against HIV PR.^{7f} All these cyclic inhibitors were found to be effective against FIV PR, suggesting being also effective against a broad range of HIV variants. The evaluation of their inhibitory activities against both wild-type HIV/FIV

PRs and some mutants of HIV PRs and the full details of the synthesis for all these cyclic inhibitors are discussed.

Results and Discussion

Chemistry

Our group previously disclosed that inhibitors with a small P3 residue, particularly **2** (TL3) (Fig. 1), are effective against HIV and its drug-resistant variants, as well as SIV and FIV.⁵ The X-ray structure of FIV PR complexed with **2** reveals that the P1 and P3 residues are positioned very closely in the neighboring hydrophobic pockets.¹⁰ This prompted us the design of the bicyclic peptidomimetic inhibitors **3** and **4**, in which the P1/P1' and P3/P3' residues are connected with the aliphatic chain in a macrocycle, which may render the solution conformation similar to the bound conformation in the active site of the protease.

The synthesis of **3** with P1 and P3 residues connected together with an amide linkage in the *meta*-position of the Phe residue is illustrated in Scheme 1. The free acid in 3-nitro-tyrosine was protected as a methyl ester followed by coupling with Boc-Val-OH. The resulting dipeptide Boc-Val-Tyr(3-NO₂)-OMe¹¹ was reacted with 5-chlorophenyl tetrazole and the hydroxyl and nitro groups in **17** were simultaneously removed and reduced, respectively after refluxing in EtOH/cyclohexene in the presence of Pd/C. The free amine was then protected with Cbz group and the protected dipeptide **18** was subjected to subsequent LiBH₄ reduction and oxidation using TEMPO/BAIB.¹² Vanadium catalyzed coupling¹³ of aldehyde **19** followed by protection and chromatographic separation of the diastereomeric mixture afforded **20** in 48% overall yield. The Cbz groups in **20** were removed and coupled with Z-Glu-O^tBu to obtain the bicyclic precursor **21** in 66% overall yield. Removal of all Boc and *t*-Bu groups in **21** with TFA followed by intramolecular amide bond formation in CH₃CN

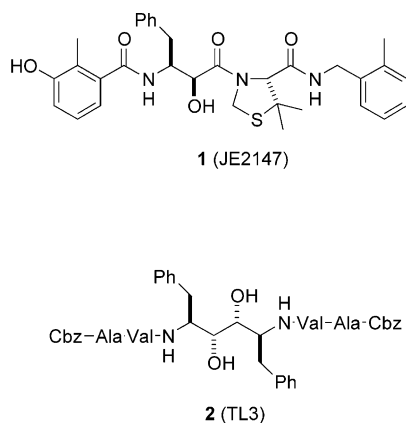


Figure 1.

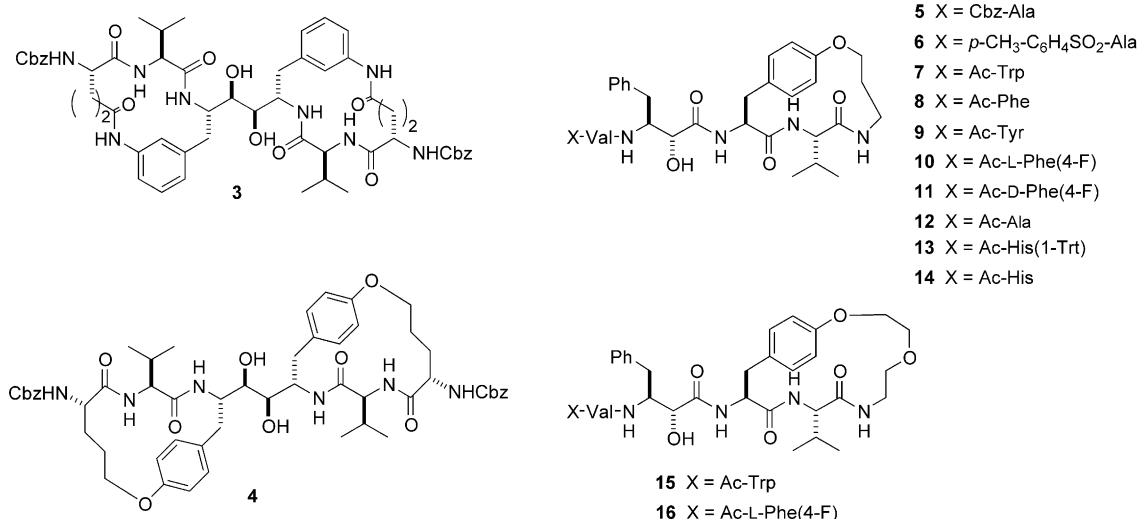
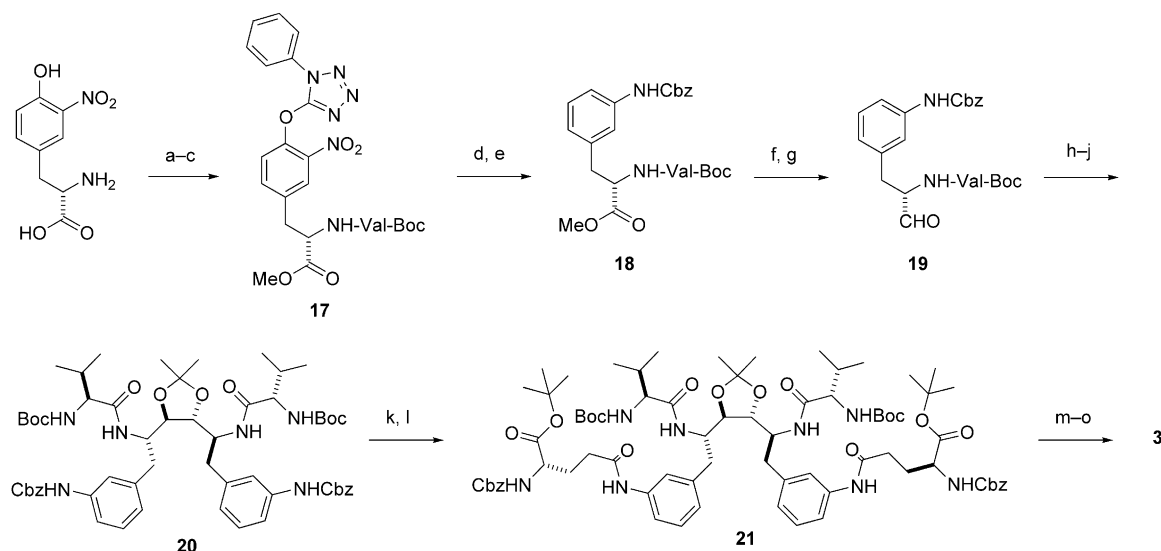


Figure 2.

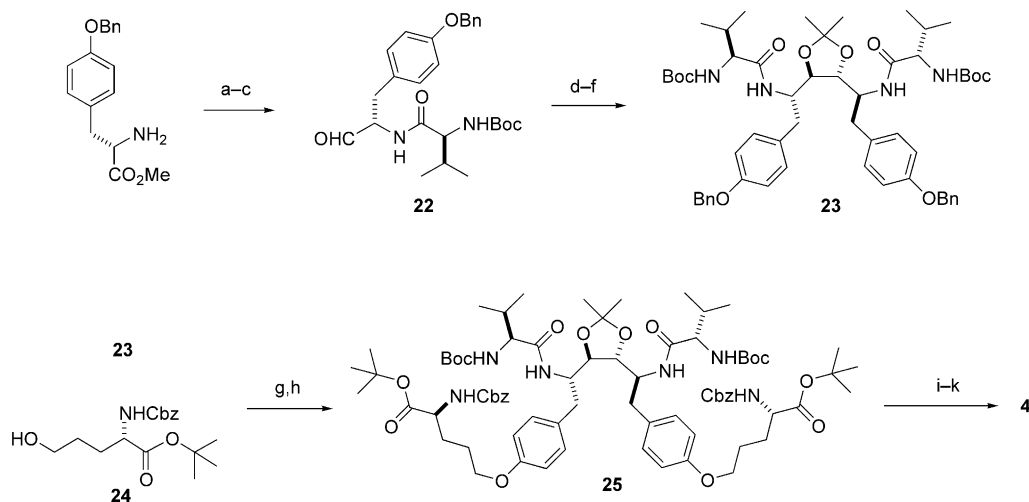


Scheme 1. Reagents and conditions: (a) AcCl, MeOH; (b) Boc-Val-OH, HBTU, DIPEA; (c) 5-chlorophenyl tetrazole, NaHCO₃, DMAC; (d) Pd/C, cyclohexene, reflux; (e) CbzCl, py; (f) LiBH₄, THF; (g) PhI(OAc)₂, TEMPO; (h) Zn, VCl₃(thf)₃; (i) 2,2-dimethoxy propane, TsOH; (j) sep. diastereomers; (k) Pd/C, H₂; (l) Z-Glu-O^tBu, HBTU, DIPEA; (m) TFA/CH₂Cl₂; (n) BOP, DIPEA, CH₃CN; (o) TFA/H₂O.

(5 mM) and unmasking the diol core with TFA/H₂O provided **3** in 60% overall yield.

In a similar manner to **3**, compound **4** was synthesized (Scheme 2). The crucial steps in the synthesis of **4** with P1 and P3 residues joined together with an ether linkage in the *para*-position of the Phe residue, included the pinacol coupling and the intramolecular cyclization reactions. The dipeptide aldehyde **22** was derived from H-Tyr(Bzl)-OMe after coupling with Boc-Val-OH and subsequent reduction and oxidation. Pinacol coupling of **22**, protection and separation of the mixture provided **23** in 60% overall yield. Deprotection of the hydroxyl groups (Pd/C, H₂) in **23** followed by Mitsunobu reaction with **24**¹⁴ afforded the bicyclic precursor **25** in 47% overall yield. Finally, deprotection of the Boc groups with TFA followed by high dilution cyclization and removal of the isopropylidene group (TFA/H₂O) afforded **4** in 46% overall yield.

Compounds **5–16** are all pentapeptide mimetics consisting of a 15- or 17-membered C-terminal macrocycle designed to mimic the P1'-P3' tripeptide (Phe-Val-Ala) of a substrate for HIV/FIV PRs. The hydroxyl-methylcarbonyl moiety among these phenylnorstatine-based inhibitors mimics the transition state of peptide hydrolysis and the hydroxyl configuration is known to be detrimental to the inhibitory activity.⁸ The *R* configuration was adopted in all these compounds since such stereochemistry around this carbinol function was previously reported to have better inhibitory activity for HIV/FIV PRs than that of the *S* isomer.⁹ Since potent peptidomimetic inhibitors for HIV/FIV PRs have been achieved either by capping the N-terminus of the basic core with a large protecting group together with a relatively small P3 residue (e.g., Ala)⁵ or vice versa,¹⁵ all our mono-cyclic inhibitors except **12** (with small P3 residue and N-terminal group) have either of these two patterns (Fig. 2). Also HIV PR inhibitors with paracyclophanes,

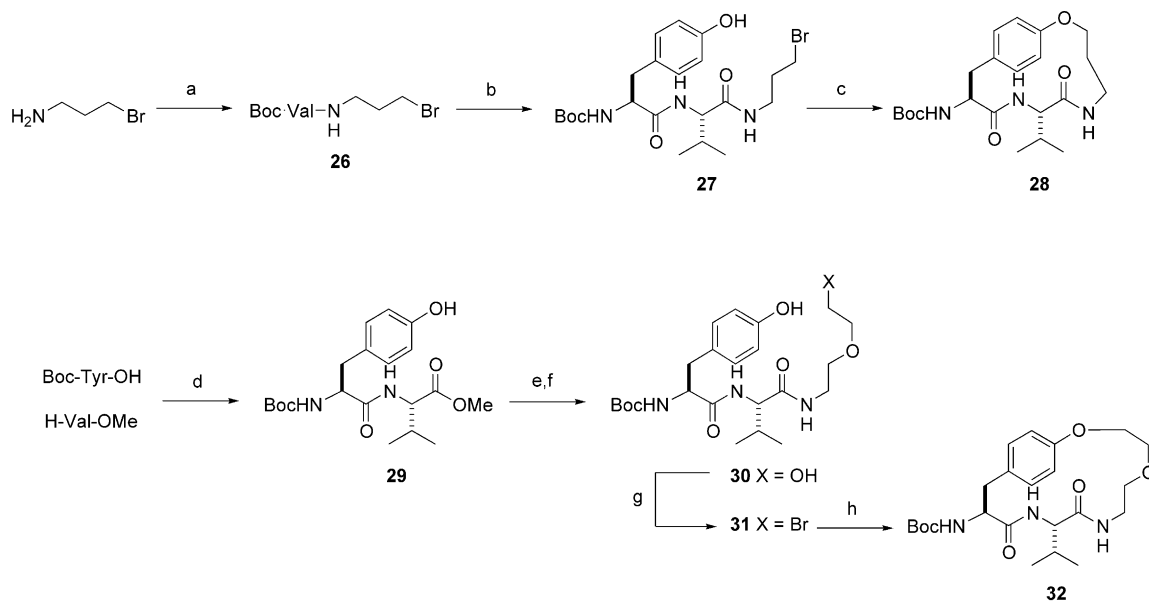


Scheme 2. Reagents and conditions: (a) Boc-Val-OH, HBTU, DIPEA; (b) LiBH₄, THF; (c) PhI(OAc)₂, TEMPO; (d) Zn, VCl₃(thf)₃; (e) 2,2-dimethoxy propane, TsOH; (f) sep. diastereomers; (g) Pd/C, H₂; (h) DIAD, PPh₃; (i) TFA/CH₂Cl₂; (j) BOP, DIPEA, CH₃CN; (k) TFA/H₂O.

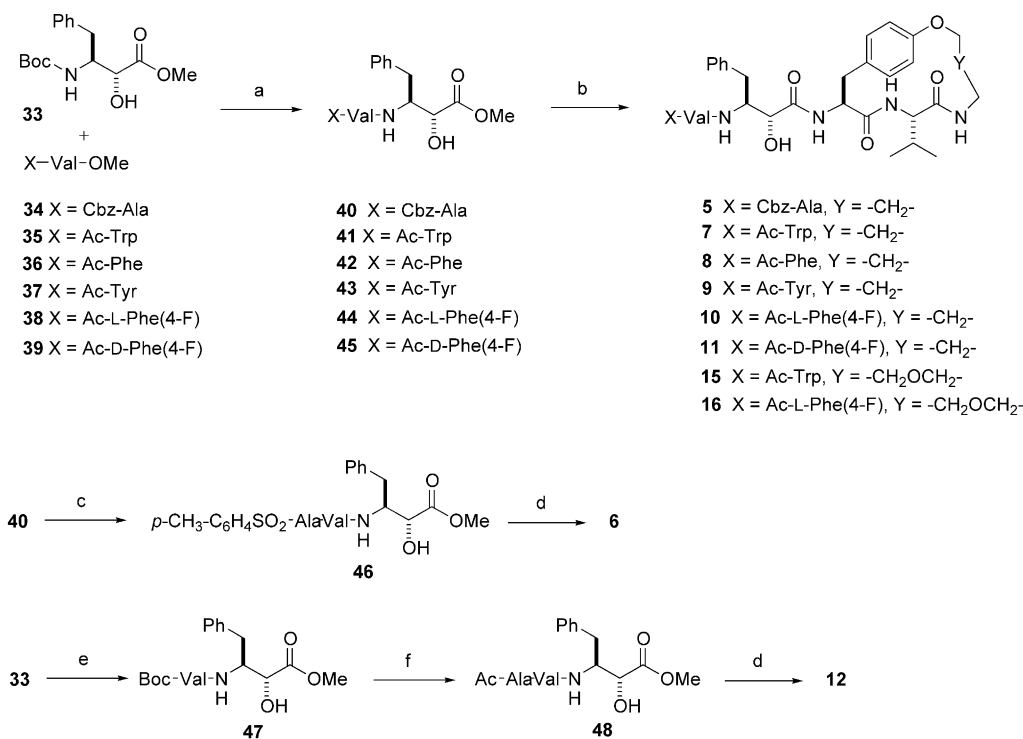
containing oxyethylene substructures, were reported to be water soluble at physiological pH and have potent antiviral activities.^{7g} Therefore, we reasoned that the incorporation of either a 15-(**28**) or 17-(**32**) membered macrocycle into our mono-cyclic inhibitors (Scheme 3), could enhance the binding and the solubility properties of these inhibitors

The mono-cyclic inhibitors **5–12**, **15** and **16** were assembled by appending the macrocycles **28** or **32** to the

appropriate acyclic components **40–46** and **48** after Boc removal and ester hydrolysis (Scheme 4). Macrocyclization of **27** and **31** were achieved efficiently using Cs₂CO₃ in CH₃CN (10 mM) in the presence of tetrabutylammonium iodide (1 mol equiv) at room temperature (Scheme 3). The NMR spectra indicate the aromatic ring in **32** is less constrained than that in **28**, where four distinct unequivalent aromatic protons can be observed. The tripeptide **40–45** were synthesized by coupling the core unit **33**¹⁶ after Boc removal and the



Scheme 3. Reagents and conditions: (a) Boc-Val-OH, HBTU, DIPEA; (b) Boc-Tyr-OH, HBTU, DIPEA; (c) CsCO₃, TBAI, CH₃CN; (d) HBTU, DIPEA; (e) LiOH, MeOH/H₂O; (f) 2-(2-aminoethoxy)ethanol, HBTU, DIPEA; (g) CBr₄, PPh₃; (h) CsCO₃, TBAI, CH₃CN.



Scheme 4. Reagents and conditions: (a) (i) LiOH, MeOH/H₂O, (ii) **33**, TFA/CH₂Cl₂, (iii) HBTU, DIPEA; (b) (i) LiOH, MeOH/H₂O, (ii) **28** or **32**, TFA/CH₂Cl₂, (iii) HBTU, DIPEA; (c) (i) Pd/C, H₂, (ii) *p*-toluene sulfonyl chloride, Et₃N; (d) (i) LiOH, MeOH/H₂O, (ii) **28**, TFA/CH₂Cl₂, (iii) HBTU, DIPEA; (e) (i) TFA/CH₂Cl₂, (ii) Boc-Val-OH, HBTU, DIPEA; (f) (i) TFA/CH₂Cl₂, (ii) Ac-Ala-OH, HBTU, DIPEA.

corresponding dipeptide methyl ester **34–39** after hydrolysis (Scheme 4). Compound **46** was derived from **40** after Cbz removal and reaction with *p*-toluene sulfonyl chloride, while **48** was obtained by coupling of Boc-removed **33** with Boc-Val-OH followed by condensation with Ac-Ala-OH (Scheme 4). In fact, **44** and **45** were prepared from the racemate of Ac-Phe(4-F)-OH and their structural identities were defined by comparing the NMR signals of the same tripeptide **53**. Compound **53** was derived from the coupling product of optically pure Boc-L-Phe (4-F)-OH and H-Val-OMe, followed by deprotection of the Boc group. The product then was coupled to AcOH followed by coupling to Boc-removed **33** to give the tripeptide **53** (Scheme 5), which has the same ^1H and ^{13}C NMR signals as **44**.

Boc removal of **28** or **32** and coupling with tripeptide **40–46** and **48** after saponification afforded mono-cyclic inhibitors **5–12**, **15** and **16** (30–70%). Compound **13** and **14** were prepared in a slightly different procedure and were shown in Scheme 6. Coupling of Boc removed **28** with **33** after hydrolysis provided **49**, which was then reacted subsequently with Boc-Val-OH and Ac-His(1-Trt)-OH under the same deprotection and coupling conditions to afford **13**. The trityl group was then removed with TFA to provide **14**. All inhibitors **5–16** were precipitated out during the work up procedure and the filtered products were pure enough for the characterization by NMR spectroscopy and high-resolution mass spectrometry.

Finally, compounds **55**, **56** were prepared through coupling of **43** after saponification with Boc removed **29** to give **55**, and Boc removed **54** to give **56** (Scheme 7).

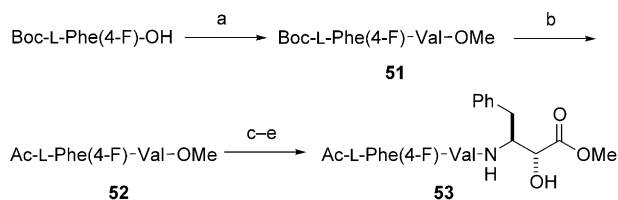
Biological evaluation and discussion

Table 1 summarizes the inhibitory activities of each cyclic compound against FIV, HIV, drug-resistant

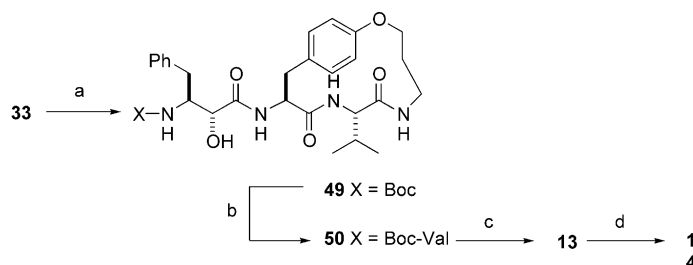
mutant HIV and TL3-resistant mutant HIV PRs. All the mutant enzymes tested here have their mutated residues within the S3 and S3' subsites, which have been identified as the important area, associated with the development of drug resistance. The beneficial effect for the conformationally constrained structures in the bicyclic inhibitors **3** and **4** was not observed to a significant extent although they have also small P3 residues. As compared to TL3 compound **3** was less effective for both HIV/FIV PRs, while compound **4** only retained similar potencies for HIV/FIV PRs as well as the drug-resistant HIV PR mutants, though it has better activities against the TL3-resistant HIV PR mutants. The cyclic inhibitors **7–10**, **15** and **16** have similar potency compared to TL3 against the mutant V82F, but less active against the drug-resistant mutant G48V. However, these inhibitors have higher potency than that of TL3 against V82A and hexa-mutant.

Amongst all the mono-cyclic inhibitors, compounds **7–10**, **15** and **16** containing a relatively large P3 residues and a small N-terminal protecting group still showed significant activity comparable to TL3, with IC_{50} values in the range of 6–10 nM, against HIV PR. They also exhibited remarkable activities toward FIV PR with IC_{50} values 2–3-fold lower compared to TL3. However, when we introduced to the mono-cyclic inhibitors a small residue (e.g., **12**) or a very large P3 residue (e.g., **13**), their activities against FIV PR decreased, while they remained effective against HIV PR. In addition, we found that the incorporation of a P3 ligand with D-configuration (e.g., **11**) lead to about 100-fold reduction in the activity against FIV PR, but did not affect the high activity against HIV PR (IC_{50} 9 nM). These results indicate that, while the P3 binding subsites in HIV PR are highly flexible and can accommodate variety of P3 ligands, however, in FIV PR they are more restricted and the balance between the size of the P3 residue and the N-terminal protecting group seems to be important in order to achieve potent inhibitors.

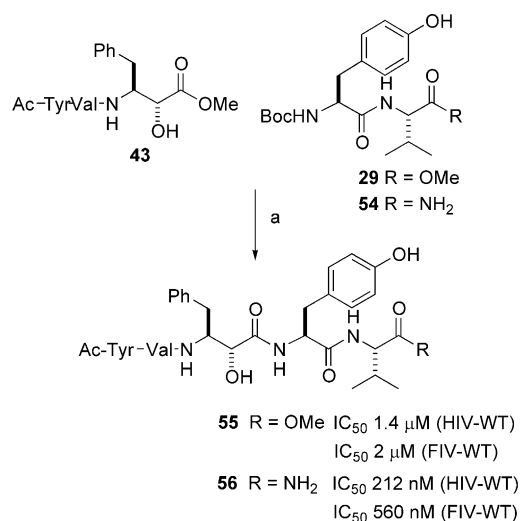
To understand the contribution of the macrocycle on the overall activity of the inhibitors, we also tested the inhibitory potency of pentapeptide **55** and **56**, which are the acyclic analogues of **9**. Compared to **9**, they displayed about 20- to 200-fold less potency against HIV/FIV PRs. Such results may be attributed to the structural mimics of tripeptide (Phe-Val-Ala) in **9** fixed in the extended strand conformation, resulting in an entropic energy gained over the acyclic compounds. Increasing



Scheme 5. Reagents and conditions: (a) H-Val-OMe, HBTU, DIPEA; (b) (i) TFA/ CH_2Cl_2 , (ii) AcOH, HBTU, DIPEA; (c) (i) LiOH, MeOH/ H_2O , (ii) **33**, TFA/ CH_2Cl_2 , (iii) HBTU, DIPEA.



Scheme 6. Reagents and conditions: (a) (i) LiOH, MeOH/ H_2O , (ii) **28**, TFA/ CH_2Cl_2 , (iii) HBTU, DIPEA; (b) (i) TFA/ CH_2Cl_2 , (ii) Boc-Val-OH, HBTU, DIPEA; (c) (i) TFA/ CH_2Cl_2 , (ii) Ac-His(1-Trt)-OH, HBTU, DIPEA; (d) TFA/ H_2O .



Scheme 7. Reagents and conditions: (a) (i) LiOH, MeOH/H₂O, (ii) TFA/CH₂Cl₂, (iii) HBTU, DIPEA.

the ring size from 15- to 17-membered macrocycle (**7**/**10–15/16**) did not affect the IC_{50} values to a significant extent, which was consistent with the results reported earlier.^{7g} The linkers between P1' and P3' may be situated outside the cleft of the active site and that the overall conformation of the P1' and P2' residues are not altered by the size of the rings. Finally, Compound **15** was found to be most effective to inhibit FIV replication in tissue culture at 1.0 μ g/mL (1.2 μ M), which is comparable to TL3 at the same concentration.

Conclusion

In summary, we have described the strategies to introduce the rigid structures in the form of a 15 to 17-membered ring into our mono- and bi-cyclic inhibitors, using the hydroxymethylcarbonyl isostere as a promi-

ing core structure for the design of HIV/FIV PR inhibitors. Several of these inhibitors that were developed in this work, exhibited very potent inhibitory activity against HIV/FIV PR, some drug-resistant and TL3-resistant mutants of HIV PRs. Compound **15**, in particular, is effective against FIV replication in tissue culture and work is continue to study its effectiveness against other FIV/HIV variants.

Experimental

In general, reagents and solvents were used as purchased without further purification. Methylene chloride (CH₂Cl₂) and acetonitrile (CH₃CN) were distilled over calcium hydride and tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone ketyl under argon. Analytical TLC was performed using silica gel 60 F₂₅₄ glass plates (Merck). Flash column chromatography was performed on silica gel 60 Geduran (35–75 μ m, EM Science). NMR (¹H, ¹³C) spectra were recorded either on a Bruker AMX-400, AMX-500 or AMX-600 MHz spectrometer. Coupling constants (*J*) are reported in hertz (δ) relative to tetramethylsilane (TMS, 0.0 ppm) or DMSO (2.49 ppm for ¹H and 39.5 ppm for ¹³C) or CD₃OD (3.30 ppm for ¹H and 49.0 ppm for ¹³C) as internal reference. Dipeptide **34** was provided by Dr. Taekyu Lee.

Method A: general procedure for peptide bond formation

To a solution of a carboxylic acid (1.0 mol equiv) and a free amine (1.0 mol equiv) in dry THF, CH₃CN or DMF (0.2–0.5 M) was added HBTU (1.1 mol equiv) followed by DIPEA (1.1 mol equiv or 2.2 mol equiv if the free amine is in the form of any acid salt). The reaction mixture was stirred at room temperature for 2–4 h and then diluted with EtOAc. The organic layer was washed with 1 M HCl, saturated NaHCO₃, brine, dried

Table 1. Biological activity (IC_{50} nM) of TL3 and cyclic inhibitors **3–16** against FIV-WT, HIV-WT, drug-resistant HIV and TL3-resistant HIV proteases

Inhibitors	FIV PR	HIV PR	Drug-resistant HIV mutants		TL3-resistant HIV mutants	
			HIV (G48V)	HIV (V82F)	HIV (V82A)	HIV (L24I, M46I, F53L, L63P, V77I, V82A)
			IC ₅₀ (nM)			
TL3	72	4	20.5 (5X) ^a	14.9 (4X)	16 (4X)	144 (36X)
3	31	389	nd ^b	nd	nd	nd
4	88	6	34 (6X)	23 (4X)	5 (1X)	23 (4X)
5	95	10	nd	nd	nd	nd
6	147	13	nd	nd	nd	nd
7	49	10	71 (7X)	30 (3X)	10 (1X)	49 (5X)
8	35	7	94 (13X)	32 (4X)	12 (2X)	79 (11X)
9	27	6	57 (9.5X)	26 (4X)	11 (2X)	70 (12X)
10	20	3	27 (9X)	20 (7X)	7 (2X)	33 (11X)
11	2000	9	nd	nd	nd	nd
12	121	6	nd	nd	nd	nd
13	138	17	nd	nd	nd	nd
14	51	18	nd	nd	nd	nd
15	45	5	33 (7X)	nd	nd	29 (6X)
16	37	5	45 (9X)	nd	nd	45 (9X)

^aNumber in parentheses denotes number of fold higher IC_{50} values in inhibition compared to that of the wild-type HIV PR.

^bNot determined.

over MgSO_4 and filtered. The filtrate was concentrated in vacuo and the crude product purified as described in the text below.

Method B: general procedure for Boc removal or hydrolysis of *t*-butyl ester. The protected peptide dissolved in 50% TFA in dry CH_2Cl_2 (~ 0.3 M) or in 4 M HCl in 1,4-dioxane (~ 0.5 M) was stirred at room temperature for 1–3 h. The solvent was removed in vacuo and the remaining TFA/HCl was removed by repeated evaporation from toluene in vacuo to give the TFA/HCl salt of the amine or the free acid.

Method C: general procedure for the hydrolysis of methyl ester. To the methyl ester of any peptide dissolved in a mixture of 40% MeOH in THF (~ 0.5 M) was added LiOH (4.0 mol equiv) and water (0.5–2 mL). The reaction was monitored by TLC and usually took about 2–4 h to complete. Most solvents were removed in vacuo and the residue was diluted in EtOAc. The organic layer was washed with 10% citric acid, brine, dried over MgSO_4 and filtered. The free acid was obtained after removal of the solvent in vacuo.

Compound 17. A mixture of Boc-Val-Tyr(3-Nitro)-OMe¹¹ (6.0 g, 14 mmol), 5-chloro-1-phenyl tetrazole (3.0 g, 17 mmol), and sodium bicarbonate (2.5 g, 30 mmol) in DMAC (70 mL) was heated to 90 °C for 2 days. The reaction mixture was cooled to 0 °C and poured into the iced cold water (450 mL). The resulting solid was filtered and washed thoroughly with water. The solid was further purified by repeated washing with ether–hexane mixture (1:1 v/v) and then dried to give **17** (7.0 g, 88%) as a bright yellow solid: ^1H NMR (500 MHz, CDCl_3) 0.91 (3H, d, $J=6.5$ Hz), 0.95 (3H, d, $J=6.8$ Hz), 1.43 (9H, s), 2.09–2.16 (1H, m), 3.21 (1H, dd, $J=14.0, 6.0$ Hz), 3.33 (1H, dd, $J=14.0, 5.8$ Hz), 3.87 (1H, dd, $J=8.4, 6.3$ Hz), 4.93 (1H, dd, $J=13.1, 6.1$ Hz), 5.01 (1H, d, $J=7.0$ Hz), 6.60 (1H, d, $J=6.9$ Hz), 7.52–7.62 (5H, m), 7.82 (2H, d, $J=8.6$ Hz), 7.99 (1H, s); ^{13}C NMR (125 MHz, CDCl_3) 17.8, 19.2, 28.2, 30.4, 37.1, 52.7, 52.8, 60.1, 80.0, 122.6, 123.9, 127.2, 129.7, 129.8, 132.6, 136.6, 136.9, 140.0, 144.9, 155.8, 159.2, 170.9, 171.8; HRMS (MALDI), calcd for MNa^+ $\text{C}_{27}\text{H}_{33}\text{N}_7\text{O}_8\text{Na}$ m/e 606.2288, found m/e 606.2273.

Compound 18. Cyclohexene (30 mL) was added to the mixture of Pd/C (10%, 0.50 g) and **17** (2.0 g, 3.4 mmol) in EtOH (40 mL) and the mixture heated to reflux under an argon atmosphere for 1 day. The solution was filtered through a pad of Celite and the solvent removed in vacuo. The crude amine was treated with CbzCl (0.80 mL, 5.6 mmol) and DIPEA (1.0 mL, 5.7 mmol) and stirred in CH_2Cl_2 (30 mL) for 1.5 h. The solvent was diluted with EtOAc and washed with saturated NaHCO_3 , brine, dried over MgSO_4 and filtered. The solvent was removed and the crude product purified by flash chromatography on silica gel (hexane–EtOAc = 3:1) to afford **18** (1.0 g, 55%) as a white foam: ^1H NMR (400 MHz, CDCl_3) 0.88 (3H, d, $J=6.8$ Hz), 0.93 (3H, d, $J=6.8$ Hz), 1.37 (9H, s), 2.02–2.13 (1H, m), 3.06 (1H, dd, $J=13.7, 4.4$ Hz), 3.13 (1H, dd, $J=13.8, 5.3$ Hz), 3.71 (3H, s), 3.95 (1H, dd, $J=9.3, 6.3$ Hz), 4.87–

4.93 (1H, m), 5.12–5.23 (2H, ABq, $J=12.1$ Hz), 5.37 (1H, d, $J=9.2$ Hz), 6.47 (1H, d, $J=8.0$ Hz), 6.71 (1H, d, $J=7.6$ Hz), 7.05 (1H, s), 7.19 (1H, t, $J=8.0$ Hz), 7.29–7.40 (5H, m), 7.55 (1H, d, $J=7.8$ Hz), 7.82 (1H, s); ^{13}C NMR (100 MHz, CDCl_3) 17.8, 19.2, 28.2, 30.5, 37.0, 52.3, 52.7, 60.1, 66.8, 80.0, 117.2, 120.1, 123.4, 128.2, 128.4, 129.2, 135.9, 136.1, 138.4, 153.5, 156.1, 171.2, 171.4; HRMS (MALDI), calcd for MH^+ $\text{C}_{28}\text{H}_{38}\text{N}_3\text{O}_7$ m/e 528.2710, found m/e 528.2714.

Aldehyde 19. To a solution of **18** (1.0 g, 1.9 mmol) in THF (15 mL) was added LiBH_4 (85 mg, 3.9 mmol) and MeOH (1 mL). The mixture was stirred at room temperature for 3 h. The reaction was quenched slowly with 1 M HCl (10 mL) and most of the THF removed. The residue was diluted with EtOAc and the aqueous layer separated. The organic layer was washed with saturated NaHCO_3 , brine, dried over MgSO_4 , filtered and the filtrate concentrated in vacuo. To a solution of the above crude alcohol in CH_2Cl_2 (10 mL) was added TEMPO (60 mg, 0.38 mmol) and BAIB (0.70 g, 2.2 mmol) and the mixture stirred at room temperature for 2 h. The mixture was diluted with EtOAc, washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$, saturated NaHCO_3 , brine, dried over MgSO_4 and filtered. The filtrate was concentrated in vacuo and the crude aldehyde **19** used in the next step without purification.

Compound 20. Under argon, Zn (84 mg, 1.3 mmol) was added to a solution of $\text{VCl}_3(\text{thf})_3$ (0.90 g, 2.4 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature until a color change from red to green. A solution of **19** (0.60 g, 1.2 mmol) in CH_2Cl_2 (5 mL) was added and the resulting mixture stirred for 5 h. An aqueous 1 M HCl (5 mL) was added and stirred for 15 min. The mixture was extracted with EtOAc and the combined organic layers washed with saturated NaHCO_3 , brine, dried over MgSO_4 and concentrated in vacuo. To a solution of the crude product in CH_2Cl_2 (10 mL) was added 2,2-dimethoxy propane (10 mL) and TsOH (40 mg) and the mixture stirred for 1 h. The solvent was removed and the desired diastereomer separated by flash chromatography on silica gel (hexane–EtOAc = 1:1) to afford **20** (0.30 g, 48%) as a white foam: ^1H NMR (600 MHz, $\text{MeOH}-d_4$) 0.60 (6H, d, $J=6.5$ Hz), 0.69 (6H, d, $J=6.6$ Hz), 1.39 (6H, s), 1.42 (18H, s), 1.80–1.90 (2H, m), 2.74–2.85 (4H, m), 3.64 (2H, s), 3.80 (2H, d, $J=6.6$ Hz), 4.37 (2H, dd, $J=9.2, 5.7$ Hz), 5.12–5.21 (4H, ABq, $J=12.5$ Hz), 6.91 (2H, d, $J=7.4$ Hz), 7.14 (2H, t, $J=7.7$ Hz), 7.22–7.42 (14H, m); ^{13}C NMR (150 MHz, $\text{MeOH}-d_4$) 18.0, 19.8, 27.8, 28.7, 31.7, 40.0, 50.2, 61.8, 67.5, 80.1, 80.7, 109.9, 118.0, 120.9, 125.1, 129.1, 129.5, 129.9, 138.2, 140.1, 155.8, 157.9, 174.2; HRMS (MALDI), calcd for MCs^+ $\text{C}_{57}\text{H}_{76}\text{N}_6\text{O}_{12}\text{Cs}$ m/e 1169.4576, found m/e 1169.4524.

Bicyclic precursor 21. Compound **20** (0.20 g, 0.19 mmol) was hydrogenated (2 h) with 10% Pd/C in MeOH to give the diamine of **20**. The crude diamine was then coupled with Z-Glu-O^tBu (0.2 g, 0.68 mmol) in CH_3CN according to the method A and purified by flash chromatography on silica gel (hexane–EtOAc = 1:1) to afford **21** (0.18 g, 66%) as a pale brown foam: ^1H NMR

(500 MHz, MeOH- d_4) 0.64 (6H, d, J = 6.5 Hz), 0.69 (6H, d, J = 6.5 Hz), 1.40 (6H, s), 1.42 (18H, s), 1.45 (18H, s), 1.80–1.90 (2H, m), 1.91–2.01 (2H, m), 2.15–2.25 (2H, m), 2.46 (4H, t, J = 7.5 Hz), 2.73–2.90 (4H, m), 3.64 (2H, s), 3.80 (2H, t, J = 6.3 Hz), 4.11 (2H, dd, J = 9.4, 4.8 Hz), 4.35–4.47 (2H, m), 5.00–5.15 (4H, ABq, J = 12.4 Hz), 6.53 (2H, d, J = 9.3 Hz), 6.97 (2H, d, J = 7.3 Hz), 7.16 (2H, t, J = 7.7 Hz), 7.23–7.45 (12H, m), 7.53 (2H, d, J = 9.3 Hz); ^{13}C NMR (125 MHz, MeOH- d_4) 18.1, 19.8, 27.8, 28.3, 28.4, 28.8, 31.8, 34.2, 40.0, 50.2, 55.9, 61.9, 67.7, 80.1, 80.7, 82.9, 110.0, 119.4, 122.2, 126.1, 128.9, 129.0, 129.5, 129.9, 138.2, 139.7, 140.1, 157.8, 158.7, 173.0, 174.3, 174.4; HRMS (MALDI), calcd for MCs^+ $\text{C}_{75}\text{H}_{106}\text{N}_8\text{O}_{18}\text{Cs}$ m/e 1539.6679, found m/e 1539.6600.

Bicyclic inhibitor 3. Boc removal and hydrolysis of *t*-Bu ester in **21** (88 mg, 0.063 mmol) were performed according to the method B. To the crude deprotected product in CH_3CN (3 mM) was added BOP (0.10 g, 0.23 mmol) and DIPEA (0.06 mL, 0.34 mmol) and the solution stirred for 38 h. Most of the solvent was removed, the solid filtered and washed with CH_3CN and Et_2O . The solid was redissolved in TFA (2 mL) and H_2O (0.2 mL) added at 0 °C. The mixture was stirred for 2 h and the solvent removed in vacuo. The residue was triturated in Et_2O and the solid filtered. The solid was washed with Et_2O to afford **3** (40 mg, 60%) as a pale brown solid: ^1H NMR (500 MHz, DMSO- d_6) 0.60–0.90 (12H, m), 1.60–2.10 (10H, m), 2.58 (2H, d, J = 15.4 Hz), 2.86 (2H, t, J = 13.4 Hz), 3.97–4.27 (6H, m), 4.69 (2H, s), 4.97 (4H, br s), 6.80–7.40 (24H, m), 7.83 (2H, br s); HRMS (MALDI), calcd for MNa^+ $\text{C}_{54}\text{H}_{66}\text{N}_8\text{O}_{12}$ m/e 1041.4692, found m/e 1041.4689.

Aldehyde 22. This was prepared from Boc-Val-Tyr (OBz)-OMe according to the procedure as described for **19** and the crude aldehyde **22** was used in the next step without purification.

Compound 23. This was prepared from **22** according to the procedure as described for **20**. Separation of the desired diastereomer by flash chromatography on silica gel (hexane–EtOAc = 2:1) afforded **23** (0.22 g, 60%) as a white foam: ^1H NMR (500 MHz, MeOH- d_4) 0.70 (6H, d, J = 5.5 Hz), 0.71 (6H, d, J = 5.5 Hz), 1.39 (6H, s), 1.43 (18H, s), 1.81–1.91 (2H, m), 2.75 (4H, d, J = 7.3 Hz), 3.63 (2H, s), 3.79 (2H, d, J = 6.6 Hz), 4.29 (2H, t, J = 7.2 Hz), 5.01 (4H, s), 6.85 (4H, d, J = 8.4 Hz), 7.11 (4H, d, J = 8.1 Hz), 7.25–7.42 (10H, m); ^{13}C NMR (150 MHz, MeOH- d_4) 18.2, 19.9, 27.7, 28.8, 31.9, 39.3, 50.5, 61.8, 71.1, 79.8, 80.7, 109.9, 116.0, 128.5, 128.8, 129.4, 131.3, 131.6, 138.9, 157.8, 159.0, 174.0; HRMS (MALDI), calcd for MNa^+ $\text{C}_{55}\text{H}_{74}\text{N}_4\text{O}_{10}\text{Na}$ m/e 973.5297, found m/e 973.5312.

Bicyclic precursor 25. Compound **23** (0.36 g, 0.47 mmol) was hydrogenated (2 h) with 10% Pd/C in MeOH to give the diamine of **25**. To a solution of the crude diamine, **24** (0.38 g, 1.2 mmol) and PPh_3 (0.50 g, 1.9 mmol) in CH_2Cl_2 (15 mL) was added DIAD (0.4 mL, 2.0 mmol). The mixture stirred for 17 h and the solvent removed. The crude product was purified by flash chromatography on silica gel (hexane–EtOAc = 2:1) to

afford **25** (0.38 g, 47%) as a white foam: ^1H NMR (500 MHz, MeOH- d_4) 0.71 (12H, d, J = 6.2 Hz), 1.39 (6H, s), 1.43 (18H, s), 1.44 (18H, s), 1.72–1.89 (8H, m), 1.90–1.97 (2H, m), 2.74 (4H, d, J = 7.4 Hz), 3.62 (2H, s), 3.75–3.82 (2H, m), 3.86–3.96 (4H, m), 4.06–4.13 (2H, m), 4.24–4.35 (2H, m), 5.03–5.14 (4H, ABq, J = 12.5 Hz), 6.39 (2H, d, J = 9.2 Hz), 6.76 (4H, d, J = 8.1 Hz), 7.09 (4H, d, J = 8.4 Hz), 7.24–7.37 (10H, m), 7.52 (2H, d, J = 9.2 Hz); ^{13}C NMR (150 MHz, MeOH- d_4) 18.3, 19.9, 26.8, 27.7, 28.3, 28.8, 29.6, 31.9, 39.4, 50.6, 56.0, 61.7, 67.6, 68.3, 79.7, 80.6, 82.8, 109.8, 115.6, 128.8, 129.0, 129.4, 131.2, 138.3, 157.8, 158.6, 159.0, 173.3, 174.0; HRMS (MALDI), calcd for MNa^+ $\text{C}_{75}\text{H}_{108}\text{N}_6\text{O}_{18}\text{Na}$ m/e 1403.7612, found m/e 1403.7599.

Bicyclic inhibitor 4. Preparation was as described for **3** and afforded **4** (11 mg, 46%) as a off-white solid: ^1H NMR (600 MHz, DMSO- d_6) 0.78 (6H, d, J = 7.0 Hz), 0.81 (6H, d, J = 6.5 Hz), 1.27–1.60 (8H, m), 1.69–1.78 (2H, m), 2.46 (2H, d, J = 10.9 Hz), 2.64 (2H, t, J = 12.3 Hz), 3.95–4.24 (10H, m), 4.58 (2H, t, J = 8.3 Hz), 4.97 (4H, s), 6.62 (2H, d, J = 8.4 Hz), 6.74 (2H, d, J = 8.0 Hz), 6.92–7.00 (4H, m), 7.06 (2H, d, J = 7.9 Hz), 7.24–7.36 (10H, m), 7.39 (2H, d, J = 10.1 Hz), 7.48 (2H, d, J = 8.8 Hz); ^{13}C NMR (125 MHz, DMSO- d_6) 18.2, 19.1, 22.0, 28.3, 31.9, 37.9, 51.1, 53.4, 56.7, 65.1, 67.5, 73.6, 116.0, 118.4, 127.7, 128.2, 128.3, 129.8, 130.6, 131.7, 137.2, 154.3, 155.2, 169.6, 170.3; HRMS (MALDI), calcd for MH^+ $\text{C}_{54}\text{H}_{69}\text{N}_6\text{O}_{12}$ m/e 993.4968, found m/e 993.4936.

Compound 26. This was prepared from 3-bromopropyl amine (2.8 g, 13 mmol) and Boc-Val-OH (2.5 g, 12 mmol) in THF according to the method A and purified by flash chromatography on silica gel (hexane–EtOAc = 2:1) to afford **26** (3.5 g, 90%) as a white solid: ^1H NMR (500 MHz, CDCl_3) 0.92 (3H, d, J = 7.0 Hz), 0.96 (3H, d, J = 6.6 Hz), 1.45 (9H, s), 2.05–2.19 (3H, m), 3.38–3.46 (4H, m), 3.84 (1H, dd, J = 8.5, 6.3 Hz), 5.05 (1H, br s), 6.27 (1H, br s); ^{13}C NMR (125 MHz, CDCl_3) 17.9, 19.3, 28.3, 30.5, 30.7, 32.0, 37.9, 60.2, 80.0, 156.0, 172.0; MS (MALDI): m/z = 237 [$\text{M}-\text{Boc}$] $^+$.

Cyclic precursor 27. This was prepared from **26** (2.9 g, 8.6 mmol) and Boc-Tyr-OH (2.3 g, 8.2 mmol) in THF according to the method A and purified by flash chromatography on silica gel (hexane–EtOAc = 1:1) to afford **27** (3.9 g, 95%) as a white foam: ^1H NMR (500 MHz, CDCl_3) 0.86 (3H, d, J = 6.5 Hz), 0.90 (3H, d, J = 6.7 Hz), 1.41 (9H, s), 1.98–2.08 (2H, m), 2.10–2.28 (1H, m), 2.85–3.05 (2H, m), 3.24–3.33 (1H, m), 3.35–3.45 (3H, m), 4.21 (1H, t, J = 7.5 Hz), 4.32–4.40 (1H, m), 5.29 (1H, d, J = 5.8 Hz), 6.76 (2H, d, J = 8.1 Hz), 6.88 (1H, d, J = 8.5 Hz), 6.98 (2H, d, J = 8.2 Hz), 7.71 (1H, s); ^{13}C NMR (125 MHz, CDCl_3) 17.7, 19.2, 28.2, 30.2, 30.7, 32.1, 37.0, 38.0, 56.2, 58.9, 80.7, 115.7, 127.2, 130.2, 155.5, 155.9, 171.3, 172.1; HRMS (MALDI), calcd for MNa^+ $\text{C}_{22}\text{H}_{34}\text{BrN}_3\text{O}_5\text{Na}$ m/e 522.1574, found m/e 522.1582.

Macrocycle 28. A solution of **27** (0.71 g, 1.4 mmol), cesium carbonate (0.55 g, 1.7 mmol) and tetrabutylammonium iodide (0.55 g, 1.5 mmol) in CH_3CN

(150 mL) was stirred at room temperature for 20 h. Most of the solvent was removed and then diluted with EtOAc. The organic layer was washed with 1 M HCl, saturated NaHCO₃, brine, dried over MgSO₄ and filtered. The crude product was purified by flash chromatography on silica gel (hexane–EtOAc = 1:3) to afford **28** (0.26 g, 44%) as a white solid: ¹H NMR (400 MHz, CDCl₃) 0.79 (3H, d, *J* = 6.7 Hz), 0.82 (3H, d, *J* = 6.6 Hz), 1.46 (9H, s), 1.70–1.85 (1H, m), 1.94–2.08 (1H, m), 2.31–2.46 (1H, m), 2.63 (1H, t, *J* = 11.7 Hz), 2.86–3.00 (1H, m), 3.23 (1H, dd, *J* = 12.6, 6.8 Hz), 3.50 (1H, t, *J* = 7.6 Hz), 3.60–3.74 (1H, m), 4.11–4.30 (2H, m), 4.42 (1H, dt, *J* = 12.6, 4.8 Hz), 5.15–5.24 (1H, m), 5.40 (1H, d, *J* = 8.5 Hz), 5.80 (1H, d, *J* = 7.3 Hz), 6.79 (1H, dd, *J* = 8.5, 2.6 Hz), 6.86 (1H, dd, *J* = 8.2, 2.3 Hz), 7.00 (1H, dd, *J* = 8.2, 2.1 Hz), 7.17 (1H, d, *J* = 8.5 Hz); ¹³C NMR (125 MHz, DMSO-*d*₆) 18.4, 18.9, 26.6, 28.1, 31.8, 35.5, 37.0, 56.9, 57.8, 67.9, 77.8, 117.7, 118.2, 129.5, 130.9, 154.9, 157.4, 169.8, 170.7; HRMS (MALDI), calcd for MNa⁺ C₂₂H₃₃N₃O₅Na *m/e* 442.2318, found *m/e* 442.2308.

Compound 29. This was prepared from Boc-Tyr-OH (0.50 g, 1.8 mmol) and H-Val-OMe-HCl (1.33 g, 2.0 mmol) in THF according to the method A. The crude product was triturated in EtOAc–Et₂O (1:3 v/v) and the solid filtered to afford **29** (0.67 g, 95%) as a white solid: ¹H NMR (600 MHz, MeOH-*d*₄) 0.91 (3H, d, *J* = 6.6 Hz), 0.92 (3H, d, *J* = 7.0 Hz), 1.37 (9H, s), 2.05–2.15 (1H, m), 2.73 (1H, dd, *J* = 13.6, 8.8 Hz), 2.80 (3H, s), 2.96 (1H, dd, *J* = 14.0, 5.9 Hz), 3.67 (3H, s), 4.27 (1H, dd, *J* = 8.5, 5.9 Hz), 4.30 (1H, d, *J* = 6.3 Hz), 6.68 (2H, d, *J* = 8.1 Hz), 7.03 (2H, d, *J* = 8.5 Hz); ¹³C NMR (150 MHz, MeOH-*d*₄) 18.4, 19.4, 28.7, 32.1, 38.3, 52.5, 57.5, 59.1, 80.6, 116.1, 129.1, 131.4, 157.2, 157.6, 173.2, 174.6; HRMS (MALDI), calcd for MNa⁺ C₂₀H₃₀N₂O₆Na *m/e* 417.1996, found *m/e* 417.2004.

Compound 30. **29** (0.73 g, 1.9 mmol) was deprotected (method C) to give the corresponding free acid followed by coupling with 2-(2-aminoethoxy)ethanol (0.20 g, 1.9 mmol) in CH₃CN–DMF (25 mL, 4:1 v/v) according to the method A. After stirring at room temperature for 2.5 h and normal aqueous work up, the crude product was purified by flash chromatography on silica gel (EtOAc) to afford **30** (0.34 g, 39%) as a white foam: ¹H NMR (400 MHz, MeOH-*d*₄) 0.92 (6H, d, *J* = 6.8 Hz), 1.37 (9H, s), 1.96–2.09 (1H, m), 2.73 (1H, dd, *J* = 13.5, 8.8 Hz), 2.97 (1H, dd, *J* = 12.6, 5.9 Hz), 3.32–3.39 (1H, m), 3.48–3.56 (4H, m), 3.62–3.69 (2H, m), 4.13 (1H, d, *J* = 7.3 Hz), 4.24 (1H, dd, *J* = 8.8, 5.9 Hz), 6.68 (2H, d, *J* = 8.5 Hz), 7.03 (2H, d, *J* = 8.2 Hz); ¹³C NMR (150 MHz, MeOH-*d*₄) 18.5, 19.6, 28.6, 32.2, 38.1, 40.3, 57.7, 60.0, 62.2, 70.4, 73.4, 80.7, 116.2, 129.2, 131.3, 157.2, 173.3, 174.4; HRMS (MALDI), calcd for MNa⁺ C₂₃H₃₇N₃O₇Na *m/e* 490.2524, found *m/e* 490.2508.

Cyclic precursor 31. To a solution of **30** (1.0 g, 2.2 mmol) and triphenylphosphine (0.64 g, 2.4 mmol) in CH₂Cl₂ (20 mL) was added carbon tetrabromide (0.80 g, 2.4 mmol). The reaction mixture was stirred at room temperature for 2 h and the solvent removed in vacuo. Purification by flash chromatography on silica gel

(CHCl₃–EtOAc = 1:1) afforded **31** (0.70 g, 66%) as a white solid: ¹H NMR (500 MHz, MeOH-*d*₄) 0.92 (3H, d, *J* = 6.3 Hz), 0.93 (3H, d, *J* = 6.6 Hz), 1.37 (9H, s), 2.00–2.10 (1H, m), 2.73 (1H, dd, *J* = 14.0, 8.8 Hz), 2.98 (1H, dd, *J* = 13.6, 5.5 Hz), 3.29–3.32 (1H, m), 3.35–3.42 (1H, m), 3.48 (2H, t, *J* = 5.9 Hz), 3.54 (2H, t, *J* = 5.5 Hz), 3.75 (2H, t, *J* = 6.2 Hz), 4.13 (1H, d, *J* = 7.3 Hz), 4.25 (1H, dd, *J* = 8.8, 5.9 Hz), 6.68 (2H, d, *J* = 8.5 Hz), 7.03 (2H, d, *J* = 8.1 Hz); ¹³C NMR (150 MHz, MeOH-*d*₄) 18.6, 19.7, 28.7, 31.3, 32.2, 38.1, 40.3, 57.7, 60.0, 70.2, 72.1, 80.7, 116.2, 129.2, 131.3, 157.2, 157.7, 173.3, 174.4; HRMS (MALDI), calcd for MNa⁺ C₂₃H₃₆BrN₃O₆Na *m/e* 552.1680, found *m/e* 552.1669.

Macrocycle 32. Preparation was as described for **28** and the crude product was purified by flash chromatography on silica gel (hexane–EtOAc = 1:3) to afford **32** (75 mg, 36%) as a white solid: ¹H NMR (500 MHz, MeOH-*d*₄) 0.80 (3H, d, *J* = 6.6 Hz), 0.82 (3H, d, *J* = 6.6 Hz), 1.44 (9H, s), 2.00–2.13 (1H, m), 2.77 (1H, t, *J* = 12.5 Hz), 2.89 (1H, dd, *J* = 12.9, 4.8 Hz), 2.59–3.06 (1H, m), 3.65–3.81 (2H, m), 4.00–4.08 (1H, m), 4.18–4.29 (2H, m), 4.30–4.39 (1H, m), 6.86 (1H, d, *J* = 7.4 Hz), 6.90 (2H, d, *J* = 8.8 Hz), 7.00 (1H, br s), 7.42 (1H, d, *J* = 8.1 Hz); ¹³C NMR (150 MHz, MeOH-*d*₄) 17.9, 19.4, 28.7, 32.9, 38.4, 41.1, 58.2, 59.5, 68.4, 71.2, 73.3, 80.5, 117.0, 129.7, 131.0, 157.4, 159.6, 172.7, 174.2; HRMS (MALDI), calcd for MNa⁺ C₂₃H₃₅N₃O₆Na *m/e* 472.2418, found *m/e* 472.2418.

Dipeptide 35. This was prepared from Ac-Trp-OH (2.0 g, 8.1 mmol) and H-Val-OMe-HCl (1.5 g, 9.0 mmol) in THF according to the method A and purified by flash chromatography on silica gel (hexane–EtOAc = 1:2 gradient to EtOAc) to afford **35** (2.6 g, 89%) as a white foam: ¹H NMR (400 MHz, MeOH-*d*₄) 0.88 (6H, d, *J* = 6.8 Hz), 1.91 (3H, s), 2.01–2.10 (1H, m), 3.08 (1H, dd, *J* = 14.4, 7.6 Hz), 3.22 (1H, dd, *J* = 14.7, 6.8 Hz), 3.61 (3H, s), 4.27 (1H, d, *J* = 6.5 Hz), 4.70 (1H, t, *J* = 7.2 Hz), 6.96–7.10 (3H, m), 7.31 (1H, d, *J* = 7.9 Hz), 7.58 (1H, d, *J* = 7.9 Hz); ¹³C NMR (150 MHz, MeOH-*d*₄) 18.5, 19.4, 22.4, 28.9, 32.0, 38.9, 52.4, 55.6, 59.2, 110.8, 112.2, 119.3, 119.7, 122.3, 124.5, 128.8, 138.0, 173.1, 173.2, 174.3; HRMS (MALDI), calcd for MNa⁺ C₁₉H₂₅N₃O₄Na *m/e* 382.1737, found *m/e* 382.1749.

Dipeptide 36. This was prepared from Ac-Phe-OH (1.0 g, 4.9 mmol) and H-Val-OMe-HCl (0.81 g, 4.9 mmol) in THF according to the method A and purified by flash chromatography on silica gel (hexane–EtOAc = 1:1) to afford **36** (1.3 g, 83%) as a white solid: ¹H NMR (400 MHz, MeOH-*d*₄) 0.92 (3H, d, *J* = 6.6 Hz), 0.93 (3H, d, *J* = 7.0 Hz), 1.88 (3H, s), 2.06–2.14 (1H, m), 2.86 (1H, dd, *J* = 13.9, 9.2 Hz), 3.09 (1H, dd, *J* = 14.0, 5.9 Hz), 3.66 (3H, s), 4.30 (1H, d, *J* = 6.3 Hz), 4.68 (1H, dd, *J* = 8.8, 5.9 Hz), 7.17–7.21 (1H, m), 7.22–7.28 (4H, m); ¹³C NMR (100 MHz, MeOH-*d*₄) 18.5, 19.4, 22.3, 31.9, 38.8, 52.5, 55.9, 59.2, 127.7, 129.4, 130.3, 138.4, 173.1, 173.2, 173.9; HRMS (MALDI), calcd for MNa⁺ C₁₇H₂₄N₂O₄Na *m/e* 343.1628, found *m/e* 343.1629.

Dipeptide 37. This was prepared from Ac-Tyr-OH (2.0 g, 9.0 mmol) and H-Val-OMe-HCl (1.5 g, 9.0 mmol)

in THF according to the method A and purified by flash chromatography on silica gel (hexane–EtOAc = 1:2 gradient to EtOAc) to afford **37** (3.0 g, 98%) as a white foam: ^1H NMR (600 MHz, MeOH- d_4) 0.91 (3H, d, J = 6.5 Hz), 0.92 (3H, d, J = 6.6 Hz), 1.90 (3H, s), 2.04–2.11 (1H, m), 2.77 (1H, dd, J = 14.0, 8.8 Hz), 2.96 (1H, dd, J = 14.0, 6.6 Hz), 3.66 (3H, s), 4.27 (1H, d, J = 6.1 Hz), 4.58 (1H, dd, J = 8.8, 6.6 Hz), 6.67 (2H, d, J = 8.3 Hz), 7.04 (2H, d, J = 8.3 Hz); ^{13}C NMR (125 MHz, MeOH- d_4) 18.5, 19.4, 22.3, 32.0, 38.1, 38.9, 52.5, 56.3, 59.2, 116.1, 128.9, 131.3, 157.3, 173.1, 173.2, 174.0; HRMS (MALDI), calcd for MNa^+ $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_5\text{Na}$ m/e 359.1577, found m/e 359.1570.

Dipeptides 38 and 39. These were prepared from a racemate of Ac-*p*-F-Phe-OH (1.0 g, 4.4 mmol) and H-Val-OMe-HCl (0.75 g, 4.5 mmol) in THF according to the method A. The crude product was triturated in Et₂O and the solid filtered to afford the diastereomeric mixture of **38** and **39** (1.4 g, 95%) as a white solid: ^1H NMR (500 MHz, MeOH- d_4) 0.78 (3H, d, J = 7.0 Hz), 0.79 (3H, d, J = 7.0 Hz), 0.91 (3H, d, J = 6.6 Hz), 0.92 (3H, d, J = 6.6 Hz), 1.89 (3H, s), 1.90 (3H, s), 1.97–2.05 (1H, m), 2.05–2.14 (1H, m), 2.85 (1H, dd, J = 14.3, 8.8 Hz), 2.88 (1H, dd, J = 13.9, 8.1 Hz), 3.03 (1H, dd, J = 13.6, 7.0 Hz), 3.05 (1H, dd, J = 14.0, 6.3 Hz), 3.67 (3H, s), 3.69 (3H, s), 4.20 (1H, d, J = 5.9 Hz), 4.29 (1H, d, J = 6.2 Hz), 4.65 (1H, dd, J = 8.5, 6.3 Hz), 4.70 (1H, t, J = 7.7 Hz), 6.95–7.01 (4H, m), 7.21–7.27 (4H, m); ^{13}C NMR (125 MHz, MeOH- d_4) 18.5, 19.4, 22.3, 22.4, 31.7, 32.0, 38.0, 38.5, 52.4, 55.9, 59.2, 59.3, 115.9 ($^2J_{\text{F-C}}$ = 21.9 Hz), 116.0 ($^2J_{\text{F-C}}$ = 21.9 Hz), 132.1 ($^3J_{\text{F-C}}$ = 6.7 Hz), 132.2 ($^3J_{\text{F-C}}$ = 6.7 Hz), 134.3, 163.2 ($^1J_{\text{F-C}}$ = 242.3 Hz), 163.3 ($^1J_{\text{F-C}}$ = 242.3 Hz), 172.9, 173.0, 173.1, 173.2, 173.4, 173.7; HRMS (MALDI), calcd for MNa^+ $\text{C}_{17}\text{H}_{23}\text{FN}_2\text{O}_4\text{Na}$ m/e 361.1534, found m/e 361.1523.

Tripeptide 40. **33** (0.47 g, 1.5 mmol) was deprotected (method B) to give the corresponding TFA salt and **34** (0.50 g, 1.6 mmol) deprotected (method C) to give the corresponding free acid. The TFA salt and the free acid were then coupled in THF according to the method A. The crude product was purified by flash chromatography on silica gel (hexane–EtOAc = 1:1 gradient to 1/2) to afford **40** (0.60 g, 77%) as a white foam: ^1H NMR (400 MHz, MeOH- d_4) 0.84 (6H, d, J = 6.8 Hz), 1.30 (3H, d, J = 7.3 Hz), 1.91–2.00 (1H, m), 2.81 (1H, dd, J = 13.5, 7.3 Hz), 2.94 (1H, dd, J = 13.2, 8.2 Hz), 3.64 (3H, s), 4.09 (1H, d, J = 1.8 Hz), 4.11–4.21 (2H, m), 4.45–4.54 (1H, m), 5.08 (2H, s), 7.15–7.40 (10H, m); ^{13}C NMR (150 MHz, MeOH- d_4) 18.2, 18.3, 19.8, 32.1, 38.5, 52.6, 54.9, 55.8, 60.0, 67.6, 71.3, 127.6, 128.9, 129.0, 129.5, 130.4, 138.2, 139.2, 158.3, 172.9, 174.8, 175.4; HRMS (MALDI), calcd for MNa^+ $\text{C}_{27}\text{H}_{35}\text{N}_3\text{O}_7\text{Na}$ m/e 536.2367, found m/e 536.2359.

Tripeptide 41. This was prepared from **33** and **35** according to the procedure as described for **40**. The crude product was triturated in EtOAc–Et₂O (1:1 v/v) and the solid filtered to afford **41** (0.54 g, 87%) as a white solid: ^1H NMR (600 MHz, MeOH- d_4) 0.81 (3H, d, J = 6.6 Hz), 0.82 (3H, d, J = 6.5 Hz), 1.89 (3H, s), 1.92–1.99 (1H, m), 2.78 (1H, dd, J = 13.7, 7.5 Hz), 2.92

(1H, dd, J = 13.2, 8.6 Hz), 3.06 (1H, dd, J = 15.0, 8.8 Hz), 3.23 (1H, dd, J = 14.9, 5.7 Hz), 3.64 (3H, s), 4.08 (1H, d, J = 2.2 Hz), 4.16 (1H, d, J = 7.0 Hz), 4.44–4.49 (1H, m), 4.71 (1H, dd, J = 8.8, 5.3 Hz), 6.98–7.02 (1H, m), 7.04–7.08 (2H, m), 7.13–7.18 (1H, m), 7.23–7.28 (4H, m), 7.29 (1H, d, J = 8.3 Hz), 7.61 (1H, d, J = 7.9 Hz); ^{13}C NMR (150 MHz, MeOH- d_4) 18.4, 19.7, 22.4, 28.7, 32.1, 38.5, 52.6, 54.9, 55.5, 60.1, 71.3, 111.1, 112.3, 119.4, 119.8, 122.4, 124.4, 127.6, 128.8, 129.5, 130.4, 138.0, 139.2, 172.9, 173.3, 174.0, 174.8; HRMS (MALDI), calcd for MNa^+ $\text{C}_{29}\text{H}_{36}\text{N}_4\text{O}_6\text{Na}$ m/e 559.2527, found m/e 559.2529.

Tripeptide 42. This was prepared from **33** and **36** according to the procedure as described for **40**. The crude product was triturated in EtOAc–Et₂O (1:5 v/v) and the solid filtered to afford **42** (0.15 g, 94%) as a white solid: ^1H NMR (500 MHz, MeOH- d_4) 0.86 (3H, d, J = 6.6 Hz), 0.87 (3H, d, J = 6.6 Hz), 1.87 (3H, s), 1.93–2.01 (1H, m), 2.78–2.87 (2H, m), 2.94 (1H, dd, J = 13.6, 8.5 Hz), 3.09 (1H, dd, J = 14.3, 5.2 Hz), 3.65 (3H, s), 4.09 (1H, d, J = 2.2 Hz), 4.14 (1H, d, J = 7.0 Hz), 4.44–4.50 (1H, m), 4.63 (1H, dd, J = 9.5, 5.1 Hz), 7.15–7.20 (2H, m), 7.22–7.29 (8H, m); ^{13}C NMR (125 MHz, MeOH- d_4) 18.5, 19.5, 22.3, 32.1, 38.6, 52.6, 54.9, 55.9, 59.2, 60.1, 71.3, 127.6, 127.7, 129.4, 129.6, 130.2, 130.4, 138.6, 139.2, 172.8, 173.2, 173.6, 174.8; HRMS (MALDI), calcd for MNa^+ $\text{C}_{27}\text{H}_{35}\text{N}_3\text{O}_6\text{Na}$ m/e 520.2418, found m/e 520.2433.

Tripeptide 43. This was prepared from **33** and **37** according to the procedure as described for **40**. The crude product was triturated in EtOAc–Et₂O (1:2 v/v) and the solid filtered to afford **43** (0.67 g, 82%) as a white solid: ^1H NMR (400 MHz, MeOH- d_4) 0.85 (3H, d, J = 6.8 Hz), 0.86 (3H, d, J = 6.8 Hz), 1.89 (3H, s), 1.93–2.01 (1H, m), 2.73 (1H, dd, J = 14.1, 9.7 Hz), 2.82 (1H, dd, J = 13.5, 7.0 Hz), 2.95 (1H, dd, J = 13.5, 9.5 Hz), 2.99 (1H, dd, J = 14.4, 5.0 Hz), 3.64 (3H, s), 4.08 (1H, d, J = 2.4 Hz), 4.17 (1H, d, J = 7.0 Hz), 4.45–4.51 (1H, m), 4.58 (1H, dd, J = 9.4, 5.0 Hz), 6.68 (2H, d, J = 8.5 Hz), 7.05 (2H, d, J = 8.5 Hz), 7.14–7.21 (1H, m), 7.23–7.32 (4H, m); ^{13}C NMR (100 MHz, MeOH- d_4) 18.5, 19.8, 22.3, 32.1, 37.9, 38.6, 52.6, 54.9, 56.3, 60.1, 71.2, 116.2, 127.6, 129.2, 129.6, 130.4, 131.2, 139.2, 157.2, 172.8, 173.2, 173.8, 174.9; HRMS (MALDI), calcd for MNa^+ $\text{C}_{27}\text{H}_{35}\text{N}_3\text{O}_7\text{Na}$ m/e 536.2367, found m/e 536.2341.

Tripeptide 44 and 45. These were prepared from **33** and a diastereomeric mixture of **38** and **39** according to the procedure as described for **40**. The crude product was purified by flash chromatography on silica gel (hexane–EtOAc = 1:4) to afford **44** and **45** (0.39 g, 51%) as white solids. Spectral data for **44**: ^1H NMR (500 MHz, MeOH- d_4) 0.85 (3H, d, J = 7.0 Hz), 0.86 (3H, d, J = 7.0 Hz), 1.88 (3H, s), 1.95–2.05 (1H, m), 2.77–2.86 (2H, m), 2.94 (1H, dd, J = 13.2, 8.5 Hz), 3.06 (1H, dd, J = 14.0, 5.2 Hz), 3.65 (3H, s), 4.09 (1H, d, J = 2.2 Hz), 4.13 (1H, d, J = 7.0 Hz), 4.44–4.51 (1H, m), 4.61 (1H, dd, J = 9.5, 5.1 Hz), 6.93–7.00 (2H, m), 7.14–7.20 (1H, m), 7.20–7.30 (6H, m); ^{13}C NMR (150 MHz, MeOH- d_4) 18.4, 19.8, 22.3, 32.1, 37.8, 38.5, 52.7, 54.9, 56.0, 60.1,

71.3, 116.0 ($^2J_{\text{F-C}}=21.8$ Hz), 127.7, 129.6, 130.4, 132.0 ($^3J_{\text{F-C}}=6.9$ Hz), 134.5, 139.2, 163.1 ($^1J_{\text{F-C}}=269.0$ Hz), 172.8, 173.3, 173.4, 174.9; HRMS (MALDI), calcd for $\text{MNa}^+ \text{C}_{27}\text{H}_{34}\text{FN}_3\text{O}_6\text{Na}$ m/e 538.2324, found m/e 538.2301.

Spectral data for 45. ^1H NMR (500 MHz, MeOH- d_4) 0.50 (3H, d, $J=7.0$ Hz), 0.57 (3H, d, $J=6.6$ Hz), 1.91–1.99 (1H, m), 2.03 (3H, s), 2.81 (1H, dd, $J=13.6$, 7.4 Hz), 2.90–3.02 (3H, m), 3.63 (3H, s), 3.98 (1H, d, $J=5.9$ Hz), 4.08 (1H, d, $J=2.6$ Hz), 4.50–4.58 (2H, m), 6.95–7.02 (2H, m), 7.15–7.20 (1H, m), 7.20–7.30 (6H, m); ^{13}C NMR (150 MHz, MeOH- d_4) 17.6, 19.5, 22.3, 30.8, 37.6, 38.6, 52.6, 55.0, 57.0, 60.1, 72.1, 116.2 ($^2J_{\text{F-C}}=21.8$ Hz), 127.6, 129.5, 130.5, 132.2 ($^3J_{\text{F-C}}=8.0$ Hz), 133.8, 139.2, 163.4 ($^1J_{\text{F-C}}=241.6$ Hz), 172.9, 173.8, 174.2, 174.3; HRMS (MALDI), calcd for $\text{MNa}^+ \text{C}_{27}\text{H}_{34}\text{FN}_3\text{O}_6\text{Na}$ m/e 538.2324, found m/e 538.2329.

Tripeptide 46. To a solution of **40** (0.10 g, 0.20 mmol) in MeOH (5 mL) was added Pd/C (30 mg) and the mixture stirred under a balloon of H_2 for 1 h. Filtration through Celite followed by concentration in vacuo yield the free amine. To the crude free amine in CH_2Cl_2 (4 mL) was added *p*-toluenesulfonyl chloride (40 mg, 0.21 mmol) followed by Et_3N (50 μL , 0.36 mmol). The reaction mixture was stirred at room temperature for 6 h and then diluted with EtOAc. The organic layer was washed with 1 M HCl, saturated NaHCO_3 , brine, dried over MgSO_4 and filtered. Purification by flash chromatography on silica gel (hexane–EtOAc=1:3) afforded **46** (83 mg, 78%) as a white solid: ^1H NMR (600 MHz, MeOH- d_4) 0.74 (3H, d, $J=6.5$ Hz), 0.77 (3H, d, $J=7.0$ Hz), 1.15 (3H, d, $J=7.0$ Hz), 1.88–1.96 (1H, m), 2.41 (3H, s), 2.81 (1H, dd, $J=13.6$, 7.5 Hz), 2.93 (1H, dd, $J=13.6$, 8.1 Hz), 3.64 (3H, s), 3.81 (1H, q, $J=7.1$ Hz), 4.04 (1H, d, $J=6.5$ Hz), 4.09 (1H, d, $J=2.2$ Hz), 4.44–4.49 (1H, m), 7.15–7.20 (1H, m), 7.23–7.29 (4H, m), 7.36 (2H, d, $J=7.9$ Hz), 7.76 (2H, d, $J=8.3$ Hz); ^{13}C NMR (150 MHz, MeOH- d_4) 18.1, 19.3, 19.7, 21.5, 31.9, 38.3, 52.7, 53.5, 54.9, 59.9, 71.4, 127.6, 128.3, 129.5, 130.4, 130.8, 138.6, 139.2, 145.0, 172.7, 174.2, 174.7; HRMS (MALDI), calcd for $\text{MNa}^+ \text{C}_{26}\text{H}_{35}\text{N}_3\text{O}_7\text{Na}$ m/e 556.2088, found m/e 556.2104.

Dipeptide 47. **33** (0.55 g, 1.8 mmol) was deprotected (method B) to give the corresponding TFA salt followed by coupling with Boc-Val-OH (0.40 g, 1.8 mmol) in CH_3CN (15 mL) according to the method A. After stirring at room temperature for 2 h and normal aqueous work up, the crude product was purified by flash chromatography on silica gel (hexane–EtOAc=2:1) to afford **47** (0.65 g, 90%) as a white solid: ^1H NMR (500 MHz, MeOH- d_4) 0.82 (3H, d, $J=7.0$ Hz), 0.84 (3H, d, $J=6.6$ Hz), 1.44 (9H, s), 1.85–1.95 (1H, m), 2.82 (1H, dd, $J=13.2$, 7.4 Hz), 2.95 (1H, dd, $J=13.6$, 8.5 Hz), 3.64 (3H, s), 3.79–3.85 (1H, m), 4.09 (1H, d, $J=2.2$ Hz), 4.44–4.52 (1H, m), 7.10–7.35 (5H, m); ^{13}C NMR (150 MHz, MeOH- d_4) 18.2, 19.8, 28.7, 32.0, 38.5, 52.6, 54.9, 61.5, 71.4, 80.5, 127.6, 129.5, 130.4, 139.3, 157.9, 173.9, 174.7; HRMS (MALDI), calcd for $\text{MNa}^+ \text{C}_{21}\text{H}_{32}\text{N}_2\text{O}_6\text{Na}$ m/e 431.2152, found m/e 431.2160.

Tripeptide 48. This was prepared from **47** and Ac-Ala-OH according to the procedure as described for **47**. The crude product was triturated in Et_2O and the solid filtered to afford **48** (0.15 g, 63%) as a white solid: ^1H NMR (600 MHz, MeOH- d_4) 0.85 (3H, d, $J=6.6$ Hz), 0.86 (3H, d, $J=7.0$ Hz), 1.30 (3H, d, $J=7.0$ Hz), 1.96 (3H, s), 1.95–2.05 (1H, m), 2.81 (1H, dd, $J=13.6$, 7.5 Hz), 2.94 (1H, dd, $J=13.6$, 8.3 Hz), 4.09 (1H, d, $J=2.2$ Hz), 4.13–4.16 (1H, m), 4.35 (1H, q, $J=7.4$ Hz), 4.45–4.51 (1H, m), 7.10–7.20 (1H, m), 7.20–7.30 (4H, m); ^{13}C NMR (150 MHz, MeOH- d_4) 17.8, 18.3, 19.8, 22.3, 32.1, 38.5, 50.4, 52.6, 54.9, 60.0, 71.4, 127.6, 129.5, 130.4, 139.2, 173.0, 173.1, 174.8, 175.0; HRMS (MALDI), calcd for $\text{MNa}^+ \text{C}_{21}\text{H}_{31}\text{N}_3\text{O}_6\text{Na}$ m/e 444.2105, found m/e 444.2123.

Cyclic inhibitor 5. **28** (35 mg, 0.084 mmol) was deprotected (method B) to give the corresponding HCl salt and **40** (42 mg, 0.084 mmol) deprotected (method C) to give the corresponding free acid. The HCl salt and the free acid were then coupled in DMF (3 mL) according to the method A. After stirring at room temperature for 19 h, water (2 mL) was added and the solid filtered. The solid was washed with Et_2O to afford **5** (35 mg, 52%) as a white solid: ^1H NMR (400 MHz, DMSO- d_6) 0.67 (6H, d, $J=6.7$ Hz), 0.70 (6H, d, $J=6.8$ Hz), 1.16 (3H, d, $J=7.0$ Hz), 1.57–1.73 (2H, m), 1.76–1.86 (1H, m), 1.94–2.06 (1H, m), 2.34 (1H, t, $J=10.8$ Hz), 2.54–2.69 (2H, m), 2.77 (1H, dd, $J=13.5$, 7.4 Hz), 3.10 (1H, dd, $J=12.3$, 6.8 Hz), 3.42 (1H, t, $J=7.6$ Hz), 3.83 (1H, dd, $J=5.8$, 2.3 Hz), 4.03–4.18 (3H, m), 4.24–4.37 (2H, m), 4.41–4.49 (1H, m), 5.00 (2H, s), 5.94 (1H, d, $J=5.8$ Hz), 6.72 (1H, dd, $J=8.2$, 2.1 Hz), 6.76–7.84 (2H, m), 6.94 (1H, d, $J=7.9$ Hz), 7.06 (1H, dd, $J=8.5$, 1.8 Hz), 7.12–7.40 (10H, m), 7.49 (1H, d, $J=7.6$ Hz), 7.53 (1H, d, $J=9.1$ Hz), 7.68 (1H, d, $J=9.1$ Hz), 7.76 (1H, d, $J=7.6$ Hz); ^{13}C NMR (125 MHz, DMSO- d_6) 17.7, 18.1, 18.7, 18.8, 19.1, 26.5, 30.9, 31.8, 35.6, 37.0, 50.1, 52.8, 54.7, 57.2, 57.9, 65.3, 67.7, 70.9, 117.6, 118.0, 126.0, 127.7, 128.1, 128.3, 129.1, 129.3, 130.8, 137.0, 138.6, 155.6, 157.4, 169.2, 169.6, 170.1, 171.0, 172.1; HRMS (MALDI), calcd for $\text{MNa}^+ \text{C}_{43}\text{H}_{56}\text{N}_6\text{O}_9\text{Na}$ m/e 823.4001, found m/e 823.4027.

Cyclic inhibitor 6. This was prepared from **28** and **46** according to the procedure as described for **5**. After stirring at room temperature for 17 h, water (2 mL) was added and the solid filtered. The solid was washed with Et_2O to afford **6** (35 mg, 59%) as a white solid: ^1H NMR (600 MHz, DMSO- d_6) 0.60 (3H, d, $J=6.5$ Hz), 0.61 (3H, d, $J=6.6$ Hz), 0.66 (3H, d, $J=7.0$ Hz), 0.69 (3H, d, $J=7.0$ Hz), 0.99 (3H, d, $J=7.0$ Hz), 1.58–1.70 (2H, m), 1.70–1.77 (1H, m), 1.95–2.04 (1H, m), 2.30–2.37 (1H, m), 2.33 (3H, s), 2.57 (1H, dd, $J=13.6$, 7.4 Hz), 2.61–2.68 (1H, m), 2.76 (1H, dd, $J=13.1$, 7.4 Hz), 3.09 (1H, dd, $J=12.3$, 6.6 Hz), 3.41 (1H, t, $J=7.0$ Hz), 3.79–3.85 (2H, m), 4.01 (1H, dd, $J=8.8$, 6.1 Hz), 4.11 (1H, ddd, $J=11.8$, 7.9, 5.7 Hz), 4.25–4.34 (2H, m), 4.43 (1H, dt, $J=10.1$, 7.2 Hz), 5.94 (1H, d, $J=6.1$ Hz), 6.73 (1H, dd, $J=8.3$, 2.2 Hz), 6.79 (1H, dd, $J=8.3$, 1.7 Hz), 6.81 (1H, dd, $J=8.6$, 2.4 Hz), 6.91 (1H, d, $J=7.9$ Hz), 7.05 (1H, dd, $J=8.3$, 1.7 Hz), 7.13–7.26 (5H, m), 7.31 (1H, d, $J=8.3$ Hz), 7.36–7.40 (1H, m),

7.61 (1H, d, $J=10.1$ Hz), 7.63 (1H, d, $J=9.2$ Hz), 7.65 (2H, d, $J=7.9$ Hz), 7.74 (1H, d, $J=7.4$ Hz), 7.86 (1H, d, $J=8.8$ Hz); ^{13}C NMR (125 MHz, DMSO- d_6) 17.6, 18.7, 18.8, 19.0, 19.3, 20.9, 26.5, 30.7, 31.8, 35.6, 37.0, 38.8, 51.5, 52.7, 54.6, 57.2, 57.9, 67.7, 70.8, 117.6, 118.0, 126.0, 126.6, 128.1, 129.1, 129.3, 129.4, 130.8, 138.3, 138.6, 142.4, 157.5, 169.2, 169.6, 169.9, 171.0; HRMS (MALDI), calcd for $\text{MNa}^+ \text{C}_{42}\text{H}_{56}\text{N}_6\text{O}_9\text{SNa}$ m/e 843.3722, found m/e 843.3753.

Cyclic inhibitor 7. This was prepared from **28** and **41** according to the procedure as described for **5**. After stirring at room temperature for 17 h and normal aqueous work up, the crude product was triturated in MeOH–H₂O (5:1 v/v) and the solid filtered. The solid was washed with Et₂O to afford **7** (0.10 g, 64%) as a white solid: ^1H NMR (500 MHz, DMSO- d_6) 0.67 (3H, d, $J=6.6$ Hz), 0.70 (3H, d, $J=6.8$ Hz), 0.71 (6H, d, $J=7.0$ Hz), 1.59–1.71 (2H, m), 1.74 (3H, s), 1.80–1.89 (1H, m), 1.95–2.05 (1H, m), 2.35 (1H, t, $J=11.4$ Hz), 2.58–2.69 (2H, m), 2.79 (1H, dd, $J=14.0$, 7.5 Hz), 2.88 (1H, dd, $J=14.5$, 10.5 Hz), 3.05–3.13 (2H, m), 3.43 (1H, t, $J=7.5$ Hz), 3.86 (1H, s), 4.07–4.18 (2H, m), 4.25–4.38 (2H, m), 4.40–4.48 (1H, m), 4.56 (1H, ddd, $J=9.5$, 8.5, 4.3 Hz), 6.72 (1H, dd, $J=8.1$, 2.2 Hz), 6.79 (1H, dd, $J=8.5$, 2.0 Hz), 6.81 (1H, dd, $J=8.4$, 2.2 Hz), 6.88 (1H, d, $J=7.7$ Hz), 6.96 (1H, t, $J=7.2$ Hz), 6.99–7.06 (2H, m), 7.10 (2H, d, $J=2.2$ Hz), 7.11–7.16 (1H, m), 7.20–7.27 (3H, m), 7.35 (1H, dd, $J=5.5$, 4.1 Hz), 7.62 (1H, d, $J=8.1$ Hz), 7.67 (1H, d, $J=5.1$ Hz), 7.69 (1H, d, $J=5.5$ Hz), 7.77 (1H, d, $J=7.4$ Hz), 8.05 (1H, d, $J=8.5$ Hz); ^{13}C NMR (100 MHz, DMSO- d_6) 17.9, 18.7, 18.9, 19.2, 22.6, 26.5, 27.4, 30.8, 31.9, 35.6, 37.1, 52.9, 53.3, 54.7, 57.5, 57.9, 67.8, 70.9, 110.5, 111.3, 117.6, 118.0, 118.2, 118.6, 120.8, 123.5, 126.1, 127.4, 128.2, 129.2, 129.3, 130.8, 136.1, 138.7, 157.5, 169.2, 169.3, 169.6, 170.2, 171.0, 171.6; HRMS (MALDI), calcd for $\text{MNa}^+ \text{C}_{45}\text{H}_{57}\text{N}_7\text{O}_8\text{Na}$ m/e 846.4161, found m/e 846.4136.

Cyclic inhibitor 8. This was prepared from **28** and **42** according to the procedure as described for **5**. After stirring at room temperature for 14 h and normal aqueous work up, the crude product was triturated in MeOH–Et₂O (1:3 v/v) and the solid filtered. The solid was washed with Et₂O to afford **8** (60 mg, 70%) as a white solid: ^1H NMR (500 MHz, DMSO- d_6) 0.67 (3H, d, $J=6.6$ Hz), 0.70 (3H, d, $J=6.6$ Hz), 0.72 (6H, d, $J=7.0$ Hz), 1.50–1.70 (2H, m), 1.72 (3H, s), 1.80–1.89 (1H, m), 1.96–2.05 (1H, m), 2.35 (1H, dd, $J=11.7$, 10.6 Hz), 2.58–2.74 (3H, m), 2.79 (1H, dd, $J=13.6$, 7.4 Hz), 2.98 (1H, dd, $J=14.0$, 3.7 Hz), 3.09 (1H, dd, $J=12.5$, 7.0 Hz), 3.43 (1H, t, $J=7.4$ Hz), 3.85 (1H, d, $J=2.6$ Hz), 4.07–4.16 (2H, m), 4.25–4.37 (2H, m), 4.41–4.48 (1H, m), 4.53 (1H, ddd, $J=10.1$, 8.5, 4.0 Hz), 6.73 (1H, dd, $J=8.5$, 2.6 Hz), 6.79 (1H, dd, $J=8.5$, 1.9 Hz), 6.82 (1H, dd, $J=8.4$, 2.2 Hz), 6.90 (1H, d, $J=8.1$ Hz), 7.03 (1H, dd, $J=8.1$, 1.9 Hz), 7.12–7.18 (2H, m), 7.19–7.28 (7H, m), 7.33–7.38 (1H, m), 7.67–7.79 (3H, m), 8.07 (1H, d, $J=8.5$ Hz); ^{13}C NMR (125 MHz, DMSO- d_6) 17.9, 18.7, 18.8, 19.1, 22.4, 26.5, 30.7, 31.8, 35.5, 36.9, 37.1, 38.6, 52.8, 53.8, 54.7, 57.5, 57.9, 67.7, 70.8, 117.6, 118.0, 126.0, 126.1, 127.9, 127.7, 128.1, 129.1, 129.2, 129.3, 130.7, 138.2, 157.4, 169.1, 169.2, 169.5, 170.1,

171.0, 171.1; HRMS (MALDI), calcd for $\text{MNa}^+ \text{C}_{43}\text{H}_{56}\text{N}_6\text{O}_8\text{Na}$ m/e 807.4052, found m/e 807.4046.

Cyclic inhibitor 9. This was prepared from **28** and **43** according to the procedure as described for **5**. After stirring at room temperature for 14 h and normal aqueous work up, the crude product was triturated in MeOH–H₂O (3:1 v/v) and the solid filtered. The solid was washed with Et₂O to afford **9** (65 mg, 68%) as a white solid: ^1H NMR (500 MHz, DMSO- d_6) 0.67 (3H, d, $J=7.0$ Hz), 0.70 (3H, d, $J=7.0$ Hz), 0.71 (6H, d, $J=7.4$ Hz), 1.59–1.71 (2H, m), 1.73 (3H, s), 1.80–1.88 (1H, m), 1.95–2.05 (1H, m), 2.35 (1H, dd, $J=12.5$, 10.6 Hz), 2.55–2.68 (3H, m), 2.79 (1H, dd, $J=13.6$, 7.4 Hz), 2.86 (1H, dd, $J=14.0$, 3.7 Hz), 3.09 (1H, dd, $J=12.5$, 6.6 Hz), 3.43 (1H, t, $J=7.7$ Hz), 3.85 (1H, dd, $J=6.3$, 2.8 Hz), 4.07–4.16 (2H, m), 4.25–4.36 (2H, m), 4.40–4.48 (2H, m), 5.92 (1H, d, $J=6.3$ Hz), 6.61 (2H, d, $J=8.4$ Hz), 6.73 (1H, dd, $J=8.3$, 2.4 Hz), 6.79 (1H, dd, $J=8.5$, 2.0 Hz), 6.82 (1H, dd, $J=8.4$, 2.2 Hz), 6.90 (1H, d, $J=8.1$ Hz), 7.03 (2H, d, $J=8.5$ Hz), 7.04 (1H, dd, $J=8.4$, 2.0 Hz), 7.13–7.18 (1H, m), 7.20–7.27 (4H, m), 7.35 (1H, dd, $J=5.6$, 4.0 Hz), 7.67 (2H, d, $J=8.8$ Hz), 7.76 (1H, d, $J=7.4$ Hz), 7.98 (1H, d, $J=8.5$ Hz); ^{13}C NMR (100 MHz, DMSO- d_6) 17.9, 18.6, 18.9, 19.2, 22.5, 26.5, 30.7, 31.8, 35.6, 36.4, 37.0, 52.8, 54.2, 54.6, 57.4, 57.9, 67.8, 70.9, 114.5, 117.6, 118.0, 126.1, 128.2, 128.3, 129.2, 129.3, 130.1, 130.8, 138.7, 155.7, 157.5, 169.1, 169.2, 169.6, 170.2, 171.0, 171.3; HRMS (MALDI), calcd for $\text{MNa}^+ \text{C}_{43}\text{H}_{56}\text{N}_6\text{O}_9\text{Na}$ m/e 823.4001, found m/e 823.3978.

Cyclic inhibitor 10. This was prepared from **28** and **44** according to the procedure as described for **5**. After stirring at room temperature for 12 h, water (3 mL) was added and the solid filtered. The solid was washed with Et₂O to afford **10** (10 mg, 30%) as a white solid: ^1H NMR (600 MHz, DMSO- d_6) 0.67 (3H, d, $J=6.5$ Hz), 0.68–0.74 (9H, m), 1.58–1.70 (2H, m), 1.72 (3H, s), 1.80–1.88 (1H, m), 1.95–2.05 (1H, m), 2.34 (1H, t, $J=11.4$ Hz), 2.56–2.72 (3H, m), 2.79 (1H, dd, $J=13.1$, 7.0 Hz), 2.95 (1H, dd, $J=14.0$, 3.3 Hz), 3.08 (1H, dd, $J=12.3$, 6.6 Hz), 3.42 (1H, t, $J=7.4$ Hz), 3.85 (1H, dd, $J=5.6$, 2.2 Hz), 4.07–4.16 (2H, m), 4.25–4.37 (2H, m), 4.41–4.48 (1H, m), 4.48–4.54 (1H, m), 5.93 (1H, d, $J=6.1$ Hz), 6.69–6.75 (1H, m), 6.76–6.84 (2H, m), 6.90 (1H, d, $J=7.9$ Hz), 7.00–7.09 (3H, m), 7.12–7.18 (1H, m), 7.19–7.32 (6H, m), 7.36–7.42 (1H, m), 7.69 (1H, d, $J=9.2$ Hz), 7.77 (1H, d, $J=7.0$ Hz), 8.07 (1H, d, $J=8.3$ Hz); ^{13}C NMR (125 MHz, DMSO- d_6) 17.9, 18.8, 18.9, 19.2, 22.4, 26.5, 30.7, 31.9, 35.6, 36.4, 37.0, 38.8, 52.9, 53.9, 54.7, 57.6, 57.9, 67.8, 70.9, 114.7 ($^2J_{\text{F-C}}=21.0$ Hz), 117.6, 118.0, 126.1, 128.2, 129.2, 129.3, 130.8, 131.0 ($^3J_{\text{F-C}}=7.6$ Hz), 134.4, 138.7, 157.5, 160.9 ($^1J_{\text{F-C}}=240.4$ Hz), 169.2, 169.3, 169.6, 170.2, 171.1; HRMS (MALDI), calcd for $\text{MNa}^+ \text{C}_{43}\text{H}_{55}\text{FN}_6\text{O}_8\text{Na}$ m/e 825.3957, found m/e 825.3923.

Cyclic inhibitor 11. This was prepared from **28** and **45** according to the procedure as described for **5**. After stirring at room temperature for 12 h, water (3 mL) was added and the solid filtered. The solid was washed with Et₂O to afford **11** (15 mg, 43%) as a pale brown solid: ^1H NMR (600 MHz, DMSO- d_6) 0.62 (6H, d,

$J=6.6$ Hz), 0.66 (3H, d, $J=7.0$ Hz), 0.69 (3H, d, $J=7.0$ Hz), 1.58–1.70 (2H, m), 1.75 (3H, s), 1.78–1.84 (1H, m), 1.95–2.04 (1H, m), 2.34 (1H, t, $J=11.0$ Hz), 2.57–2.71 (3H, m), 2.77 (1H, dd, $J=13.1$, 7.4 Hz), 2.90 (1H, dd, $J=13.6$, 5.7 Hz), 3.09 (1H, dd, $J=12.7$, 7.0 Hz), 3.83 (1H, dd, $J=6.6$, 2.6 Hz), 4.07–4.15 (2H, m), 4.25–4.34 (2H, m), 4.39–4.46 (1H, m), 4.60–4.66 (1H, m), 5.90 (1H, d, $J=6.5$ Hz), 6.73 (1H, dd, $J=7.9$, 2.2 Hz), 6.78 (1H, dd, $J=8.8$, 2.2 Hz), 6.81 (1H, dd, $J=8.3$, 2.2 Hz), 6.91 (1H, d, $J=7.9$ Hz), 7.01–7.07 (3H, m), 7.12–7.17 (1H, m), 7.19–7.29 (5H, m), 7.35–7.39 (1H, m), 7.67 (1H, d, $J=9.2$ Hz), 7.76 (1H, d, $J=7.4$ Hz), 7.92 (1H, d, $J=9.2$ Hz), 8.12 (1H, d, $J=8.3$ Hz); ^{13}C NMR (100 MHz, DMSO- d_6) 17.9, 18.8, 18.9, 19.1, 22.5, 26.5, 30.6, 31.9, 35.7, 35.9, 37.3, 37.5, 53.0, 53.9, 54.8, 57.5, 56.0, 67.8, 70.9, 114.7 ($^2J_{\text{F-C}}=19.7$ Hz), 117.7, 118.1, 126.2, 128.3, 129.2, 129.3, 129.4, 130.8, 131.1 ($^3J_{\text{F-C}}=7.6$ Hz), 134.0, 138.7, 157.5, 161.0 ($^1J_{\text{F-C}}=239.6$ Hz), 169.2, 169.3, 169.7, 170.2, 171.0, 171.1; HRMS (MALDI), calcd for MH^+ $\text{C}_{43}\text{H}_{56}\text{FN}_6\text{O}_8$ m/e 803.4138, found m/e 803.4151.

Cyclic inhibitor 12. This was prepared from **28** and **48** according to the procedure as described for **5**. After stirring at room temperature for 2 h, water (2 mL) was added and the solid filtered. The solid was washed with Et_2O to afford **12** (30 mg, 47%) as a white solid: ^1H NMR (600 MHz, DMSO- d_6) 0.67 (3H, d, $J=6.6$ Hz), 0.68–0.72 (9H, m), 1.14 (3H, d, $J=7.0$ Hz), 1.60–1.71 (2H, m), 1.81 (3H, s), 1.80–1.87 (1H, m), 1.95–2.04 (1H, m), 2.36 (1H, dd, $J=12.2$, 10.6 Hz), 2.59 (1H, dd, $J=13.1$, 7.4 Hz), 2.62–2.68 (1H, m), 2.74–2.81 (1H, m), 3.09 (1H, dd, $J=12.3$, 6.6 Hz), 3.42 (1H, t, $J=7.4$ Hz), 3.84 (1H, dd, $J=6.2$, 2.6 Hz), 4.06–4.16 (2H, m), 4.24–4.36 (3H, m), 4.40–4.48 (1H, m), 6.73 (1H, dd, $J=8.3$, 2.2 Hz), 6.79 (1H, dd, $J=8.3$, 1.7 Hz), 6.82 (1H, dd, $J=8.8$, 2.6 Hz), 6.89 (1H, d, $J=8.3$ Hz), 7.06 (1H, dd, $J=8.3$, 1.8 Hz), 7.13–7.18 (1H, m), 7.18–7.26 (4H, m), 7.32–7.38 (1H, m), 7.55 (1H, d, $J=9.2$ Hz), 7.60 (1H, d, $J=9.2$ Hz), 7.75 (1H, d, $J=7.5$ Hz), 8.02 (1H, d, $J=7.9$ Hz); ^{13}C NMR (150 MHz, DMSO- d_6) 17.7, 18.0, 18.7, 18.8, 19.1, 22.4, 26.5, 30.6, 31.8, 35.6, 36.9, 38.7, 48.0, 52.8, 54.7, 57.3, 57.9, 67.7, 70.9, 117.6, 118.0, 126.0, 128.1, 129.2, 129.3, 130.8, 138.6, 157.4, 169.0, 169.3, 169.6, 170.1, 171.0, 172.1; HRMS (MALDI), calcd for MNa^+ $\text{C}_{37}\text{H}_{52}\text{N}_6\text{O}_8\text{Na}$ m/e 731.3739, found m/e 731.3709.

Cyclic inhibitor 15. This was prepared from **28** and **41** according to the procedure as described for **5**. After stirring at room temperature for 2 h, water (2 mL) was added and the solid filtered. The solid was washed with Et_2O to afford **15** (35 mg, 61%) as a white solid: ^1H NMR (600 MHz, DMSO- d_6) 0.69–0.74 (12H, m), 1.74 (3H, s), 1.80–2.00 (2H, m), 2.60–2.68 (2H, m), 2.77–2.85 (2H, m), 2.88–2.94 (2H, m), 3.08 (1H, dd, $J=14.9$, 4.0 Hz), 3.40–3.47 (1H, m), 3.60–3.67 (2H, m), 3.88 (1H, dd, $J=6.1$, 2.2 Hz), 3.92 (1H, dd, $J=8.8$, 6.6 Hz), 4.17 (1H, dd, $J=8.8$, 6.5 Hz), 4.18–4.30 (2H, m), 4.34–4.41 (1H, m), 4.46–4.52 (1H, m), 4.53–4.59 (1H, m), 5.95 (1H, d, $J=6.4$ Hz), 6.83 (2H, d, $J=8.3$ Hz), 6.91 (2H, d, $J=8.3$ Hz), 6.96 (1H, t, $J=7.4$ Hz), 7.04 (1H, t, $J=7.4$ Hz), 7.10 (1H, d, $J=2.0$ Hz), 7.12–7.17 (1H, m), 7.18–7.26 (4H, m), 7.30 (1H, d, $J=7.9$ Hz), 7.61 (1H, d,

$J=7.9$ Hz), 7.67 (2H, d, $J=8.3$ Hz), 7.89 (1H, d, $J=7.4$ Hz), 7.94 (1H, s), 8.04 (1H, d, $J=8.3$ Hz); ^{13}C NMR (125 MHz, DMSO- d_6) 17.7, 18.2, 18.9, 19.1, 22.5, 27.4, 30.7, 31.3, 35.8, 37.1, 37.7, 52.7, 53.3, 53.6, 57.4, 57.5, 66.6, 69.5, 70.8, 71.4, 110.4, 111.2, 115.2, 118.1, 118.5, 120.8, 123.4, 126.0, 127.3, 128.0, 128.1, 129.2, 129.6, 136.0, 138.6, 157.3, 169.1, 169.6, 169.7, 170.1, 170.9, 171.5; HRMS (MALDI), calcd for MNa^+ $\text{C}_{46}\text{H}_{59}\text{N}_7\text{O}_9\text{Na}$ m/e 876.4266, found m/e 876.4240.

Cyclic inhibitor 16. This was prepared from **28** and **44** according to the procedure as described for **5**. After stirring at room temperature for 2 h, water (2 mL) was added and the solid filtered. The solid was washed with Et_2O to afford **16** (25 mg, 45%) as a white solid: ^1H NMR (600 MHz, DMSO- d_6 , 60 °C) 0.70–0.76 (12H, m), 1.75 (3H, s), 1.80–2.00 (2H, m), 2.60–2.70 (2H, m), 2.79–2.96 (4H, m), 3.00 (1H, dd, $J=14.0$, 4.4 Hz), 3.30–3.43 (3H, m), 3.60–3.70 (2H, m), 3.87–3.97 (2H, m), 4.11 (1H, dd, $J=8.3$, 6.6 Hz), 4.20–4.30 (2H, m), 4.33–4.41 (1H, m), 4.47–4.57 (2H, m), 5.76 (1H, d, $J=6.1$ Hz), 6.81–6.89 (3H, m), 6.92–7.05 (4H, m), 7.11–7.17 (1H, m), 7.20–7.30 (5H, m), 7.40 (1H, d, $J=8.3$ Hz), 7.46 (1H, d, $J=9.2$ Hz), 7.57 (1H, d, $J=8.3$ Hz), 7.79 (1H, d, $J=7.5$ Hz), 7.90 (1H, d, $J=8.3$ Hz); ^{13}C NMR (150 MHz, DMSO- d_6 , 60 °C) 17.5, 17.7, 18.6, 18.8, 22.1, 30.2, 30.9, 36.1, 36.5, 37.6, 52.6, 53.6, 53.9, 57.4, 57.6, 66.7, 69.3, 70.9, 71.1, 114.3 ($^2J_{\text{F-C}}=19.7$ Hz), 115.3, 115.4, 125.7, 127.8, 128.0, 128.1, 128.8, 129.3, 130.6 ($^3J_{\text{F-C}}=7.6$ Hz), 134.0, 138.4, 157.2, 161.5, 168.9, 169.5, 169.6, 169.7, 170.7, 170.8; HRMS (MALDI), calcd for MNa^+ $\text{C}_{44}\text{H}_{57}\text{FN}_6\text{O}_9\text{Na}$ m/e 855.4063, found m/e 855.4039.

Compound 49. **28** (0.11 g, 0.26 mmol) was deprotected (method B) to give the corresponding TFA salt and **33** (81 mg, 0.26 mmol) deprotected (method C) to give the corresponding free acid. The TFA salt and the free acid were then coupled in THF (6 mL) according to the method A. After stirring at room temperature for 2 h and normal aqueous work up, the crude product was triturated in hexane–EtOAc (1:2 v/v) and the solid filtered. The solid was washed with Et_2O to afford **49** (0.10 g, 64%) as a white solid: ^1H NMR (500 MHz, MeOH- d_4) 0.76 (3H, d, $J=7.0$ Hz), 0.77 (3H, d, $J=7.0$ Hz), 1.31 (9H, s), 1.71–1.82 (2H, m), 2.13–2.22 (1H, m), 2.61 (1H, t, $J=11.8$ Hz), 2.75 (1H, dd, $J=13.2$, 8.5 Hz), 2.81 (1H, ddd, $J=14.0$, 7.3, 3.0 Hz), 2.89 (1H, dd, $J=13.6$, 6.6 Hz), 3.16 (1H, dd, $J=12.5$, 6.6 Hz), 3.45 (1H, d, $J=7.4$ Hz), 3.49 (1H, ddd, $J=13.9$, 9.2, 2.9 Hz), 4.03 (1H, d, $J=2.2$ Hz), 4.11–4.16 (1H, m), 4.20 (1H, ddd, $J=12.5$, 8.8, 5.2 Hz), 4.35 (1H, dt, $J=12.5$, 5.2 Hz), 4.50 (1H, dd, $J=11.0$, 6.6 Hz), 6.80–6.87 (2H, m), 6.94 (1H, dd, $J=8.1$, 2.2 Hz), 7.13 (1H, dd, $J=8.5$, 1.8 Hz), 7.15–7.29 (5H, m); ^{13}C NMR (100 MHz, MeOH- d_4) 19.3, 19.4, 27.9, 28.7, 33.5, 37.3, 38.9, 39.3, 56.2, 56.9, 60.3, 68.9, 72.9, 80.1, 118.8, 119.0, 127.3, 129.4, 130.3, 130.5, 130.6, 132.4, 139.8, 157.6, 159.6, 172.0, 172.3, 174.6; HRMS (MALDI), calcd for MNa^+ $\text{C}_{32}\text{H}_{44}\text{N}_4\text{O}_7\text{Na}$ m/e 619.3102, found m/e 619.3085.

Compound 50. **49** (60 mg, 0.10 mmol) was deprotected (method B) to give the corresponding HCl salt followed by coupling with Boc-Val-OH (25 mg, 0.12 mmol) in

DMF (3 mL) according to the method A. After stirring at room temperature for 18 h and normal aqueous work up, the crude product was triturated in EtOAc–Et₂O (1:2 v/v) and the solid filtered. The solid was washed with Et₂O to afford **50** (40 mg, 58%) as a white solid: ¹H NMR (500 MHz, DMSO-*d*₆) 0.66 (6H, d, *J* = 6.6 Hz), 0.69 (6H, d, *J* = 6.6 Hz), 1.37 (9H, s), 1.59–1.72 (2H, m), 1.74–1.84 (1H, m), 1.94–2.05 (1H, m), 2.36 (1H, t, *J* = 11.4 Hz), 2.57 (1H, dd, *J* = 13.4, 7.9 Hz), 2.62–2.70 (1H, m), 2.79 (1H, dd, *J* = 13.6, 7.2, 3.0 Hz), 3.09 (1H, dd, *J* = 12.5, 7.0 Hz), 3.42 (1H, d, *J* = 7.4 Hz), 3.74 (1H, d, *J* = 8.1 Hz), 3.85 (1H, dd, *J* = 5.5, 2.6 Hz), 4.06–4.15 (1H, m), 4.24–4.35 (2H, m), 4.43–4.49 (1H, m), 5.98 (1H, d, *J* = 5.9 Hz), 6.42 (1H, d, *J* = 8.5 Hz), 6.72 (1H, dd, *J* = 8.5, 2.2 Hz), 6.77–6.84 (2H, m), 6.88 (1H, d, *J* = 8.1 Hz), 7.06 (1H, dd, *J* = 8.5, 1.9 Hz), 7.13–7.29 (5H, m), 7.31–7.37 (1H, m), 7.54 (1H, d, *J* = 9.2 Hz), 7.72 (1H, d, *J* = 7.7 Hz); ¹³C NMR (125 MHz, DMSO-*d*₆) 17.8, 18.7, 18.8, 19.2, 26.5, 28.2, 30.4, 31.8, 35.6, 36.8, 38.7, 52.9, 54.7, 57.9, 59.5, 67.8, 71.0, 77.9, 117.6, 118.1, 126.0, 128.1, 129.2, 129.3, 130.8, 138.7, 155.4, 157.5, 169.3, 169.6, 170.7, 171.0; HRMS (MALDI), calcd for MNa⁺ C₃₇H₅₃N₅O₈Na *m/e* 718.3786, found *m/e* 718.3804.

Cyclic inhibitor 13. This was prepared from **50** and Ac-His(1-Trt)-OH according to the procedure as described for **50**. After stirring at room temperature for 4 h, water (5 mL) was added and the solid filtered. The solid was washed with Et₂O to afford **13** (43 mg, 73%) as a white solid: ¹H NMR (500 MHz, DMSO-*d*₆) 0.66 (6H, d, *J* = 7.0 Hz), 0.69 (6H, d, *J* = 6.3 Hz), 1.59–1.69 (1H, m), 1.72 (3H, s), 1.78–1.88 (1H, m), 1.92–2.04 (1H, m), 2.37 (1H, t, *J* = 11.4 Hz), 2.55 (1H, dd, *J* = 13.2, 7.7 Hz), 2.59–2.69 (2H, m), 2.78 (1H, dd, *J* = 14.0, 7.7 Hz), 2.82–2.87 (1H, m), 3.08 (1H, dd, *J* = 13.2, 7.7 Hz), 3.43 (1H, t, *J* = 7.3 Hz), 3.77–3.87 (1H, m), 4.02 (1H, s), 4.05–4.15 (2H, m), 4.22–4.35 (2H, m), 4.41–4.52 (2H, m), 5.92 (1H, d, *J* = 5.9 Hz), 6.62–6.70 (2H, m), 6.76–6.85 (2H, m), 6.95 (1H, d, *J* = 8.1 Hz), 6.99–7.10 (7H, m), 7.10–7.27 (6H, m), 7.27–7.42 (10H, m), 7.56 (1H, d, *J* = 8.1 Hz), 7.69–7.79 (2H, m), 8.00 (1H, d, *J* = 8.4 Hz); ¹³C NMR (125 MHz, DMSO-*d*₆) 17.5, 18.7, 19.1, 22.4, 26.5, 30.5, 30.7, 31.7, 35.5, 35.8, 36.6, 52.5, 52.8, 54.7, 57.5, 57.9, 67.7, 70.9, 74.4, 117.6, 118.0, 118.9, 126.0, 127.9, 128.1, 129.1, 129.2, 129.3, 130.8, 137.3, 137.5, 138.6, 142.3, 157.4, 162.3, 169.0, 169.2, 169.6, 170.1, 171.1, 171.2; HRMS (MALDI), calcd for MNa⁺ C₅₉H₆₈N₈O₈Na *m/e* 1039.5052, found *m/e* 1039.5013.

Cyclic inhibitor 14. **13** (32 mg, 0.032 mmol) was dissolved in 10% H₂O in TFA (1 mL) and stirred at room temperature for 1 h. The solvent was removed in vacuo and the remaining TFA and water were removed by repeated evaporation from toluene in vacuo. The crude product was triturated in Et₂O and the solid filtered. The solid was washed with Et₂O to afford **14** (24 mg, 97%) as a white solid: ¹H NMR (600 MHz, DMSO-*d*₆) 0.60–0.75 (12H, m), 1.57–1.72 (2H, m), 1.81 (3H, s), 1.77–1.88 (1H, m), 1.96–2.06 (1H, m), 2.33 (1H, t, *J* = 10.7 Hz), 2.57–2.69 (2H, m), 2.74–2.82 (1H, m), 2.85–2.93 (1H, m), 2.96–3.05 (1H, m), 3.06–3.13 (1H, m), 3.85 (1H, s), 4.03–4.21 (2H, m), 4.24–4.38 (2H, m), 4.40–4.48 (1H, m), 4.59–4.67 (1H, m), 6.02 (1H, br s),

6.72 (1H, d, *J* = 7.4 Hz), 6.76–6.86 (2H, m), 7.04 (1H, d, *J* = 7.9 Hz), 7.12–7.37 (9H, m), 7.38–7.45 (1H, m), 7.73–7.82 (1H, m), 8.15–8.25 (1H, m), 8.91 (1H, s); ¹³C NMR (125 MHz, DMSO-*d*₆) 17.6, 18.7, 18.8, 19.1, 22.4, 26.5, 27.2, 30.6, 31.8, 35.6, 37.1, 38.8, 51.4, 52.9, 54.7, 57.6, 57.9, 67.7, 70.7, 117.6, 118.0, 126.1, 127.0, 127.5, 127.9, 128.2, 129.1, 129.2, 129.6, 130.7, 138.6, 157.5, 169.2, 169.4, 169.5, 169.9, 170.4, 171.0; HRMS (MALDI), calcd for MNa⁺ C₄₀H₅₄N₈O₈Na *m/e* 797.3957, found *m/e* 797.3978.

Dipeptide 51. This was prepared from Boc-*p*-F-Phe-OH (0.50 g, 1.8 mmol) and H-Val-OMe-HCl (0.30 g, 1.8 mmol) in CH₃CN according to the method A. The crude product was triturated in Et₂O–hexane (1:2 v/v) and the solid filtered. The filtrate was concentrated to afford **51** (0.68 g, 97%) as a white solid: ¹H NMR (400 MHz, MeOH-*d*₄) 0.92 (3H, d, *J* = 6.8 Hz), 0.93 (3H, d, *J* = 6.7 Hz), 1.37 (3H, s), 2.05–2.20 (1H, m), 2.81 (1H, dd, *J* = 13.9, 9.0 Hz), 3.04 (1H, dd, *J* = 13.8, 5.9 Hz), 3.68 (3H, s), 4.31 (1H, d, *J* = 5.9 Hz), 4.33 (1H, dd, *J* = 9.1, 5.8 Hz), 6.93–7.04 (2H, m), 7.18–7.30 (2H, m); ¹³C NMR (150 MHz, MeOH-*d*₄) 18.4, 19.4, 28.6, 32.0, 38.3, 52.5, 57.2, 59.1, 80.6, 115.9 (²*J*_{F–C} = 21.8 Hz), 132.1 (³*J*_{F–C} = 6.9 Hz), 134.5, 157.6, 163.2 (¹*J*_{F–C} = 241.6 Hz), 173.2, 174.3; HRMS (MALDI), calcd for MNa⁺ C₂₀H₂₉FN₂O₅Na *m/e* 419.1953, found *m/e* 419.1939.

Dipeptide 52. **51** (0.70 g, 1.8 mmol) was deprotected to the corresponding TFA salt (method B) followed by coupling with acetic acid (0.20 mL, 3.5 mmol) (method A). The crude product was triturated in Et₂O–MeOH (10:1 v/v) and the solid filtered to afford **52** (0.38 g, 64%) as a white solid: ¹H NMR (500 MHz, MeOH-*d*₄) 0.91 (3H, d, *J* = 6.6 Hz), 0.92 (3H, d, *J* = 7.0 Hz), 1.89 (3H, s), 2.05–2.15 (1H, m), 2.85 (1H, dd, *J* = 14.0, 8.8 Hz), 3.06 (1H, dd, *J* = 13.6, 6.3 Hz), 3.67 (3H, s), 4.28 (1H, d, *J* = 6.3 Hz), 4.64 (1H, dd, *J* = 8.8, 6.3 Hz), 6.95–7.01 (2H, m), 7.21–7.27 (2H, m); ¹³C NMR (150 MHz, MeOH-*d*₄) 18.5, 19.4, 22.3, 32.0, 38.3, 52.5, 55.9, 59.2, 115.9 (²*J*_{F–C} = 21.8 Hz), 132.1 (³*J*_{F–C} = 8.0 Hz), 134.3, 163.3 (¹*J*_{F–C} = 241.5 Hz), 173.1, 173.2, 173.7; HRMS (MALDI), calcd for MNa⁺ C₁₇H₂₃FN₂O₄Na *m/e* 361.1534, found *m/e* 361.1538.

Tripeptide 53. **33** (0.27 g, 0.87 mmol) was deprotected (method B) to give the corresponding TFA salt and **52** (0.30 g, 0.88 mmol) deprotected (method C) to give the corresponding free acid. The TFA salt and the free acid were then coupled in THF (8 mL) according to the method A. The crude product was purified by flash chromatography on silica gel (CHCl₃–EtOAc = 1:3 gradient to EtOAc) to afford **53** (0.20 g, 45%) as a white solid. Spectral data of **53** are the same as those of **44**.

Dipeptide 54. This was prepared from Boc-Tyr-OH (0.50 g, 1.8 mmol) and H-Val-NH₂-HCl (0.28 g, 1.8 mmol) in THF according to the method A. The crude product was triturated in Et₂O and the solid filtered to afford **54** (0.60 g, 90%) as a white solid: ¹H NMR (400 MHz, MeOH-*d*₄) 0.93 (3H, d, *J* = 7.0 Hz), 0.95 (3H, d, *J* = 7.0 Hz), 1.37 (9H, s), 2.02–2.12 (1H, m), 2.73 (1H, dd, *J* = 13.8, 9.1 Hz), 3.00 (1H, dd, *J* = 13.8, 5.3 Hz), 4.20 (1H, d, *J* = 6.5 Hz), 4.25 (1H, dd, *J* = 8.8,

5.3 Hz), 6.68 (2H, d, $J=8.2$ Hz), 7.04 (2H, d, $J=8.5$ Hz); ^{13}C NMR (150 MHz, MeOH- d_4) 18.2, 19.7, 28.7, 32.0, 38.0, 57.7, 59.5, 80.7, 116.2, 129.2, 131.3, 157.2, 157.7, 174.5, 175.8; HRMS (MALDI), calcd for MNa^+ $\text{C}_{19}\text{H}_{29}\text{N}_3\text{O}_5\text{Na}$ m/e 402.1999, found m/e 402.2013.

Pentapeptide 55. 29 (80 mg, 0.20 mmol) was deprotected (method B) to give the corresponding HCl salt and **43** (92 mg, 0.18 mmol) deprotected (method C) to give the corresponding free acid. The HCl salt and the free acid were then coupled in DMF (3 mL) according to the method A. The crude product was triturated in MeOH–Et₂O (1:5 v/v) and the solid filtered. The solid was washed with Et₂O to afford **55** (50 mg, 32%) as a white solid: ^1H NMR (600 MHz, DMSO- d_6) 0.65 (3H, d, $J=7.0$ Hz), 0.66 (3H, d, $J=6.5$ Hz), 0.85 (3H, d, $J=6.6$ Hz), 0.88 (3H, d, $J=6.5$ Hz), 1.72 (3H, s), 1.77–1.85 (1H, m), 1.97–2.04 (1H, m), 2.52–2.59 (2H, m), 2.72–2.79 (2H, m), 2.83 (1H, dd, $J=14.5$, 3.9 Hz), 2.87 (1H, dd, $J=14.0$, 6.2 Hz), 3.62 (3H, s), 3.75 (1H, dd, $J=6.6$, 2.6 Hz), 4.08–4.14 (2H, m), 4.28 (1H, ddd, $J=16.6$, 7.4, 2.2 Hz), 4.41 (1H, ddd, $J=12.3$, 8.3, 4.0 Hz), 4.52–4.57 (1H, m), 6.16 (1H, d, $J=6.2$ Hz), 6.54 (2H, d, $J=8.8$ Hz), 6.61 (2H, d, $J=8.3$ Hz), 6.84 (2H, d, $J=8.3$ Hz), 7.01 (2H, d, $J=8.8$ Hz), 7.12–7.27 (5H, m), 7.57 (1H, d, $J=9.2$ Hz), 7.63 (1H, d, $J=8.3$ Hz), 7.65 (1H, d, $J=8.8$ Hz), 7.99 (1H, d, $J=8.3$ Hz), 8.39 (1H, d, $J=7.9$ Hz); ^{13}C NMR (100 MHz, DMSO- d_6) 17.7, 18.4, 19.0, 19.1, 22.5, 30.0, 30.8, 36.4, 36.9, 37.3, 51.8, 52.7, 52.9, 54.2, 57.4, 57.6, 70.7, 114.8, 126.1, 126.8, 128.3, 129.2, 130.1, 130.4, 138.7, 155.7, 155.8, 169.2, 170.1, 170.7, 171.0, 171.4, 171.9; HRMS (MALDI), calcd for MNa^+ $\text{C}_{41}\text{H}_{53}\text{N}_5\text{O}_{10}\text{Na}$ m/e 798.3685, found m/e 798.3706.

Pentapeptide 56. This was prepared from **54** and **43** according to the procedure as described for **55**. The crude product was triturated in MeOH–Et₂O (1:5 v/v) and the solid filtered. The solid was washed with Et₂O to afford **56** (20 mg, 33%) as a white solid: ^1H NMR (600 MHz, DMSO- d_6) 0.65 (6H, d, $J=6.5$ Hz), 0.82 (3H, d, $J=8.3$ Hz), 0.84 (3H, d, $J=7.0$ Hz), 1.72 (3H, s), 1.77–1.85 (1H, m), 1.90–1.97 (1H, m), 2.53–2.62 (2H, m), 2.74–2.92 (5H, m), 3.78 (1H, d, $J=2.2$ Hz), 4.04–4.13 (1H, m), 4.26–4.33 (1H, m), 4.36–4.44 (1H, m), 4.46–4.53 (1H, m), 6.55 (2H, d, $J=7.4$ Hz), 6.62 (2H, d, $J=7.9$ Hz), 6.82 (2H, d, $J=8.3$ Hz), 7.01 (2H, d, $J=8.3$ Hz), 7.08 (1H, s), 7.11–7.17 (1H, m), 7.19–7.27 (4H, m), 7.46 (1H, s), 7.60 (1H, d, $J=9.2$ Hz), 7.64–7.71 (2H, m), 8.07 (1H, d, $J=8.3$ Hz), 8.14 (1H, d, $J=8.8$ Hz); ^{13}C NMR (125 MHz, DMSO- d_6) 17.7, 18.3, 19.1, 19.4, 22.5, 30.5, 30.7, 36.4, 36.8, 36.9, 52.9, 53.0, 54.3, 57.5, 57.8, 70.7, 114.8, 126.0, 126.8, 128.2, 129.2, 130.0, 130.4, 138.8, 155.8, 169.2, 170.0, 170.1, 170.7, 171.1, 171.4, 172.9; HRMS (MALDI), calcd for MNa^+ $\text{C}_{40}\text{H}_{52}\text{N}_6\text{O}_9\text{Na}$ m/e 783.3688, found m/e 783.3683.

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References and Notes

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