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Structure–Activity Studies of FIV and HIV Protease Inhibitors Containing Allophenylnorstatine

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Abstract—The interaction of P1 and P3 side chains with the combining S1 and S3 hydrophobic subsites of HIV and FIV proteases has been explored using asymmetric competitive inhibitors. The inhibitors evaluated contained (*2S,3S*)-3-amino-2-hydroxy-4-phenylbutyric acid (allophenylnorstatine) as the hydroxymethylcarbonyl isostere, (*R*)-5,5-dimethyl-1, 3-thiazolidine-4-carbonyl as P1′, Val as P2 and P2′ residues, and a variety of amino acids at the P3 and P3′ positions. All inhibitors showed competitive inhibition of both enzymes with higher potency against the HIV protease in vitro. Within this series, **31** (VLE776) is the most effective inhibitor against FIV protease, and it contains Phe at P3, but no P3′ residue. VLE776 also exhibited potent antiviral activities against the drug-resistant HIV mutants (G48V and V82F) and the **TL3**-resistant HIV mutants. Explanation of the inhibition activities was described. In addition, a new strategy was described for development of bifunctional inhibitors, which combine the protease inhibitor and another enzyme inhibitor in one molecule.

Introduction

Human immunodeficiency virus protease (HIV PR) has been identified as an important target enzyme for inhibition in order to suppress HIV replication. In the last several years, an extensive research effort has been devoted to the search for therapeutically useful inhibitors of the enzyme to stop the progression of human acquired immunodeficiency syndrome (AIDS). Five competitive inhibitors of the enzyme have already been approved and several others are in clinical trials.[1] However, recent reports[2] indicate that 45 distinct drug-resistant single mutations in HIV PR have been identified, and the number of mutations has increased by 250% over a 3-year period. The development of drug-resistance is the consequence of incomplete suppression of HIV replication. The rapid replication rate of HIV and its inherent genetic variation result in the generation of numerous viral variants.[2,3] This genetic flexibility of HIV creates a new challenge for the development of the next generation of HIV inhibitors. Previous attempts to tackle the drug-resistance problems have been focused on the modification of inhibitors to overcome the effects of single mutations,[3a] or have relied on combination therapy.[3g,h] However, clinically isolated drug-resistant HIV variants often contain multiple mutations in their protease.[2,3c,e] The higher number of substitutions in the enzyme also increases the chance of developing cross-resistance to a wide range of structurally diverse inhibitors.[3c,e] This suggests that combination therapy with multiple HIV PR inhibitors may not be a solution to combat resistance selection. Therefore, it is necessary to develop new protease inhibitors which are efficacious against both the wild-type and drug-resistant HIV proteases and less prone to resistance development.

As a first step toward this goal, we have developed potent inhibitors against feline immunodeficiency virus protease (FIV PR), which has been shown to be a useful model for drug-resistant HIV PRs.[4] FIV is a retrovirus which causes an immunodeficiency syndrome in cats comparable to AIDS in humans.[5] FIV PR is also a C_2-symmetric homodimeric aspartic protease and is responsible for processing both the structural proteins of *gag* and the enzymes encoded by *pol* from polyprotein during FIV replication.[6] This enzyme has a superimposable active site structure and identical mechanism of catalysis to HIV PR.[4c,7] Furthermore, six mutated residues in HIV PR causing drug resistance (K20I, V32I, I50V, N88D, L90M, Q92K)[2,8] are found in the structurally aligned native residues of FIV PR.[7] In addition, FIV PR also contains five other amino acid

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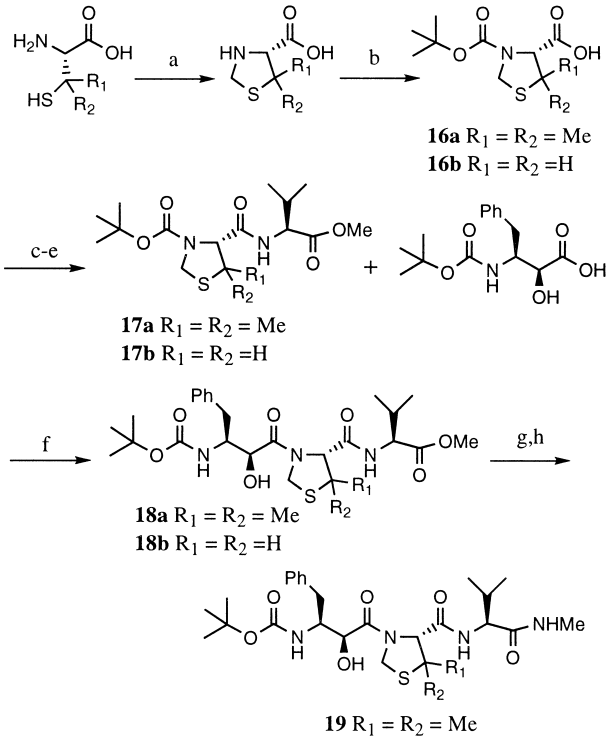
residues (L17, N39, I57, I85, I98)[7] closely related to mutations observed in drug-resistant HIV PRs, i.e., T12I, E34Q, G48V, A71V, P81T, respectively.[2] Many HIV protease mutants have a shrunken P3 binding site, which is a structural characteristic of FIV protease.[4,7] Kinetic studies have also demonstrated that various structurally diverse potent HIV PR inhibitors lost their efficiency as inhibitors against FIV PR by a factor of 100 or more.[4] These observations suggest that FIV PR may serve as a model for drug-resistant HIV PRs containing multiple mutations and may contribute to the understanding of HIV resistance to inhibitors. Furthermore, the cat may be used as an animal model to test the effectiveness of potential therapeutic drugs in vivo to accelerate the drug development process.

Our first investigation[4a,b] on the development of broad-based protease inhibitors efficacious against both HIV and FIV was focused on the systematic analysis of the S3 and S3′ subsite specificities of the enzymes. A series of C_2-symmetric inhibitors containing (1*S*, 2*R*, 3*R*, 4*S*)-1,4-diamino-1,4-dibenzyl-2,3-butan-diol as P1 and P1′ core were studied and these efforts led to the development of the potent FIV PR inhibitor TL3, which has a remarkable versatility to control FIV, HIV, and SIV infections in tissue culture with virtually the same degree of effectiveness.[4b] Although TL3 showed highly potent anti-HIV activity, it displays low oral bioavailability in cat and mouse. In the present study, we described our continuing effort to generate novel small-sized HIV and FIV protease inhibitors.



Scheme 1. (a) HCHO, py, H_2O, 85%; (b) BOC_2O, THF/H_2O, $NaHCO_3$, 77%; (c) Val-OMe, HBTU, DMF, Et_3N, 90%; (d) 4 N HCl, dioxane; (e) pH7; (f) HBTU, DMF, Et_3N, 89%; (g) LiOH, 20% MeOH/THF, H_2O, 100%; (h) NHS, HOBt, DCC, DCE then $MeNH_2$ 78%.

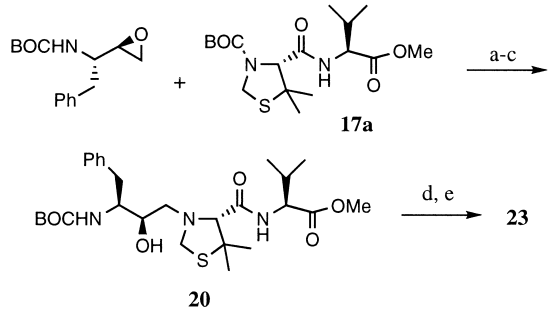
Results and Discussion

Chemistry

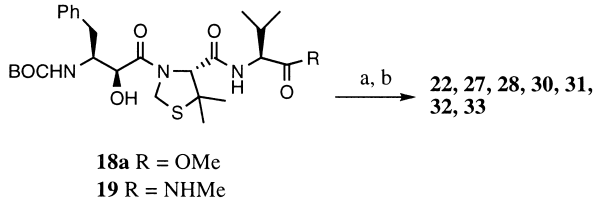
Scheme 1 illustrates the procedures to synthesize the tripeptide derivatives **18a**, **b** and **19**. BOC-protected 1,3-thiazolidine-4-carboxylic acid derivatives **16a, b** were prepared according to known procedures.[9,10] Compounds **17a, b** were prepared in good yields from the acids **16a, b** by using valine methyl ester and HBTU as a condensation reagent. Removal of the BOC group in **17a, b** followed by coupling of the acid[11] gave the tripeptides **18a,b**. Hydrolysis of the ester **18a** with LiOH followed by activation of the acid with *N*-hydroxysuccinimide gave the activated ester. This activated ester was condensed with aqueous methylamine to give the tripeptide **19** in good yields.

Scheme 2 illustrates the synthesis of compound **23**, which began with the removal of the BOC group in **17a** followed by condensation with an epoxide[4a] to give compound **20**. Deprotection of the BOC group in **20** followed by peptide coupling with Cbz-AlaVal-OH gave compound **23** in 80% yield.

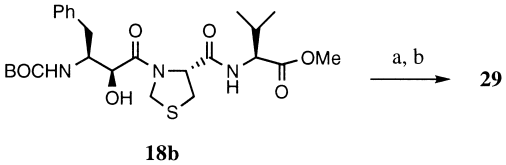
The inhibitors **22**, **27**–**33** were prepared from the corresponding tripeptides **18a**, **b** and **19** and are shown in Schemes 3 and 4.



Scheme 2. (a) 4 N HCl, dioxane; (b) pH7; (c) MeOH, Et_3N, 80 °C, 90%; (d) 4 N HCl, dioxane; (e) Cbz-Ala-Val-OH, HBTU, DMF, Et_3N, 68%.



Scheme 3. (a) 4 N HCl, dioxane; (b) dipeptide, HBTU, DMF, Et_3N, 70–90%.



Scheme 4. (a) 4 N HCl, dioxane; (b) Ac-Trp-Val-OH, HBTU, DMF, Et_3N, 82%.

Structure–activity relationship

Our first effort to improve the activity of TL3 involves structural modification of P4 and P4′ and the results are shown in Table 1. All the *C2*-symmetric diols tested in this study showed competitive inhibition of both the feline and human lentivirus PRs, but with higher potency against HIV PR by at least an order of magnitude. The sulfonamides **3**–**7** and the amide **8** derivatives displayed approximately 1–3-fold less active against FIV PR and about 1–20-fold less active against HIV PR. Two notable exceptions are compounds **2** and **9**, which displayed the highest potency with IC_{50} values of 17 and 62 nM against FIV PR respectively. However, the urea derivatives **10**–**13** showed only 37–61% inhibition at 200 μM against FIV PR. Compounds **2** and **9** were tested against drug-resistant mutant HIV PRs, G48V and V82F, and were found to be quite effective.

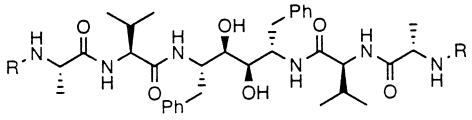
In order to ascertain the optimal length of the *C2*-symmetrical inhibitors derived from TL3, we next examined asymmetrically substituted derivatives **14** and **15** (Fig. 1). The chain length significantly affected the inhibitory activity. We found that removal of the P3′ residue from TL3 reduces the potency against HIV and FIV PRs by 4-fold and 22-fold respectively. Compound **15**, which contains no P3′ and P2′ residues, exhibited marginal activity with IC_{50} value of 200 μM against FIV PR and 100 nM against HIV PR. Such reduction in potency in **14** and **15** may also be attributed to Cbz group not properly bound in S2 and S3 pockets and so contribute to the poor activity.

In an effort to increase the antiviral activity and pharmacokinetic profiles of **TL3** derivatives, we used allophenylnorstatine ((2*S*,3*S*)-3-amino-2hydroxy-4-phenylbutyric acid) as a transition-state isostere.[10] Using hydroxymethyl-carboxamide as a transition-state mimic has produced the potent HIV PR inhibitor JE-2147 now in clinical trials.[12] Compounds **21**–**24** contain a thiazolidine ring, a bio-isostere of proline, at the P1′ portion; they were tested against both the wild-type FIV and HIV PRs and the results are summaries in Table 2. Compound **21** bearing the same residues as TL3, except for the P1′ residue, exhibited similar FIV PR inhibitory activity (IC_{50} = 95 nM), but lost its potency against HIV PR by 5-fold. Removal of the P3′ residue from compound **21** resulted in a 2-fold decrease in FIV PR inhibitory activity, but still retained its potency against HIV PR (IC_{50} = 18 nM). Deletion of the 1-oxo group in **22** led to compound **23**, which showed a significant loss of FIV PR activity (IC_{50} = 5.2 μM), but still retained its binding affinity to HIV PR. The configuration of the hydroxyl, which forms hydrogen bonds with the catalytic aspartic acids, plays an important role in binding: the (2*R*)-alcohol **24** displays a 96- and 26-fold reduction in potency against FIV and HIV PRs respectively as compared to the (2*S*)-alcohol **22**. This is in line with the results reported by Mimoto et al.[13]

In the course of our study on C_2 symmetrical diol inhibitors, we have observed that large hydrophobic P3 groups reduced the potency of inhibitors against FIV PR considerably,[4a] as in the case of compound **25**. However, compound **26**, which contains a tryptophan as P3 residue and *N*-acetyl as the N-terminal group, has a reasonable binding affinity with FIV PR (212 nM). This observation was in agreement with an independent study reported by Dunn laboratory,[14] indicating that in this case the P3 residue has moved away from the P3 binding site and oriented toward outside the cleft.

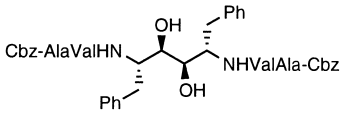
In the allophenylnorstatine series, compound **27**, a tryptophan as a P3 residue and *N*-Cbz as the terminal group, shows an IC_{50} value of 1 μM against FIV PR (Table 3). Interestingly, compound **28**, with an *N*-acetyl

Table 1. Structure and activity of TL3 derivatives against FIV, HIV and drug-resistant HIV proteases[a]



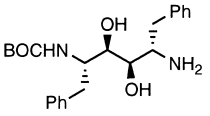
Inhibitor	R	FIV PR[b] IC_{50} (nM)	HIV PR[c] IC_{50} (nM)	HIV (G48V)[c] IC_{50} (nM)	HIV (V82F)[c] IC_{50} (nM)
TL3	CBz	100	4	21 (X5)	15 (X4)
1	CBz-Ser	128	17	202 (X6)	58 (X3)
2	4-$MePhSO_2$	17	5	28 (X6)	6 (X1)
3	$PhSO_2$	138	46		
4	4-$BrPhSO_2$	141	70		
5	4-O_2NPhSO_2	228	79		
6	4-$MeOPhSO_2$	310	20		
7	$PhCH_2SO_2$	118	23		
8	PhCO	156	17		
9	3-Pyr-CO	62	11	53 (X5)	43 (X4)
10	4-$F_3COPhNHCO$	119,000	1800		
11	4-$F_3CPhNHCO$	55% (200 μM)	2000		
12	4-MePhNHCO	37% (200 μM)	160		
13	4-MeOPhNHCO	61% (200 μM)	14		

[a]IC_{50} values were determined in duplicate.
[b]Data obtained at pH 5.25 at 37 °C in 0.1 M NaH_2PO_4, 0.1 M sodium citrate, 0.2 M NaCl, 0.1 mM DTT, 5% glycerol, and 5% DMSO in volume.
[c]Data obtained at pH 5.25 at 37 °C in 0.1M MES, 5% glycerol, and 5% DMSO in volume.

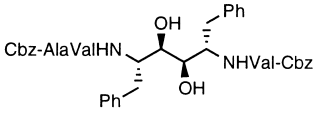


TL3

IC_{50} = 4 nM, HIV-WT
100 nM, FIV-WT

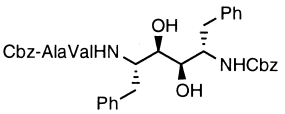


14a



14

IC_{50} = 17 nM, HIV-WT (X4)
2.2 μM, FIV-WT (X22)

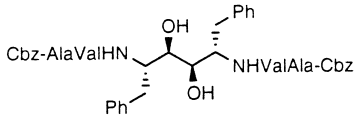


15

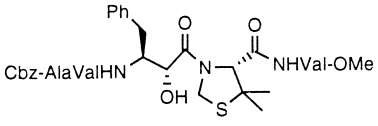
IC_{50} = 100 nM, HIV-WT (X25)
200 μM, FIV-WT (X2000)

Figure 1. Inhibition of TL3 and its derivatives against the wild-type HIV and FIV proteases.

Table 2. Structure and activity of unsymmetrically substituted inhibitors of HIV and FIV proteases



TL3



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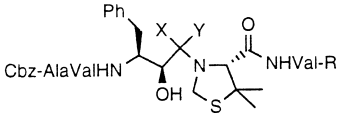


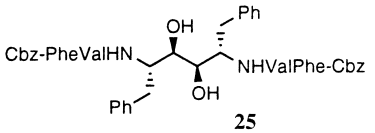
2*S*, 3*S*-isomer

21 R = Ala-Cbz, X = Y = O
22 R = OMe, X = Y = O
23 R = OMe, X = Y = H

	Inhibitors				
Wild-type proteases	TL3	**21**	**22**	**23**	**24**
FIV PR (IC_{50}, nM)	100	95	200	5200	19,200
HIV PR (IC_{50}, nM)	4	20	18	15	475

group, displays a 4-fold higher activity. Removal of the dimethyl group (**29**) from the thiazolidine ring reduces the potency of compound **28** against FIV PR by 5-fold, whereas no effect was observed against HIV PR. Conversion of the methyl ester **28** into methyl amide **30** was found to increase the inhibitory activity against FIV PR by a factor of 3. Replacing the tryptophan group in **28** with a phenylalanine group in **31** (VLE776) as the P3 site resulted in a 2- and 5-fold increase in the binding affinity to HIV and FIV PRs respectively. However, compound **33**, with the alanine group at the P3 site shows only a 1.4-fold increase in IC_{50} against FIV PR compared to that of **28**. Therefore, current observation suggests that the steric interaction between neighboring P1 and P3 side chains is still a crucial factor to facilitate proper binding in the active site of FIV PR. With phenylalanine as the P3 binding site, it is not too big or too small compared to tryptophan and alanine, respectively.

Table 3. Structure and activity of unsymmetrically substituted inhibitors of HIV and FIV proteases



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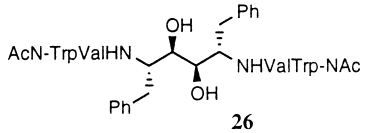

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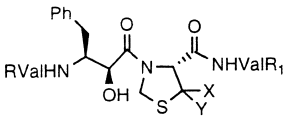


27 R=CbzTrp, R_1=OMe, X=Y =Me
28 R=AcTrp, R_1=OMe, X=Y=Me
29 R=AcTrp, R_1=OMe, X=Y=H
30 R=AcTrp, R_1=NHMe, X=Y=Me
31 R=AcPhe, R_1=OMe, X=Y=Me
32 R=AcPhe, R_1=NHMe, X=Y=Me
33 R=AcAla, R_1=OMe, X=Y=Me

	Inhibitors								
Wild-type proteases	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**
FIV PR (IC_{50}, nM)	92,000	212	1000	256	1200	80	48	117	182
HIV PR (IC_{50}, nM)	10	12	25	18	12	15	8	10	8

Therefore with phenylalanine in both P1 and P3 is the appropriate combination for good binding of **31**.

Based on the X-ray crystallography studies of LP130 complex with FIV PR[14] and JE2147 complex with HIV PR,[15] a chemical structure of VLE776 with binding pockets were constructed and is shown in Figure 2. The orientation of the phenylalanine side-chain in HIV PR is completely different from that observed in FIV PR, due to the presence of the Phe53 side chain in the flap region of HIV PR. The phenyl ring at P3 is tightly packed between Pro81 and Phe53. In FIV PR, the phenyl ring at P3 rotates away from the flap and is in closed contact with the three residues, Q99, I98 and I57.

A resistance surmountable inhibitors, 31/VLE776

HIV PR also develops in vitro a high level of resistance to TL3 by acquiring mutations in the protease-encoding gene, though it takes a relatively long time.[16] Mutations conferring TL3-resistance were L24I, M46I, F53L, L63P, V77I and V82A. The IC_{50} values of TL3 against wild-type HIV PR and TL3-resistant HIV PR were 4 and 144 nM respectively. In this study, compound **31** (**VLE776**) was found to be active against both wild-type HIV PR (IC_{50} = 8 nM) and the TL3-resistant protease (IC_{50} = 40 nM). Other FDA approved drugs were also tested against the TL3-resistant HIV PR and they showed about 12–22-fold decrease in potency as compared to the wild-type HIV PR. (Table 4).

Preliminary study on the synthesis of bifunctional inhibitors

Our initial effort in this regard is to incorporate a gp-120 glycosidase inhibitor as the *N*-terminal protecting

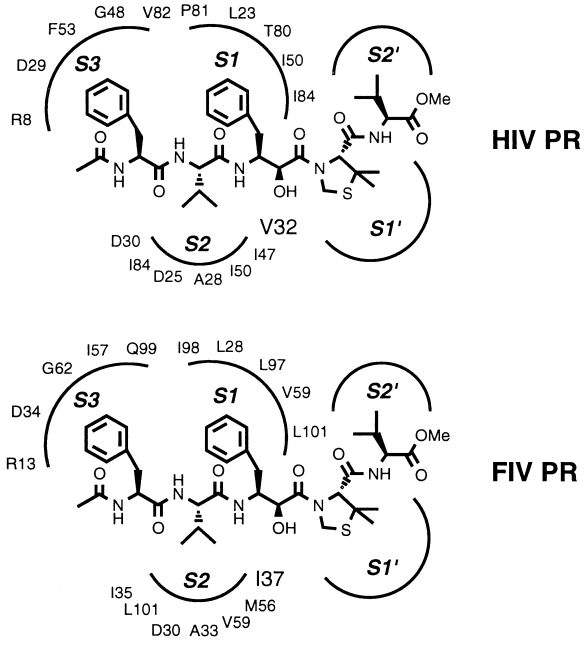


Figure 2. Comparison of subsites of HIV and FIV proteases.

group of an HIV protease inhibitor effective against the wild-type and some resistant mutants. Previous studies indicate that the N-terminal protecting group of inhibitors with a small P3 group has little effect on the activity.[4] We therefore decided to attach deoxynojirimycin,[17] a gp-120 glycosidase inhibitor, to the N-terminus of the protease inhibitor **35**[4a] via a linker (Scheme 5). Compound **36** was shown to be active against HIV protease ($IC_{50} = 39$ nM) and work is in progress to investigate its activity against different glycosidases.

Conclusion

In summary, we have designed and synthesized a series of novel TL3 derivatives containing allophenylnorstatine with a hydroxymethylcarboxamide isostere as transition-state analogue inhibitors of HIV and FIV proteases. From our SAR study on HIV and FIV protease inhibition, we have identified VLE776 as the best FIV PR inhibitor to date. Also VLE776 showed a strong inhibition against the drug-resistant mutant PRs (G48V and V82F) and the TL3-resistant HIV PR. Studies to determine the pharmacokinetic profiles of VLE776 are currently in progress.

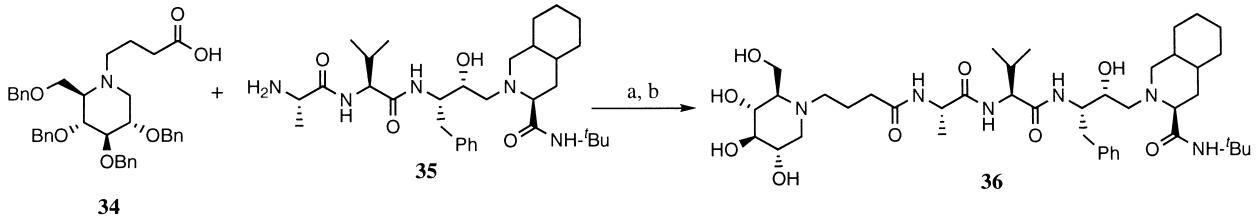
Experimental

Analytical TLC was performed on pre-coated plates (Merck, silica gel 60F-254). Silica gel used for flash column chromatography was Mallinckrodt Type 60 (230–400 mesh). NMR (^1H, ^{13}C) spectra were recorded either on a Bruker AMX-400, AMX-500 or AMX-600 MHz fourier transform spectrometer. Coupling constants (*J*) are reported in hertz, and chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (TMS, 0.0 ppm) or DMSO (2.49 ppm for ^1H and 39.5 ppm for ^{13}C) or CD_3OD (3.30 ppm for ^1H and 49.0 ppm for ^{13}C) as internal reference. All new compounds were homogeneous by TLC and were characterized by satisfactory ^1H, ^{13}C NMR, and mass spectra.

Compound 1. To a solution of compound TL3[4a,4b] (1 g, 1.10 mmol) in 2,2-dimethoxypropane (20 mL) was added catalytic amounts of *p*-TsOH. The reaction mixture was heated at room temperature for 24 h then

Table 4. Comparation of inhibitory activity of FDA approved drugs and **31** against HIV-WT, drug-resistant and TL3-resistant proteases

	IC_{50}, nM					
Inhibitors	WT	G48V	V82F	V82A	V82A, F53L M46I	V82A, V77I, L63P F53L, M46I, L24I
TL3	4	21(5X)	15(4X)	13(3X)	51(3X)	144(36X)
SQV	2	ND	ND	7(4X)	20(10X)	37(19X)
NFV	3	ND	ND	6(2X)	19(6X)	35(12X)
RTV	2	ND	ND	7((4X)	25(13X)	43(22X)
31	8	68(8X)	28(4X)	16(2X)	ND	40(5X)



34 **35** **36**

Scheme 5. (a) HBTU, DMF, Et_3N, 60% (b) H_2, Pd/C, AcOH, 56%.

diluted with EtOAc. The organic solution was washed with satd aq $NaHCO_3$ and satd aq NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo to give acetonide as a white solid. The above acetonide in MeOH (30 mL) containing 10% Pd/C (170 mg) was stirred under H_2 (1atm) at 20 °C for 6 h. The reaction mixture was filtered through Celite and then concentrated in vacuo to give diamine in nearly quantitative yields. To the above diamine (20 mg, 0.029 mmol) in DMF (2 mL) were added Cbz-Ser-OH (14 mg, 0.058 mmol) and HBTU (22.4 mg, 0.058 mmol). The reaction mixture was stirred at room temperature overnight then diluted with EtOAc. The organic solution was washed with satd aq $NaHCO_3$ and satd aq NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was dissolved in MeOH (2 mL) and *p*TsOH (4 mg) was added. The reaction mixture was stirred for 24 h and then water (2 mL) was added. Compound **1** which precipitated out was collected and dried (78%): ^{1}H NMR (600 MHz, DMSO-d_6) 8.08 (d, 1H, $J=7.4$), 7.62 (d, 1H, $J=9.0$), 7.29–7.37 (m, 7H), 7.14–7.16 (m, 3H), 7.07–7.10 (m, 1H), 5.02 (d, 1H, $J=12.7$), 5.00 (d, 1H, $J=12.7$), 4.41–4.45 (m, 1H), 4.28 (dt, 1H, $J=14.1$, 7.0), 4.09 (dd, 1H, $J=13.8$, 6.4), 4.03 (dd, 1H, $J=8.6$, 6.9), 3.58 (dd, 1H, $J=10.9$, 5.8), 3.52 (dd, 1H, $J=10.8$, 6.7), 3.22 (s, 1H), 2.74 (dd, 1H, $J=13.9$, 10.3), 2.59 (dd, 1H, $J=13.7$, 3.8), 1.75–1.81 (m, 1H), 1.15 (d, 3H, $J=7.0$), 0.69 (d, 3H, $J=6.7$), 0.62 (d, 3H, $J=6.7$); ^{13}C NMR (150 MHz, DMSO-d_6) 171.8, 170.3, 169.9, 155.9, 138.9, 136.9, 129.1, 128.3, 127.8, 127.7, 125.7, 73.2, 65.5, 61.8, 58.0, 57.0, 50.4, 48.3, 38.5, 30.4, 19.2, 18.1, 18.0; HRMS (FAB+), calcd for $C_{56}H_{74}N_8O_{14}Na$ *m/e* 1105.5222, found *m/e* 1105.5181.

Compound 2. To the above diamine (31 mg, 0.046 mmol) in dry pyridine (2 mL) at 0 °C was added a solution of *p*-toluenesulfonyl chloride (17.4 mg, 0.091 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at room temperature for 24 h then diluted with EtOAc. The organic solution was washed with 1 N HCl, satd aq $NaHCO_3$ and satd aq NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was dissolved in MeOH (2 mL) and *p*TsOH (4 mg) was added. The reaction mixture was stirred for 24 h and then water (2 mL) was added. Compound **2** which precipitated out was collected and dried (88%): ^{1}H NMR (500 MHz, DMSO-d_6) 7.85 (d, 1H, $J=8.5$), 7.64 (d, 2H, $J=8.0$), 7.58 (d, 1H, $J=8.5$), 7.32 (m, 4H), 7.14 (m, 7H), 4.64 (s, 2H), 4.45 (m, 1H), 3.91 (dd, 1H, $J=9.0$, 6.5), 3.82 (m, 1H), 3.18 (m, 1H), 2.75 (m, 1H), 2.57 (m, 1H), 2.34 (s, 3H), 1.70 (m, 1H), 0.95 (d, 3H, $J=7.0$), 0.58 (d, 3H, $J=7.0$), 0.54 (d, 3H, $J=7.0$); HRMS (FAB+), calcd for $C_{48}H_{64}N_6O_{10}S_2Cs$ *m/e* 1081.3180, found *m/e* 1081.3219.

The preparations of compounds **3**–**13** were carried out using the general procedures for coupling and deprotection.

Compound 3. In the same manner, diamine was reacted with phenylsulfonyl chloride followed by deprotection to give compound **3** (58%) as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6) 8.00 (d, 1H, $J=8.5$), 7.78 (m, 2H), 7.46–7.64 (m, 4H), 7.33 (d, 1H, $J=9.5$), 7.15–7.16 (m, 5H), 7.07–7.10 (m, 1H), 4.65 (s, 1H), 4.46 (m, 1H), 3.93 (dd, 1H, $J=9.0$, 6.5), 3.87 (m, 1H), 3.20 (s, 1H), 2.74 (dd, 1H, $J=13.5$, 10.0), 2.60 (dd, 1H, $J=14.0$, 10.0), 1.73 (m, 1H), 0.97 (d, 3H, $J=7.0$); HRMS (FAB+), calcd for $C_{46}H_{60}N_6O_{10}S_2Cs$ *m/e* 1053.2867, found *m/e* 1053.2904.

Compound 4. In the same manner, diamine was reacted with 4-bromophenylsulfonyl chloride followed by deprotection to give compound **4** (70%) as a white solid; ^{1}H NMR (500 MHz, DMSO-d_6), 8.09 (bs, 1H), 7.65–7.75 (m, 5H), 7.32 (d, 1H, $J=9.5$), 7.14–7.15 (m, 1H), 7.07–7.10 (m, 1H), 4.65 (s, 2H), 4.44 (m, 1H), 3.84–3.92 (m, 2H), 3.19 (s, 1H), 2.73 (dd, 1H, $J=14.0$, 10.0), 2.56 (m, 1H), 1.65–1.70 (m, 1H), 1.00 (d, 3H, $J=7.0$), 0.58 (d, 3H, $J=7.0$), 0.54 (d, 3H, $J=7.0$); HRMS (FAB+), calcd for $C_{46}H_{58}N_6O_{10}S_2Br_2Cs$ *m/e* 1211.1056, found *m/e* 1211.1021.

Compound 5. In the same manner, diamine was reacted with 4-nitrophenylsulfonyl chloride followed by deprotection to give compound **5** (74%) as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6), 8.35 (d, 2H, $J=8.5$), 8.02 (d, 2H, $J=8.5$), 7.70 (d, 1H, $J=8.5$), 7.34 (d, 1H, $J=9.0$), 7.13–7.14 (m, 5H), 7.08 (m, 1H), 4.64 (s, 2H), 4.42 (m,1H), 4.00 (m, 1H), 3.89 (dd, 1H, $J=8.5$, 6.5), 3.18 (s, 1H), 2.72 (m, 1H), 2.54 (m, 1H), 1.65 (m, 1H), 1.01 (d, 1H, $J=.0$), 0.56 (d, 1H, $J=6.5$), 0.5 (d, 1H, $J=6.5$).

Compound 8. In the same manner, diamine was reacted with benzoyl chloride followed by deprotection to give compound **8** (88%) as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6), 8.52 (d, 1H, $J=7.4$), 7.88 (d, 2H, $J=7.0$), 7.40–7.61 (m, 6H), 7.06–7.18 (m, 6H), 4.50–4.55 (m, 1H), 4.43–4.49 (m, 1H), 4.07 (dd, 1H, $J=8.4$, 6.6), 3.27 (s, 1H), 2.77 (dd, 1H, $J=13.6$, 10.3), 1.81–1.88 (m, 1H), 1.30 (d, 3H, $J=7.4$), 0.70 (d, 3H, $J=7.0$), 0.66 (d, 3H, $J=7.0$); ^{13}C NMR (125 MHz, DMSO-d_6), 171.9, 170.2, 166.2, 138.9, 134.1, 131.3, 129.0, 128.2, 127.7, 127.4, 125.6, 73.2, 57.8, 50.4, 48.9, 38.5, 30.4, 19.3, 17.8, 17.6; HRMS (FAB+), calcd for $C_{48}H_{60}N_6O_8Na$ *m/e* 871.4370, found *m/e* 871.4373.

Compound 9. In the same manner, diamine was coupled with 6-methylnicotinic acid followed by deprotection to give compound **9** (55%) as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6), 8.91 (s, 1H), 8.67 (d, 1H, $J=7.4$), 8.11 (d, 1H, $J=8.0$), 7.64 (d, 1H, $J=8.8$), 7.42 (d, 1H, $J=9.6$), 7.35 (d, 1H, $J=8.1$), 7.08–7.28 (m, 7H), 4.68 (s, 1H), 4.47–4.53 (m, 2H), 4.06 (m, 1H), 3.26 (s, 1H), 2.76 (m, 1H), 2.61 (m, 1H), 2.55 (s, 3H),1.82-1.86 (m, 1H), 1.29 (d, 3H, $J=7.0$), 0.70 (d, 3H, $J=6.6$), 0.66(d, 3H, $J=6.6$); ^{13}C NMR (125 MHz, DMSO-d_6), 179.8, 174.2, 170.4, 157.6, 148.5, 144.9, 138.5, 137.6, 137.3, 136.4, 135.1, 132.1, 82.9, 67.3, 59.9, 58.4, 51.2, 40.0, 33.6, 28.8, 27.4, 27.1; HRMS (FAB+), calcd for $C_{48}H_{62}N_8O_8Na$ *m/e* 901.4583, found *m/e* 901.4608.

Compound 10. In the same manner, diamine was reacted with 4-trifuoromethylphenyl isocyanate followed by deprotection to give compound **10** (67%) as a white

solid: ^{1}H NMR (400 MHz, DMSO-d_6), 8.87 (s, 1H), 7.84 (d, 1H, J = 8.9), 7.44 (d, 2H, J = 8.9), 7.13–7.21 (m, 8H), 7.08–7.10 (m, 1H), 6.43 (d, 1H, J = 7.6), 4.67 (s, 1H), 4.46–4.51 (m, 1H), 4.26–4.33 (m, 1H), 4.06 (dd, 1H, J = 8.6, 7.0), 3.24 (s, 1H), 2.76 (dd, 1H, J = 13.8, 10.5), 2.58–2.63 (m, 1H), 1.77–1.86 (m, 1H), 1.14 (d, 3H, J = 6.8), 0.70 (d, 3H, J = 6.8), 0.65 (d, 3H, J = 6.5); HRMS (FAB+), calcd for $C_{50}H_{60}N_8O_{10}F_6Cs$ m/e 1179.3391, found m/e 1179.3350.

Compound 12. In the same manner, diamine was reacted with 4-methylylphenyl isocyanate followed by deprotection to give compound **12** (70%) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6), 8.46 (d, 1H, J = 7.3), 7.79 (d, 2H, J = 7.9), 7.59 (d, 1H, J = 9.1), 7.42 (d, 1H, J = 9.4), 7.26 (d, 2H, J = 7.9), 7.08–7.17 (m, 5H), 4.38–4.51 (m, 4H), 4.06 (dd, 1H, J = 8.8, 6.4), 3.25 (s, 1H), 2.76 (dd, 1H, J = 13.8, 10.3), 2.61 (dd, 1H, J = 13.8, 3.8), 2.35 (s, 3H), 1.80–1.88 (m, 1H), 1.28 (d, 3H, J = 7.04), 0.69 (d, 3H, J = 7.0), 0.65 (d, 3H, J = 6.8); ^{13}C NMR (100 MHz, DMSO-d_6), 172.1, 170.3, 166.1, 141.2, 139.0, 131.3, 129.1, 128.8, 128.1, 127.8, 127.5, 125.7, 73.3, 57.8, 50.4, 48.9, 38.6, 30.5, 21.0, 20.8, 19.3, 17.8, 17.6; HRMS (FAB+), calcd for $C_{50}H_{64}N_6O_8Na$ m/e 899.4683, found m/e 899.4690.

Compound 13. In the same manner, diamine was reacted with 4-methoxyphenyl isocyanate followed by deprotection to give compound **13** (70%) as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6), 8.45 (s, 1H), 7.80 (d, 1H, J = 9.0), 7.33 (d, 1H, J = 8.9) 7.25 (d, 1H, J = 8.6), 7.14–7.17 (m, 4H), 7.08–7.11 (m, 1H), 6.74 (d, 1H, J = 0.3), 6.25 (d, 1H, J = 7.7), 4.65 (s, 1H), 4.48 (m, 1H), 4.27 (dt, 1H, J = 13.8, 6.7), 4.05 (t, 1H, J = 7.5), 3.70 (s, 3H), 3.25 (s, 1H), 2.76 (dd, 1H, J = 13.8, 10.7), 2.60 (dd, 1H, J = 13.7, 3.5), 1.79–1.85 (m, 1H), 1.14 (d, 3H, J = 6.74), 0.70 (d, 3H, J = 6.7), 0.65 (d, 3H, J = 6.6); HRMS (FAB+), calcd for $C_{50}H_{66}N_8O_{10}Cs$ m/e 1071.3956, found m/e 1071.3929.

Compound 14. To a solution of amine **14a**[18] (50 mg, 0.13 mmol) in DMF (2 mL) was added Cbz-AlaVal-OH (40.3 mg, 0.13 mmol) and HBTU (47.4 mg, 0.13 mmol). The reaction mixture was stirred for 2 h then diluted with EtOAc. The organic solution was washed with satd aq $NaHCO_3$ and satd aq NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was dissolved in 4 N HCl in dioxane (2 mL) and stirred for 2 h. After removal of the solvents to dryness, the residue was dissolved in DMF and Cbz-Val-OH (31 mg, 0.13 mmol) and HBTU (47 mg) and Et_3N (52 μL, 0.38 mmol) was added. The reaction mixture was stirred for 6 h then diluted with EtOAc. The organic solution was washed with satd aq $NaHCO_3$ and satd aq NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo to give compound **14** (65%): ^{1}H NMR (500 MHz, DMSO-d_6), 7.09–7.35 (m, 20H), 5.04 (d, 2H, J = 12.5), 5.02 (s, 2H), 4.71–4.77 (m, 2H), 4.47–4.50 (m, 2H), 4.14 (m, 1H), 4.08 (t, 2H, J = 8.1), 3.76 (t, 1H, J = 8.8), 3.25 (m, 3H), 2.76 (m, 2H), 2.60 (m, 2H), 1.80 (m, 2H), 1.18 (d, 3H, J = 7.0), 1.15 (d, 3H, J = 7.0), 0.61–0.72 (m, 12H); HRMS (FAB+), calcd for $C_{47}H_{59}N_5O_9Na$ m/e 860.4313, found m/e 860.4390.

Compound 15. In the same manner, amine was coupled with Cbz-Cl to give compound **15** (70%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) 7.13–7.35 (m, 15H), 6.39–6.47 (m, 1H), 5.09 (s, 2H), 5.04 (s, 2H), 4.05–4.30 (m, 4H), 3.76 (m, 2H), 2.75–2.87 (m, 4H), 1.82–1.90 (m, 1H), 1.20 (d, 3H, J = 7.2), 0.86 (m, 3H), 0.75 (m, 3H); HRMS (FAB+), calcd for $C_{42}H_{50}N_4O_8Na$ m/e 761.3629, found m/e 761.3640.

Compound 17a. To a solution of acid **16a**[9] (261 mg, 1 mmol) in DMF (4 mL) was added Val-OMe.HCl (168 mg, 1 mmol), HBTU (379 mg, 1 mmol) and Et_3N (0.28 mL). The reaction mixture was stirred overnight and then diluted with EtOAc. The organic solution was washed with satd aq $NaHCO_3$ and satd aq NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography in 10% EtOAc/Hexane to give compound **17a** (85%): ^{1}H NMR (500 MHz, CD_3OD) 4.65 (d, 1H, J = 9.1), 4.60 (d, J = 9.1), 4.21–4.37 (m, 2H), 3.70 (s, 3H), 2.12–2.19 (m, 1H), 1.56 (s, 3H), 1.43 (s, 9H), 1.38 (s, 3H), 0.98 (m, 6H); HRMS (FAB+), calcd for $C_{17}H_{30}N_2O_5SNa$ m/e 397.1768, found m/e 397.1787.

Compound 17b. In the similar manner, acid **16b**[9] was coupled with ValOMe.HCl to give compound **17b** (80%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) 4.73 (bs, 1H), 4.66 (m, 1H), 4.53 (m, 1H), 4.38 (bs, 1H), 3.73 (s, 3H), 2.14–2.20 (m, 1H), 1.50 (s, 9H), 0.93 (d, 3H, J = 6.6), 0.89 (d, 3H, J = 6.6); ^{13}C NMR (125 MHz, $CDCl_3$) 171.6, 169.8, 153.7, 81.7, 56.9, 51.8, 49.2, 31.1, 27.9, 18.7, 17.3; HRMS (FAB+), calcd for $C_{15}H_{26}N_2O_5SNa$ m/e 369.1455, found m/e 369.1490.

Compound 18a. To a solution of compound **17a** (374 mg, 1 mmol) in CH_2Cl_2 (4 mL) was added 4 N HCl in dioxane (4 mL). The reaction mixture was stirred for 4 h and the solvent was removed to dryness. To a solution of this residue in DMF (8 mL) was added the acid[11] (295 mg, 1 mmol) HBTU (379 mg, 1 mmol) and Et_3N (0.14 mL). The reaction mixture was stirred overnight and then diluted with EtOAc. The organic solution was washed with satd aq $NaHCO_3$ and satd aq NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography in 20% EtOAc/Hexane to give compound **18a** (72%): ^{1}H NMR (600 MHz, CD_3OD) 7.14–7.26 (m, 5H), 5.05 (d, 1H, J = 9.2), 4.93 (d, 1H, J = 9.2), 4.62 (s, 1H), 4.50 (d, 1H, J = 3,9), 4.44 (d, 1H, J = 5.7), 4.01 (m,1H), 3.70 (s, 3H), 2.81 (dd, 1H, J = 14.0, 3.5), 2.62 (dd, 1H, J = 13.6, 11.0), 2.17 (m, 1H), 1.60 (s, 3H), 1.44 (s, 3H), 1.31 (s, 9H), 0.96 (t, 6H, J = 7.0); ^{13}C NMR (150 MHz, CD_3OD) 173.4, 172.3, 170.9, 157.8, 140.2, 130.6, 129.2, 127.1, 80.1, 73.3, 73.1, 59.0, 56.0, 52.4, 35.7, 32.0, 30.1, 28.7, 25.3, 19.5, 18.4; HRMS (FAB+), calcd for $C_{27}H_{41}N_3O_7SNa$ m/e 574.2665, found m/e 574.2693.

Compound 18b. To a solution of compound **17b** (346 mg, 1 mmol) in CH_2Cl_2 (4 mL) was added 4 N HCl in dioxane (4 mL). The reaction mixture was stirred for 4 h and the solvent was removed to dryness. To a solution of this residue in DMF (8 mL) was added the acid (295 mg, 1 mmol), HBTU (379 mg, 1 mmol) and Et_3N

(0.14 mL). The reaction mixture was stirred overnight and then diluted with EtOAc. The organic solution was washed with satd aq $NaHCO_3$ and satd aq NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography in 20% EtOAc/Hexane to give compound **18b** (68%); ^{1}H NMR (500 MHz, CD_3OD) 7.13–7.29 (m, 5H), 5.00 (d, 1H, $J=9.5$), 4.96 (t, 1H, $J=7.0$), 4.77 (d, 1H, $J=9.9$), 4.59 (d, 1H, $J=3.3$), 4.41 (d, 1H, $J=5.5$), 4.02–4.05 (m, 2H), 3.70 (s, 3H), 3.40 (dd, 1H, $J=11.7$, 7.7), 3.14 (dd, 1H, $J=11.7$, 6.6), 2.89 (dd, 1H, $J=14.0$, 3.0), 2.66 (m, 1H), 2.16 (m, 1H), 1.32 (s, 9H), 0.95 (d, 6H, $J=6.6$); ^{13}C NMR (125 MHz, CD_3OD) 173.4, 172.2, 171.8, 157.7, 140.0, 130.5, 129.1, 127.1, 80.0, 73.3, 65.3, 64.0, 61.4, 59.1, 56.0, 52.5, 51.0, 34.0, 32.0, 28.7, 19.5, 18.4; HRMS (FAB+), calcd for $C_{25}H_{37}N_3O_7SNa$ *m/e* 546.2244, found *m/e* 546.2239.

Compound 19. To a solution of compound **18a** (551 mg, 1 mmol) in 20% MeOH in THF (8 mL) was added a solution of LiOH (72 mg, 3 mmol) in water (0.5 mL). The reaction mixture was stirred for 4 h and then diluted with EtOAc. The organic solution was washed with 10% citric acid and water, dried over $MgSO_4$, filtered and concentrated in vacuo. To a solution of the residue in 1,2-dichloroethane (10 mL) was added *N*-hydroxysuccinimide (115 mg, 1 mmol), HOBt (153 mg, 1 mmol) and DCC (206 mg, 1 mmol). The reaction mixture was stirred for 24 h and excess of solvents was removed to dryness. The residue was dissolved in THF (10 mL) and methylamine (0.7 mL, 2 M in THF, 1.4 mmol) was added. The reaction mixture was stirred for 1 h and the precipitate which forms was removed by filtration. Excess of solvents were removed and the crude product was purified by flash chromatography to give **c**ompound **19** (90%) as a white solid: ^{1}H NMR (500 MHz, CD_3OD) 7.13–7.18 (m, 5H), 5.09 (d, 1H, $J=9.6$), 4.95 (d, 1H, $J=8.8$), 4.57 (s, 1H), 4.54 (d, 1H, $J=4.4$), 4.18 (m, 1H), 3.94 (m, 1H), 2.90 (m, 1H), 2.70 (s, 3H), 2.03 (m, 1H), 1.57 (s, 3H), 1.40 (s, 3H), 1.31 (s, 9H), 0.96 (d, 3H, $J=6.6$), 0.91 (d, 3H, $J=7.0$); ^{13}C NMR (125 MHz, CD_3OD) 173.9, 172.5, 170.5, 157.7, 140.0, 130.5, 129.1, 127.1, 80.0, 73.5, 61.4, 56.1, 52.3, 35.9, 32.0, 30.4, 28.7, 26.3, 26.1, 25.1, 20.9, 19.7, 19.1 14.5; HRMS (FAB+), calcd for $C_{27}H_{42}N_4O_6SNa$ *m/e* 573.2717, found *m/e* 573.2726.

Compound 20. To a solution of compound **17a** (374 mg, 1 mmol) in CH_2Cl_2 (4 mL) was added 4 N HCl in dioxane (4 mL). The reaction mixture was stirred for 4 h and the solvent was removed to dryness. The residue was dissolved in water and neutralized with 2 MNaOH. The aqueous solution was extracted with EtOAc and the organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. To a solution of this residue in dry MeOH (10 mL) was added epoxide[4a] (263 mg, 1 mmol) and Et_3N (0.28 mL). The reaction mixture was stirred at 80 °C for 24 h. After allowing to cool to room temperature, excess of solvent was removed and the crude product was purified by flash chromatography to give compound **20** (62%): ^{1}H NMR (500 MHz, $CDCl_3$) 7.97 (d, 1H, $J=9.0$), 7.17–7.30 (m, 5H), 4.71 (d, 1H, $J=8.7$), 4.52 (d, 1H, $J=10.0$), 4.48 (dd, 1H, $J=9.4$, 4.9), 4.42 (d, 1H, $J=4.7$), 3.95 (d, 1H, $J=10.0$), 3.80 (m, 1H), 3.75 (s, 3H), 3.59 (m, 1H), 3.16 (s, 1H), 2.98 (d, 2H, $J=12.3$), 2.86 (dd, 1H, $J=12.7$, 9.6), 2.76 (m, 1H), 2.21 (m, 1H), 1.63 (s, 3H), 1.41 (s, 3H), 1.31 (s, 9H), 0.98 (d, 3H, $J=6.9$), 0.93 (d, 3H, $J=6.8$); ^{13}C NMR (125 MHz, $CDCl_3$) 174.4, 171.4, 155.5, 138.0, 129.4, 128.2, 126.2, 80.7, 79.2, 72.0, 62.0, 60.3, 58.6, 56.8, 55.6, 54.6, 52.5, 35.9, 30.4, 29.6, 28.2, 25.3, 19.4, 17.7, 14.1; HRMS (FAB+), calcd for $C_{27}H_{43}N_3O_6SNa$ *m/e* 560.2765, found *m/e* 560.2742.

Compound 23. To a solution of compound **20** (54 mg, 0.1 mmol) in CH_2Cl_2 (2 mL) was added 4 N HCl in dioxane (2 mL). The reaction mixture was stirred for 4 h and the solvent was removed to dryness. To a solution of crude amine in DMF (2 mL) was added Cbz-AlaVal-OH (32 mg, 0.1 mmol), HBTU (38 mg, 0.1 mmol) and Et_3N (28 μL, 0.2 mmol). The reaction mixture was stirred for 12 h and then diluted with EtOAc. The organic solution was washed with satd aq $NaHCO_3$ and satd aq NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography in 15% EtOAc/Hexane to give compound **23** (80%) as a white solid: ^{1}H NMR (600 MHz, CD_3OD) 7.12–7.35 (m, 10H), 5.09 (s, 2H), 5.05 (s, 1H), 4.53 (d, 1H, $J=9.5$), 4.34 (dd, 1H, $J=10.6$, 5.4), 3.95–4.18 (m, 4H), 3.73 (s, 3H), 2.94–2.98 (m, 1H), 2.72–2.76 (m, 2H), 2.16–2.21 (m, 1H), 1.87–1.92 (m, 1H), 1.57 (s, 3H), 1.37 (s, 3H), 1.32 (d, 3H, $J=7.1$), 0.94–0.96 (m, 6H), 0.77 (t, 3H, $J=7.0$), 0.60 (t, 3H, $J=7.0$); ^{13}C NMR (150 MHz, CD_3OD), 175.5, 174.3, 173.6, 173.1, 158.4, 140.0, 138.1, 130.6, 129.5, 129.3, 129.0, 127.2, 82.6, 74.1, 67.7, 61.5, 60.4, 58.7, 58.5, 55.5, 53.1, 54.9, 52.8, 52.1, 37.0, 32.0, 31.4, 30.3, 26.7, 19.9, 19.7, 18.4, 18.0; HRMS (FAB+), calcd for $C_{38}H_{55}N_5O_8SNa$ *m/e* 764.3664, found *m/e* 764.3689.

Compound 24. ^{1}H NMR (600 MHz, CD_3OD) 8.27 (d, 1H, $J=8.76$), 7.86 (d, 1H, $J=9.24$), 7.26–7.34 (m, 10H), 7.18–7.20 (m, 1H), 5.10 (d, 1H, $J=12.7$), 5.06 (d, 1H, $J=12.2$), 4.65 (d, 1H, $J=8.3$), 4.53 (m, 1H), 4.47 (d, 1H, $J=7.86$), 4.35 (s, 1H), 4.30–4.32 (m, 2H), 4.18 (dd, 1H, $J=14.0$, 7.0), 4.13 (t, 1H, $J=6.6$), 3.67 (s, 3H), 2.99 (dd, 1H, $J=12.6$, 8.8), 2.87 (dd, 1H, $J=12.3$, 6.6), 2.11 (dt, 1H, $J=21.1$, 14.5, 7.5), 1.91–1.93 (m, 1H), 1.53 (s, 3H), 1.35 (s, 3H), 1.32 (d, 3H, $J=7.0$), 0.94 (t, 3H, $J=5.7$), 0.80 (dd, 3H, $J=9.7$, 7.0); ^{13}C NMR (150 MHz, CD_3OD,) 173.3, 173.1, 172.1, 171.7, 171.6, 158.5, 139.3, 138.1, 130.5, 129.6, 129.5, 129.0, 128.7, 127.7, 73.4, 70.6, 67.7, 60.1, 59.3, 52.9, 52.6, 52.4, 51.9, 38.8, 32.0, 31.9, 31.3, 24.3, 20.0, 19.5, 18.7, 18.5, 18.0; HRMS (FAB+), calcd for $C_{38}H_{53}N_5O_9SNa$ *m/e* 778.3564, found *m/e* 778.3590.

Compound 25. See ref 4a.

Compound 26. ^{1}H NMR (600 MHz, DMSO-d_6), 8.10 (d, 1H, $J=8.3$), 7.68 (d, 1H, $J=9.2$), 7.60 (d, 1H, $J=7.9$), 7.46 (d, 1H, $J=7.9$), 7.31 (d, 1H, $J=7.9$), 6.95–7.21 (m, 15H), 4.52–4.55 (m, 1H), 4.44–4.48 (m, 1H), 4.08 (dd, 1H, $J=8.8$, 6.5), 3.29 (s, 1H), 3.01 (dd, 1H, $J=12.6$, 1.6), 2.85 (dd, 1H, $J=14.9$, 10.5), 2.76–2.81 (m, 1H), 2.64 (dd, 1H, $J=14.0$, 4.0), 1.83–1.86 (m, 1H), 1.74 (s,

3H), 0.68 (d, 3H, $J=7.0$), 0.65 (d, 3H, $J=7.0$); ^{13}C NMR (150 MHz, DMSO-d_6), 171.6, 170.3, 169.2, 139.0, 136.0, 129.1, 128.8, 128.0, 127.8, 127.3, 125.7, 125.5, 123.3, 120.8, 118.5, 118.1, 111.2, 110.5, 73.3, 57.9, 53.2, 50.6, 38.6, 30.5, 27.4, 22.5, 19.3, 17.9; HRMS (FAB+), calcd for $C_{54}H_{66}N_8O_8Na$ *m/e* 977.4896, found *m/e* 977.4882.

General procedure for the synthesis of compounds 22, 27, 28, 29 and 31

To a solution of compound **18a** (551 mg, 1 mmol) or **18b** (523 mg, 1 mmol) or **19** (550 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added 4 N HCl in dioxane (10 mL). The reaction mixture was stirred for 4 h and the solvent was removed to dryness. To a solution of the amine (49 mg, 0.1 mmol) in DMF (2 mL) was added dipeptide (0.1 mmol), HBTU (38 mg, 0.1 mmol) and Et_3N (28 μL, 0.2 mmol). The reaction mixture was stirred for 12 h and then diluted with EtOAc. The organic solution was washed with satd aq $NaHCO_3$ and satd aq NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography in 15% EtOAc/Hexane to give the title compound.

Compound 22. The above amine (49 mg, 0.1 mmol) was coupled with Cbz-AlaVal-OH (32 mg, 0.1 mmol) to give compound **22** (75%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) 7.11–7.34 (m, 10H), 5.07 (s, 2H), 5.04 (m, 1H), 4.62 (s, 1H), 4.35–4.48 (m, 3H), 4.05–4.13 (m, 2H), 3.70 (s, 3H), 2.79–2.86 (m, 2H), 2.13–2.16 (m, 1H), 1.60 (s, 3H), 1.45 (s, 3H), 0.93–0.97 (m, 9H), 0.77–0.79 (m, 3H); HRMS (FAB+), calcd for $C_{38}H_{53}N_5O_9SNa$ *m/e* 778.3564, found *m/e* 778.3580.

Compound 29. The above amine (46 mg, 0.1 mmol) was coupled with Ac-TrpVal-OH (35 mg, 0.1 mmol) to give compound **29** (66%) as a white solid: ^{1}H NMR (500 MHz, CD_3OD) 7.60 (m, 1H), 6.94–7.32 (m, 9H), 5.14 (d, 1H, $J=9.2$), 4.87 (d, 1H, $J=9.2$), 4.64 (s, 1H), 4.53 (m, 1H), 4.34–4.43 (m, 3H), 4.05 (d, 1H, $J=6.3$), 3.70 (s, 3H), 3.15–3.20 (m, 1H), 3.06 (m, 1H), 2.69 (m, 1H), 3.15–3.20 (m, 1H), 3.06 (m, 1H), 2.88 (m, 1H), 2.69 (m, 1H), 2.13 (m, 1H), 1.90 (s, 3H), 1.60 (s, 3H), 1.45 (s, 3H), 0.94 (t, 3H, $J=7.0$), 0.40 (dd, 3H, $J=24.6$, 7.0); HRMS (FAB+), calcd for $C_{38}H_{50}N_6O_8SNa$ *m/e* 773.3411, found *m/e* 773.3450.

Compound 30. The above amine (49 mg, 0.1 mmol) was coupled with Ac-PheVal-OH (35 mg, 0.1 mmol) to give compound **30** (55%) as a white solid: ^{1}H NMR (500 MHz, CD_3OD) 7.58 (d, 1H, $J=7.7$), 7.32 (d, 1H, $J=8.0$), 7.17–7.24 (m, 6H), 7.03–7.14 (m, 2H), 6.97–7.00 (m, 1H), 5.04 (d, 1H, $J=9.2$), 4.86 (d, 1H, $J=9.2$), 4.65 (m, 1H), 4.52 (dd, 1H, $J=9.2$, 3.7), 4.32 (m, 1H), 4.07–4.14 (m, 2H), 3.18 (dd, 1H, $J=14.7$, 5.9), 3.04 (dd, 1H, $J=14.7$, 8.1), 2.90 (m, 1H), 2.75–2.80 (m, 1H), 2.70 (s, 3H), 1.94–1.98 (m, 2H), 1.54 (s, 3H), 1.40 (s, 3H), 0.89–0.95 (m, 6H), 0.72 (d, 3H, $J=8.0$), 0.70 (d, 3H, $J=7.0$); ^{13}C NMR (125 MHz, CD_3OD,) 174.1, 173.9, 173.4, 173.2, 172.3, 170.7, 139.9, 138.1, 130.6, 129.3, 127.5, 124.6, 122.4, 119.8, 119.4, 112.3, 110.9, 73.5, 72.6, 60.5, 60.4, 55.5, 55.0, 52.5, 34.8, 31.9, 31.6, 30.3, 28.7, 26.1, 25.2, 22.5, 19.8, 19.7, 19.6, 19.2, 18.5; HRMS (FAB+), calcd for $C_{40}H_{55}N_7O_7SNa$ *m/e* 800.3776, found *m/e* 800.3793.

Compound 31. The above amine (49 mg, 0.1 mmol) was coupled with Ac-PheVal-OH (31 mg, 0.1 mmol) to give compound **31** (72%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) 7.15–7.31 (m, 10H), 5.08 (d, 1H, $J=9.4$), 4.91 (d, 1H, $J=9.4$), 4.63 (s, 1H), 4.57 (d, 1H, $J=10.0$, 5.3), 4.50 (d, 1H, $J=3.52$), 4.43 (d, 1H, $J=5.88$), 4.34–4.37 (m, 1H), 4.07 (d, 1H, $J=7.3$), 3.70 (s, 3H), 2.98 (dd, 1H, $J=14.1$, 5.0), 2.73–2.87 (m, 3H), 2.11–2.19 (m, 1H), 1.90–1.97 (m, 1H), 1.86 (s, 3H), 1.60 (s, 3H), 1.45 (s, 3H), 0.95 (dd, 3H, $J=6.8$, 3.2), 0.81 (d, 3H, $J=6.8$); ^{13}C NMR (100 MHz, CD_3OD), 173.7, 173.5, 173.2, 173.1, 172.0, 170.9, 139.9, 138.5, 130.6, 130.2, 129.4, 129.3, 127.7, 127.3, 73.0, 72.7, 60.3, 59.1, 56.0, 54.8, 52.5, 52.4, 38.5, 34.7, 32.0, 30.2, 25.3, 22.3, 19.7, 19.5, 18.6, 18.5; HRMS (FAB+), calcd for $C_{38}H_{53}N_5O_8SNa$ *m/e* 762.3507, found *m/e* 762.3539.

Compound 32. The above amine (49 mg, 0.1 mmol) was coupled with Ac-PheVal-OH (31 mg, 0.1 mmol) to give compound **32** (79%) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) 8.03 (d, 1H, $J=8.8$), 7.30 (d, 1H, $J=7.4$), 7.18–7.22 (m, 10H), 5.08 (d, 1H, $J=9.4$), 4.91 (m, 1H), 4.58 (dd, 1H, $J=11.4$, 5.0), 4.55 (s, 1H), 4.52 (d, 1H, $J=4.1$), 4.33–4.38 (m, 1H), 4.16 (d, 1H, $J=8.2$), 4.09 (d, 1H, $J=7.3$), 3.00 (dd, 1H, $J=9.4$, 5.0), 2.90 (dd, 1H, $J=14.1$, 3.2), 2.79 (dd, 1H, $J=14.1$, 10), 2.70 (s, 3H), 1.96–2.00 (m, 1H), 1.86 (s, 3H), 1.56 (s, 3H), 1.40 (s, 3H), 0.96 (m, 3H), 0.79 (t, 3H, $J=6.8$); ^{13}C NMR (100 MHz, CD_3OD,) 173.9, 173.6, 173.4, 172.8, 172.2, 170.6, 139.9, 138.5, 130.5, 130.2, 129.4, 129.3, 127.7, 127.3, 73.4, 72.8, 60.4, 60.3, 55.9, 54.9, 52.5, 38.5, 34.9, 32.0, 31.9, 30.3, 26.1, 25.2, 22.3, 19.8, 19.6, 18.6, 17.7; HRMS (FAB+), calcd for $C_{38}H_{54}N_6O_7SNa$ *m/e* 761.3667, found *m/e* 761.3640.

Compound 33. The above amine (49 mg, 0.1 mmol) was coupled with Ac-AlaVal-OH (23 mg, 0.1 mmol) to give compound **33** (85%) as a white solid: ^{1}H NMR (600 MHz, CD_3OD) 7.16–7.25 (m, 5H), 5.07 (d, 1H, $J=9.2$), 4.92 (d, 1H, $J=9.2$), 4.62 (s, 1H), 4.48 (d, 1H, $J=3.5$), 4.43 (d, 1H, $J=5.7$), 4.39 (m, 1H), 4.32 (dd, 1H, $J=14.0$, 7.0), 4.06 (d, 1H, $J=7.4$), 3.71 (s, 3H), 2.83 (dd, 1H, $J=14.0$, 3.5), 2.73 (dd, 1H, $J=14.0$, 11.0), 2.16 (m, 1H), 1.95 (s, 3H), 1.60 (s, 3H), 1.45 (s, 3H), 0.96 (t, 3H, $J=7.0$), 0.80 (t, 3H, $J=6.5$); ^{13}C NMR (150 MHz, CD_3OD) 175.0, 173.5, 173.3, 173.2, 172.0, 170.9, 139.8, 130.5, 129.3, 127.2, 73.0, 72.8, 60.4, 59.1, 54.6, 52.5, 52.4, 50.4, 34.9, 32.0, 31.9, 30.1, 25.3, 22.3, 19.7, 19.5, 18.5, 17.7; HRMS (FAB+), calcd for $C_{32}H_{49}N_5O_8SNa$ *m/e* 686.3302, found *m/e* 686.3320.

Compound 34. To a solution of deoxynojirimycin tetrabenzyl ether[19] (2.62 g, 5 mmol) in dry DMF (10 mL) was added ethyl 4-bromobutyrate (0.98 g, 5 mmol) and tetra-*n*-butylammonium iodide (1.85 g, 5 mmol). The reaction mixture was stirred at 80 °C for 12 h and then diluted with EtOAc. The organic solution was washed with 1 *N* HCl and satd aq NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash

chromatography in 10% EtOAc/Hexane to give ester (3 g, 94%); ^{1}H NMR (500 MHz, $CDCl_3$) 7.26–7.33 (m, 18H), 7.13 (m, 2H), 4.96 (d, 1H, $J=11.1$), 4.86 (d, 1H, $J=10.9$), 4.80 (d, 1H, $J=11.1$), 4.68 (d, 1H, $J=11.6$), 4.65 (d, 1H, $J=11.6$), 4.47 (d, 1H, $J=12.1$), 4.43 (d, 1H, $J=12.0$), 4.41 (d, 1H, $J=10.9$), 4.11 (d, 1H, $J=7.1$), 4.08 (d, 1H, $J=7.1$), 3.60–3.68 (m, 3H), 3.55 (t, 1H, $J=9.2$), 3.47 (t, 1H, $J=9.0$), 3.10 (dd, 1H, $J=11.2$, 4.9), 2.73 (m, 1H), 2.59 (m, 1H), 2.34 (m, 1H), 2.13–2.26 (m, 3H), 1.72 (m, 2H), 1.23 (t, 3H, $J=7.2$); ^{13}C NMR (125 MHz, $CDCl_3$) 173.2, 138.9, 138.4, 138.3, 137.7, 128.2, 128.2, 127.7, 127.5, 127.4, 127.3, 87.2, 78.5, 78.4, 75.2, 75.0, 73.2, 72.6, 65.7, 63.8, 60.2, 54.3, 51.4, 31.9, 19.5, 14.2; HRMS (FAB+), calcd for $C_{40}H_{48}NO_6$ *m/e* 638.3476, found *m/e* 638.3503.

To a solution of the above ester (2.55 g, 4 mmol) in 20% MeOH in THF (8 mL) was added a solution of LiOH (192 mg, 8 mmol) in water (1 mL). The reaction mixture was stirred for 4 h and then diluted with EtOAc. The organic solution was washed with 10% citric acid and water, dried over $MgSO_4$, filtered and concentrated in vacuo to give the acid **34** (2.3 g, 95%) as a white solid; ^{1}H NMR (600 MHz, $CDCl_3$) 7.26–7.31 (m, 18H), 7.09 (m, 2H), 4.92 (d, 1H, $J=11.1$), 4.84 (d, 1H, $J=10.8$), 4.76 (d, 1H, $J=11.1$), 4.72 (d, 1H, $J=11.3$), 4.66 (d, 1H, $J=11.3$), 4.44 (s, 2H), 4.42 (d, 1H, $J=11.0$), 4.10 (m, 1H), 3.90 (dd, 1H, $J=11.6$, 4.4), 3.83 (t, 1H, $J=9.3$), 3.75 (d, 1H, $J=10.6$), 3.56 (t, 1H, $J=8.9$), 3.50 (m, 1H), 3.22 (m, 1H), 3.02 (m, 1H), 2.90 (d, 1H, $J=7.8$), 2.59 (t, 1H, $J=11.3$), 2.30 (m, 2H), 1.82 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) 175.7, 138.0, 137.5, 137.3, 136.8, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 107.8, 84.9, 75.6, 75.5, 75.0, 73.4, 73.1, 67.5, 64.9, 64.1, 52.5, 52.2, 31.5, 29.0, 23.8, 20.8, 18.1.

Compound 36. To a solution of acid **34** (2.03 g, 3.3 mmol) in DMF (10 mL) was added amine **35** (1.91 g, 3.3 mmol), HBTU (1.26 g, 3.3 mmol) and Et_3N (0.46 mL). The reaction mixture was stirred overnight and then diluted with EtOAc. The organic solution was washed with satd aq $NaHCO_3$ and satd aq NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography in 20% EtOAc/Hexane to give coupling product (2.33 g, 60%) as colorless foam: ^{1}H NMR (600 MHz, CD_3OD) 7.18–7.35 (m, 25H), 7.10 (m, 4H), 4.89 (d, 1H, $J=11.3$), 4.78 (d, 1H, $J=10.9$), 4.74 (d, 1H, $J=11.1$), 4.68 (d, 1H, $J=11.6$), 4.62 (d, 1H, $J=11.6$), 4.48 (d, 1H, $J=11.9$), 4.42 (d, 1H, $J=11.0$), 4.40 (d, 1H, $J=11.9$), 4.32 (m, 1H), 4.26 (dd, 1H, $J=14.3$, 7.1), 4.03 (d, 1H, $J=7.0$), 3.82 (m, 1H), 3.67 (s, 2H), 3.57 (dt, 1H, $J=14.1$, 9.9, 4.9), 3.48 (t, 1H, $J=9.2$), 3.40 (t, 1H, $J=9.0$), 3.14 (dd, 1H, $J=11.3$, 4.8), 3.05 (dd, 1H, $J=11.7$, 2.2), 3.01 (dd, 1H, $J=14.3$, 3.1), 2.70–2.75 (m, 2H), 2.56–2.66 (m, 3H), 2.32 (d, 1H, $J=9.5$), 1.92–2.23 (m, 9H), 1.75 (m, 4H), 1.62 (m, 1H), 1.53 (m, 4H), 1.38 (m, 4H), 1.30 (s, 9H), 1.25 (d, 3H, $J=7.1$), 0.78 (d, 3H, $J=7.0$), 0.77 (d, 3H, $J=6.9$); ^{13}C NMR (150 MHz, $CDCl_3$) 176.0, 175.6, 174.9, 172.9, 140.3, 140.2, 140.0, 139.8, 139.3, 130.5, 129.6, 129.4, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 127.1, 88.2, 79.7, 79.4, 76.3, 76.2, 74.3, 73.5, 72.2, 66.8, 65.3, 60.4, 59.7, 55.2, 54.6, 52.9, 51.9, 50.6, 37.4, 35.0, 34.7, 34.3, 32.0, 31.5, 28.9, 27.3, 27.0, 22.0, 21.3, 19.9, 18.5, 17.8; HRMS (FAB+), calcd for $C_{70}H_{95}N_6O_9S$ *m/e* 1163.7155, found *m/e* 1163.7139.

To the above coupling product (1.16 g, 10 mmol) in AcOH (20 mL) containing 10% Pd/C (170 mg) was stirred under H_2 (1atm) at 20 °C for 2 days. The reaction mixture was filtered through Celite and then concentrated in vacuo to give **36** (444 mg, 56%) as a white solid (lympholizer); ^{1}H NMR (400 MHz, D_2O) 7.29–7.32 (m, 5H), 4.99 (m, 4H), 4.75 (m, 1H), 4.67 (m, 1H), 4.22 (m, 2H), 4.02–4.11 (m, 3H), 3.75 (m, 2H), 3.65 (m, 2H), 3.02 (m, 1H), 2.91 (m, 3H), 2.53 (m, 2H), 1.82–2.01 (m, 9H), 1.63–1.70 (m, 6H), 1.47 (m, 4H), 1.35 (m, 4H), 1.22 (s, 9H), 1.15 (d, 3H, $J=7.0$), 0.70 (t, 6H, $J=6.4$); HRMS (FAB+), calcd for $C_{42}H_{71}N_6O_9$ *m/e* 803.5204, found *m/e* 803.5309.

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