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The Synthesis of Novel HIV-Protease Inhibitors

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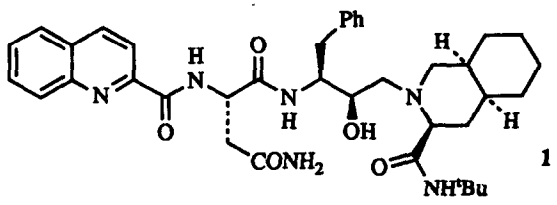
Abstract—The syntheses, enzyme inhibition and antiviral activity of potent HIV-protease inhibitors containing novel β-hydroxy ether and thioethers based on the transition state mimetic concept are discussed.

Introduction

Pseudopeptides containing hydroxyethylamine and related transition state mimics have been found to be potent inhibitors of the aspartic protease of HIV-1.[1] Inactivation of this enzyme results in premature termination of the post-translational processing of the viral *gag* and *gag-pol* polyprotein gene products generating non-infectious virions.[2] Based on the initial pepstatin lead[3] several laboratories have reported the synthesis and biological activity of HIV-protease inhibitors containing a hydroxyethylamine moiety.[4] The most advanced compound in this class is the isoquinoline derivative Ro31-8959 (**1**),[4a] claimed to be, at this time, in phase II clinical trials. This substance, however, is relatively poorly absorbed when given orally to mice and monkeys[5] and there is a clear need to discover more bioavailable and effective HIV-protease inhibitors. We were particularly interested in hydroxyethylamine pseudopeptides that are not readily susceptible to undesirable cleavage and inactivation by mammalian peptidases.

We reasoned that the nitrogen heterocycles vicinal to the hydroxyl group in these inhibitors (structure **1**) may not be a critical factor for activity although a substantial hydrophobic group was thought to be essential for



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optimal binding to the protease. An investigation of this hypothesis revealed that sulfur and oxygen ligands carrying simpler hydrophobic moieties can be readily introduced and yet maintain very good anti-HIV activity. We now wish to report the results of this study, a series of potent HIV-protease inhibitors containing novel β-hydroxy ether and thioether dipeptide isostere surrogates. To the best of our knowledge pseudopeptides containing these novel nonhydrolyzable dipeptide replacements have not been explored as inhibitors of HIV-protease or as inhibitors of other aspartic proteases.

Results and Discussion

To conduct a systematic study the P1 and P2 sites of the inhibitors (Figure 1) were initially maintained in our examples while modifications to the P1' moiety and the stereochemical requirements of the critical hydroxyl group were investigated. The IC_{50} values for recombinant HIV-protease enzyme inhibition were determined using the scintillation proximity assay (SPA) and the most active compounds were then tested in the HIV antiviral assay[6] (see Experimental Section for details). The initial targets synthesized to test the utility of these isosteres are shown in the table (entries 2–5) and led us to make certain conclusions. Compounds derived from the *tert*-butyl amides of thiosalicylic (entries 2 and 3) and salicylic (entries 4 and 5) acids are potent inhibitors of HIV-protease. The inhibitors show a slight preference in the enzyme assay for the oxygen ligand (X = O), but this pattern is not evident in the antiviral assay.

Interestingly, unlike inhibitors of similar size containing related dipeptide isosteres,[4a,7] the configuration of the hydroxyl group does not appear to be a critical factor for activity. However, other HIV-protease inhibitors which differ with respect only to the configuration of the secondary hydroxyl group have been reported with similar biological activities.[4a,b] Compounds in this series with hydroxyl groups in the *S*-configuration (entries 2 and 4) are marginally more active.

To optimize the activity, we further investigated the role played in potency by the amide appendage in the thiosalicylic acid moiety of **2**, by synthesizing and evaluating positional isomers (entries 6 and 7). As the table indicates both the *meta*- and *para*-substituted phenyl analogues **6** and **7** were less active. Analysis of the reported X-ray data[8] of enzyme–inhibitor complexes reveal that the carbonyl groups in the P1' residues of related inhibitors such as **1** with a similar array of functional groups to the salicylates **2–5** play an important structural role by hydrogen bonding to the flap water molecule, connecting the inhibitor to the active site of the enzyme. These interactions may be somewhat reduced in compound **6**, but considerably so or even absent in the case of the

para-isomer **7**, due to the relatively remote disposition of the carboxamide functionalities and hence resulting in reduced potency. Having established that an aromatic 1,2-disubstitution is beneficial for enhanced activity we attempted to optimize the potency of the inhibitors by probing the P1' binding domain for larger aromatic groups

Table 1. HIV-protease inhibitors containing aromatic β-hydroxy ether and thioether transition state mimics

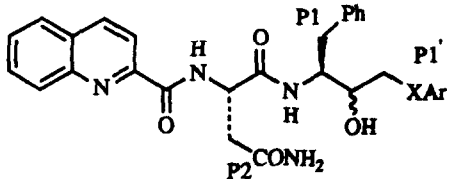
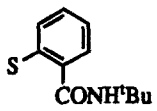
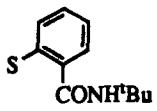
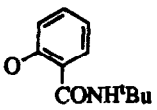
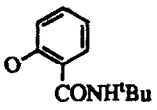
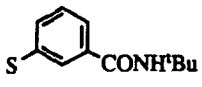
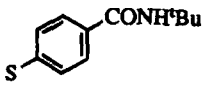
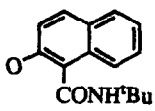
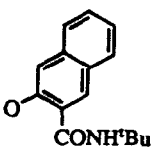
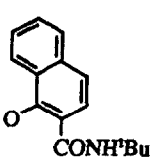


Figure 1.

Entry	XAr	Carbinol Configuration§	Enzyme IC_{50}(nM)†	Antiviral ID_{50}(μM)†
2			90	0.25
3			140	0.62
4			45	2.9
5			64	0.72
6			200	N.T.*
7			900	N.T.*
8			139	0.24
9			78	0.24
10			220	0.67

*N.T. = not tested, §N.B. there is a priority change in configuration assignment on going from N to O or S, †see Experimental Section for details. In the enzyme assay Ro31-8959[4a] has an IC_{50} = 45 nM.

such as the naphthalenes (entries 8–10). All three isomers are effective HIV-protease inhibitors, but **8** and **9** appear to be more active than **10**.

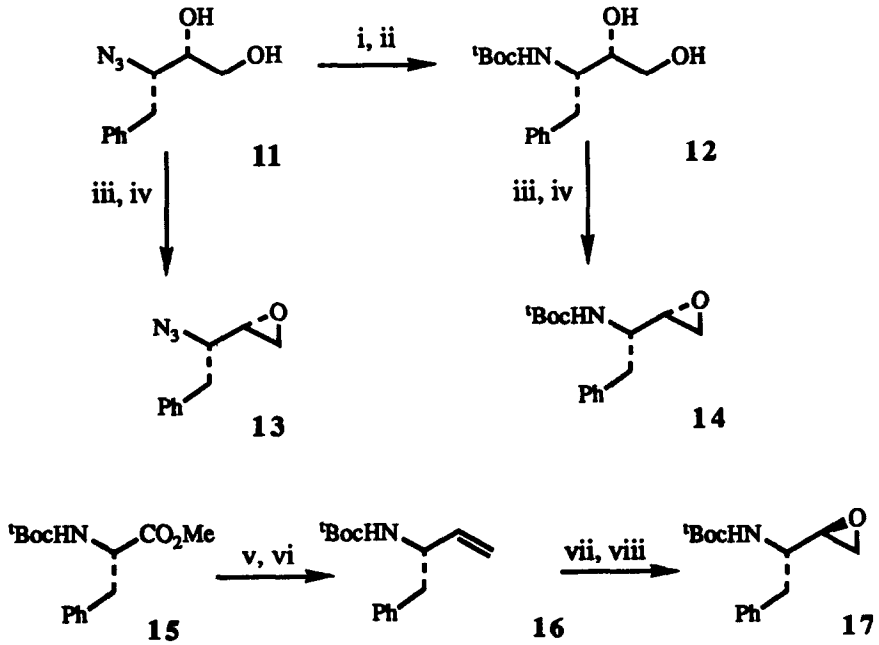
Most of the potent HIV-protease inhibitors were evaluated for their antiviral activity against the HTLV III strain of HIV-1 in CEM cell lines. As evident from the table, compounds **2**, **3**, **5**, **8**, **9**, and **10** have excellent anti-HIV activity and show a good correlation between enzyme IC_{50} and antiviral ID_{50} values indicative of effective cell penetration and stability to assay conditions. The pharmacokinetic properties of these compounds are currently being investigated.

Chemistry

In order to prepare and investigate the stereochemical preferences of the inhibitors in this text, gram quantities of the azido oxirane **13** and the diastereoisomeric carbamyl epoxides **14** and **17** were required (Scheme I). From the common intermediate **11**,[9a,b] a known azido diol, both *erythro*-epoxides **13** and **14** were prepared. The azido derivative **13** was synthesized from **11** via selective tosylation followed by exposure of the resulting primary tosylate to sodium hydride in dimethylformamide. Catalytic hydrogenolysis of the azide **11** produced the corresponding amino diol which was protected, prior to purification, with *tert*-butyl pyrocarbonate to the carbamyl diol **12**. Tosylation and ring closure with sodium hydride generated the desired carbamyl epoxide **14**. Using a modification of the methodology of Luly and co-workers[10] and *t*-Boc-L-phenylalanine methyl ester **15**, the *threo*-carbamate **17** was constructed in three steps—partial reduction with diisobutylaluminum hydride provided the corresponding known intermediate aldehyde[11] which was converted, in crude form, with two equivalents of methylenetriphenylphosphorane to the alkene **16**. MCPBA oxidation generated the desired *threo*-isomer **17**. This product required purification by crystallization in order to remove the minor, more crystalline *erythro*-diastereomer **14**. Varying degrees of isomerization occurred as a result of enolization during the Wittig step. However, the epoxide **17** derived from the mother liquor was used in subsequent transformations to prepare target compounds such as the thioether **3** and ether **5** without detectable amounts of other diastereomers (400 Mz ^1H NMR).

The syntheses of thioether protease inhibitors **2** and **3** are shown at the top of Scheme II. Thiosalicylic acid was *S*-alkylated with the epoxides **14** and **17** to yield the hydroxy acids which were transformed to the corresponding *tert*-butyl amides **18** and **19** via active ester formation and subsequent treatment with *tert*-butylamine. Acidolysis of **18** and **19** followed by independent coupling[12] of the resulting amines with the acid **20** gave the target compounds **2** and **3**, respectively. The acid **20** was constructed from commercial L-Asn-O^{t}Bu in two steps (see below) by condensation of quinaldic acid providing the *tert*-butyl ester of *N*-(2-quinolinylcarbonyl)-L-asparagine, which was cleaved to the desired acid **20** with trifluoroacetic acid.

The *meta* and *para* positional isomers **6** and **7**, respectively, were constructed using the known acids[13] **21** and **22**, which, were converted into the corresponding *tert*-butyl amides **23** and **24**. These xanthates were hydrolyzed in the presence of the epoxide **14**, yielding the alcohols **25** and **26**. Using the aforementioned chemistry described for the transformation of **14** and **17** to **2** and **3**, the carbamates **25** and **26** were converted to the pseudopeptides **6** and **7**.

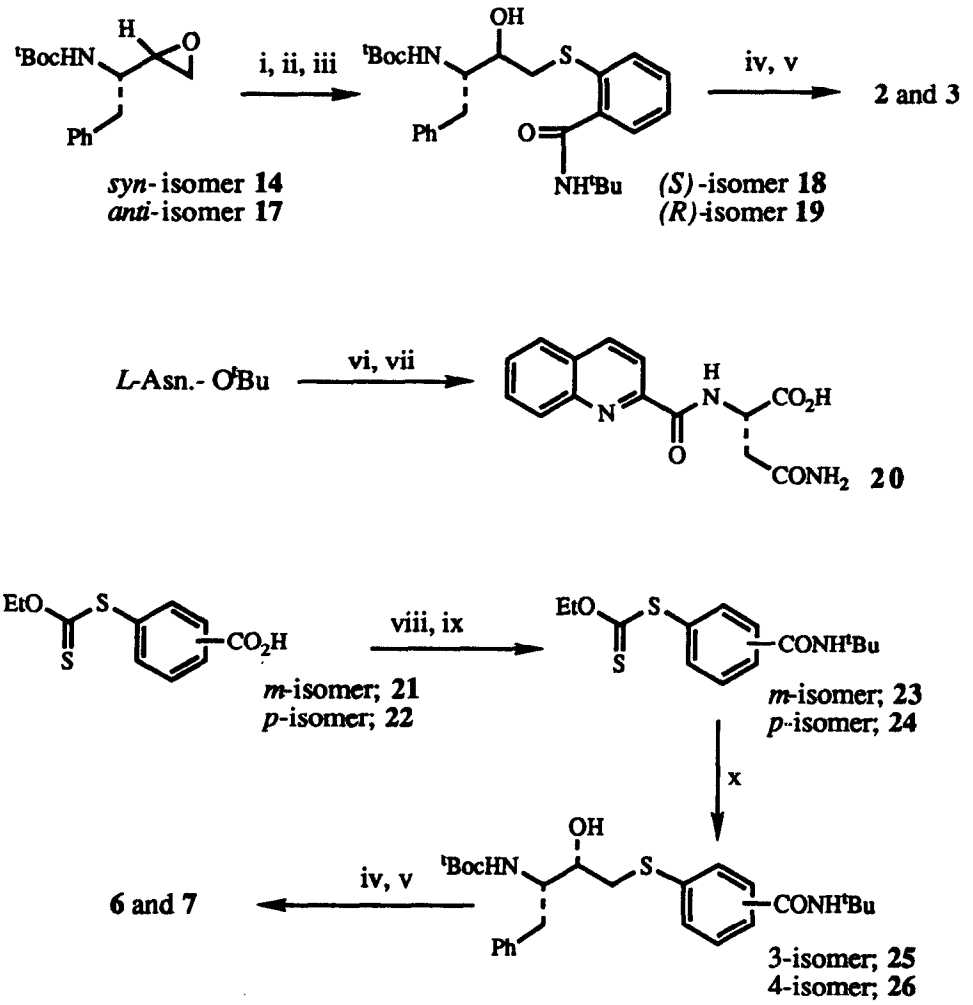


Reagents and conditions: i, H_2, 10 % Pd-C, ethanol, 25 °C, 1 atm.; ii, ^{t}BuOCOOCOO^{t}Bu, Et_3N, dioxane, 25 °C; iii, MeC_6H_4-*p*-SO_2Cl, cat. DMAP, pyridine, 0 °C; iv, NaH, dimethylformamide, 0–25 °C; v, 2.5 eq. DIBAL-H, toluene, –78 °C; vi, 2 eq. Ph_3PCH_3Br, 2 eq. NaHMDS, tetrahydrofuran, 25 °C; vii, MCPBA, dichloromethane, 25 °C; viii, crystallization.

Scheme I.

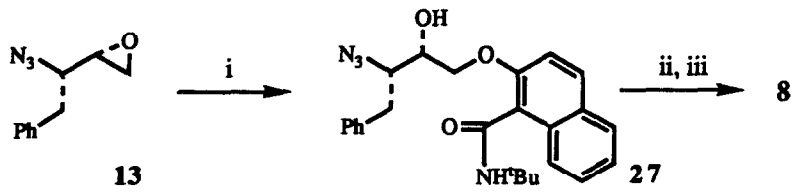
Using the naphthalene derivative **8** as an example, the synthesis of the target compounds containing the β-hydroxyether dipeptide replacement is outlined in Scheme III. The critical addition of *N-tert*-butyl-2-hydroxy-1-naphthalene carboxamide to the azido-epoxide **13** was achieved by heating both components together in dimethylformamide at 120 °C, overnight (approx. 16 h), which provided the ether **27** in 55 % yield. Typically, 50–70 % yields of the desired products were obtained following column chromatography on silica gel. Catalytic hydrogenation followed by coupling the resulting amine to the acid **20** provided the inhibitor **8**.

In summary, potent inhibitors of HIV-protease incorporating novel β-hydroxy ether and thioether dipeptide isostere surrogates have been constructed in an efficient, convergent manner from inexpensive starting materials such as salicylic and thiosalicylic acids. These enzyme inhibitors are also effective antiviral agents and prevent the spread of HTLV III strain of HIV-1 in CEM cell lines.



Reagents and conditions: i, 2.2 eq. NaOH, aq. ethanol, HSC_6H_4-*o*-CO_2H, 25 °C, followed by aq. HCl; ii, DCC, *N*-hydroxysuccinimide (NOS), dioxane, 25 °C; iii, $^tBuNH_2$; iv, TFA, dichloromethane, 25 °C, followed by excess Et_3N; v, BOP reagent, Et_3N, dichloromethane, acid **20**, 25 °C; vi, BOP reagent, Et_3N, quinaldic acid, dichloromethane, 25 °C; vii, TFA, dichloromethane, 25 °C. viii, DCC, NOS, tetrahydrofuran, 25 °C; ix, $^tBuNH_2$, dioxane, 25 °C; x, 3.2 eq. NaOH, aq. ethanol, epoxide **14**.

Scheme II.



Reagents and conditions: i, *N-tert*-butyl-2-hydroxy-1-naphthalene carboxamide, dimethylformamide, 120 °C; ii, H_2, 10 % Pd-C, ethanol, 25 °C, 1 atm.; iii, BOP reagent, Et_3N, dichloromethane, acid **20**, 25 °C.

Scheme III.

Experimental Section

Chemistry

Optical rotations ($[\alpha]_D$) were measured on a Perkin–Elmer 243B polarimeter. ^1H NMR spectra were recorded on a Varian Model XL-400. Chemical shifts were reported as δ units relative to tetramethylsilane as internal standard and all *J* values are in Hz. Low-resolution mass spectra were determined on a Finnigan Model MAT-312 double focusing mass spectrometer at 3 KV. High-resolution mass spectra were determined on a VG-ZAB-SE double focusing mass spectrometer at 8 KV. Melting points were determined with a Fisher–Johns melting point apparatus and are uncorrected.

All reactions were carried out under an atmosphere of nitrogen with anhydrous solvents unless otherwise stated. Anhydrous solvents were purchased from Aldrich chemical company and used without further purification. Reagents were from commercial sources and were used without purification. E. Merck silica gel 60 (230–40 mesh) was used for column chromatography. All solvents for chromatography were reagent grade and were obtained from Fisher Scientific. Organic solutions were dried by brief exposure to magnesium sulfate.

(1,1- Dimethylethyl)- [2,3- dihydroxy -1- (phenylmethyl)-propyl]carbamate (12). A suspension of the azide **11** (1.37 g; 6.7 mmol) and 10 % Pd-C (0.25 g) in ethanol (50 mL) was stirred under an atmosphere of hydrogen at room temperature, overnight (approx. 16 h). The crude reaction product was filtered through a pad of Celite and the solid was washed thoroughly with EtOAc. The filtrate was concentrated to yield the intermediate amine (1.05 g; 87 %), as a yellow foam, used in the procedure directly below without purification: NMR ($CDCl_3$) δ 2.61 (1H, dd, *J* = 13.4 and 10.1), 2.93 (1H, dd, *J* = 13.4 and 4.2), 3.30–3.36 (1H, m), 3.60–3.65 (1H, m), 3.76 (1H, dd, *J* = 11.8 and 3.9), 3.91 (1H, dd, *J* = 11.8 and 4.4) and 7.17–7.36 (5H, m).

Triethylamine (0.98 mL; 7mmol) was added dropwise to a stirred solution of the crude amine (1.05 g; 5.8 mmol) and di-*tert*-butyl pyrocarbonate (1.40 g; 6.4 mmol) in dioxane (25 mL) while cooled in an ice bath. When the addition was complete, the resulting mixture was stirred at room temperature for 3 h, concentrated under reduced pressure and the residue was purified by column chromatography using EtOAc–hexane (6:4) as eluant to give the desired carbamate **12** (1.31 g; 80 %), a white solid: mp:123–125 °C; NMR ($CDCl_3$) δ 1.38 (9H, s), 2.91 (1H, dd, *J* = 14.3 and 7.9), 3.10 (1H, dd, *J* = 14.3 and 4.1), 3.32–3.40 (1H, m), 3.59–3.71 (2H, m), 3.79–3.88 (1H, m), 4.55 (1H, d, *J* = 8.2), 7.21–7.27 (3H, m) and 7.29–7.35 (2H, m). HRFABMS: MH^+, 282.1707. $C_{15}H_{24}NO_4$ requires 282.1705.

(1,1-Dimethylethyl)-[1-oxiranyl-2-phenylethyl] carbamate (14). 4-Dimethylaminopyridine (29 mg; 0.23 mmol) was added to a stirred solution of the diol **12** (1.31 g; 4.7 mmol) and *p*-toluenesulfonyl chloride (0.90 g; 4.7 mmol) in pyridine (15 mL), cooled in an ice bath. The resulting mixture was stirred at room temperature for 3 h and partitioned between EtOAc and 5 % aq. HCl. The organic phase was separated, washed with water (× 3), dried and concentrated. The residue was purified by column chromatography to give the intermediate primary tosylate (1.67 g; 82 %), as a white solid, which was used immediately in the procedure set forth directly below.

A solution of the tosylate (0.82 g; 1.9 mmol) in DMF (2 mL) was added dropwise to a stirred suspension of sodium hydride (0.18 g of a 50 % dispersion in mineral oil; 3.8 mmol; washed ×3 with hexane) in DMF (5 mL), cooled in an ice bath. The resulting mixture was stirred at room temperature for 30 min and ice was added before partitioning between EtOAc and water. The organic phase was separated washed with water (×3), dried and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc–hexane (1:5) as eluant to provide the epoxide **14** (0.42 g; 84 %), a white solid: mp: 123–124 °C; NMR ($CDCl_3$) δ 1.39 (9H, s), 2.73–3.01 (5H, m), 3.70 (1H, br. s), 4.44 (1H, br. s) and 7.19–7.37 (5H, m). In agreement with previously reported data.[9c]

(1,1- Dimethylethyl)- [1- (phenylmethyl) -2- propenyl]-carbamate (16). Diisobutylaluminum hydride (99.0 mL of a 1.0 M solution in THF; 99.0 mmol) was added dropwise to a stirred solution of *t*-Boc-L-phenylalanine methyl ester **15** (11.00 g; 39 mmol) in toluene (170 mL) at –78 °C. After 6 min, methanol (10 mL), followed by Rochelles salt were added. The mixture was allowed to warm to room temperature and partitioned between EtOAc and water. The organic phase was separated, washed with water (× 3), dried and concentrated to yield the crude, intermediate aldehyde which was used in the procedure set forth directly below, without purification.

Sodium bis(trimethylsilyl)amide (79 mL of a 1.0 M solution in THF; 79 mmol) was added dropwise to a stirred suspension of methyltriphenylphosphonium bromide (28.17 g; 79 mmol) in THF (320 mL) and the resulting orange mixture was stirred at room temperature for a period of 0.5 h. The crude aldehyde in THF (20 mL) was added and the reaction was stirred for a further period of 3 h before adding to a mixture of EtOAc and water. The organic phase was washed with water (× 3), dried and concentrated to yield a red oil (25.27 g) which was adsorbed on silica gel (50.00 g) before purification by column chromatography using EtOAc–hexane (1:10) as eluant to give the desired alkene **16** (6.47 g; 66 % overall), as a white solid mp: 57–60 °C; NMR ($CDCl_3$) δ 1.40 (9H, s), 2.84 (2H, d, *J* = 6.3), 4.42 (2H, br. s), 5.05–5.14 (2H, m), 5.74–5.85 (1H, m) and 7.16–7.32 (5H, arylC-H).

(1,1-Dimethylethyl)-[1-oxiranyl-2-phenylethyl] carbamate (17). *m*-Chloroperoxybenzoic acid (9.12 g of approx. 80 % pure material; approx. 44 mmol) was added slowly to a stirred solution of the alkene **16** (6.47 g; 26 mmol) in chloroform (250 mL), while cooled in an ice bath. The resulting mixture was allowed to warm to room temperature and stirred for a period of 4 days before

adding to a mixture of EtOAc and 10 % aq. $Na_2S_2O_3$. The organic phase was separated, washed with aq. $Na_2S_2O_3$ (× 3), sat. aq. $NaHCO_3$ (×3), dried and concentrated. The crude reaction product was purified by fractional crystallization (EtOAc–hexane), each time retaining the filtrate. Concentration yielded the desired epoxide **17** (3.11 g; 45 %) as a white semi-solid. NMR ($CDCl_3$) δ 1.40 (9H, s), 2.58 (1H, br s), 2.70 (1H, t, J = 4.3), 2.83–3.04 (3H, m), 4.12 (1H, br s), 4.47 (1H, br s) and 7.14–7.38 (arylC–H). In good agreement with previously reported data.[9c]

(1-Azido-2-phenylethyl)oxirane (13). Using the diol **11** (3.32 g; 16 mmol), *p*-toluenesulfonyl chloride (3.09 g; 16 mmol), 4-dimethylaminopyridine (0.20 g; 1.6 mmol) in pyridine (30 mL) and the aforegoing procedure set forth for the conversion of diol **12** to epoxide **14**, the corresponding intermediate primary tosylate (4.34 g; 75 %) was obtained following column chromatography (EtOAc–hexane; 1:5). Continued elution provided recovered diol **14** (0.64 g; 18 %). The tosylate was immediately treated with sodium hydride (0.70 g of a 50 % dispersion in mineral oil; 15 mmol; washed ×3 with hexane) in DMF (30 mL) followed by column chromatography (EtOAc–hexane; 1:20) to provide the oxirane **13** (2.11 g; 93 %), a colorless oil, $[\alpha]_D$ +14.3 ° (c = 1.3, $CHCl_3$), NMR ($CDCl_3$) δ 2.79–2.85 (3H, m), 2.99 (1H, dd, J = 14.0 and 4.6), 3.04–3.08 (1H, m), 3.57–3.62 (1H, m) and 7.20–7.37 (5H, m). In excellent agreement with previously reported data.[9a]

(1,1-Dimethylethyl)- [3- [[2- [[(1,1-dimethylethyl) amino]-carbonyl]phenyl]thio]-2-hydroxy-1-(phenylmethyl)propyl]-carbamate (18). Sodium hydroxide (0.48 g; 12 mmol) was added to a stirred solution of the epoxide **14** (1.44 g; 5.5 mmol) and thiosalicylic acid (0.84 g; 5.5 mmol) in ethanol (70 mL) at room temperature. After stirring for 3 h, the reaction was added to a mixture of EtOAc and excess 5 % aq. HCl. The organic phase was separated, washed with water (× 3), dried and concentrated to give the desired intermediate hydroxy-acid (2.25 g; 98 %) which was transformed to the corresponding *tert*-butylamide **18**, described below, without prior purification. NMR (d_6-DMSO) δ 1.28 (9H, s), 2.57 (1H, dd, J = 13.8 and 10.4), 2.86 (1H, dd, J = 12.7 and 8.6), 3.04 (1H, dd, J = 13.8 and 2.9), 3.12 (1H, dd, J = 12.7 and 2.4), 3.56–3.74 (2H, m), 5.37 (1H, br. s), 6.79 (1H, d, J = 8.8), 7.12–7.30 (arylC–H), 7.36 (1H, d, J = 8.2), 7.45–7.52 (1H, m), 7.86 (1H, dd, J = 7.7 and 1.3) and 13.0 (1H, br. s).

1,3-Dicyclohexylcarbodiimide (1.21 g; 5.9 mmol) was added to a stirred solution of the crude acid (2.22 g; 5.3 mmol), and *N*-hydroxysuccinimide (0.68 g; 5.9 mmol) in dioxane (25 mL), while cooled in an ice bath. The resulting mixture was stirred at room temperature for 2 h and replaced in an ice bath before adding *tert*-butylamine (1.68 mL; 16 mmol). After stirring for a further 3 h at room temperature, the reaction was added to a mixture of EtOAc and water. The organic phase was separated, washed with water (× 3), dried and concentrated. The residue was purified by column chromatography using EtOAc–hexane (3:7) as eluant to give the amide **18** (2.23 g; 88 %), a white solid; mp; 56–58 °C; NMR ($CDCl_3$) δ 1.31 (9H, s), 1.50 (9H, s), 2.75–2.87 (2H, m), 2.92–3.02 (1H, m), 3.08–3.17 (1H, m), 3.52–3.61 (1H, m), 3.78–3.87 (1H, m), 4.70 (1H, br. s), 5.87 (1H, br. s), 7.13–7.40 (8H, arylC–H) and 7.55 (1H, d, arylC–H). HRFABMS: MH^+, 473.2490. $C_{26}H_{37}N_2O_4S$ requires 473.2474).

N^1*-[3-[[2-[[(1,1-Dimethylethyl)amino] carbonyl] phenyl]-thio]-2(S)-hydroxy-1-(S)-(phenylmethyl)propyl]-(S)-2-[(2-quinolinylcarbonyl)amino]butanediamide (2).* Trifluoroacetic acid (10 mL) was added to a stirred solution of the carbamate **18** (1.07 g; 2.3 mmol) in dichloromethane (10 mL), while cooled in an ice bath. The resulting mixture was stirred at room temperature for 3 h, concentrated under reduced pressure, dissolved in EtOAc and cooled in an ice bath. Excess triethylamine was added and the mixture was washed with water (× 3), dried and concentrated to yield the crude intermediate amine (0.84 g), which was used in the procedure set forth directly below without purification. NMR ($CDCl_3$) δ 1.49 (9H, s), 2.48 (1H, dd, J = 13.6 and 9.9), 2.90–3.02 (2H, m), 3.10–3.18 (1H, m), 3.24 (1H, dd, J = 13.6 and 3.0), 3.48–3.56 (1H, m), 5.95 (1H, br s), 7.14–7.40 (8H, arylC-H) and 7.55 (1H, dd, J = 7.4 and approx. 1).

Triethylamine (2 × 0.44 mL; 2 × 3.1 mmol) was added, approximately 30 min apart to a stirred suspension of the crude amine (1.08 g; 2.9 mmol), the acid **20** (see below) (0.87 g; 3.0 mmol) and BOP reagent (1.41 g; 3.1 mmol) in dichloromethane (10 mL), while cooled in an ice bath. When the addition was complete, the resulting mixture was stirred at room temperature for 3 h and added to a mixture of EtOAc and water. The organic phase was separated, washed with water (× 3), dried and concentrated. Column chromatography of the residue using EtOAc–MeOH (10:1) as eluant gave the desired pseudopeptide **2** (1.00 g; 54 %), as a pale-yellow solid: NMR (d_6-DMSO) δ 1.37 (9H, s), 2.50–2.67 (3H, m), 2.82 (1H, dd, J = 13.4 and 9.2), 3.01 (1H, dd, J = 13.9 and 3.3), 3.24 (1H, dd, J = 13.4 and 3.6), 3.52–3.60 (1H, m), 3.92–4.01 (1H, m), 4.66–4.73 (1H, m), 5.32 (1H, d, J = 6.6), 6.90 (1H, br s), 6.96 (1H, t, J = 7.3), 7.03–7.09 (2H, m), 7.14–7.20 (3H, m), 7.23–7.32 (2H, m), 7.40–7.46 (2H, m), 7.71–7.77 (1H, m), 7.84 (1H, br s), 7.85–7.92 (1H, m), 7.99 (1H, d, J = 9.2), 8.06–8.19 (3H, m), 8.59 (1H, d, J = 8.3) and 8.87 (1H, d, J = 8.0). HRFABMS: MH^+, 642.2761. $C_{35}H_{40}N_5O_5S$ requires 642.2750.

N^1*-[3-[[2-[[(1,1-Dimethylethyl) amino] carbonyl] phenyl]-thio]-2(R)-hydroxy-1-(S)-(phenylmethyl)propyl]-(S)-2-[(2-quinolinylcarbonyl)amino]butanediamide (3).* Using the aforegoing procedure described for the transformation of carbamate **18** to the target compound **2**, the carbamate **19** (1.62 g; 3.4 mmol) was treated with trifluoroacetic acid (10 mL) in dichloromethane (10 mL) and the resulting amine was coupled to the acid **20** (0.99 g; 3.4 mmol) with BOP reagent (1.52 g; 3.4 mmol) and triethylamine (1.05 mL; 7.6 mmol) in dichloromethane (10 mL) providing the pseudopeptide **3** (1.14 g; 52 %) after column chromatography (EtOAc–MeOH; 10:1); NMR ($CDCl_3$) δ 1.44 (9H, s), 2.77 (1H, dd, J = 15.3 and 7.3), 2.81–2.95 (4H, m), 2.99 (1H, dd, J = 13.7 and 3.6), 3.56–3.63 (1H, m), 4.15–4.23 (1H, m), 4.98–5.07 (1H, m), 5.83 (1H, br s), 6.05 (1H, s), 6.41 (1H, br s), 6.92–6.97 (1H, m), 7.00–7.07 (2H, m), 7.09–7.14 (2H, m), 7.16–7.36 (4H, m), 7.38–7.42

(1H, m), 7.58–7.64 (1H, m), 7.72–7.78 (1H, m), 7.84 (1H, d, J = 8.2), 8.13 (1H, d, J = 8.6). 8.17 (1H, d, J = 8.5), 8.26 (1H, d, J = 8.6) and 9.07 (1H, d, J = 8.2). FAB-MS: M^++23 (Na), 664.3 (100 %).

N-(2-Quinolinylcarbonyl)-L-asparagine (20). Triethylamine (6.1 mL; 44 mmol) was added dropwise to a stirred suspension of quinaldic acid (3.86 g; 22 mmol), BOP reagent (10.80 g; 24 mmol) and the hydrochloride salt of L-Asn-O^{t}Bu (5.00 g; 22 mmol) in dichloromethane (10 mL), while cooled in an ice bath. After stirring at room temperature for 1 h a further portion of triethylamine (3.1 mL; 22 mmol) was added. Stirring was continued for a further 1 h before the reaction was added to a mixture of water and EtOAc. The organic phase was separated, dried and concentrated. The residue was purified by column chromatography using EtOAc–hexane (1:1) as eluant to provide *N*-(2-Quinolinylcarbonyl)-L-asparagine-1,1-dimethylethyl ester (5.70 g; 75 %) as a white solid; NMR ($CDCl_3$) δ 1.52 (9H, s), 2.97 (1H, dd, J = 16.1 and 4.7), 3.03 (1H, dd, J = 16.1 and 5.3), 4.93–4.97 (1H, m), 5.48 (1H, br s), 5.98 (1H, br s), 7.59–7.65 (1H, m), 7.74–7.79 (1H, m), 7.86 (1H, dd, J = approx. 7.5 and approx. 1.5), 8.17 (1H, d, J = 8.5), 8.24 (1H, d, J = 8.4), 8.29 (1H, d, J = 8.5) and 9.15 (1H, d, J = 8.2). HRFABMS: MH^+, 344.1601. $C_{18}H_{22}N_3O_4$ requires 344.1610.

Trifluoroacetic acid (20 mL) was added dropwise to a stirred solution of the ester above (1.05 g; 3.1 mmol) in dichloromethane (20 mL), while cooled in an ice bath. The resulting mixture was stirred overnight at room temperature and the volatiles were removed under reduced pressure. Methanol was added to the residue and the desired acid **20** (0.65 g; 74 %), was collected as a white solid: mp: 201–203 °C; $[\alpha]_D$ +23.7 ° (c = 1.02, MeOH), NMR (d_6-DMSO), δ 2.73 (1H, dd, J = 15.9 and 4.6), 2.86 (1H, dd, J = 15.9 and 5.8), 4.79–4.87 (1H, m), 7.00 (1H, s), 7.50 (1H, s), 7.72–7.78 (1H, m), 7.86–7.92 (1H, m), 8.08–8.16 (2H, m), 8.18 (1H, d, J = 8.5), 8.60 (1H, d, J = 8.3), 9.16 (1H, d, J = 8.6) and 12.56 (1H, br s). Found: C, 58.3; H, 4.6; N, 14.6. $C_{14}H_{13}N_3O_4$ requires: C, 58.6; H, 4.6; N, 14.6 %.

3-(Ethoxythiocarbonyl)-N-(1,1-dimethylethyl)-benzamide (23). 1,3-Dicyclohexylcarbodiimide (1.87 g; 9.1 mmol) was added to a stirred solution of the acid **21** (2.00 g; 8.3 mmol) and *N*-hydroxysuccinimide (1.04 g; 9.1 mmol) in tetrahydrofuran (50 mL) at 0 °C (ice bath). The resulting mixture was stirred at room temperature for 3 h and added to a mixture of EtOAc and water. The organic phase was separated, washed with water (× 3), dried and concentrated to yield the crude intermediate succinimidyl ester (3.25 g). Dioxane (50 mL) was added and the resulting solution was cooled in an ice bath before adding *tert*-butylamine (2.60 mL; 25 mmol). After stirring at room temperature overnight, the reaction was added to a mixture of EtOAc and water. The organic phase was separated, washed with water (× 3), dried and concentrated. The residue was purified by column chromatography using EtOAc–hexane (1:10) as eluant to give the amide **23** (1.07 g; 44 %), a white solid: mp: 101–103 °C; NMR ($CDCl_3$) δ 1.31 (3H, t, J = 7.1), 1.44 (9H, s), 4.59 (2H, q, J = 7.1), 5.91 (1H, br s), 7.46 (1H, t, J = 7.9), 7.59 (1H, d, J = 7.9) and 7.78–7.85 (2H, m).

(1,1-Dimethylethyl[3-[[3-[[(1,1-dimethylethyl)amino]carbonyl] phenyl] thio]-2-hydroxy-1-(phenylmethyl) propyl]-carbamate (25). Sodium hydroxide (0.051 g; 1.3 mmol) was added to a stirred solution of the epoxide **14** (0.101 g; 0.38 mmol) and the xanthate **23** (0.114 g; 0.38 mmol) in a mixture of ethanol (5 mL) and water (1 mL). The resulting mixture was stirred at room temperature for 3 h and added to a mixture of EtOAc and water. The organic phase was separated, washed with water (× 3), dried and concentrated. The residue was purified by column chromatography using EtOAc–hexane (3:7) as eluant to give the desired alcohol **25** (0.145 g; 80 %), a white solid: mp: 82–84 °C; NMR ($CDCl_3$) δ 1.34 (9H, s), 1.47 (9H, s), 2.77–2.88 (1H, m), 2.92–3.02 (2H, m), 3.20 (1H, dd, J = 13.8 and 3.4), 3.70–3.80 (1H, m), 3.84–3.95 (1H, m), 4.58–4.67 (1H, m), 5.97 (1H, br s), 7.15–7.36 (6H, arylC–H), 7.46 (1H, d, J = 7.9), 7.53 (1H, d, J = 7.7) and 7.75 (1H, s). HRFABMS: MH^+, 473.2485. $C_{26}H_{37}N_2O_4S$ requires 473.2474.

N^1-[3-[[3-[[(1,1-Dimethylethyl) amino] carbonyl] phenyl]-thio]-2(S)-hydroxy-1-(S)-(phenylmethyl)propyl]-(S)-2-[(2-quinolinylcarbonyl)amino]butanediamide (6). Using the aforegoing procedure describing the conversion of carbamate **18** to pseudopeptide **2**, the carbamate **25** (0.061 g; 0.13 mmol) was converted to the corresponding intermediate amine (0.048 g; 100 %) with trifluoroacetic acid (1 mL) in dichloromethane (1 mL). The amine (0.041 g; 0.11 mmol) was condensed to the acid **20** (0.035 g; 0.12 mmol) using BOP reagent (0.054 g; 0.12 mmol) and triethylamine (2 × 0.016 mL; 2 × 0.11 mmol) in dichloromethane (1 mL) to give the pseudopeptide **6** (0.027 g; 38 %), crystallized from the crude reaction product (EtOAc). Still a considerable amount of product remained in the mother liquor but was not pursued: mp: 168–170 °C; NMR (d_6-DMSO) δ 1.37 (9H, s), 2.55–2.68 (3H, m), 2.88 (1H, dd, J = 13.4 and 9.1), 3.02 (1H, dd, J = 13.7 and 3.0), 3.35 (1H, dd, J = 13.2 and 3.4), 3.56–3.63 (1H, m), 3.93–4.02 (1H, m), 4.66–4.74 (1H, m), 5.32 (1H, d, J = 6.8), 6.92–6.97 (2H, m), 7.05 (2H, t, J = 7.5), 7.14–7.18 (2H, m), 7.32 (1H, t, J = 7.7), 7.42–7.48 (2H, m) 7.56 (1H, d, J = 7.7), 7.72–7.76 (2H, m), 7.79 (1H, br s), 7.86–7.92 (1H, m), 8.01 (1H, d, J = 9.1), 8.09–8.16 (3H, m), 8.59 (1H, d, J = 8.6) and 8.86 (1H, d, J = 8.1). HRFABMS: MH^+, 642.2761. $C_{35}H_{40}N_5O_5S$ requires 642.2750.

N^1-[3-[[4-[[(1,1-Dimethylethyl) amino] carbonyl] phenyl]-thio]-2(S)-hydroxy-1-(S)-(phenylmethyl)propyl]-(S)-2-[(2-quinolinylcarbonyl)amino]butanediamide (7). NMR (d_6-DMSO) δ 1.38 (9H, s), 2.55–2.68 (3H, m), 2.88 (1H, dd, J = 13.3 and 9.0), 3.03 (1H, dd, J = 14.0 and 3.4), 3.37 (1H, dd, J = 13.3 and 3.3), 3.56–3.64 (1H, m), 3.92–4.01 (1H, m), 4.67–4.74 (1H, m), 5.35 (1H, d, J = approx. 7), 6.90–6.97 (2H, m), 7.06 (2H, t, J = 7.5), 7.17 (2H, d, J = 7.2), 7.34 (2H, d, J = 8.3), 7.42 (1H, br s), 7.66 (1H, br s), 7.71 (2H, d, J = 8.3), 7.71-7.77 (1H, m), 7.87–7.92 (1H, m), 8.00 (1H, d, J = 9.1), 8.10 (1H, d, J = 8.3), 8.14 (1H, d, J = 8.4), 8.17 (1H, d, J = 8.5), 8.59 (1H, d, J = 8.7) and 8.86 (1H, d, J = approx. 8). HRFABMS: MH^+, 642.2767. $C_{35}H_{40}N_5O_5S$ requires 642.2750.

2-(3(S)-Azido -2(S)- hydroxy -4- phenylbutoxy) -N- (1,1-dimethylethyl)-1-naphthalenecarboxamide (27). A solution of the *N*-(1,1-dimethylethyl)-2-hydroxy-1-naphthalenylcarboxamide (0.0713 g; 0.29 mmol) and the epoxide **13** (0.050 g; 0.27 mmol) in dimethylformamide (1 mL) was heated to 130 °C (oil bath) for 16 h After cooling, the reaction was added to a mixture of EtOAc and water. The organic phase was separated, washed with water (× 3), dried and concentrated. The residue was purified by column chromatography using EtOAc–hexane (1:5) as eluant to give the alcohol **27** (0.063 g; 55 %): NMR ($CDCl_3$) δ 1.56 (9H, s), 2.79 (1H, dd, *J* = 14.1 and 9.0), 3.25–3.32 (1H, m), 3.70–3.78 (2H, m), 4.35 (1H, dd, *J* = 10.6 and 5.3), 4.42 (1H, dd, *J* = 10.6 and 2.2), 4.79 (1H, br s), 5.84 (1H, s), 7.22–7.32 (6H, m), 7.39–7.44 (1H, m), 7.50–7.55 (1H, m) and 7.79–7.88 (3H, m). FABMS: MH^+, 432.9 (100 %).

N^1- *[3- [[1- [[(1,1- Dimethylethyl) amino] carbonyl]-2-naphthalenyl] oxy] -2(S)- hydroxy -1(S)- (phenylmethyl)-propyl] -(S)-2- [(2- quinolinylcarbonyl) amino] butanediamide (8).* 10 % Pd-C (0.015 g) was added to a solution of the azide **27** (0.054 g; 0.13 mmol) in ethanol (1 mL) and the resulting black suspension was stirred under an atmosphere of hydrogen at room temperature for 16 h. The reaction was filtered through a pad of Celite and the solid was washed thoroughly with EtOAc. The filtrate was concentrated to yield the crude intermediate amine (0.051 g), used in the procedure set forth directly below.

The amine was dissolved in dichloromethane (2 mL) and the acid **20** (0.039 g; 0.14 mmol) followed by BOP reagent (0.060 g; 0.14 mmol) and triethylamine (0.017 mL; 0.12 mmol) were added. The resulting mixture was stirred at room temperature for 15 min and a further portion of triethylamine (0.017 mL; 0.12 mmol) was added. After stirring for a further 3 h, the reaction was added to a mixture of EtOAc and water. The organic phase was separated, washed with water (× 3), dried and concentrated. Column chromatography of the residue using EtOAc–methanol (20:1) as eluant gave the desired pseudopeptide **8** (0.043 g; 52 %): NMR (CD_3OD) δ 1.50 (9H, s), 2.63–2.74 (2H, m), 2.86 (1H, dd, *J* = 13.9 and 9.9), 3.18 (1H, dd, *J* = 13.9 and 3.9), 3.93–3.99 (1H, m), 4.18–4.29 (2H, m), 4.32 (1H, dd, *J* = 10.4 and 3.1), 6.83 (1H, t, *J* = 7.4), 6.98 (2H, t, *J* = 7.6), 7.19–7.23 (2H, m), 7.36 (2H, d, *J* = 8.9), 7.44–7.50 (1H, m), 7.66–7.85 (5H, m), 7.97 (1H, d, *J* = 7.9), 8.06 (1H, d, *J* = 8.4), 8.11 (1H, d, *J* = 8.3) and 8.36 (1H, d, *J* = 8.3). HRFABMS: MH^+, 676.3152. $C_{39}H_{42}N_5O_6$ requires 676.3135.

N^1-*[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenoxy]-2(S)- hydroxy -1-(S)- (phenylmethyl)- propyl](S)-2- [(2-quinolinylcarbonyl)amino]butanediamide (4).* NMR (d_6-DMSO) δ 1.39 (9H, s), 2.53–2.66 (2H, m), 2.73 (1H, dd, *J* = 13.8 and 9.8), 3.09 (1H, dd, *J* = 13.8 and 3.4), 3.76–3.84 (1H, m), 3.98–4.09 (2H, m), 4.27 (1H, dd, *J* = 10.1 and 2.5), 4.65–4.71 (1H, m), 5.35 (1H, d, *J* = 6.4), 6.91 (1H, br s), 6.92–6.98 (1H, m), 7.00–7.12 (4H, m), 7.18–7.21 (2H, m), 7.40–7.45 (2H, m), 7.72–7.76 (1H, m), 7.84–7.92 (2H, m), 8.01 (1H, d, *J* = 9.0), 8.08–8.14 (2H, m), 8.17 (1H, d, *J* = 8.5), 8.20 (1H, br s), 8.59 (1H, d, *J* = 8.5) and 8.85 (1H, d, *J* = 8.1). HRFABMS: MH^+, 626.2984. $C_{35}H_{40}N_5O_6$ requires 626.2979.

N^1-*[3-[2-[[(1,1-Dimethylethyl)amino]carbonyl]phenoxy]-2(R)- hydroxy -1- (S)- (phenylmethyl)- propyl] (S) -2- [(2-quinolinyl)carbonyl)amino]butanediamide (5).* NMR (d_6-DMSO) δ 1.34 (9H, s), 2.64 (1H, dd, *J* = 15.4 and 5.8), 2.68–2.82 (2H, m), 2.92 (1H, dd, *J* = 13.4 and 6.1), 3.89–3.95 (1H, m), 3.96–4.02 (1H, m), 4.05–4.11 (1H, m), 4.13–4.21 (1H, m), 4.74–4.82 (1H, m), 5.37 (1H, d, *J* = 5.5), 6.95 (1H, br s), 7.00–7.09 (3H, m), 7.12–7.17 (2H, m), 7.22–7.26 (2H, m), 7.41–7.48 (2H, m), 7.72–7.77 (1H, m), 7.79 (1H, dd, *J* = 7.7 and 1.8), 7.87–7.92 (1H, m), 7.94 (1H, d, *J* = 9.2), 7.99 (1H, br s), 8.10 (1H, d, *J* = 7.7), 8.14 (1H, d, *J* = 8.4), 8.17 (1H, d, *J* = 8.4), 8.59 (1H, d, *J* = 8.4) and 9.03 (1H, d, *J* = 7.8). HRFABMS: MH^+, 626.2983. $C_{35}H_{40}N_5O_6$ requires 626.2979.

N^1- *[3- [[2- [[(1,1- Dimethylethyl) amino] carbonyl] -3-naphthalenyl] oxy] -2(S)- hydroxy -1(S)- (phenylmethyl)-propyl] -(S) -2- [(2-quinolinylcarbonyl) amino] butanediamide (9).* NMR (CD_3OD) δ 1.50 (9H, s), 2.67–2.78 (2H, m), 2.88 (1H, dd, *J* = 13.9 and 9.8), 3.23 (1H, dd, *J* = 13.9 and 3.9), 4.02–4.08 (1H, m), 4.22–4.34 (2H, m), 4.37 (1H, dd, *J* = 10.2 and 2.8), 4.88 (1H, t, *J* = 6.5), 6.80–6.85 (1H, m), 6.96–7.02 (2H, m), 7.20–7.24 (2H, m), 7.33–7.38 (2H, m), 7.42–7.47 (1H, m), 7.65–7.70 (1H, m), 7.74 (1H, d, *J* = 8.1), 7.78–7.84 (2H, m), 7.96 (1H, d, *J* = 8.5), 8.08–8.12 (2H, m), 8.29 (1H, s) and 8.36 (1H, d, *J* = 8.3). HRFABMS: MH^+, 676.3171. $C_{39}H_{42}N_5O_6$ requires 676.3135.

N^1- *[3- [[2- [[(1,1- Dimethylethyl) amino] carbonyl] -1-naphthalenyl] oxy] -2(S)- hydroxy -1(S)- (phenylmethyl)-propyl] -(S) -2- [(2-quinolinylcarbonyl) amino] butanediamide (10).* NMR (CD_3OD) δ 1.53 (9H, s), 2.68 (1H, dd, *J* = 15.5 and 5.6), 2.79 (1H, dd, *J* = 15.5 and 6.8), 2.93 (1H, dd, *J* = 13.8 and 8.9), 3.10 (1H, dd, *J* = 13.8 and 4.9), 4.05–4.19 (3H, m), 4.28–4.34 (1H, m), 4.87–4.91 (1H, m), 6.90–6.95 (1H, m), 7.03–7.09 (2H, m), 7.21–7.25 (2H, m), 7.40–7.45 (2H, m), 7.57–7.60 (2H, m), 7.64–7.69 (1H, m), 7.73–7.81 (2H, m), 7.84–7.93 (2H, m), 8.01 (1H, d, *J* = 8.5), 8.14–8.17 (1H, m) and 8.24 (1H, d, *J* = 8.1). HRFABMS: (MH^+, 676.3164. $C_{39}H_{42}N_5O_6$ requires 676.3135).

Biology

Inhibition of proteolytic activity of HIV-1 protease as determined by scintillation proximity assay (SPA). The SPA assay for HIV-1 protease has been developed by Amersham Corporation, Arlington Heights, Illinois, and is available for commercial use. In this system the substrate for HIV-protease, AcN-(I^{125})Tyr-Arg-Ala-Arg-Val-Phe-Phe-Val-Arg-Ala-Ala-Lys-SPA bead, is cleaved by the HIV-protease at the Phe-Phe bond releasing the I^{125}-labeled peptide fragment from the SPA bead. This event causes removal of detectable signal from the microsphere bead indicated by reduction in radioactivity (measured in CPM), which is proportional to the proteolytic activity. The substrate (10 nM) and the HIV-1 protease (13 nM) were incubated in the presence of synthetic compounds in

various dilutions at room temperature for 40 min, and the concentration of the compound required to inhibit the proteolytic activity by 50 % was determined.

Antiviral activity: HIV cytopathogenic effect (CPE) inhibition assay. HIV-CPE inhibition assays were performed at IIT Research Institute, Chicago, Illinois. CEM-T4 cells were infected in the presence of test compounds with HIV-1 strain HTLV-III_B at a multiplicity of 0.05. Infected cells were then incubated at 37 °C in 5 % CO_2 atmosphere. At 8 days post-infection, the ability of the synthetic compounds to prevent cytopathogenicity caused by HIV was determined by MTT assay[6] and the 50 % effective dose (ID_{50}) was calculated using the dose effect analysis software of Chou and Chou (Elsevier–Biosoft).

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