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Preliminary communication

Synthesis and anti-HIV activity of α-thiophenoxy-hydroxyethylamide derivatives

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Abstract – A series of new anti-HIV derivatives containing a novel α-thiophenoxyhydroxyethylamide core have been synthesized, using S-phenylbenzenethiosulfonate as the thiosulfenylating reagent. Some of the new synthesized compounds (**1a**, **1c**, **1g**, **1i**, **1j** and **1l**) inhibited HIV replication in cell culture assays (syncytia formation) with effective concentrations (EC_{50}) ranging from 0.1–1 μM. Incorporation of thiophenoxy substitution within various pseudomimetic peptide backbones provided a series of highly potent HIV inhibitors. © 1999 Éditions scientifiques et médicales Elsevier SAS

HIV inhibitors / α-thiophenoxy-hydroxyethylamide isostere / anti-AIDS agents

1. Introduction

We have previously reported [1] that the specific replacement of the Phe residue by an α-thiophenoxy glycine in a peptidic sequence, conferred anti-HIV properties for the resulting mimetic peptide. Moreover, we have also shown that the introduction of a thiophenoxy moiety in particular cyclic oxamides [2] led to potent HIV inhibitors. The finding which supported our efforts for the design of these thiophenoxy containing classes of compounds was that α-thiophenoxy amide, upon hydrolysis, generated an unstable thiophenoxy aminal intermediate, which lead to the release of thiophenol as reported in literature by Kingsbury et al. [3, 4] and is shown in *figure 1*.

It should be also underlined that molecular modelling studies showed that the bioisosteric replacement of a methylene group by a sulfur atom in a benzyl group of various enzymatic substrates, correctly matched the preferred low energy conformation of the two bioisosters [2, 5].

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In the present paper, both synthesis and anti-HIV properties of a novel class of compounds incorporating an α-thiophenoxy-hydroxyethyl motif, represented by structures **1** and **2**, are described *(figure 2)*.

In our approach, we directly proceed to in vitro evaluation of anti-HIV activity of the new analogues on HIV-infected MT_4 cells (observation of syncytia formation). The most active compounds emergent from this preliminary screening were then submitted to further screenings on other HIV-infected cell types, different HIV virus strains, and also anti-HIV protease inhibition studies.

2. Chemistry

All the compounds **1a–j** and **2a–c** outlined in *table I* were synthesized following the general synthetic pathway illustrated in *schemes 1* and *2* using 1,3-diamino-2-hydroxypropane **3** as starting material. Compound **3** was condensed on various substituted benzaldehydes, the

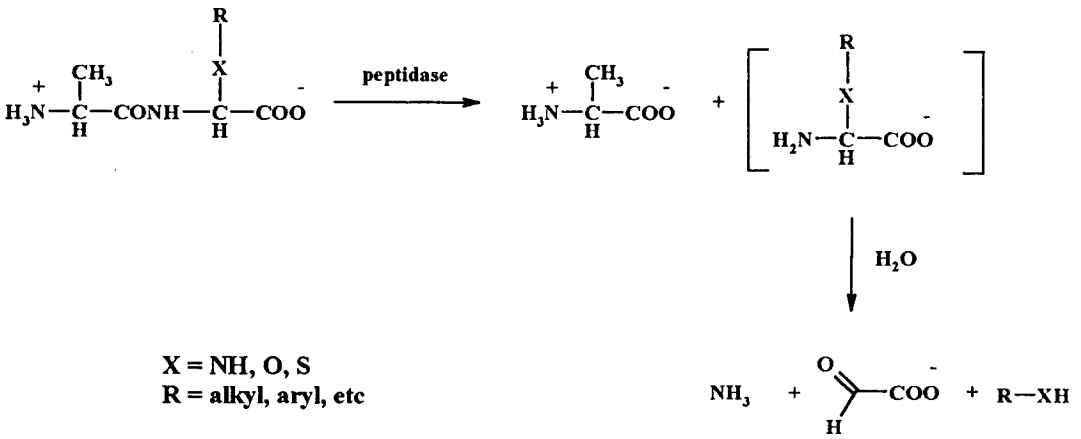
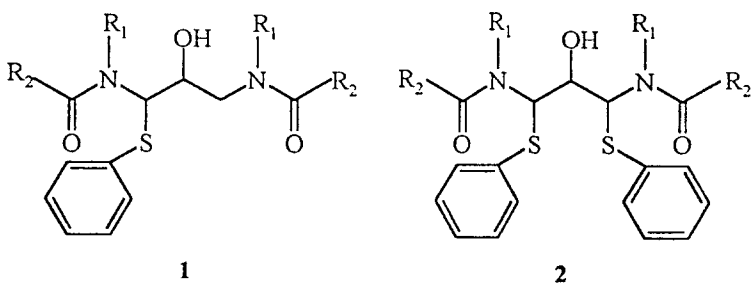


Figure 1. Kingsbury et al. [4].

resulting diimines **4a** and **4b** were reduced to the corresponding diamines **5a** and **5b** using sodium borohydride in ethanol.

The condensation of **5a** on Boc_2O gave diurethane **6a**. Compounds **6b–c** and **6h** were obtained respectively from **5a** and **5b** by alkoxycarbonylation using the appropriate alkylchloroformate. N,N′-disuccinimidyl carbonate in the presence of triethylamine in dry CH_3CN was used specifically to synthesize analogues **6d** and **6e** using respectively (S)-3-hydroxytetrahydrofuran and benzyl alcohol through a mixed carbonate condensation on diamine **5a** [6]. Analogues **6f** and **6i** were obtained respectively after condensation of diamines **5a** and **5b** on N-methyl-N-phenyl carbamoyl chloride. Using a carbodiimide mediate-coupling, analogues **6g** and **6j** were obtained respectively from condensation of L-Boc-Val-OH on diamine **5a** and 1,3-diamino-2-hydroxypropane **3**. It can be underlined that whatever the synthetic routes, analogues **6a–j** were obtained in good yields (*scheme 1*).

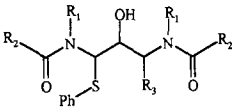
As shown in *scheme 2*, in order to prepare ketone analogues **7a–j**, oxidation of the corresponding hydroxy analogues **6a–j** was achieved using the nitroxy radical TEMPO ((2,2,6,6-tetramethyl)-1-piperidinyloxy) [7]. This method was employed since it is known that this reagent is more favourable for the oxidation of secondary alcohols rather than the corresponding primary alcohols [8]. Introduction of a thiophenoxy group at the α position of the ketone represents the limiting step of the presented synthesis. This was overcome using S-phenyl benzenethiosulfonate [8] as the reagent in the presence of n-butyllithium in dry dichloroethane. The use of n-butyllithium to generate the α-carbanion is crucial since it allows specifically only the formation of the monocarbanion leading to the α-monothiophenoxy ketones **8a–j**. In contrast, the use of a mixture of

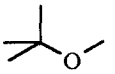
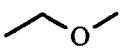
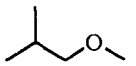
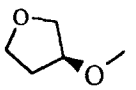
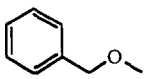
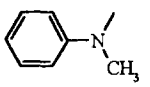
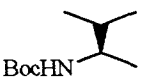
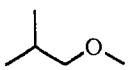
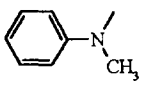
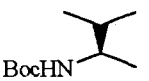
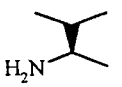
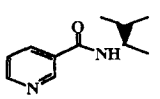
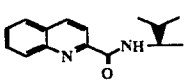
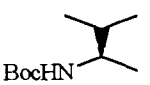


1 2

Figure 2. R_1 and R_2 represent various substituents listed in *table I*.

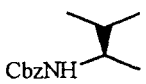
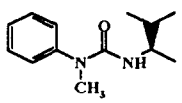
Table I. Anti-HIV potencies of new α-thiophenoxy hydroethylamide isosteres.



No.	R_1	R_2	R_3	Mw	Log P[a]	EC_{50}[b] μM	CC_{50}[c] μM	SI[d]
1a	$PhCH_2$		H	578	8.37	1–0.1	50	50–500
1b	$PhCH_2$		H	522	6.98	inactive	50	–
1c	$PhCH_2$		H	578	8.74	0.1	50	500
1d	$PhCH_2$		H	606	5.46	10	50	5
1e	$PhCH_2$		H	646	9.47	10	100	10
1f	$PhCH_2$		H	644	10.05	10/Tox	50	5
1g	$PhCH_2$		H	776	9.97	1	50	50
1h	$p(MeO)PhCH_2$		H	638	8.57	10	50	5
1i	$p(MeO)PhCH_2$		H	704	9.88	1–0.1	10	10–100
1j	H		H	596	5.22	0.1	50	500
1k	$PhCH_2$		H	576	6.41	10	50	5
1l	$PhCH_2$		H	786	8.74	1	100	10
1m	$PhCH_2$		H	842	10.01	10	50	5
2a	H		PhS	704	8.61	inactive	100	–

[a]Log P determinations were performed using ACD software (Advanced Chemistry Development) /Log P 1.0 base calculations. [b]EC_{50} = concentration required to inhibit syncytia formation by 50% on MT_4 cells. [c]CC_{50} = concentration required to cause 50% death of uninfected MT_4 cells. [d]SI = selectivity index (CC_{50}/EC_{50}).

Table I. Anti-HIV potencies of new α-thiophenoxy hydroethylamide isosteres (continued).

No.	R_1	R_2	R_3	Mw	Log P[a]	EC_{50}[b] μM	CC_{50}[c] μM	SI[d]
2b	H		PhS	770	8.41	10	50	5
2c	H		PhS	772	9.70	inactive	10	–

[a]Log P determinations were performed using ACD software (Advanced Chemistry Development) /Log P 1.0 base calculations. [b]EC_{50} = concentration required to inhibit syncytia formation by 50% on MT_4 cells. [c]CC_{50} = concentration required to cause 50% death of uninfected MT_4 cells. [d]SI = selectivity index (CC_{50}/EC_{50}).

n-butyllithium and sodium hydride (1.2–1.5 eq.) allows predominantly the formation of α,α′-dithiophenoxy ketone **9** through the generation, in situ, of the corresponding dicarbanion. This observation is in good agreement with literature reports, on mono- and dicarbanion formations [9]. It should be also underlined that the use of diphenyldisulfide as the sulfenylation reagent [10] led to lower yields. The last step of the synthesis required the specific reduction of the α-thiophenoxy ketones **8a–j** and **9**. This was achieved using sodium borohydride reagent in ethanol according to known procedures [11]. The corresponding α-thiophenoxy alcohols **1a–j** and **2a**, were isolated in good yields. In order to obtain various valinyl derivatives with different peripheral groups, deprotection using trifluoroacetic acid (TFA) of analogue **1g** provided compound **1k**. Condensation of free amine derivative **1k** with nicotinic acid and quinaldic acid using BOP reagent coupling [12] gave respectively analogues **1l** and **1m**. Boc deprotection of compound **2a** followed by condensation with N-methyl-N-phenyl carbamoyl chloride or benzylchloroformate provided respectively analogues **2b** and **2c** in good yields.

In this first approach, the stereochemistry of the different chiral centres was not considered. Indeed enantioselective synthesis or HPLC separation of the obtained racemic mixtures on chiral phase will be performed only on racemic mixtures which will demonstrate a remarkable activity on HIV-infected cell cultures.

3. Antiviral evaluation and discussion

All new analogues were first evaluated for their inhibitory effects on HIV replication in MT_4 cell culture *(table I)*. Under assay conditions among all tested analogues, the most active compounds **1a**, **1c**, **1g**, **1i**, **1j** and **1l** elicited anti-HIV activity with EC_{50} values ranging from 0.1–1 μM. Examination of the antiviral potencies of the various thiophenoxy analogues revealed several trends:

i. Symmetrical dithiophenoxy analogues are ineffective or less active compared to the corresponding monothiophenoxy analogues.

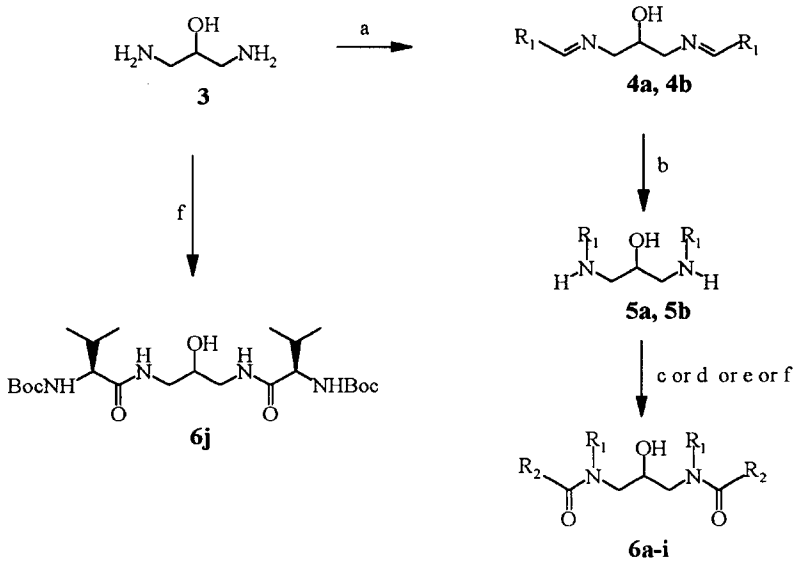
ii. The presence of R_1 substituents is actually detrimental for anti-HIV activity, since the N-unsubstituted compound **1j** showed a better activity versus the N-substituted analogue **1g**.

iii. In contrast, the N-substitution with various R_2 substituents confers higher anti-HIV activities, since carbamates **1a** and **1c**, urea **1i** and N-substituted-(L)-Val **1g** and **1j** analogues were found to be active.

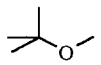
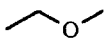
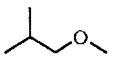
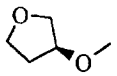
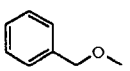
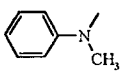
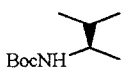
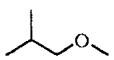
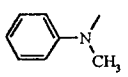
It can be also observed that these new analogues are relatively cytotoxic since their CC_{50} values ranged from 100–10 μM. The most active compounds exhibited selectivity index (SI) values of about 500.

Since high lipophilicity constitutes a significant obstacle to the development of peptidic inhibitors [13], we have determined the relative lipophilicity of the new designed thiophenoxy analogues through the calculation of their partition coefficient. For this purpose, using ACD software [14], the partition coefficient of each studied compound was calculated. As shown in *table I* the new analogues have Log P values ranging from 5.22–10.05.

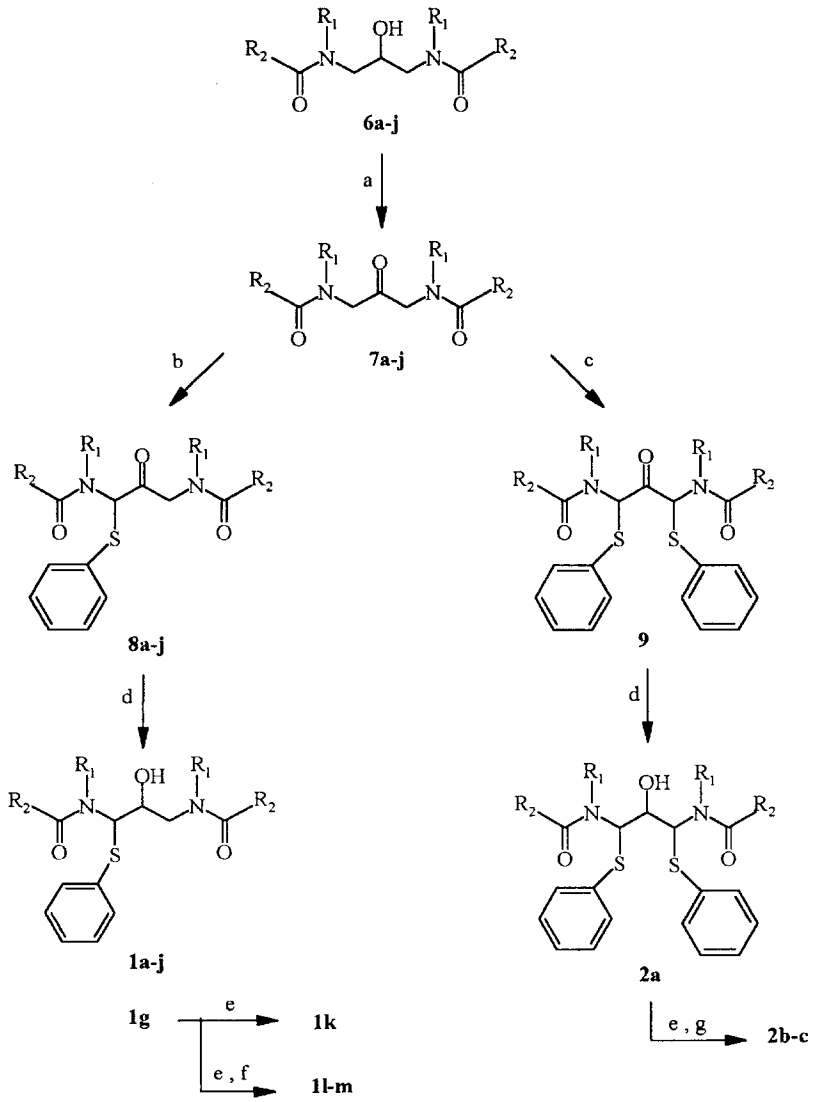
Comparison of Log P values for the most active compounds (**1a**, **1c**, **1g**, **1i** and **1l**) ranging from 8.37–9.97, indicates that these compounds with similar high lipophilic properties should easily penetrate the cells. As a consequence, these lipophilic analogues display a relatively high cellular cytotoxicity. In order to investigate the possible mechanism of action by which these thiophenoxy analogues elicited their antiviral activ-



(a) R_1CHO, Na_2SO_4, CH_2Cl_2, rt, overnight, 93% ; (b) $NaBH_4$, EtOH, rt, overnight, 100% ; (c) Boc_2O, CH_2Cl_2, rt, 100% or (d) R_2COCl, Et_3N, CH_2Cl_2, rt, 98–100% or (e) Alkylsuccinimidyl carbonate, Et_3N, CH_3CN, rt, 93% or (f) Boc-Val-OH, DCC, HOBT, Et_3N, DMF, rt, overnight, 95%.

Compound	R_1	R_2
6a	$PhCH_2$	
6b	$PhCH_2$	
6c	$PhCH_2$	
6d	$PhCH_2$	
6e	$PhCH_2$	
6f	$PhCH_2$	
6g	$PhCH_2$	
6h	p(MeO)$PhCH_2$	
6i	p(MeO)$PhCH_2$	

Scheme 1.



(a) TEMPO, KBr, NaOCl solution (pH = 8), CH_2Cl_2/$NaHCO_3$, rt, 85–93% (b) $PhSO_2$-SPh, n-Buli, Dichloroethane, −25°C to rt, 30–45%; (c) $PhSO_2$-SPh, n-Buli, NaH, Dichloroethane, −25°C to rt, 22%; (d) $NaBH_4$, MeOH, rt, 95–100%; (e) TFA, CH_2CL_2, rt, 81%; (f) RCOOH, BOP, Et_3N, CH_2Cl_2, rt, 60%; (g) RCOCl, Et_3N, CH_2Cl_2, rt, 52–82%.

Scheme 2.

ity, we have verified that when analogue **1a** was submitted to acidic hydrolysis, thiophenol release was spectrophotometrically measured (λmax = 412 nm). Thiophenol production was followed by the use of Ellman's reagent [15]. Unfortunately, this technique was not applicable to suspension of MT_4 HIV-infected cells since the limit of detection of thiophenol by the Ellman's reagent method is around 10 μM, while the active concentration of the thiophenoxy analogue was around 0.1–1 μM. At this point the possible role of intracellular thiophenol

release in the observed HIV inhibiting properties could not be confirmed by this technique.

In conclusion, we have discovered a new series of potent anti-HIV analogues. These compounds contain a novel 2-thiophenoxy-1-hydroxyethylamide isostere. Some of the compounds inhibit MT_4 syncytia formation at EC_{50} values ranging from 0.1–1 μM. These results indicate that this new isostere synthon could be suitable for solid phase combinatorial anti-HIV chemistry since it could be incorporated in various peptidic backbones.

Experiments are underway in order to bring to light the role played by the thiophenoxy moiety in the observed anti-HIV activity, and to verify if thiophenol release occurs within the infected cell during the viral replication process. In this case, this new concept of 2-thiophenoxy-1-hydroxyethylamide isostere could represent a promising approach for the design of anti-HIV drugs.

4. Experimental protocols

4.1. Chemistry

Nuclear magnetic resonance spectra were recorded with a Brucker AC-250 (^{1}H NMR); chemical shifts are expressed as δ units (parts per million) downfield from TMS. Fast atom bombardment mass spectral analyses were obtained by Dr Astier (Laboratoire de Mesures Physiques- RMN, USTL, Montpellier, France) on a Jeol DX-100 using a caesium ion source and glycerol/thioglycerol (1:1) or *m*-nitrobenzyl alcohol (NOBA) as matrix. Mass calibration was performed using caesium iodide. Microanalyses were carried out by Service Central d'Analyses du CNRS (Venaison, France) and were within ± 0.4% of the theoretical values. Thin layer chromatography (TLC) and preparative layer chromatography (PLC) were performed using silica gel plates 0.2, 1 or 2 mm thick ($60F_{254}$ Merck). Preparative flash column chromatography was carried out on silica gel (230–240 mesh, G60 Merck).

All reagents were of commercial quality (Aldrich Company) from freshly opened containers.

4.1.1. 1,3-di-(N-benzylamino)-2-hydroxypropane **5a**

To a suspension of 1,3-diamino-2-hydroxypropane **3** (7 g, 77 mmol) and Na_2SO_4 (22 g, 155 mmol) in CH_2Cl_2 (75 mL) was added, in portions, benzaldehyde (16 g, 155 mmol) at 0 °C. The reaction mixture was then stirred overnight at room temperature, filtered and concentrated in vacuo. The crude diimine **4a** was taken off in ethanol (50 mL) and treated with $NaBH_4$ (3 g, 77 mmol) at 0 °C. The solution was allowed to warm to room temperature and stirred overnight. After removal of solvent, the residue was partitioned between CH_2Cl_2 (60 mL) and aqueous 1 N NaOH (30 mL). The organic layer was dried over Na_2SO_4 and evaporated in vacuo to provide **5a** as an oil (20.14 g, 97%). Rf = 0.42 (CH_2Cl_2/MeOH 8.5:1.5). ^{1}H NMR ($CDCl_3$) δ 2.5 (m, 4H, NH-C*H*$_2$-CH(OH)); 3.0 (br, 2H, N*H*); 3.6 (s, 4H, PHC*H*$_2$-NH); 3.7 (m, 1H, C*H*-OH); 7.1 (m, 10H, ar). MS (FAB) m/z 271 MH^+. Anal. $C_{17}H_{22}N_2O$ (C, H, N, O).

4.1.2. 1,3-di-[N-(4-methoxybenzyl)amino)]-2-hydroxypropane **5b**

Compound **5b** was prepared using 4-methoxybenzaldehyde (2.8 mL, 19.70 mmol) as described for **5a** and obtained as an oil (4.50 g, 92%). Rf = 0.22 (CH_2Cl_2/MeOH 9:1). ^{1}H NMR ($CDCl_3$) δ 2.7 (m, 4H, NH-C*H*$_2$-CH(OH)), 3.4 (br, 2H, N*H*); 3.7 (s, 4H, PHC*H*$_2$-NH); 3.9 (s, 6H, OC*H*$_3$); 4.1 (m, 1H, C*H*-OH); 6.8 (d, 4H, *J* = 13.4 Hz, ar); 7.2 (d, 4H, *J* = 13.4 Hz, ar). MS (FAB) m/z 331 MH^+. Anal. $C_{19}H_{26}N_2O_3$ (C, H, N, O).

4.1.3. 1,3-di-[N-benzyl-N-[(tert-butyloxy)carbonyl]amino]-2-hydroxypropane **6a**

A solution of 1,3-di-(N-benzylamino)-2-hydroxypropane **5a** (1 g, 3.70 mmol) in CH_2Cl_2 (10 mL) was reacted with Boc_2O (1.77 g, 8.14 mmol) at 0 °C under N_2 atmosphere. After being allowed to warm to room temperature and stirred for 2 h, the resulting solution was diluted with CH_2Cl_2 (10 mL) and washed with 5% aqueous citric acid (15 mL), then saturated brine (15 mL), dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography using hexane/EtOAc 8:2 to give **6a** as an oil (1.70 g, 98%). Rf = 0.26 (hexane/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 1.3 (s, 18H, *t*-Bu); 2.8 (m, 4H, N-C*H*$_2$-CH(OH)); 3.6 (s, 4H, PhC*H*$_2$-N); 4.2 (m, 1H, C*H*-OH); 7.1 (m, 10H, ar). MS (FAB) m/z 471 MH^+. Anal. $C_{27}H_{38}N_2O_5$ (C, H, N, O).

4.1.4. 1,3-di-[N-benzyl-N-[(ethyloxy)carbonyl]amino]-2-hydroxypropane **6b**

A solution of **5a** (0.50 g, 1.85 mmol) in dry CH_2Cl_2 (5 mL) was treated with ethylchloroformate (0.39 mL, 4.07 mmol) at 0 °C in the presence of Et_3N (0.57 mL, 5.50 mmol). After being allowed to warm to room temperature for 1 h, the resulting solution was diluted with CH_2Cl_2 (10 mL) and washed with 5% aqueous citric acid (5 mL), then saturated brine (5 mL), dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography using hexane/EtOAc 95:5 to give **6b** as an oil (0.76 g, 100%). Rf = 0.28 (hexane/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 1.2 (brt, 6H, C*H*$_3$-CH$_2$); 3.2 (m, 4H, N-C*H*$_2$-CH(OH)); 4.0 (m, 1H, C*H*-OH); 4.2 (s, 4H,

PhCH_2-N); 4.5 (q, 4H, O-CH_2-CH_3); 7.1 (m, 10H, ar). MS (FAB) m/z 415 MH^+. Anal. $C_{23}H_{30}N_2O_5$ (C, H, N, O).

4.1.5. 1,3-di-[N-benzyl-N-[(isobutyloxy)carbonyl]amino] -2-hydroxypropane **6c**

Compound **6c** was prepared from condensation of isobutylchloroformate (0.52 g, 4.70 mmol) on **5a** according to the method described for **6b** and obtained as an oil (0.85 g, 98%). Rf = 0.28 (hexane/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 0.8 (d, 12H, J = 13.4 Hz, ((CH_3)$_2$CH); 1.6 (m, 2H, CH(CH_3)$_2$); 2.8–3.2 (br, 4H, N-CH_2-CH(OH)); 3.6 (m, 1H, CH-OH); 3.8 (s, 4H, PhCH_2-N); 4.3 (br, 4H, *i*Pr-CH_2-O); 7.1 (m, 10H, ar). MS (FAB) m/z 471 MH^+. Anal. $C_{27}H_{38}N_2O_5$ (C, H, N, O).

4.1.6. 1,3-di-[N-benzyl-N-[(tetrahydrofuran-3-oxy)carbonyl]amino]-2-hydroxypropane **6d**

To a stirred solution of 3-hydroxytetrahydrofuran (0.20 g, 2.26 mmol) in dry CH_3CN (5 mL) at room temperature were added disuccinimidyl carbonate (0.64 g, 2.48 mmol) and Et_3N (0.24 mL, 2.48 mmol). The reaction mixture was stirred until disappearance of starting alcohol on TLC. After concentration in vacuo, the residue was diluted with CH_2Cl_2 (10 mL) and washed with 5% aqueous citric acid (5 mL), then saturated brine (10 mL), dried over Na_2SO_4 and evaporated in vacuo. The crude mixed carbonate was dissolved in dry CH_2Cl_2 (5 mL) and added to a stirred solution of 1,3-di-(N-benzylamino)-2-hydroxypropane **5a** (0.50 g, 1.85 mmol) in dry CH_2Cl_2 (5 mL). The resulting mixture was stirred at room temperature for 3 h, diluted in CH_2Cl_2 (10 mL) and washed with 5% aqueous citric acid (10 mL), then saturated brine (10 mL), dried over Na_2SO_4 and evaporated in vacuo, the residue was purified by flash chromatography using hexane/EtOAc 5:5 to give **6d** as an oil (0.87 g, 95%). Rf = 0.14 (hexane/EtOAc 4:6). ^{1}H NMR ($CDCl_3$) δ 1.8–2.2 (br, 4H, *HH′*-4); 3.1–3.4 (br, 4H, N-CH_2-CH(OH)); 3.8 (br, 8H, *HH′*-2 and *HH′*-2); 4.0 (m, 1H, CH-OH); 4.3 (s, 4H, PhCH_2-N); 5.1 (m, 2H, *HH′*-3); 6.9–7.2 (m, 10H, ar). MS (FAB) m/z 499 MH^+. Anal. $C_{27}H_{34}N_2O_7$ (C, H, N, O).

4.1.7. 1,3-di-[N-benzyl-N-[(benzyloxy)carbonyl]amino]-2-hydroxypropane **6e**

Compound **6e** was prepared using benzyl alcohol (0.50 g, 4.70 mmol)) according to the method described for **6d** and obtained as an oil (1.06 g, 85%). Rf = 0.47 (toluene/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 2.9–3.1 (br, 4H, N-CH_2-CH(OH)); 3.9 (m, 1H, CH-OH); 4.4 (s, 4H, PhCH_2-N); 5.0 (s, 4H, PhCH_2-O); 6.9–7.1 (m, 20H, ar). MS (FAB) *m/z* 539 MH^+. Anal. $C_{33}H_{34}N_2O_5$ (C, H, N, O).

4.1.8. 1,3-di-[N-benzyl-N-[((N-methyl-N-phenyl)amino) carbonyl]amino]-2-hydroxypropane **6f**

A solution of **5a** (0.50 g, 1.85 mmol) in dry CH_2Cl_2 (5 mL) was treated with N-methyl-N-phenyl carbamoyl-chloride (0.69 g, 4.07 mmol) at 0 °C in the presence of Et_3N (0.57 mL, 5.50 mmol). After being allowed to warm to room temperature and stirred for 1h, the resulting solution was diluted in CH_2Cl_2 (10 mL) and washed with 5% aqueous citric acid (10 mL), then saturated brine (10 mL), dried over Na_2SO_4 and evaporated in vacuo, the residue was purified by flash chromatography using hexane/EtOAc 6:4 to give **6f** as an oil (0.99 g, 99%). Rf = 0.31 (hexane/EtOAc 5:5). ^{1}H NMR ($CDCl_3$) δ 2.8 (dd, J = 7.16, 15.6 Hz, 2H, N-CH(H)-CH(OH)), 3.0 (s, 6H, N-CH_3); 3.2 (dd, J = 4.76, 15.6 Hz, 2H, N-CH(*H*)-CH(OH)); 3.7 (m, 1H, CH-OH), 4.1 (s, 4H, PhCH_2-N); 7.12 (m, 20 H, ar). MS (FAB) m/z 537 MH^+. Anal.$C_{33}H_{36}N_4O_3$ (C, H, N, O).

4.1.9. 1,3-Bis[N-benzyl-N-[N-[(tert-butyloxy)carbonyl] valinyl]amino]-2-hydroxypropane **6g**

A mixture of (L)-Boc-Val-OH (5 g, 23 mmol), DCC (4.74 g, 23 mmol), HOBT (3.10 g, 23 mmol), Et_3N (4.50 mL, 33 mmol) and 1,3-di-(N-benzylamino)-2-hydroxypropane **5a** (3 g, 11 mmol), in DMF (75 mL) was stirred from 0 °C to room temperature overnight. After filtration of solid DCU, the resulting solution was concentrated under reduced pressure. The residual oil was partitioned between EtOAc (40 mL) and saturated brine (20 mL). The organic layer was washed with aqueous 5% $NaHCO_3$ (20 mL), then 5% aqueous citric acid, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel flash column chromatography to provide **6g** as an oil (6.98 g, 95%).

Rf = 0.18 (toluene/EtOAc 9:1). Signals in ^{1}H NMR ($CDCl_3$) could not be assigned because of their breadth. MS (FAB) *m/z* 669 MH^+. Anal. $C_{37}H_{56}N_4O_7$ (C, H, N, O).

4.1.10. 1,3-di[N-(4-methoxybenzyl)-N-[(isobutyloxy)carbonyl]amino]-2-hydroxypropane **6h**

Compound **6h** was prepared using isobutylchloroformate (0.50 g, 3.03 mmol) and diamine **5b** (0.5 g, 1.51 mmol) according to the method already described for **6b** and obtained as an oil (0.79 g, 98%). Rf = 0.36 (hexane/EtOAc 7:3). ^{1}H NMR ($CDCl_3$) δ 0.7 (d, 12H, J = 13.4 Hz, (CH_3)$_2$CH); 1.7 (m, 1H, CH(CH_3)$_2$); 2.8–3.2 (br, 4H, N-CH_2-CH(OH)); 3.6 (s, 6H, OCH_3); 3.7 (s, 4H, PhCH_2-N); 3.9 (m, 1H, CH-OH); 4.5 (br, 4H, *i*Pr-CH_2-O); 6.7 (d, 4H, J = 11.8 Hz, ar); 7.0 (d, 4H, J = 11.8 Hz, ar). MS (FAB) *m/z* 531 MH^+. Anal. $C_{29}H_{42}N_2O_5$ (C, H, N, O).

4.1.11. 1,3-di-[N-(4-methoxybenzyl)-N-[[(N-methyl-N-phenyl)amino]carbonyl]amino]-2-hydroxypropane **6i**

Compound **6i** was prepared using N-methyl-N-phenyl carbamoylchloride (0.51 g, 3.03 mmol) and diamine **5b** (0.5 g, 1.51 mmol) according to method described for **6f** and obtained as an oil (0.89 g, 98%). Rf = 0.33 (hexane/EtOAc 4:6). ^{1}H NMR ($CDCl_3$) δ 2.9 (dd, *J* = 2.8, 14.3 Hz, 2H, N-C*H*(H)-CH(OH)); 3.1 (s, 6H, CH_3N); 3.2 (dd, *J* = 8.3, 14.3 Hz, 2H, N-CH(*H*)-CH(OH)); 3.7 (s, 6H, CH_3O); 3.8 (m, 1H, C*H*-OH); 4.1 (AB, quartet 4H, *p*(MeO)PhCH_2-N); 5.0 (d, *J* = 3.7 Hz, 1H, CH-O*H*); 6.8 (d, *J* = 8.2 Hz, 4H, ar); 7.0 (d, *J* = 8.2 Hz, 4H, ar); 7.1–7.3 (m, 10H, ar). MS (FAB) *m/z* 597 MH$^+$. Anal. $C_{35}H_{40}N_4O_5$ (C, H, N, O).

4.1.12. 1,3-Bis[N-[N-[(tert-butyloxy)carbonyl]valinyl]amino]-2-hydroxypropane **6j**

Compound **6j** was prepared using 1,3-diamino-2-hydroxypropane **3** (0.62 g, 6.90 mmol) according to the method already described for **6g** and obtained as an oil (3.10 g, 91%). Rf = 0.6 (EtOAc). ^{1}H NMR ($CDCl_3$) δ 0.7 (d, *J* = 6.5 Hz, 12H, (CH_3)$_2$CH); 1.3 (s, 18H, *t*-Bu); 1.8 (m, 2H, C*H*(CH$_3$)$_2$); 3.1 (br, 4H, NH-CH_2-CH(OH)); 3.8 (br, 2H, BocNH-C*H*(iPr)-CO); 4.1 (m, 1H, C*H*-OH); 5.0 (d, *J* = 8.9 Hz, 2H, BocN*H*-CH(iPr)); 7.2 (br, 2H, N*H*-CH$_2$-CO). MS (FAB) *m/z* 489 MH$^+$. Anal. $C_{23}H_{44}N_4O_7$ (C, H, N, O).

4.1.13. General procedure A for the preparation of compounds **7a–7j**: *oxidation of alcohol to ketone using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)*

In a biphasic mixture of CH_2Cl_2/saturated aqueous $NaHCO_3$ (v:v / 3:1) was added the alcohol compound radical TEMPO (catalytic amount, 10 mg) and KBr (50 mg). The mixture was stirred for 30 min in an ice bath. A solution of NaOCl (5 mL) with pH controlled at 8 was added in portions with vigorous stirring to the above mixture at room temperature. The resulting solution became red. After 1 h, NaOCl solution was added and stirring was continued until disappearance of starting material on TLC. The biphasic solution was separated and the organic layer was washed with 5% aqueous citric acid, then saturated brine dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography was performed using the appropriate solvent.

4.1.13.1. 1,3-di-[N-benzyl-N-[(tert-butyloxy)carbonyl]-propanone **7a**

Starting from **6a** (0.5 g, 1.06 mmol), the title compound was prepared according to general procedure A and obtained as an oil (0.46 g, 93%). Rf = 0.42 (hexane/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 1.3 (s, 18H, *t*-Bu); 3.7 (s, 4H, CH_2-CO); 4.3 (1, 4H, PhCH_2-N); 7.0–7.2 (m, 10H, ar). MS (FAB) *m/z* 469 MH$^+$. Anal. $C_{27}H_{36}N_2O_5$ (C, H, N, O).

4.1.13.2. 1,3-di-[N-benzyl-N-[(ethyolxy)carbonyl]-propanone **7b**

Starting from **6b** (0.5 g, 1.20 mmol), the title compound was prepared according to general procedure A and obtained as an oil (0.46 g, 93%). Rf = 0.35 (hexane/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 1.0 (t, 6H, CH_3-CH$_2$); 3.8 (d, *J* = 14.1 Hz, 4H, CH_2-CO); 4.0 (s, 4H, CH$_3$-CH_2-O); 4.3 (q, 4H, PhCH_2-N); 7.0–7.2 (m, 10H, ar). MS (FAB) *m/z* 413 MH$^+$. Anal. $C_{23}H_{28}N_2O_5$ (C, H, N, O).

4.1.13.3. 1,3-di-[N-benzyl-N-[(isobutyloxy)carbonyl]-propanone **7c**

Starting from **6c** (0.5 g, 1.06 mmol), the title compound was prepared according to general procedure A and obtained as an oil (0.45 g, 90%). Rf = 0.33 (hexane/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 0.8 (d, *J* = 13.2 Hz, 12H, (CH_3)$_2$CH); 1.8 (m, 2H, C*H*(CH$_3$)$_2$); 3.7 (br, 8H, N-CH_2-CO and PhCH_2-N); 4.4 (d, *J* = 9.2 Hz, 4H, *i*Pr-CH_2-O); 7.2 (m, 10H, ar). MS (FAB) *m/z* 469 MH$^+$. Anal. $C_{27}H_{36}N_2O_5$ (C, H, N, O).

4.1.13.4. 1,3-di-[N-benzyl-N-[(tetrahydrofuran-3-oxy) carbonyl]-propanone **7d**

Starting from **6d** (0.7 g, 1.40 mmol), the title compound was prepared according to general procedure A and obtained as an oil (0.62 g, 88%). Rf = 0.24 (hexane/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 1.9–2.2 (m, 4H, *HH′*-4); 3.1–3.3 (m, 12H, CH_2-CO and *HH′*-2 and *HH′*-5); 4.4 (br, 4H, PhCH_2-N); 5.2 (br, 2H, *HH′*-3); 7.0–7.2 (m, 10H, ar). MS (FAB) *m/z* 497 MH$^+$. Anal. $C_{27}H_{32}N_2O_7$ (C, H, N, O).

4.1.13.5. 1,3-di-[N-benzyl-N-[(benzyloxy)carbonyl]-propanone **7e**

Starting from **6e** (0.8 g, 1.49 mmol), the title compound was prepared according to general procedure A and obtained as an oil (0.68 g, 85%). Rf = 0.36 (toluene/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 3.6 (d, *J* = 12.0 Hz, 2H, N-C*H*(H)-CO); 3.8 (d, *J* = 12.0 Hz, 2H, N-CH(*H*)-CO); 4.3 (s, 4H, PhCH_2-N); 5.1 (s, 4H, PhCH_2-O); 7.0–7.2 (m, 10H, ar). MS (FAB) *m/z* 537 MH$^+$. Anal. $C_{33}H_{32}N_2O_5$ (C, H, N, O).

4.1.13.6. 1,3-di-[N-benzyl-N-[((N-methyl-N-phenyl) amino)carbonyl)amino]-propanone **7f**

Starting from **6f** (0.5 g, 0.93 mmol), the title compound was prepared according to general procedure A and obtained as an oil (0.45 g, 91%). Rf = 0.42 (hexane/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 3.0 (s, 6H,

CH_3N); 3.5 (s, 4H, N-CH_2-CO); 4.1 (s, 4H, PhCH_2-N); 6.8–7.2 (m, 20H, ar). MS (FAB) *m/z* 535 MH^+. Anal. $C_{33}H_{34}N_4O_3$ (C, H, N, O).

4.1.13.7. 1,3-Bis[N-benzyl-N-[N-[(tert-butyloxy)carbonyl]valinyl]amino]-propanone **7g**

Compound **7g** was prepared from **6g** (6 g; 8.90 mmol) according to general procedure A and obtained as an oil (5.20 g, 98%). Rf = 0.32 (toluene/EtOAc 9:1). Signals in ^1H NMR ($CDCl_3$) could not be assigned because of their breadth. MS (FAB) *m/z* 667 MH^+. Anal. $C_{37}H_{54}N_4O_7$ (C, H, N, O).

4.1.13.8. 1,3-di-[N-(4-methoxybenzyl)-N-[(isobutyloxy) carbonyl]-propanone **7h**

Starting from **6h** (0.6 g, 1.13 mmol), the title compound was prepared according to general procedure A and obtained as an oil (0.54 g, 90%). Rf = 0.42 (hexane/EtOAc 7:3). ^1H NMR ($CDCl_3$) δ 0.7 (d, *J* = 13.2 Hz, 12H, $(CH_3)_2CH$); 1.7 (m, 2H, $CH(CH_3)_2$); 3.5 (s, 6H, CH_3O); 3.7 (br, 8H, CH_2-CO and *p*(MeO)PhCH_2-N); 4.2 (d, *J* = 9.7 Hz, 4H, *i*Pr-CH_2-O); 6.5 (d, *J* = 8.4 Hz, 4H, ar); 6.9 (d, *J* = 8.4 Hz, 4H, ar). MS (FAB) *m/z* 529 MH^+. Anal. $C_{29}H_{40}N_2O_5$ (C, H, N, O).

4.1.13.9. 1,3-di-[N-(4-methoxybenzyl)-N-[((N-methyl-N-phenyl)amino)carbonyl)amino]-propanone **7i**

Starting from **6i** (0.5 g, 0.84 mmol), the title compound was prepared according to general procedure A and obtained as an oil (0.46 g, 93%). Rf = 0.53 (hexane/EtOAc 1:1). ^1H NMR ($CDCl_3$) δ 3.0 (s, 6H, CH_3N); 3.5 (s, 4H, N-CH_2-CO); 3.6 (s, 6H, CH_3O); 3.9 (s, 4H, *p*(MeO)PhCH_2-N); 6.9–7.1 (m, 10H, ar); 7.2 (d, *J* = 8.4 Hz, 4H, ar); 7.4 (d, *J* = 8.4 Hz, 4H, ar); MS (FAB) *m/z* 595 MH^+. Anal. $C_{35}H_{38}N_4O_5$ (C, H, N, O).

4.1.13.10. 1,3-Bis[N-[N-[(tert-butyloxy)carbonyl]valinyl]amino]-propanone **7j**

Starting from **6j** (5 g, 10.3 mmol), the title compound was prepared according to general procedure A and obtained as an oil (4.85 g, 97%). Rf = 0.36 (EtOAc:hexane 7:3). ^1H NMR ($CDCl_3$) δ 0.7 (d, *J* = 6.9 Hz, 12H, $(CH_3)_2CH$); 1.3 (s, 18H, *t*-Bu); 1.8 (m, 2H, $CH(CH_3)_2$); 3.8 (brd, *J* = 6.2 Hz, 4H, NH-CH_2-CO); 4.0 (br, 2H, BocNH-C*H*(iPr)-CO); 5.1 (br, 2H, BocN*H*-CH(iPr)); 7.3 (br, 2H, N*H*-CH_2-CO). MS (FAB) *m/z* 487 MH^+. Anal. $C_{23}H_{42}N_4O_7$ (C, H, N, O).

4.1.14. General procedure B for the preparation of compounds **8a–8i**: *sulfenylation of ketone to the α-phenylsulfenyl-ketone compounds*

A solution of 1 eq. of ketone and 1.1 eq. S-phenyl benzene thiosulfonate ($PhSO_2$-SPh) in dry dichloroethane was treated with a solution of 1.1 eq. of n-butyllithium in dichloroethane under N_2 atmosphere at –25 °C. After being allowed to warm to room temperature with stirring for 1 h, the resulting solution was diluted with CH_2Cl_2 and washed with 5% aqueous citric acid, then saturated brine, dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography using the appropriate solvent elution.

4.1.14.1. 1,3-di-[N-benzyl-N-[(tert-butyloxy)carbonyl)]-1-phenylsulfenyl-propanone **8a**

Compound **8a** was prepared from **7a** (0.3 g, 0.63 mmol) according to general procedure B and obtained as an oil (0.15 g, 42%). Rf = 0.6 (hexane/EtOAc 8:2). ^1H NMR ($CDCl_3$) δ 1.3 (s, 9H, *t*-Bu); 1.4 (s, 9H, *t*-Bu); 3.6 (br, 2H, N-CH_2-CO); 4.2 (s, 4H, PhCH_2-N); 4.9 (s, 1H, C*H*-PhS); 7.2 (m, 15H, ar). MS (NOBA) m/z 577 MH^+. Anal. $C_{33}H_{40}N_2O_5S$ (C, H, N, O).

4.1.14.2. 1,3-di-[N-benzyl-N-[(ethyloxy)carbonyl)]-1-phenylsulfenyl-propanone **8b**

Compound **8b** was prepared from **7b** (0.4 g, 0.97 mmol) according to general procedure B and obtained as an oil (0.23 g, 45%). Rf = 0.40 (hexane/EtOAc 8:2). ^1H NMR ($CDCl_3$) δ 0.9 (brt, 3H, CH_3-CH_2); 1.1 (brt, 3H, CH_3-CH_2); 3.3 (br, 2H, N-CH_2-CO); 3.7 (q, 2H, CH_3-CH_2-O), 4.0 (q, 2H, CH_3-CH_2-O); 4.5 (br, 4H, PhCH_2-N); 5.2 (s, 1H, C*H*-PhS); 7.0–7.3 (m, 15H, ar). MS (NOBA) m/z 521 MH^+. Anal. $C_{27}H_{32}N_2O_5S$ (C, H, N, O).

4.1.14.3. 1,3-di-[N-benzyl-N-[(isobutyloxy)carbonyl)]-1-phenylsulfenyl-propanone **8c**

Compound **8c** was prepared from **7c** (0.4 g, 0.85 mmol) according to general procedure B and obtained as an oil (0.22 g, 45%). Rf = 0.49 (hexane/EtOAc 8:2). ^1H NMR ($CDCl_3$) δ 0.6 (br, 6H, $(CH_3)_2CH$); 0.8 (br, 6H, $(CH_3)_2CH$); 1.7 (m, 1H, $CH(CH_3)_2$); 1.8 (m, 1H, $CH(CH_3)_2$); 3.6 (br, 2H, N-CH_2-CO); 3.9 (brs, 4H, PhCH_2-N); 4.3–4.6 (br, 4H, *i*Pr-CH_2-O); 5.2 (s, 1H, C*H*-PhS); 6.9–7.2 (m, 15H, ar). MS (NOBA) m/z 577 MH^+. Anal. $C_{33}H_{40}N_2O_5S$ (C, H, N, O).

4.1.14.4. 1,3-di-[N-benzyl-N-[(tetrafuran-3-oxy)carbonyl)]-1-phenylsulfenyl-propanone **8d**

Compound **8d** was prepared from **7d** (0.35 g, 0.70 mmol) according to general procedure B and obtained as an oil (0.16 g, 37%). Rf = 0.23 (hexane/EtOAc 5:5). ^1H NMR ($CDCl_3$) δ 1.8–2.2 (br, 4H, *HH′*-4); 3.5–3.8 (br, 10H, N-CH_2-CO) and *HH′*-2 and *HH′*-5); 4.5 (br, 4H, PhCH_2-N), 5.2 (s, 1H, C*H*-PhS), 5.6 (m, 2H, *HH′*-3), 7.1–7.3 (m, 15H, ar); MS (NOBA) *m/z* 605 MH^+. Anal. $C_{33}H_{36}N_2O_7S$ (C, H, N, O).

4.1.14.5. 1,3-di-[N-benzyl-N-[(benzyloxy)carbonyl)]-1-phenylsulfenyl-propanone **8e**

Compound **8e** was prepared from **7e** (0.25 g, 0.47 mmol) according to general procedure B and obtained as an oil (0.12 g, 40%). Rf = 0.13 (hexane/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 3.6 (d, *J* = 11.6 Hz, 2H, PhC*H*(H)-N); 3.8 (d, *J* = 11.6 Hz, 2H, PhCH(*H*)-N); 4.2 (d, *J* = 9.0 Hz, 2H, N-C*H*(H)-CO); 4.3 (d, *J* = 9.0 Hz, 1H, N-CH(*H*)-CO); 4.5 (s, 4H, PhCH_2-O), 5.1 (s, 1H, C*H*-PhS); 7.1–7.3 (m, 25H, ar). MS (FAB) *m/z* 645 MH$^+$. Anal. $C_{39}H_{36}N_2O_5S$ (C, H, N, O).

4.1.14.6. 1,3-di-[N-benzyl-N-[[(N-methyl-N-phenyl) amino]carbonyl]amino]-1-phenylsulfenyl-propanone **8f**

Compound **8f** was prepared from **7f** (0.4 g; 0.75 mmol) according to general procedure B and obtained as an oil (0.22 g, 45%). Rf = 0.35 (hexane/EtOAc 6.5:3.5). ^{1}H NMR ($CDCl_3$) δ 2.9 (s, 3H, CH_3N); 3.0 (s, 3H, CH_3N); 3.7 (d, *J* = 8.7 Hz, 1H, N-C*H*(H)-CO); 4.0 (d, *J* = 8.7 Hz, 1H, N-CH(*H*)-CO); 4.2 (d, *J* = 9.5 Hz, 4H, PhCH_2-N); 5.2 (s, 1H, C*H*-PhS); 6.7–7.2 (m, 25H, ar). MS (NOBA) *m/z* 643 MH$^+$. Anal. $C_{39}H_{38}N_4O_3S$ (C, H, N, O).

4.1.14.7. 1,3-Bis[N-benzyl-N-[N-[(tert-butyloxy)carbonyl]valinyl]amino]-1-phenylsulfenyl-propanone **8g**

Compound **8g** was prepared from **7g** (1.5 g, 2.25 mmol) according to general procedure B and obtained as an oil (0.74 g, 42%). Rf = 0.28 (hexane/EtOAc 8:2). Signals in ^{1}H NMR ($CDCl_3$) could not be assigned because of their breadth. MS (NOBA) *m/z* 775 MH$^+$. Anal. $C_{43}H_{60}N_4O_7S$ (C, H, N, O).

4.1.14.8. 1,3-di-[N-(4-methoxybenzyl)-N-[(isobutyloxy) carbonyl]-1-phenylsulfenyl-propanone **8h**

Compound **8h** was prepared from **7h** (0.35 g, 0.67 mmol) according to general procedure B and obtained as an oil (0.19 g, 44%). Rf = 0.35 (hexane/EtOAc 6:4). ^{1}H NMR ($CDCl_3$) δ 0.7 (d, *J* = 13.1 Hz, 6H, (CH_3)$_2$CH); 0.8 (d, *J* = 13.1 Hz, 6H, (CH_3)$_2$CH); 1.7 (m, 2H, C*H*(CH_3)$_2$; 3.5 (s, 3H, OCH_3); 3.6 (s, 3H, OCH_3), 3.8 (s, 2H, N-CH_2-CO); 4.1 (br, 4H, *p*(MeO)PhCH_2-N); 4.4–4.5 (br, 4H, *i*Pr-CH_2-O), 5.5 (s, 1H, C*H*-SPh); 6.5 (m, 4H, ar); 6.9 (m, 4H, ar); 7.1–7.2 (m, 5H, ar). MS (NOBA) *m/z* 637 MH$^+$. Anal. $C_{35}H_{44}N_2O_7S$ (C, H, N, O).

4.1.14.9. 1,3-di-[N-(4-methoxybenzyl)-N-[[(N-methyl-N-phenyl]amino)carbonyl]-1-phenyl sulfenyl-propanone **8i**

Compound **8i** was prepared from **7i** (0.2 g, 0.34 mmol) according to general procedure B and obtained as an oil (0.09 g, 40%). Rf = 0.31 (hexane/EtOAc 8:2).^{1}H NMR ($CDCl_3$) δ 3.0 (s, 3H, CH_3N); 3.1 (s, 3H, CH_3N); 3.6 (s, 3H, OCH_3); 3.7 (s, 3H, OCH_3); 3.9 (d, *J* = 8.7 Hz, 1H, N-C*H*(H)-CO); 4.1 (d, *J* = 9.7 Hz, 4H, p(MeO)PhCH_2-N); 4.2 (d, *J* = 8.7 Hz, 1H, N-CH(*H*)-CO); 4.7 (s, 1H, CH-SPh); 6.7 (d, *J* = 11.6 Hz, 4H, ar), 6.8–7.0 (m, 10H, ar); 7.1–7.2 (m, 5H, ar); 7.4 (d, *J* = 11.6 Hz, 4H, ar); MS (NOBA) *m/z* 703 MH$^+$. Anal. $C_{41}H_{44}N_4O_5S$ (C, H, N, O).

4.1.15. 1,3-Bis[N-[N-[(tert-butyloxy)carbonyl]valinyl] amino]-1-phenylsulfenyl-propanone **8j**

A solution of **7j** (1 g, 2.06 mmol) and $PhSO_2$-SPh (1.13 g, 0.54 mmol) in dry dichloroethane (10 mL) was treated with a solution of n-BuLi 1.6 M in hexane (1.4 mL, 2.26 mmol) under N_2 atmosphere at –25 °C. After 30 min of stirring, NaH (90 mg, 2.26 mmol) was added. The reaction mixture was allowed to warm to room temperature while stirring for 3 h. The resulting solution was diluted with CH_2Cl_2 (10 mL) and washed with two portions of 5% aqueous citric acid (10 mL), then saturated brine (10 mL), dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by silica gel chromatography using hexane/EtOAc (7:3) to give **8j** (0.44 g, 35%). Rf = 0.17 (hexane/EtOAc 7:3). ^{1}H NMR ($CDCl_3$) δ 0.7 (d, *J* = 6.5 Hz, 6H, (CH_3)$_2$CH); 0.7 (d, *J* = 6.5 Hz, 6H, (CH_3)$_2$CH); 1.31 (s, 9H, *t*-Bu); 1.33 (s, 9H, *t*-Bu); 1.8 (m, 2H, C*H*(CH_3)$_2$); 3.8 (br, 3H, BocNH-C*H*(*i*Pr)-CO and NH-C*H*(H)-CO); 4.3 (dd, *J* = 5.2, 17.5 Hz, 1H, NH-CH(*H*)-CO); 5.1 (d, *J* = 8.8 Hz, 1H, BocN*H*-CH(*i*Pr)-CO); 5.2 (d, *J* = 8.8 Hz, 1H, BocN*H*-CH(*i*Pr)); 5.6 (d, *J* = 8.2 Hz, 1H, C*H*(PhS)-NH); 6.8 (br, 1H, N*H* CH_2-CO); 7.1–7.3 (m, 6H, ar and N*H*-CH(SPh)). MS (NOBA) *m/z* 595 MH$^+$. Anal. $C_{29}H_{46}N_4O_7S$ (C, H, N, O).

4.1.16. 1,3-Bis[N-[N-[(tert-butyloxy)carbonyl]valinyl]amino]-1,3-diphenylsulfenyl-propanone **9**

After purification using hexane/EtOAc (9:1) as eluent, compound **9** was obtained from reaction procedure of **8j** as a white solid (0.36 g, 25%). Rf = 0.51 (hexane:EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 0.9 (d, *J* = 6.9 Hz, 12H, (CH_3)$_2$CH); 1.2 (s, 18H, *t*-Bu); 1.9 (m, 2H, C*H*(CH_3)$_2$); 4.0 (br, 2H, BocNH-C*H*(*i*Pr)-CO); 5.1 (d, *J* = 7.9 Hz, 2H, BocN*H*-CH(iPr)); 6.2 (d, *J* = 8.5 Hz, 2H, NH-C*H*(PhS)), 6.8 (d, *J* = 8.5 Hz, 2H, CH(PhS)-N*H*); 7.1–7.2 (m, 10H, ar). MS (NOBA) *m/z* 703 MH$^+$. Anal. $C_{35}H_{50}N_4O_7S_2$ (C, H, N, O).

4.1.17. General procedure C for the preparation of compounds **1a–1j** *and* **2a**: *reduction of phenylthio-ketone*

A solution of phenylthio-ketone (1.0 eq.) in ethanol was treated with $NaBH_4$ (1.5 eq.) from 0 °C to room temperature until disappearance of starting material on TLC. After removal of solvent, the residue was taken off in CH_2Cl_2 and washed with 5% aqueous citric acid, then saturated brine, dried over Na_2SO_4 and evaporated in

vacuo. The residue was purified by preparative layer chromatography using the appropriate eluent.

4.1.17.1. 1,3-di-[N-benzyl-N-[(tert-butyloxy)carbonyl]-1-phenylsulfenyl-2-hydroxypropane **1a**

Compound **1a** was prepared from **8a** (0.1 g, 0.13 mmol) according to general procedure C and obtained quantitatively as an oil. Rf = 0.51 (hexane/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 1.3 (s, 9H, *t*-Bu); 1.4 (s, 9H, *t*-Bu); 3.3 (br, 2H, N-CH_2-CH(OH)); 3.6 (m, 1H, C*H*-OH); 4.3 (brs, 4H, PhCH_2-N); 5.2 (br, 1H, C*H*-SPh); 7.2 (m, 15H, ar). MS (NOBA) *m/z* 579 MH^+. Anal. $C_{33}H_{42}N_2O_5S$ (C, H, N, O).

4.1.17.2. 1,3-di-[N-benzyl-N-[(ethyloxy)carbonyl]-1-phenylsulfenyl-2-hydroxypropane **1b**

Compound **1b** was prepared from **8b** (0.8 g, 0.15 mmol) according to general procedure C and obtained quantitatively as an oil. Rf = 0.30 (hexane/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 3H, CH_3-CH_2); 1.1 (t, 3H, CH_3-CH_2); 3.6 (br, 2H, CH_2-CH(OH)); 3.8 (m, 1H, C*H*-OH); 4.0 (br, 4H, PhCH_2-N); 4.3 (q, 2H, CH_3-CH_2-O); 4.5 (q, 2H, CH_3-CH_2-O); 5.5 (br, 1H, C*H*-SPh); 7.1 (m, 15H, ar). MS (NOBA) *m/z* 523 MH^+. Anal. $C_{27}H_{34}N_2O_2S$ (C, H, N, O).

4.1.17.3. 1,3-di-[N-benzyl-N-[(isobutyloxy)carbonyl]-1-phenylsulfenyl-2-hydroxypropane **1c**

Compound **1c** was prepared from **8c** (0.1 g, 0.13 mmol) according to general procedure C and obtained quantitatively as an oil. Rf = 0.36 (hexane/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 0.6 (d, 6H, $(CH_3)_2$CH); 0.8 (d, 6H, $(CH_3)_2$CH); 1.8 (m, 2H C*H*$(CH_3)_2$); 3.3 (br, 2H, N-CH_2-CH(OH)); 3.8 (br, 4H, PhCH_2-N); 4.0 (m, 1H, C*H*-OH); 4.3–4.5 (br, 4H, *i*Pr-CH_2-O); 5.4 (br, 1H, C*H*-SPh); 7.0–7.2 (m, 15H, ar). MS (NOBA) *m/z* 579 MH^+. Anal. $C_{33}H_{42}N_2O_5S$ (C, H, N, O).

4.1.17.4. 1,3-di-[N-benzyl-N-[(tetrafuran-3-oxy)carbonyl]-1-phenylsulfenyl-2-hydroxypropane **1d**

Compound **1d** was prepared from **8d** (0.1 g, 0.16 mmol) according to general procedure C and obtained as an oil (0.095 g, 95%). Rf = 0.10 (hexane/EtOAc 5:5). Signals in ^{1}H NMR ($CDCl_3$) could not be assigned because of their breadth. MS (NOBA) *m/z* 607 MH^+. Anal. $C_{33}H_{38}N_2O_7S$ (C, H, N, O).

4.1.17.5. 1,3-di-[N-benzyl-N-[(benzyloxy)carbonyl]-1-phenylsulfenyl-2-hydroxypropane **1e**

Compound **1e** was prepared from **8e** (0.05 g, 0.08 mmol) according to general procedure C and obtained quantitative as an oil. Rf = 0.10 (hexane/EtOAc 5:5). ^{1}H NMR ($CDCl_3$) δ 3.0–3.1 (br, 2H, N-CH_2-CH(OH)); 4.0 (m, 1H, C*H*-OH); 4.3 (brs, 4H, PhCH_2-N); 5.1 (s, 4H, PhCH_2-O); 5.4 (br, 1H, CH-SPh); 6.9–7.2 (m, 25H). MS (FAB) *m/z* 647 MH^+. Anal. $C_{39}H_{38}N_2O_5S$ (C, H, N, O).

4.1.17.6. 1,3-di-[N-benzyl-N-[[(N-methyl-N-phenyl)amino]carbonyl]amino]-1-phenylsulfenyl-2-hydroxypropane **1f**

Compound **1f** was prepared from **8f** (0.1 g, 0.12 mmol) according to general procedure C and obtained as an oil (0.098 g, 98%). Rf = 0.26 (hexane/EtOAc 6:4). ^{1}H NMR ($CDCl_3$) δ 2.8 (s, 3H, CH_3N); 3.0 (s, 3H, CH_3N); 3.1 (dd, *J* = 8.7, 11.4 Hz, 1H, N-C*H*(H)-CH(OH)); 3.4 (dd, *J* = 2.9, 11.4 Hz, 1H, N-C*H*(H)-CH(OH)); 3.8 (m, 1H, C*H*-OH); 4.0 (AB, quartet, 4H, PhCH_2-N), 4.5 (br, 1H, CH-O*H*); 4.8 (d, *J* = 8.3 Hz, 1H, C*H*-SPh); 6.8–7.2 (m, 25H, ar). MS (NOBA) *m/z* 645 MH^+. Anal. $C_{39}H_{40}N_4O_3S$ (C, H, N, O).

4.1.17.7. 1,3-Bis[N-benzyl-N-[N-[(tert-butyloxy)carbonyl]valinyl]amino]-1-phenylsulfenyl-2-hydroxypropane **1g**

Compound **1g** was prepared from **8g** (0.40 g, 0.51 mmol) according to general procedure C and obtained as an oil (395 mg, 98%). Rf = 0.18 (hexane/EtOAc 8:2). Signals in ^{1}H NMR ($CDCl_3$) could not be assigned because of their breadth. MS (NOBA) *m/z* 777 MH^+. Anal. $C_{43}H_{62}N_4O_7S$ (C, H, N, O).

4.1.17.8. 1,3-di-[N-(4-methoxybenzyl)-N-[(isobutyloxy)carbonyl)]-1-phenylsulfenyl-2-hydroxypropane **1h**

Compound **1h** was prepared from **8h** (0.08 g, 0.13 mmol) according to general procedure C and obtained quantitatively as an oil. Rf = 0.19 (hexane/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 0.6 (d, *J* = 13.1 Hz, 6H, $(CH_3)_2$CH); 0.8 (d, *J* = 13.1 Hz, 6H, $(CH_3)_2$CH); 1.5 (m, 1H, C*H*$(CH_3)_2$); 1.7 (m, 1H, C*H*$(CH_3)_2$); 3.5 (s, 6H, OCH_3); 3.7 (br, 2H, N-CH_2-CH(OH)); 4.1 (m, 1H, C*H*-OH); 4.3 (brs, 4H, *p*(MeO)PhCH_2-N); 4.5 (br, 2H, *i*Pr-CH_2-O); 4.4 (br, 2H, *i*Pr-CH_2-O); 5.2 (br, 1H, C*H*-SPh); 6.8 (m, *J* = 11.6 Hz, 4H, ar), 7.0–7.2 (m, 5H, ar); 7.3 (m, *J* = 11.6 Hz, 4H, ar). MS (NOBA) *m/z* 639 MH^+. Anal. $C_{35}H_{46}N_2O_7S$ (C, H, N, O).

4.1.17.9. 1,3-di-[N-(4-methoxybenzyl)-N-[[(N-methyl-N-phenyl)amino]carbonyl)amino]-1-phenylsulfenyl-2-hydroxypropane **1i**

Compound **1i** was prepared from **8i** (0.05 g, 0.07 mmol) according to general procedure C and obtained quantitative as an oil. Rf = 0.20 (hexane/EtOAc 8:2). ^{1}H NMR ($CDCl_3$) δ 2.9 (s, 3H, CH_3N); 3.1 (s, 3H, CH_3N); 3.2 (dd, *J* = 7.1, 12.9 Hz, 1H, N-C*H*(H)-CH(OH)); 3.4 (dd, *J* = 3.1, 12.9 Hz, 1H, N-CH(*H*)-

CH(OH)); 3.7 (s, 6H, CH_3O); 3.9 (m, 1H, C*H*-OH); 4.1 (AB, 4H, *p*(MeO)PhCH_2-N); 4.9 (br, 1H, CH-O*H*); 5.2 (d, J = 8.1 Hz, 1H, C*H*-SPh); 6.8 (m, J = 11.6 Hz, 4H, ar); 7.0–7.2 (m, 15H, ar); 7.3 (m, J = 11.6 Hz, 4H, ar). MS (NOBA) *m/z* 705 MH^+. Anal. $C_{41}H_{44}N_4O_5S$ (C, H, N, O).

4.1.17.10. 1,3-Bis[N-[N-[(tert-butyloxy)carbonyl]valinyl]amino]-1-phenylsulfenyl-2-hydroxypropane **1j**

Compound **1j** was obtained from **8j** (0.1 g, 0.17 mmol) following general procedure C. Purification by PLC using hexane/EtOAc (5:5) as solvent afforded the title compound as a white solid (0.09 g, 97%). Rf = 0.39 (hexane/EtOAc 5:5). Signals in ^1H NMR ($CDCl_3$) could not be assigned because of their breadth. MS (NOBA) *m/z* 597 MH^+. Anal. $C_{29}H_{48}N_4O_7S$ (C, H, N, O).

4.1.18. 1,3-Bis[N-benzyl-N-(valinyl)amino]-1-phenylsulfenyl-2-hydroxypropane **1k**

A solution of **1g** (0.1 g, 0.13 mmol) in TFA (2 mL) was stirred at room temperature until the disappearance of the starting material on TLC (2 h). The reaction mixture was concentrated under reduced pressure and the residue was purified by PLC using CH_2Cl_2/MeOH (8:2) as solvent to give **1k** (0.06 g, 83%). Rf = 0.17 (CH_2Cl_2/MeOH 9:1). Signals in ^1H NMR ($CDCl_3$) could not be assigned because of their breadth. MS (NOBA) *m/z* 577 MH^+. Anal. $C_{33}H_{44}N_4O_3S$ (C, H, N, O).

4.1.19. 1,3-Bis[N-benzyl-N-[N-[(2-pyridinyl)carbonyl]valinyl]amino]-1-phenylsulfenyl-2-hydroxypropane **1l**

A solution of **1g** (0.08 g, 0.09 mmol) in TFA (2 mL) was stirred at room temperature until disappearance of starting material on TLC (2 h). After evaporation of solvent, the crude residue was taken off in dry CH_2Cl_2 (5 mL). Nicotinic acid (0.03 g, 0.24 mmol), BOP reagent (0.1 g, 0.24 mmol) and Et_3N (100 µL, 0.72 mmol) were added to the above solution, and the reaction mixture was stirred at room temperature for 3 h, then concentrated in vacuo. The residue was taken off in EtOAc (10 mL) and washed with saturated brine (5 mL), dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by PLC using CH_2Cl_2/MeOH (9:1) as solvent to give **1l** (0.04 g, 60%). Rf = 0.52 (CH_2Cl_2/MeOH 9:1). Signals in ^1H NMR ($CDCl_3$) could not be assigned because of their breadth. MS (NOBA) *m/z* 787 MH^+. Anal. $C_{45}H_{50}N_6O_5S$ (C, H, N, O).

4.1.20. 1,3-Bis[N-benzyl-N-[N-(quinaldyl)valinyl]amino]-1-phenylsulfenyl-2-hydroxypropane **1m**

Compound **1m** was prepared from quinaldic acid (0.04 g, 0.24 mmol) as described for **1l** and obtained as an oil (0.06 g, 75%). Rf = 0.29 (EtOAc/hexane 7:3). Signals in ^1H NMR ($CDCl_3$) could not be assigned because of their breadth. MS (NOBA) *m/z* 839 MH^+. Anal. $C_{49}H_{54}N_6O_5S$ (C, H, N, O).

4.1.21. 1,3-Bis[N-[N-[(tert-butyloxy)carbonyl]valinyl]amino]-1,3-diphenylsulfenyl-2-hydroxypropane **2a**

Compound **2a** was obtained from **9** (150 mg, 0.22 mmol) following general procedure C. Purification by PLC using hexane/EtOAc (8:3) as solvent afforded the title compound as a white solid (0.15 g, 96%). Rf = 0.39 (EtOAc:hexane 7:3). ^1H NMR ($CDCl_3$) δ 0.6 (d, J = 6.7 Hz, 6H, $(CH_3)_2CH$); 0.8 (d, J = 6.7 Hz, 6H, $(CH_3)_2CH$); 1.2 (s, 9H, *t*-Bu); 1.3 (s, 9H, *t*-Bu); 1.8 (m, 2H, C*H*$(CH_3)_2$); 3.6 (br, 1H, CH-O*H*); 3.8 (t, J = 6.7 Hz, 1H, BocNH-C*H*(*i*Pr)-CO); 4.0 (d, J = 6.7 Hz, 1H, BocNH-C*H*(*i*Pr)-CO); 4.3 (m, 1H, C*H*-OH); 4.9 (d, J = 8.3 Hz, 1H, BocN*H*-CH(iPr)); 5.0 (d, J = 8.3 Hz, 1H, BocN*H*-CH(iPr)); 5.1 (dd, J = 5.5, 9.3 Hz, 1H, C*H*(PhS)-NH); 5.2 (dd, J = 3.1, 8.5 Hz, 1H, C*H*(PhS)-NH); 7.1–7.2 (m, 10H, ar); 7.9 (d, J = 9.3 Hz, 1H, N*H*-CH(PhS)); 8.1 (d, J = 9.3 Hz, 1H, N*H*-CH(PhS)). MS (NOBA) *m/z* 705 MH^+. Anal. $C_{35}H_{52}N_4O_7S_2$ (C, H, N, O).

4.1.22. 1,3-Bis[N-[N-[[(N-methyl, N-phenyl)]amino)]carbonyl]valinyl]amino]-1,3-diphenylsulfenyl-2-hydroxypropane **2b**

A solution of **2a** (0.10 g, 0.14 mmol) in TFA (2 mL) was stirred at room temperature until there was no remaining starting material on TLC. After evaporation to dryness, the crude residue was taken off in CH_2Cl_2 (5 mL) and treated with N-methyl-N-phenyl carbamoyl chloride (0.05 g, 0.30 mmol) for 1 h in the presence of Et_3N (97 µL, 0.7mmol). The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 5% aqueous citric acid (5 mL), then saturated brine (5 mL), dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by PLC using EtOAc/hexane 6:4 as solvent to give **2b** (0.09 g, 82%). Rf = 0.48 (EtOAc/hexane 6:4). ^1H NMR ($CDCl_3$) δ 0.6 (d, J = 6.9 Hz, 6H, $(CH_3)_2CH$); 0.7 (d, J = 6.9 Hz, 6H, $(CH_3)_2CH$); 1.7 (m, 2H, C*H*$(CH_3)_2$); 3.2 (s, 6H, CH_3N); 3.9 (br, 1H, CH-O*H*); 4.1 (t, J = 8.5 Hz, 2H, BocNH-C*H*(*i*Pr)-CO); 4.2 (m, 1H, C*H*-OH); 4.7 (d, J = 8.3 Hz, 1H, BocN*H*-CH(iPr); 4.9 (d, J = 8.3 Hz, 1H, CH(*i*Pr)-N*H*Boc); 5.6 (dd, J = 5.7, 9.5 Hz, 1H, C*H*(PhS)-NH); 5.7 (dd, J = 3.3, 9.5 Hz, 1H, C*H*(PhS)-NH); 7.1–7.2 (m, 20H, ar); 8.2 (d, J = 9.5 Hz, 1H, N*H*-CH(PhS)); 8.6 (d, J = 9.5 Hz, 1H, N*H*-CH(PhS)). MS (NOBA) *m/z* 771 MH^+. Anal. $C_{41}H_{50}N_6O_5S_2$ (C, H, N, O).

4.1.23. 1,3-Bis[N-[N-[(benzyloxy)carbonyl]valinyl]amino]-1,3-diphenylsulfenyl-2-hydroxypropane **2c**

A solution of **2a** (0.05 g, 0.07 mmol) in TFA (2 mL) was stirred at room temperature until the disappearance

of starting material on TLC (2 h). After evaporation of solvent, the crude residue was taken of in CH_2Cl_2 (5 mL) and treated with benzylchloroformate (21 μL, 0.15 mmol) for 1 h in the presence of Et_3N (30 μL, 0.21 mmol). The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with 5% aqueous citric acid (5 mL), then saturated brine (5 mL), dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by PLC using toluene/EtOAc 6:4 as solvent to give **2c** (52%, 0.03 g). Rf = 0.38 (toluene/EtOAc 6:4). ^{1}H NMR ($CDCl_3$) δ 0.6 (d, J = 6.8 Hz, 6H, $(CH_3)_2CH$); 0.7 (d, J = 6.8 Hz, 6H, $(CH_3)_2CH$); 1.8 (m, 2H, $CH(CH_3)_2$); 3.9 (br, 1H, CH-O*H*); 4.1 (t, J = 7.6 Hz, 2H, BocNH-C*H*(*i*Pr)-CO); 4.2 (m, 1H, C*H*-OH); 4.2 (AB, 4H, PhCH_2-O); 5.3 (d, J = 7.2 Hz, 2H, BocN*H*-CH(*i*Pr); 5.6 (dd, J = 5.7, 9.5 Hz, 1H, C*H*(PhS)-NH); 5.7 (dd, J = 3.3, 9.5 Hz, 1H, C*H*(PhS)-NH); 7.1–7.3 (m, 20H, ar); 7.6 (d, J = 9.5 Hz, 1H, N*H*-CH(PhS)); 7.8 (d, J = 9.5 Hz, 1H, N*H*-CH(PhS)). MS (NOBA) *m/z* 773 MH^+. Anal. $C_{41}H_{48}N_4O_7S_2$ (C, H, N, O).

4.2. Anti-HIV evaluation assay

The CEM cell line and the T Leukaemia virus type one (HTLV-1) CD4-positive T cell line were cultured in RPMI/10% FCS and re-fed twice a week.

The laboratory-adapted strain HIV^{LAV} clade B stock was prepared from the supernatant of an infected CEM cell line and aliquots were kept frozen at –80 °C until use [16].

Anti-HIV activity was monitored by the efficiency of drug compounds to inhibit syncytia formation after HIV infection of MT_4 as already described [17, 18]. Briefly, 3 × 10^5 MT_4 cells were first pre-incubated with 100 μL of various concentrations of drug compounds dissolved in phosphate buffered saline solution for 1 h at 37 °C. Then 100 μL of an appropriate virus dilution was added to the mixture and further incubated at 37 °C for 1 h. After three washes, cells were resuspended in culture medium in the presence or not of drug compounds. Cultures were then grown for 7 d at 37 °C, under 5% CO_2 atmosphere and re-fed at day 3 post-infection with culture medium supplemented or not with drug compounds. Each culture well was done in duplicate. The appearance of syncytia was followed each day with an inverted optical microscope. Typically, the virus dilution used in the assay (multiplicity of infection of 0.1 $TCID_{50}$/CELL) allowed syncytia formation at day 5 post infection. The inhibitory concentration of drug compounds was expressed as the concentration that caused 50% inhibition of syncytia formation (EC_{50}) without direct toxicity to cells. Cytotoxicity concentration (CC_{50}) of drug compounds was monitored on growth of non-infected cells by trypan blue exclusion assay and corresponded to the concentration required to cause 50% cell death.

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