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HIV Protease Inhibitor HOE/BAY 793, Structure–Activity Relationships in a Series of C_2-Symmetric Diols

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Abstract—A detailed structure–activity relationship of C_2-symmetric diol inhibitors of HIV-1 protease leads to inhibitor **6** (HOE/BAY 793) which is outstanding in the inhibition of the enzyme and in the inhibition of viral replication in HIV infected cell culture (IC_{50}: 0.3 nM; EC_{50}: 3 nM). There are well defined steric requirements for the design of the side chains P1–P3 of the inhibitors. In addition, all three side chains need to be lipophilic. While the enzyme tolerates hydrophilic substituents in some cases, drastic reductions in anti-HIV activity are observed in cell culture, most likely due to insufficient cell penetration.

Introduction

The rapid and global spread of the acquired immune deficiency syndrome (AIDS) pandemic has initiated intensive efforts to treat this aggressive disease. The etiological cause of AIDS is the human immunodeficiency virus (HIV), a retrovirus that belongs to the group of lentiviruses. By analogy to the processing of proteins of other retroviruses, some HIV proteins are first translated into long precursor proteins, which later have to be cleaved to the active proteins by a virus encoded protease. This specific processing of the HIV gag and gag pol polyprotein gene products by HIV protease is essential for viral maturation. Therefore, inhibition of HIV protease is considered a promising target for antiviral chemotherapy.[1]

The HIV protease belongs to the aspartic protease family and therefore the design of inhibitors was influenced by the knowledge obtained in the study of renin and other related enzymes. The most potent inhibitors reported so far are pseudopeptidic compounds containing transition-state inserts instead of the cleavage sites in the natural or unnatural peptide substrates.[2] Recently several non-peptide inhibitors of the HIV-protease have been reported.[3]

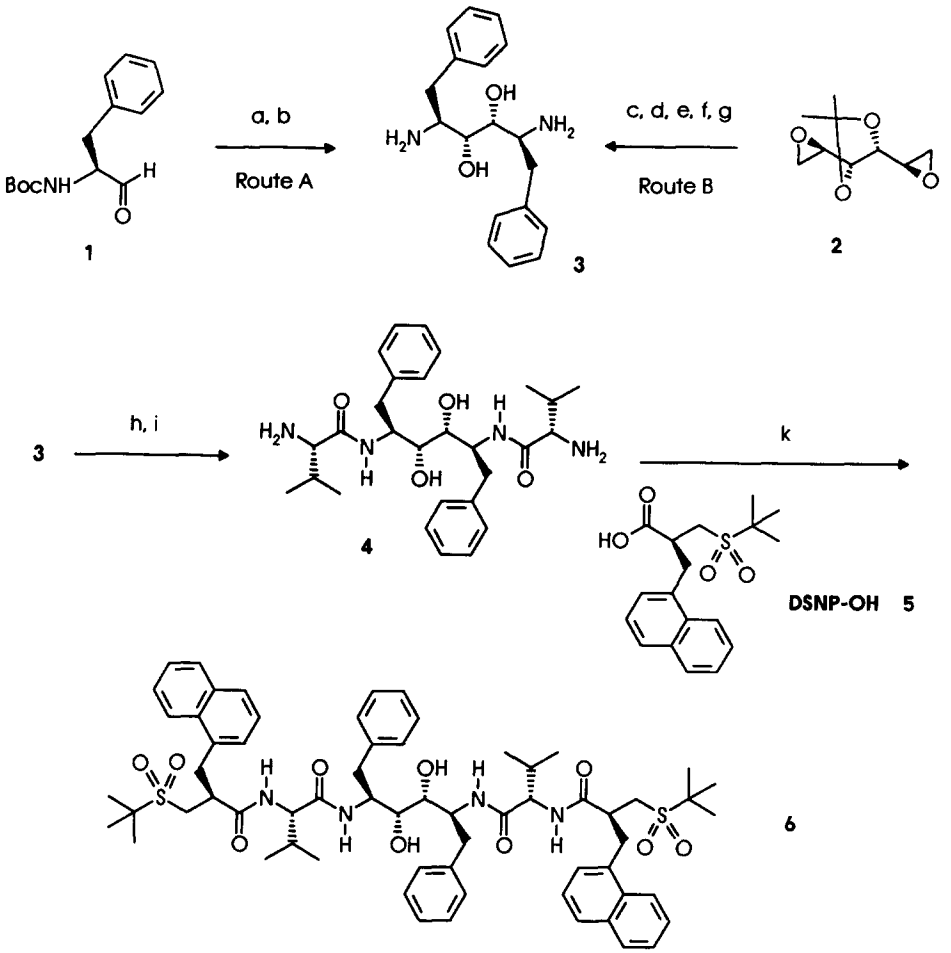
While the active center of typical aspartic proteases is located on a single protein chain, the HIV protease is enzymatically active only upon association to a C_2 symmetric dimer.[4] This prompted us[5] to synthesize C_2 symmetric inhibitors. In previous reports we described a series of inhibitors with a central phosphinic acid or a hydroxymethylphosphinic acid unit in a C_2 symmetric peptidic environment.[6]

In this article we concentrate on C_2-symmetric compounds with a vicinal diol group as a central unit. The same approach has been concurrently followed by Kempf *et al.*[7] In this paper we present detailed structure–activity relationships (SARs) both for enzyme inhibition and for *in vitro* activity. Interestingly the two SARs are not at all parallel: while good enzyme inhibition is an absolute requirement, it does not necessarily result in good antiviral *in vitro* activity. The systematic variation of substituents of P1, P2 and P3 led to the inhibitor HOE/BAY 793 (compound **6**) with outstanding potency, especially in HIV infected cell culture.

Chemistry

The synthesis of the central building blocks and inhibitors is outlined in Scheme 1 which shows the synthesis of compound **6** as a representative example. Methods similar to those shown in Scheme 1 have also been reported by several groups.[7–9] The synthesis of the symmetric diamino diol moiety **3** was achieved in two ways. Route A starts from the N-protected phenylalaninal **1** which is converted into **3** by reductive pinacol coupling. When samarium(II) iodide is used as reducing agent the three isomers *SRRS*, *SRSS*, *SSSS* are obtained in the ratio 2.3:1:1.4. For the stereospecific synthesis of the pure *SRRS* isomer $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ is used, which has been shown[8] to yield the isomers in a 6:1.5:1 ratio. Kammermeier *et al.*[8b] describe a suitable synthesis for the large scale preparation of **6**. Route B starts from the D-mannitol based bisepoxide **2** which is reacted with $(C_6H_5)_2CuLi$ and the resulting free hydroxyl groups are subsequently converted into amino groups. This chiral pool derived route has the advantage of a correctly preformed stereochemistry.

The central building blocks of the inhibitors **12**, **13** and **17** were obtained by route A, those of **18–22** by route B.



Scheme 1. Representative synthesis of inhibitors. (a) SmI_2 or $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$; (b) HCl/MeOH or H_2/Pd/C; (c) $(C_6H_5)_2CuLi$; (d) *p*-$O_2NC_6H_4SO_2Cl$; (e) NaN_3/DMF; (f) H_2/Pd; (g) HCl/MeOH; (h) 1. Z-Val-OH, TOTU, (i) H_2/Pd/C; (k) DCC, HOOBt.

Active ester coupling of **4** and the terminal unit **5**[10] with DCC and HOOBT yielded inhibitor **6**. The synthesis of inhibitors **14** and **15** (Scheme 2) is achieved by conversion of the N-Boc protected **3** into the cyclic sulfite **7** and subsequent ring opening by azide. Compound **15** is obtained from **14** by catalytic hydrogenation.

Compounds **10**, **11**, **16** and **23–51** were obtained in analogy to **6** by application of various suitable protecting groups.

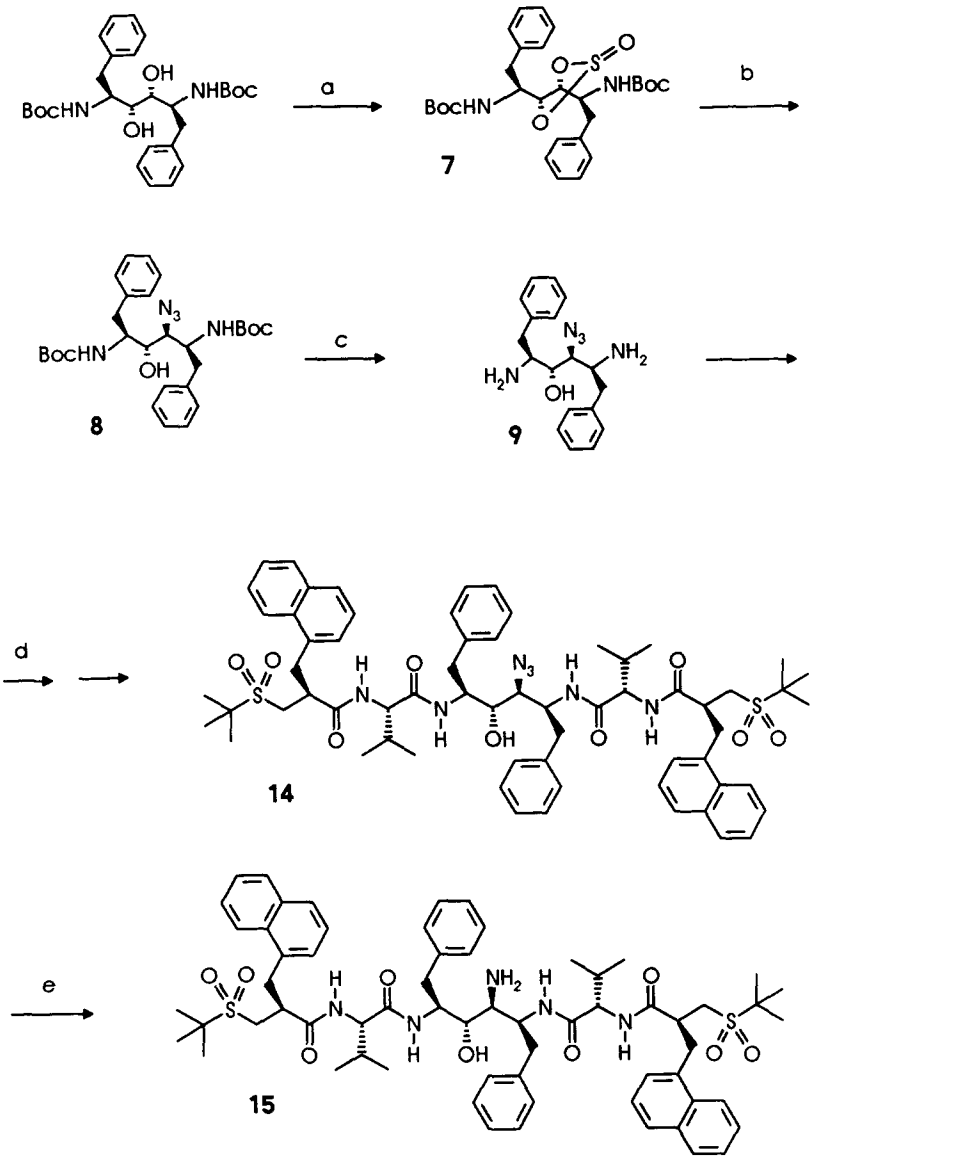
Results and Discussion

Tables 1–5 give a representative selection of the inhibitors that were evaluated for their ability to inhibit HIV-protease and in the HIV infected cell culture. Values for inhibition of the enzyme (IC_{50} values) were determined by a peptide hydrolysis assay that employs the synthetic heptapeptide substrate H_2N-Ser-Phe-Asn-Phe-Opr-Gln-Ile-OH, where Opr stands for 5-oxaproline, and quantitation via HPLC.[11] The EC_{50} values represent the ability of the compound to inhibit the replication of the virus by 50% based on the cytopathic effect of HIV-1[12a] or on reduction of viral antigen in the supernatant of infected human T-cells.[12b]

Transition state mimic

Tables 1 and 2 demonstrate the influence of different groups in the center of this type of inhibitor. As expected, hydroxyl groups strongly enhance the inhibition of the enzyme. Compound **11** containing the bis-hydroxyl moiety shows fifty-fold better activity compared to the hydrocarbon-centered inhibitor **10**. This reflects the binding contribution of the diol transition state mimic. Nevertheless some activity is achieved even without hydroxyl groups, provided that other parts of the inhibitor (in this case P2 and P3) provide enough binding energy. Although **11** is a very good inhibitor of the enzyme, it is only slightly active in the cell culture assay. The main reason seems to be the missing lipophilic substituent in P1, which is needed for cell penetration.

Contrary to our expectations the configuration of the hydroxyl groups has not much impact on the interaction of the inhibitor with HIV protease as can be seen from Table 2. Compound **6** (*RR*-configuration) for example is only somewhat more active than its isomers **12** and **13** (*SS*- and *RS*-configurations). However, a strong influence of the hydroxyl group configuration on the HIV inhibitory activity in cell culture is observed. Compound **6** is about thirty times more active than the unsymmetrical isomer **13**. At the moment we do not have an explanation for this result.



Scheme 2. (a) $SOCl_2$; (b) NaN_3, DMF; (c) 1. HCl/dioxane; (d) 1. Boc-Val-OH, TOTU, Et_3N; 2. HCl/dioxane; 3. **5**, TOTU, Et_3N; (e). H_2/Pd/C.

Interestingly one hydroxyl group is sufficient for both enzyme and cell culture inhibition, as found in **16**. Substitution of one hydroxyl group by an amino group as in **15** does not weaken the enzyme inhibitory activity as compared with **13**, but leads to a nearly complete loss of activity in the cell culture assay. This could be due to the basic nature of the amino group impairing cell penetration. Substitution by the neutral, but larger azide group in **14** leads to a loss of activity by a factor of 30 already at the enzyme level.

P1-position

Table 3 summarizes data on the influence of side chains filling the P1 position. Medium sized lipophilic side groups (e.g. in **6** and **22**) are favourable for enzyme inhibition as well as for activity in cell culture. The best result is obtained with the benzyl group in **6**. Elongation of the alkyl side chain by one methylene group in **17** (or possibly **21**) dramatically decreases activity compared to **6**. Enlargement of its volume as in **20** also leads to a decrease of activity. While the introduction of hydrophilic substituents in P_1 as the tyrosine side chain in inhibitor **18** still yields fairly good enzyme inhibition, the activity in the cell assay is decreased by a factor of a hundred, probably because of diminished cell penetration. The fact that P1 side chains are more important for activity in cell culture than for simple enzyme inhibition is demonstrated by compound **11** lacking the P1 side chain, which is highly active on the enzyme and almost inactive in cell culture.

P2-position

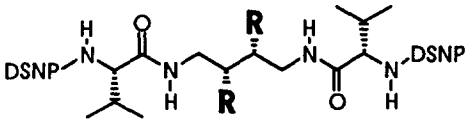
The best activity in enzyme and cell assay is shown by compounds with small alkyl side chains in P2 (see Table 4) which are branched in the β-position, e.g. **6**, **23**, **24**, **25** or **26**. However, branching in the β-position is not an absolute requirement, the propyl substituent in

27 also leads to excellent inhibition. Again, the introduction of hydrophilic substituents as in **30** and **31** is compatible with good activity in the enzyme assay, but not with *in vitro* inhibition. Interestingly the enzyme does not tolerate the amide side chain in **29** nor the imidazole side chain in **32**. The enzyme also reacts very sensitively to changes in the backbone of the inhibitor: elongation by a methylene group as in **28** or even more dramatically the fixing of the backbone conformation by a proline residue as in **33** leads to a loss in activity.

P3-position

Table 5 shows data on some representative inhibitors that carry optimized residues in the positions P1 (benzyl) and P2 (isopropyl), varying in the P3-position. Compound **40** is almost identical with the inhibitor A-77003, selected for clinical development by Abbott,[7a] except for the *RS*-geometry at the hydroxyl groups.

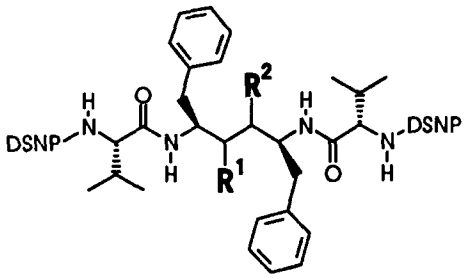
Table 1. Influence of OH-groups in the central building block on HIV-1 protease inhibition and antiviral activity; DSNP: see Scheme 1



No.	R	IC_{50}[nM][a]	EC_{50}[nM][b]
10	H	100	3,000
11	OH	2.2	10,000

(a) Concentration of test compound at which 50% inhibition of the activity of HIV-1 protease was observed.[11]; (b) concentration which inhibited 50% of the cytopathic effect of HIV-1 or the production of p24 antigen in lymphocytes[12].

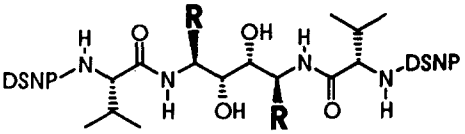
Table 2. Influence of configuration and functionality in the central building block on HIV-1 protease inhibition and antiviral activity. DSNP: see Scheme 1

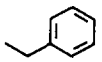
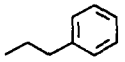
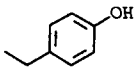
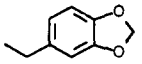
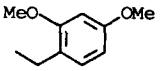
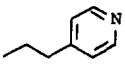


No.	R1 (config.)	R2 (config.)	IC_{50} [nM][a]	EC_{50} [nM][b]
6	OH (R)	OH (R)	0.3	3
12	OH (S)	OH (S)	0.3	20
13	OH (R)	OH(S)	0.5	217
14	OH (R)	N_3 (S)	60	10^5
15	OH (R)	NH_2 (S)	2.1	$> 10^5$
16[c]	OH (S)	H	0.3	17

(a,b) See Table 1; (c) geometry *S* corresponds to *R* in the diol case due to CIP-rules.

Table 3. Influence of variations in P1 on HIV-1 protease inhibition and antiviral activity. DSNP: see Scheme 1



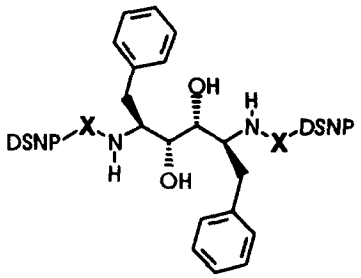
No.	R-	IC_{50}[nM][a]	EC_{50}[nM][b]
6		0.3	3
11	-H	2.2	10000
17		360	n.d.
18		2.9	300
19		0.4	20
20		18	175
21		140	n.d.
22		1.0	7.5

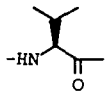
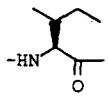
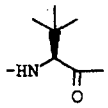
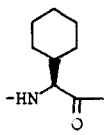
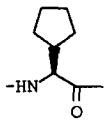
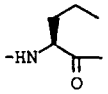
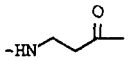
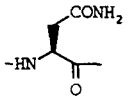
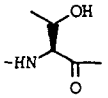
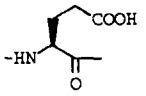
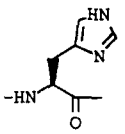
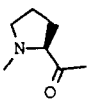
(a,b) see Table 1

Regarding enzyme inhibition Table 5 further shows that the use of structurally very diverse terminal groups like positively or negatively charged residues, e.g. **34, 35** or **36**, polyhydroxy or neutral groups, e.g. **42** or **38** result in highly active HIV protease inhibitors. However, regarding antiviral efficacy, only two of the tested residues, **41** and **43**, lead to really good inhibitors in the cell culture assay.

The terminus of **43**[10] served as a lead structure for more detailed investigations, that are summarized in Table 6. With the sulfonyl group held in place, enzyme inhibition can be obtained with quite different structures. Comparison of **43** and **47** demonstrates that a side chain in P3 is not a requirement for high activity. Only compound **49** obviously carries a terminal chain which is too long for the P3 pocket of the enzyme. For virus inhibition we get the same overall picture as for P1. The lipophilic side chain is useful for enzyme inhibition, but mandatory for viral suppression in the cell culture assay. Every increase of the hydrophilic character as in the pyridyl compound **45**, the *N*-oxide **46** or even the methoxy derivative **44** and the hydroxyethyl derivative **48** has to be paid for with loss of virustatic activity. In a similar way substitution of the *tert*-butylsulfonyl group by the more polar sulfonamide containing moiety in **51** is unfavorable for activity in cell culture. On the other hand enhancement of lipophilic properties by substitution of the phenyl residue in **43** by a naphthyl residue leads to the extremely potent inhibitor **6** (HOE/BAY 793).

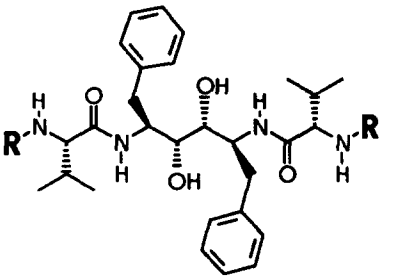
Table 4. Influence of variations in P2 on inhibitory activity. DSNP: see Scheme 1

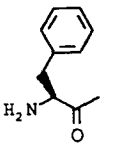
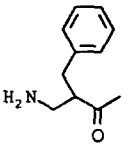
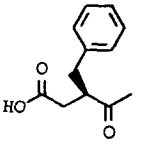
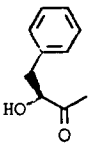
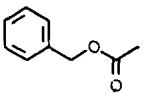
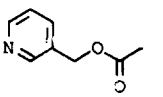
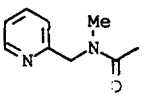
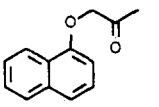
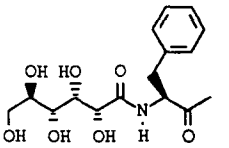
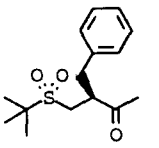


No.	X-	IC_{50} (nM)[a]	EC_{50} (nM)[b]
6		0.3	3
23		0.3	10
24		0.5	15
25		1.7	60
26		0.3	7
27		0.4	4
28		50	10,000
29		100	10,000
30		0.3	2,000
31		0.75	> 100.000
32		340	> 10,000
33		20,000	n.d.

(a,b) see Table 1

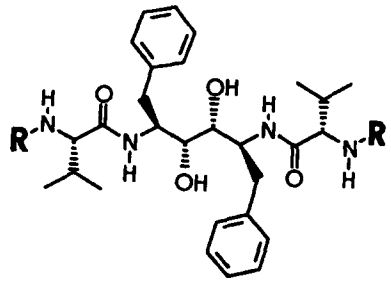
Table 5. Influence of variations in terminus on inhibitory activity

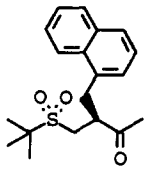
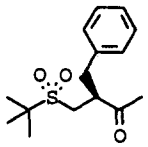
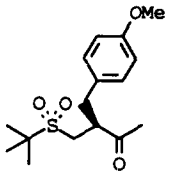
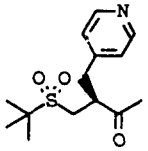
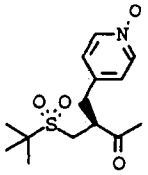
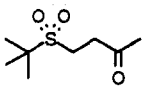
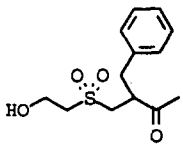
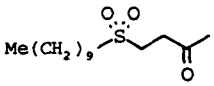
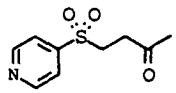
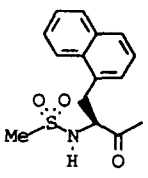


No.	R-	IC_{50} (nM)[a]	EC_{50} (nM)[b]
34		0.85	> 25000
35		25	> 25000
36		1.4	>25000
37		22	100
38		2	100
39		1.3	253
40		15	958
41		38	41
42		0.9	> 25000
43		0.3	23

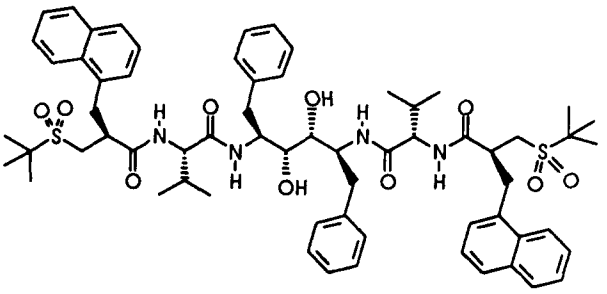
(a,b) see Table 1

Table 6. Influence of variations in terminus on inhibitory avtivity



No.	R-	IC_{90}(nM)[a]	EC_{90}(nM)[b]
6		0.3	3
43		3.2	25
44		0.34	80-400
45		0,8	25,000
46		7	50000
47		4	1,000
48		4.8	6,000
49		> 10000	25000
50		4	1200
51		0.8	500

(a,b) see Table 1



6 (HOE/BAY 793)
Figure 1.

Conclusions

The detailed structure–activity relationship presented here does give a clear picture of the requirements for the P1–P3 sidechains in combination with the central C_2-symmetric building block. All three side chains need to be lipophilic. While the enzyme tolerates hydrophilic substituents in some cases, drastic reductions in anti-HIV activity are observed, most likely due to insufficient cell penetration. The best results are obtained with compound **6** (HOE/BAY 793) which is outstanding in both enzyme and *in vitro* virus inhibition.

Experimental

Chemistry

Proton magnetic resonance spectra were recorded on a Bruker AM 270 spectrometer. Chemical shifts were recorded as δ units relative to tetramethylsilane as internal standard. FAB mass spectra were taken on a VG Analytical 11-250J spectrometer, and relevant data are tabulated as m/z. Anhydrous solvents were obtained as follows: methylene chloride, distillation from P_2O_5 or drying over 4Å molecular sieves; tetrahydrofuran, distillation from lithium aluminium hydride or use of Aldrich Sure-Seal solvent without further purification; dimethylformamide, drying over 4Å molecular sieves. Flash chromatography was performed on silica gel 60 (230–400 mesh, E. Merck). All solvents for chromatography were reagent grade. Thin layer chromatography was performed with E. Merck or Riedel-de Haën silica gel 60 F-254 (0.25 mm) plates and visualized with phosphomolybdic acid or ninhydrin. The following abbreviations are used: EA, ethylacetate; MC methylene chloride; NEM, *N*-ethylmorpholine; DMF, dimethylformamide; THF, tetrahydrofuran; DCC, dicyclohexylcarbodiimide; HOBT, 1-hydroxybenzotriazole hydrate; HOOBT, 1-hydroxybenzotriazine; TOTU, *O*-[(ethoxycarbonyl)cyanomethylenamino]-*N,N,N',N'*-tetramethyluronium-tetrafluoroborate.[13]

The synthesis of inhibitors **38**, **39**, **40** and 3*S*-hydroxy-2*S*,5*S*-diamino-1,6-diphenylhexane was carried out as published.[7]

2S,5S-Diamino-1,6-diphenylhexane-3R,4R-diol (**3**), *Route A.* (a) *tert*-Butoxycarbonyl-L-phenylalaninal **1** (17 g) was dissolved in 500 mL of dry THF and the solution was cooled to 0 °C under argon. One liter of 0.1 molar SmI_2 solution in THF was added in the course of about 20 min and the mixture was subsequently stirred at rt for 30 min. It was acidified to pH 1–2 with 0.1 N aqueous HCl. The mixture was diluted with EA and the organic phase was separated and extracted with 0.1 N HCl, 2 times with $Na_2S_2O_3$ solution and 2 times with water. After drying over $MgSO_4$, the extract was concentrated and the residue was chromatographed over silica gel (EA:petroleum ether, 1:2). The fraction containing *N,N'*-bis-(*tert*-butoxycarbonyl)-2*S*,5*S*-diamino-1,6-diphenylhexane-3*R*,4*R*-diol was recrystallized from ethanol/water (yield 1.61 g).

N,N'-bis-(*tert*-Butoxycarbonyl)-2*S*,5*S*-diamino-1,6-diphenylhexane-3*S*,4*S*-diol (1.0g) was obtained from the fraction containing the 3*S*,4*S* and the 3*R*,4*S* isomer by crystallization from MC/isopropyl ether/heptane. The mother liquor was chromatographed on RP18 silica gel to obtain 0.71 g of *N,N'*-bis-(*tert*-butoxycarbonyl)-2*S*,5*S*-diamino-1,6-diphenylhexane-3*R*,4*S*-diol (acetonitrile:water 4:6).

R_f values [silica gel, ethylacetate:hexane, 1:2]: 0.18 (3*R*,4*R*), 0.41 (3*S*,4*S*), 0.39 (3*R*,4*S*), MS (FAB): 501 $(M + H)^+$, 401, 345, 327 (all three isomers); ^{1}H NMR (270 MHz, DMSO-d_6): 3*R*,4*R* isomer: 1.30 (*s*, 18H), 2.54–2.80 (*m*, 4H), 3.24 (*m*, 2H), 4.12 (*m*, 2H), 4.43 (*m*, 2H), 6.16 (*d*, 2H), 7.08–7.27 (*m*, 10H). 3*S*,4*S* Isomer: 1.30 (*s*, 18H), 2.63 (*dd*, *J* = 14 Hz, 9 Hz, 2H), 3.04 (*dd*, *J* = 14 Hz, 4 Hz, 2H), 3.42 (*m*, 2H), 3.71 (*m*, 2H), 4.57 (*d*, *J* = 7 Hz, 2H), 6.60 (*d*, 2H), 7.11–7.29 (*m*, 10H). 3*R*,4*S* Isomer: 1.24 (*s*, 9H), 1.32 (*s*, 9H), 2.62–2.83 (*m*, 4H), 3.27–3.46 (*m*, 2H), 3.91–4.12 (*m*, 2H), 4.94 (*d*, *J* = 4 Hz, 1H), 4.62 (*d*, *J* = 4 Hz, 1H), 6.28 (*d*, 1H), 6.31 (*d*, 1H), 7.08–7.32 (*m*, 10H).

(b) The 2*S*,5*S*-diamino-1,6-diphenylhexane-3,4-diol isomers were obtained from the corresponding *N,N'*-bis-(*tert*-butoxycarbonyl)-2*S*,5*S*-diamino-1,6-diphenylhexane-3,4-diol isomers by treatment with 3 N HCl in methanol for 15 min at 25 °C and were used without further purification.

2S,5S-Diamino-1,6-diphenyl-3,4-O-isopropylidenehexane-3R,4R-diol (**3b**). Route B. (a) 1,2*R*-5*R*,6-Diepoxy-3,4-*O*-isopropylidene-3*R*,4*R*-diol **2**[16] (1.12 g) was added to a solution of 36 mmol of $(C_6H_5)_2CuLi$ in 60 mL of dry ether at –78 °C under argon. The cooling bath was removed and the mixture was allowed to warm to rt, while stirring. EA (250 mL) was added to the mixture and the mixture was extracted 3 times with a mixture of 25% ammonia and ammonium chloride. The EA phase was washed with NaCl solution, dried and concentrated. The residue was purified over silica gel (methylene chloride:ethylacetate, 97:3 to 90:10). 2*R*,5*R*-Dihydroxy-1,6-diphenyl-3,4-*O*-isopropylidene-3*R*,4*R*-diol (1.86 g) was obtained. MS (FAB): 343 $(M + H)^+$, 327, 285, 267; ^{1}H NMR (270 MHz, DMSO-d_6): 1.39 (*s*, 6H), 2.58 (*dd*, *J* = 13 Hz, 9 Hz, 2H), 3.43 (*dd*, *J* = 13 Hz, 3 Hz, 2H), 3.68 (*m*, 2H), 3.83 (*m*, 2H), 5.05 (*d*, *J* = 6 Hz, 2H), 7.14–7.32 (*m*, 10H).

(b) 2*R*,5*R*-Dihydroxy-1,6-diphenyl-3,4-*O*-isopropylidenehexane-3*R*,4*R*-diol (5.6 g) was dissolved in 300 mL of chloroform together with 7.9 g of DMAP. *p*-Nitrobenzenesulfonyl chloride (14.5 g) was added at rt and the mixture was stirred at 50 °C for 3 h. MC was added and the solution was extracted with bicarbonate solution, $KHSO_4$ solution and NaCl solution. The organic phase was dried and concentrated. 2*R*,5*R*-Di-(4-nitrophenylsulfonyloxy)-1,6-diphenyl-3,4-*O*-isopropylidenehexane-3*S*,4*S*-diol (11.8 g) was obtained. MS (FAB): 713 $(M + H)^+$, 697, 510; ^{1}H NMR (270 MHz, DMSO-d_6): 1.42 (*s*, 6H), 2.87 (*dd*, *J* = 15 Hz, 9 Hz, 2H), 3.11 (*dd*, *J* = 15 Hz, 3 Hz, 2H), 4.41 (*s*, 2H), 5.07 (*dm*, *J* = 9 Hz, 2H), 6.95–7.11 (*m*, 10H), 7.73 (*d*, *J* = 9 Hz, 4H), 8.18 (*d*, *J* = 9 Hz, 4H).

(c) 2*R*,5*R*-Di-(4-nitrophenylsulfonyloxy)-1,6-diphenyl-3,4-*O*-isopropylidenehexane-3*S*,4*S*-diol (8.5 g) was dissolved in 300 mL of DMF and the solution was heated at 50 °C with about 9.2 g of NaN_3 and 6.3 g of 18-crown-6 for 4 h. The solvent was evaporated, the residue was taken up in ether and the mixture was extracted with aqueous $NaHCO_3$ solution. After washing with water, the organic phase was dried and concentrated. The residue was chromatographed on silica gel (toluene:*n*-heptane, 2:5 to 2:3). 2*S*,5*S*-Diazido-1,6-diphenyl-3,4-*O*-isopropylidenehexane-3*R*,4*R*-diol (2.37 g) was obtained. ^{1}H NMR (270 MHz, DMSO-d_6): 1.48 (*s*, 6H), 2.92–3.12 (*m*, 4H), 3.74 (*dd*, *J* = 10 Hz, 5 Hz, 2H), 4.15 (*s*, 2H), 7.21–7.39 (*m*, 10H).

(d) 2*S*,5*S*-Diazido-1,6-diphenyl-1,6-*O*-isopropylidenehexane-3*R*,4*R*-diol (2.3 g) was dissolved in 50 mL of methanol and hydrogenated using about 0.2 g of palladium-on-charcoal (10%) under normal pressure for 2 h. The catalyst was filtered off, the solution was concentrated and the residue was chromatographed on silica gel (MC:ethanol, 99:1). The yield was 1.33 g. MS (FAB): 341 $(M + H)^+$; ^{1}H NMR (270 MHz, DMSO-d_6): 1.29 (*m*, 4H), 1.37 (*s*, 6H), 2.71 (*dd*, *J* = 12 Hz, 5 Hz, 2H), 2.87 (*m*, 2H), 3.32 (*m*, 2H), 3.95 (*s*, 2H), 7.12–7.33 (*m*, 10H).

N,N'-bis-(L-Valyl)-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol dihydrochloride (**4**). (a) 2*S*,5*S*-Diamino-1,6-diphenyl-3,4-*O*-isopropylidenehexane-3*R*,4*R*-diol **3b** (136 mg) was dissolved in 2 mL of dry EA with 0.54 mL of NEM and 260 mg of *N*-*tert*-butoxycarbonyl-L-valine. A 50% propanephosphonic anhydride (0.97 mL) solution in EA was added at –10 °C. The mixture was stirred at 0 °C for 1 h and then at rt overnight. The solution was diluted with EA and extracted with saturated $NaHCO_3$ solution, 10% $KHSO_4$ solution and water. The organic phase was dried over anhydrous $MgSO_4$ and concentrated and the residue was purified by chromatography on silica gel (methylene chloride:ethanol, 97:3). *N,N*-bis-(*tert*-Butoxycarbonyl-L-valyl)-2*S*,5*S*-diamino-1,6-diphenyl-3,4-*O*-isopropylidene-

hexane-3*R*,4*R*-diol (230 mg) was obtained. MS (FAB): 739 $(M + H)^+$, 681, 639, 569, 539.

(b) *N,N'*-bis-(*tert*-Butoxycarbonyl-L-valyl)-2*S*,5*S*-diamino-1,6-diphenyl-3,4-*O*-isopropylidenehexane-3*R*,4*R*-diol (220 mg) was stirred into 10 mL of an approximately 3 N solution of HCl in dioxane: methanol, 1:1 at rt for 1 h. The volatile constituents of the solution were removed *in vacuo* and the residue was dried under a high vacuum. The substance was used without further purification. Yield: 184 mg; MS (FAB): 499 $(M + H)^+$, 481, 463.

N,N'-bis-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl]-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol (**6**). *N,N'*-bis-(L-Valyl)-2*S*,5*S*-diamino-1,6-diphenylhexane-3*R*,4*R*-diol dihydrochloride **4** (57 mg), (2*S*-(1,1-dimethylethyl-sulfonyl-methyl)-3-(1-naphthyl)-propionic acid **5**[10] (95 mg), HOBt (41 mg) and TBTU (96 mg) were dissolved in 1 mL of dry DMF. N-ethyldiisopropylamine (0.11 mL) was added at rt and the mixture was stirred for 1 h. The solvent was evaporated, the residue was taken up in 30 mL of EA and the mixture was extracted with bisulfate solution, bicarbonate solution and water. After drying over Na_2SO_4, the extract was concentrated and the crude material was purified by chromatography on silica gel (MC:methanol, 97:3). The product was obtained in a yield of 31 mg. MS (FAB): 1153 $(M + Na)^+$, 1131; ^1H NMR (270 MHz, DMSO-d_6): 0.69 (*d*, *J* = 7 Hz, 6H), 0.76 (*d*, *J* = 7 Hz, 6H), 1.10 (*s*, 18H), 1.86 (*m*, 2H), 2.63–2.87 (*m*, 6H), 3.08 (*m*, 2H), about 3.25–3.44 (*m*, about 2H), 3.52–3.63 (*m*, 2H), 4.08 (*m*, 2H), 7.32 (*d*, *J* = 8Hz, 2H), 7.38–7.48 (*m*, 4H), 7.47–7.62 (*m*, 4H), 7.81 (*m*, 2H), 7.92 (*m*, 2H), 8.12–8.25 (*m*, 4H).

1-Sulfoxy-2,5-dioxy-3R,4R-di-[1S-tert-butyloxycarbonylamino-2-phenylethyl]-cyclopentane (**7**). 2*S*,5*S*-Di-*tert*-butyloxycarbonylamino-1,6-diphenylhexane-3*R*,4*R*-diol). (300 mg, 0.6 mmol) was suspended in 10 mL MC and 1 mL absolute pyridine and treated at 0 °C with 86 mg (0.72 mol) $SOCl_2$. The mixture was diluted with methylenechloride, washed with brine and water, dried over Na_2SO_4, concentrated and chromatographed over silica (toluene:ethylacetate, 7:3). 320 mg (97%) of **7** were obtained. MS (FAB): 553.3 $(M + Li^+)$.

2S,5S-Di-tert-butyloxycarbonylamino-3R-hydroxy-4R-azido-1,6-diphenylhexane (**8**). Compound **7** (870 mg, 1.6 mmol) in 15 mL absolute DMF was treated with 311 mg (6.4 mmol) LiN_3 at 100 °C for 22 h. The solvent was removed by distillation, the product was dissolved in EA, washed with brine and water, dried over Na_2SO_4, concentrated and chromatographed over silica (toluene: EA 9:1). Compound **8** (286 mg) was obtained. MS (FAB): 531.8 $(M + Li^+)$. ^1H NMR (270 MHz, DMSO-d_6): 1.25 (*s*, 9H), 1.32 (*s*, 9H), 2.28 (*d*,2H), 2.54–2.68 (*m*, 2H), 3.57 (*dd*, 1H), 3.95–4.20 (*m*, 3H), 7.08 (*d*, 1H), 7.13–7.32 (*m*, 10H).

2S,5S-Diamino-3R-hydroxy-4R-azido-1,6-diphenylhexane (**9**). Compound **8** (200 mg, 0.4 mmol) was dissolved in 10 mL 4.4 N HCl/dioxane and stirred at 0 °C for 1 h. The solvent was evaporated, the product was treated with diethylether, filtered and dried. Compound **9** (155 mg) was obtained and used without further purification.

N,N'-bis-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl]-1,4-diaminobutane (**10**). Synthesis in analogy to **3**: MS (FAB): 941 $(M + Na)^+$, 919 $(M + H)^+$; ^1H NMR (270 MHz, DMSO-d_6): 0.82 (*d*, *J* = 6 Hz, 12H), 1.19 (*s*, 18H), 1.32 (*m*, 4H), 1.89 (*m*, 2H), 2.98 (*m*, 4H), 3.32 (*m*, 2H), 3.42 (*m*, 6H), 3.54 (*dd*, *J* = 12.8 Hz, 8 Hz, 2H), 4.04 (*t*, *J* = 8 Hz, 2H), 7.38 (*m*, 4H), 7.53 (*m*, 6H), 7.79 (*m*, 2H), 7.92 (*m*, 2H), 8.08 (*d*, *J* = 8 Hz, 2H), 8.21 (*m*, 2H).

N,N'-bis-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl]-1,4-diaminobutane-2R,3R-diol (**11**). Synthesis in analogy to **6** from 1,4-diaminobutane-2*R*,3*R*-diol dihydrochloride. MS (FAB): 973 $(M + Na)^+$; 951 $(M + H)^+$; ^1H NMR (270 MHz, DMSO-d_6): 0.82 (*d*, *J* = 6 Hz, 12H), 1.17 (*s*, 18H), 1.92 (*m*, 2H), 2.92–3.08 (*m*, 4H), 3.16–3.53 (*m*, 10H), 3.53 (*dd*, *J* = 12.8 Hz, 8.8 Hz, 2H), 4.11 (*dd*, *J* = 8.0 Hz, 7.2 Hz, 2H), 4.55 (*d*, *J* = 4.8 Hz, 2H), 7.38–7.67 (*m*, 10H), 7.80 (*m*, 2H), 7.92 (*m*, 2H), 8.12 (*d*, *J* = 8.4 Hz, 2H), 8.20 (*d*, *J* = 8 Hz, 2H)

N,N'-bis-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl]-2S,5S-diamino-1,6-diphenylhexane-3S,4S-diol (**12**). Synthesis in analogy to **6**; MS (FAB): 1131 $(M + H)^+$, 716; ^1H NMR (270 MHz, DMSO-d_6): 0.77 (*d*, *J* = 7 Hz, 6H), 0.80 (*d*, *J* = 7 Hz, 6H), 1.12 (*s*, 18H), 1.87 (*m*, 2H), 2.75 (*m*, 2H), 2.83 (*m*, 2H), 2.92–3.03 (*m*, 2H), 3.10–3.22 (*m*, 2H), about 3.27–3.49 (*m*, 6H), 3.54–3.67 (*m*, 2H), 4.02–4.15 (*m*, 4H), 4.66 (*d*, *J* = 6 Hz, 2H), 7.01–7.09 (*m*, 2H), 7.10–7.25 (*m*, 8H), 7.28–7.43 (*m*, 4H), 7.48–7.68 (*m*, 6H), 7.79 (*d*, *J* = 8 Hz, 2H), 7.88–7.95 (*m*, 2H), 8.15–8.25 (*m*, 4H).

N,N'-bis-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl]-2S,5S-diamino-1,6-diphenylhexane-3R,4S-diol (**13**). Synthesis in analogy to **6**. MS (FAB): 1153 $(M + Na)^+$, 1131.

N,N'-bis-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl]-2S,5S-diamino-1,6-diphenyl-3R-hydroxy-4S-azidohexane (**14**). Synthesis in analogy to **6** from **9**. MS (FAB): 1162.6 $(M + Li)^+$, 1156.6.

N,N'-bis-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl]-2S,5S-diamino-1,6-diphenyl-3R-hydroxy-4S-aminohexane (**15**). Compound **14** (89 mg, 0.08 mmol) was dissolved in 15 mL methanol and hydrogenated over 100 mg Pd/C (10%), 1 atm for 12 h. The catalyst was filtrated, the solvent was evaporated and the residue chromatographed over silica (MC:methanol, 9:1) and 36 mg (41%) of **15** was obtained. MS (FAB): 1136.7 $(M + Li)^+$, 1130.7.

N,N'-*bis*-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl]-2S,5S-diamino-1,6-diphenyl-3S-hydroxyhexane (**16**). Synthesis in analogy to **6** starting from 3*S*-hydroxy-2*S*,5*S*-diamino-1,6-diphenylhexane.[7] MS (FAB): 1137 (M + Na)$^+$, 1115.

N,N'-*bis*-([2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl]-L-valyl)-3S,6S-diamino-1,8-diphenyloctane-4R,5R-diol (**17**). Synthesis in analogy to **6** from 3*S*,6*S*-diamino-1,8-diphenyloctane-4*R*,5*R*-diol dihydrochloride (the latter compound was prepared in analogy to **3** from **2** and benzyllithium). MS (FAB(LiI)): 1165 (M + Li)$^+$; ^{1}H NMR (270 MHz, DMSO-d_6): 0.92 (*d*, *J* = 7 Hz, 12H), 1.13 (*s*, 18H), 1.6–1.85 (*m*, 4H), 2.04 (*m*, 2H), 2.40–2.64 (*m*, 4H), 2.82 (*dm*, *J* = 14 Hz, 2H), 3.18 (*m*, 2H), 3.32–3.52 (*m*, 6H), 3.58 (*m*, 2H), 4.08 (*m*, 2H), 4.22 (*t*, *J* = 8 Hz, 2H), 7.1–7.56 (*m*, 20H), 7.72 (*dd*, *J* = 4 Hz, 2H), 7.88 (*m*, 2H), 8.14 (*m*, 2H), 8.32 (*d*, *J* = 8 Hz, 2H).

N,N'-*bis*-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl]-2S,5S-diamino-1,6-di-(4-hydroxyphenyl)-hexane-3R,4R-diol (**18**). Synthesis in analogy to **6** from 2*S*,5*S*-diamino-1,6-bis-(4-hydroxyphenyl)-hexane-3*R*,4*R*-diol dihydrochloride. MS (FAB): 1185 (M + Na)$^+$, 1163.

N,N'-*bis*-([2S-1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl]-L-valyl)-2S,5S-diamino-1,6-bis-(3,4-methylenedioxyphenyl)-hexane-3R,4R-diol (**19**). Synthesis in analogy to **6** from 2*S*,5*S*-diamino-1,6-bis-(3,4-methylenedioxyphenyl)-hexane-3*R*,4*R*-diol dihydrochloride (the latter compound was prepared in analogy to **3** from **2** and 3,4-methylenedioxyphenyllithium). MS (FAB): 1241 (M + Na)$^+$, 1219 (M + H)$^+$; ^{1}H NMR (270 MHz, DMSO-d_6): 0.73 (*d*, *J* = 7 Hz, 6H), 0.78 (*d*, *J* = 7 Hz, 6H), 1.10 (*s*, 18H), 1.89 (*m*, 2H), 2.55–2.72 (*m*, 4H), 2.79 (*dm*, *J* = 14 Hz, 2H), 3.08 (*dd*, *J* = 14 Hz, 10 Hz, 2H), about 3.22–3.43 (*m*, about 6H), 3.58 (*dd*, *J* = 14 Hz, 10 Hz, 2H), 4.07 (*m*, 2H), 4.45 (*m*, 2H), 4.49 (*m*, 2H), 5.75 (*s*, 2H), 5.78 (*s*, 2H), 6.68 (*s*, 2H), 6.80 (*s*, 2H), 7.25 (*d*, *J* = 9 Hz, 2H), 7.39–7.45 (*m*, 4H), 7.54 (*m*, 6H), 7.80 (*m*, 2H), 7.92 (*m*, 2H), 8.15–8.25 (*m*, 4H).

N,N'-*bis*-([2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl]-L-valyl)-2S,5S-diamino-1,6-bis-(2,4-dimethoxyphenyl)-hexane-3R,4R-diol (**20**). Synthesis in analogy to **3** from 2*S*,5*S*-diamino-1,6-bis-(2,4-dimethoxyphenyl)-hexane-3*R*,4*R*-diol dihydrochloride (the latter compound was prepared in analogy to **3** from **2** and 2,4-dimethoxyphenyllithium). MS (FAB): 1251 (M + H)$^+$.

N,N'-*bis*-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl]-3S,6S-diamino-1,8-di-(4-pyridyl)-octane-4R,5R-diol (**21**). Synthesis in analogy to **6** from 3*S*,6*S*-diamino-1,8-di-(4-pyridyl)-octane-4*R*,5*R*-diol-tetrahydrochloride (the latter compound was obtained in analogy to **3** starting from **2** and 4-picolyllithium. MS (FAB): 1161 (M + H)$^+$; ^{1}H NMR (270 MHz, DMSO-d_6): 0.83 (*m*, 12H), 1.14 (*s*, 18H), 1.66 (*m*, 2H), 1.82 (*m*, 2H), 2.00 (*m*, 2H), 2.50–2.78 (*m*, 4H), 2.86 (*m*, 2H), 3.06–3.63 (*m*, 10H), 4.02 (*m*, 2H), 4.14 (*m*, 2H), 4.69 (*m*, 2H), 7.30-7.60 (*m*, 14H), 7.74 (*d*, *J* = 8 Hz, 2H), 7.87 (*m*, 2H), 8.16 (*m*, 2H), 8.32 (*d*, *J* = 8 Hz, 2H), 8.58 (*m*, 4H)

N,N'-*bis*-([2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl]-L-valyl)-6S,9S-diaminotetradecane-7R,8R-diol (**22**). Synthesis analogous to **6** from 6*S*,9*S*-diaminotetradecane-7*R*,8*R*-diol dihydrochloride (the latter compound was prepared in analogy to **3** from **2** and *n*-butyllithium). MS (FAB(LiI)): 1097 (M + Li)$^+$; ^{1}H NMR (270 MHz, DMSO-d_6): 0.76 (*m*, 6H), 0.88 (*d*, *J* = 7 Hz, 12H), 1.12 (*s*, 18H), about 1.10–1.54 (*m*, 16H), 2.02 (*m*, 2H), 2.82 (*dd*, *J* = 12 Hz, 2 Hz, 2H), 3.16 (*dd*, *J* = 12 Hz, 16 Hz, 2H), 3.24 (*m*, 2H), 3.36–3.52 (*m*, 4H), 3.58 (*dd*, *J* = 8 Hz, 13 Hz, 2H), 3.98 (*m*, 2H), 4.16 (*t*, *J* = 6 Hz, 2H), 4.44 (*s*, 2H), 7.18 (*d*, *J* = 10 Hz, 2H), 7.42–7.48 (*m*, 4H), 7.49–7.62 (*m*, 4H), 7.81 (*m*, 2H), 7.92 (*m*, 2H), 8.20 (*d*, *J* = 8 Hz, 2H), 8.30 (*d*, *J* = 8.4 Hz, 2H).

N,N'-*bis*-([2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl]-L-isoleucyl)-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol (**23**). Synthesis in analogy to **6**. MS (FAB): 1181 (M + Na)$^+$; ^{1}H NMR (270 MHz, DMSO-d_6): 0.63 (*d*, *J* = 7 Hz, 6H), 0.73 (*t*, *J* = 7 Hz, 6H), 0.99 (*m*, 2H), 1.11 (*s*, 18H), 1.32 (*m*, 2H), 1.64 (*m*, 2H), 2.63–2.88 (*m*, 6H), 3.07 (*dd*, *J* = 15 Hz, 11 Hz, 2H), about 3.28–3.43 (*m*, about 6H), 3.58 (*dd*, *J* = 14 Hz, 9 Hz, 2H), 4.09 (*t*, *J* = 8 Hz, 2H), 4.48–4.62 (*m*, 4H), 7.03 (*m*, 2H), 7.12–7.31 (*m*, 10H), 7.43 (*m*, 4H), 7.54 (*m*, 4H), 7.81 (*m*, 2H), 7.92 (*m*, 2H), 8.15–8.25 (*m*, 4H).

N,N'-*bis*-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-phenyl-propionyl)-L-tert-butylglycyl]-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol (**24**). Synthesis in analogy to **6**. MS (FAB): 1181 (M + Na)$^+$, 1159 (M + H)$^+$; ^{1}H NMR (270 MHz, DMSO-d_6): 0.83 (*s*, 18H), 1.12 (*s*, 18H), 2.39 (*dd*, *J* = 11 Hz, 14 Hz, 2H), 2.56–2.72 (*m*, 4H), 2.73–2.90 (*m*, 4H), about 3.25–3.40 (*m*, about 4H), 3.53 (*dd*, *J* = 10 Hz, 14 Hz, 2H), 4.20 (*d*, *J* = 9 Hz, 2H), 4.54 (*m*, 2H), 4.62 (*m*, 2H), 6.98 (*m*, 2H): 7.07–7.36 (*m*, 18H), 7.37 (*d*, *J* = 9 Hz, 2H), 7.98 (*d*, *J* = 9 Hz, 2H).

N,N'-*bis*-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-cyclohexylglycyl]-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol (**25**). Synthesis in analogy to **6**. MS (FAB): 1233 (M + Na)$^+$, 1211 (M + H)$^+$.

N,N'-*bis*-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-cyclopentylglycyl]-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol (**26**). Synthesis in analogy to **6**. MS (FAB): 1205 (M + Na)$^+$, 1183 (M + H)$^+$.

N,N'-*bis*-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-propylglycyl]-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol (**27**). Synthesis in analogy to **6**. MS (FAB): 1153 (M + Na)$^+$, 1131 (M + H)$^+$.

N,N'-*bis*-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl)-homoglycyl]-2S,5S-diamino-1,6-diphenylhexane-3R,4R-*diol* (**28**). Synthesis in analogy to **6**. MS (FAB): 1097 $(M + Na)^+$, 1075 $(M + H)^+$.

N,N'-*bis*-([2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl]-L-asparaginyl)-2S,5S-diamino-1,6-diphenylhexane-3R,4R-*diol* (**29**). Synthesis in analogy to **6**. MS (FAB): 1183 $(M + Na)^+$; ^1H NMR (270 MHz, DMSO-d_6): 1.17 (*s*, 18H), 2.22 (*m*, 2H): 2.37–2.76 (*m*, 10H), 2.90 (*m*, 2H), 3.25 (*m*, 4H), 3.58 (*m*, 2H), 4.25 (*m*, 2H), 4.40 (*m*, 2H), 4.62 (*m*, 2H), 6.93–7.60 (*m*, 24H), 7.77 (*m*, 2H), 7.90 (*m*, 2H), 8.22 (*d*, J = 8 Hz, 2H), 8.33 (*d*, J = 8 Hz, 2H).

N,N'-*bis*-([2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl]-L-threonyl)-2S,5S-diamino-1,6-diphenylhexane-3R,4R-*diol* (**30**). Synthesis in analogy to **6**. MS (FAB): 1157 $(M + Na)^+$, 1135 $(M + H)^+$.

N,N'-*bis*-([2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl]-L-glutaryl)-2S,5S-diamino-1,6-diphenylhexane-3R,4R-*diol* (**31**). Synthesis in analogy to **6**. MS (FAB): 1213 $(M + Na)^+$, 1191 $(M + H)^+$.

N,N'-*bis*-([2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl]-L-histidyl-2S,5S-diamino-1,6-diphenylhexane-3R,4R-*diol* (**32**). Synthesis in analogy to **6**. MS (FAB): 1229 $(M + Na)^+$, 1207 $(M + H)^+$.

N,N'-*bis*-([2S-(1,1-Dimethylethylsulfonylmethyl)-3-(1-naphthyl)-propionyl]-L-prolyl)-2S,5S-diamino-1,6-diphenylhexane-3R,4R-*diol* (**33**). Synthesis in analogy to **6**. MS (FAB): 1149 $(M + Na)^+$, 1127 $(M + H)^+$.

N,N'-*bis*-(L-Phenylalanyl-L-valyl)-2S,5S-diamino-1,6-diphenylhexane-3R,4R-*diol dihydrochloride* (**34**). (a) Compound **4** (100 mg) was dissolved in DMF (1.5 mL) together with *N*-*tert*-butoxycarbonyl-L-phenylalanine (111 mg), NEM (0.57 mL) and HOBt (60 mg). After addition of EDAC (85 mg) at 0 °C, stirring was continued at 0 °C for 1 h and then at rt overnight. The solvent was evaporated, the residue was taken up in EA and the mixture was extracted with saturated $KHCO_3$ solution, 10% $KHSO_4$ solution and water. The organic phase was dried with anhydrous Na_2SO_4 and concentrated. The residue was recrystallized from ethanol–water. The yield of *N,N'*-bis-(*tert*-butoxycarbonyl-L-phenylalanyl-L-valyl)-2*S*,5*S*-diamino-1,6-diphenylhexane-3*R*,4*R*-diol was 92 mg. MS (FAB): 993 $(M + H)^+$, 975, 893, 793; ^1H NMR (270 MHz, DMSO-d_6): 0.72 (*d*, J = 6 Hz, 6H), 0.75 (*d*, J = 6 Hz, 6H), 1.29 (*s*, 18H), 1.86 (*m*, 2H), 2.60–2.96 (*m*, 8H), 3.30 (*m*, 2H), 4.17 (*m*, 2H), 4.45 (*m*, 2H),. 4.68 (*m*, 2H), 7.03 (*d*, J = 9 Hz, 2H), 7.05–7.30 (*m*, 22H), 7.53 (*d*, J = 9 Hz, 2H).

(b) *N,N'*-bis-(tert-Butyloxycarbonyl-L-phenylalanyl-L-valyl)-2*S*,5*S*-diamino-1,6-diphenylhexane-3*R*,4*R*-diol (80 mg) was treated with a mixture of 2 mL of 5 N HCl in dioxane and 1 mL of HCl in methanol at rt for 30 min. The volatile constituents were removed *in vacuo*, the residue was washed with ether and the substance was dried under a high vacuum. The yield was 50 mg; MS (FAB): 793 $(M + H)^+$, 775.

N,N'-*bis*-[(3-Amino-2-benzyl)-propionyl-L-valyl]-2S,5S-*diamino-1,6-diphenylhexane-3R,4R-diol dihydrochloride* (**35**). Synthesis in analogy to **34** from **4** and 2-benzyl-3-*tert*-butoxycarbonylaminopropionic acid. MS (FAB): 843 $(M + Na)^+$, 821 $(M + H)^+$.

N,N'-*bis*-[(2R-Benzyl-3-carboxyl)-propionyl-L-valyl]-2S,5S-*diamino-1,6-diphenylhexane-3R,4R-diol* (**36**). (a) Compound **4** (45 mg) was dissolved in DMF (2 mL) with 2*R*-benzyl-3-*tert*-butoxycarbonylpropionic acid (75 mg) (prepared after lit. 17), and HOBt (37 mg), TBTU (87 mg) and ethyldiisopropylamine (112 µL) were added. The mixture was stirred at rt for 15 min, the DMF was removed *in vacuo*, the residue was taken up in EA and the mixture was extracted with $KHSO_4$ solution, $NaHCO_3$ solution and water. The organic phase was dried over $MgSO_4$ and concentrated. The residue was triturated with diethyl ether and filtered off. *N,N'*-bis-[(2*R*-Benzyl-3-*tert*-butoxycarbonyl)-prop-ionyl-L-valyl]-2*S*,5*S*-diamino-1,6-diphenylhexane-3*R*,4*R*-diol (44 mg) was obtained. MS (FAB): 1013 $(M + Na)^+$, 991 $(M + H)^+$; ^1H NMR (270 MHz, DMSO-d_6): 0.69 (*d*, J = 6 Hz, 6H), 0.74 (*d*, J = 6 Hz, 6H), 1.31 (*s*, 18H), 1.83 (*m*, 2H), 1.95 (*m*, 2H), 2.32–2.47 (*m*, 4H), 2.60–2.87 (*m*, 6H), 2.98 (*m*, 2H), 3.29 (*m*, 2H), 4.09 (*dd*, J = 8 Hz, 7 Hz, 2H), 4.46 (*m*, 2H), 4.64 (*m*, 2H), 7.02–7.31 (*m*, 10H), 7.38 (*d*, J = 9 Hz, 2H), 7.80 (*d*, J = 8 Hz, 2H).

(b) *N,N'*-bis-[(2*R*-benzyl-3-carboxyl)-propionyl-L-valyl]-2*S*,5*S*-diamino-1,6-diphenylhexane-3*R*,4*R*-diol **36** (15 mg) was obtained from *N,N'*-bis-[(2*R*-benzyl-3-*tert*-butoxyarbonyl)-propionyl-L-valyl]-2*S*,5*S*-diamino-1,6-diphenylhexane-3*R*,4*R*-diol (30 mg) by treatment with trifluoroacetic acid. MS (FAB): 901 $(M + Na)^+$, 879 $(M + H)^+$.

N,N'-*bis*-[(2S-Hydroxy-3-phenylpropionyl)-L-valyl]-2S,5S-*diamino-1,6-diphenylhexane-3S,4S-diol* (**37**). HOBt (27 mg), of TBTU (64 mg) and then, slowly, diisopropylethylamine (0.088 mL) were added to *N,N'*-bis-[-L-valyl]-2*S*,5*S*-diamino-1,6-diphenylhexane-3*S*,4*S*-diol dihydrochloride (0.065 mmol) and *S*-phenyllactic acid (33 mg) in DMF (4 mL). After 15 min at rt, the DMF was removed *in vacuo*, the residue was taken up in EA and the mixture was extracted with $KHSO_4$ solution, $NaHCO_3$ solution and water. The organic phase was dried with $MgSO_4$ and concentrated, and the residue was triturated with ether and filtered. The yield was 43 mg. MS (FAB): 795 $(M + H)^+$; ^1H NMR (270 MHz, DMSO-d_6): 0.63 (*d*, J = 7 Hz, 6H), 0.67 (*d*, J = 7 Hz, 6H), 1.82 (*m*, 2H), 2.64–2.79 (*m*, 4H), 2.91–3.04 (*m*, 4H), 3.38 (*m*, 2H), 3.97–4.17 (*m*, 6H), 4.72 (*d*, J = 6 Hz, 2H), 5.77 (*d*, J = 6 Hz, 2H), 7.08–7.29 (*m*, 20H), 7.38 (*d*, J = 9 Hz, 2H), 7.85 (*d*, J = 8 Hz, 2H).

N,N'-*bis*-([1-Naphthyloxy]-acetyl-L-valyl)-2S,5S-*diamino-1,6-diphenylhexane-3R,4R-diol* (**41**). Synthesis analogous to **6** from **4** and 1-naphthyloxyacetic acid. MS (FAB): 866 $(M + H)^+$.

N,N'-bis-[D-Gluconyl-L-phenylalanyl-L-valyl]-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol (**42**). (a) *N,N'-bis-[2,3,4,5,6-Penta-O-acetyl-D-gluconyl-L-phenylalanyl-L-valyl]-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol.* Synthesis by coupling of 2,3,4,5,6-penta-*O*-acetyl-D-gluconic acid[18] and **34** in analogy to **6**. MS (FAB): 1569 $(M + H)^+$.

(b) Compound **42** was obtained from *N,N'*-bis-[2,3,4,5,6-penta-*O*-acetyl-D-gluconyl-L-phenylalanyl-L-valyl]-2*S*,5*S*-diamino-1,6-diphenylhexane-3*R*,4*R*-diol with a saturated solution of ammonia in methanol. MS (FAB): 1171 $(M + Na)^+$.

N,N'-bis-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-phenylpropionyl)-L-valyl]-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol (**43**). Synthesis in analogy to **6**. MS (FAB): 1053 $(M + Na)^+$, 1031 $(M + H)^+$; ^1H NMR (270 MHz, DMSO-d_6): 0.72 (*d*, *J* = 7 Hz, 6H), 0.78 (*d*, *J* = 7 Hz, 6H), 1.14 (*s*, 18H), 1.85 (*m*, 2H), 2.62–2.94 (*m*, 8H), about 3.20–3.35 (*m*, about 4H), 3.53 (*dd*, *J* = 10 Hz, 14 Hz, 2H), 4.02–4.13 (*m*, 2H), 4.50 (*m*, 2H), 4.64 (*m*, 2H), 7.01–7.10 (*m*, 2H), 7.12–7.39 (*m*, 22H), 8.05 (*J* = 8 Hz, 2H).

N,N'-bis-[(2S-(1,1-Dimethylethylsulfonylmethyl)-3-(4-methoxyphenyl)propionyl)-L-valyl]-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol (**44**). Synthesis in analogy to **6**. MS (FAB): 1113 $(M + Na)^+$, 1091 $(M + H)^+$.

N,N'-bis-([2S-(1,1-Dimethylethylsulfonylmethyl)-3-(4-pyridyl)-propionyl]-L-valyl)-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol dihydrochloride (**45**). Synthesis in analogy to **6**; 2*S*-(1,1-dimethylethylsulfonylmethyl)-3-(4-pyridyl)-propionic acid is synthesized in analogy to Ref. 10. MS (FAB): 1055 $(M + Na)^+$, 1033 $(M + H)^+$; ^1H NMR (270 MHz, DMSO-d_6): 0.68 (*d*, *J* = 7 Hz, 6H), 0.74 (*d*, *J* = 7 Hz, 6H), 1.19 (*s*, 18H), 1.83 (*m*, 2H), 2.53–2.94 (*m*, 10H), about 3.2–3.45 (*m*, about 10H), 3.53 (*dd*, *J* = 14 Hz, 9 Hz, 2H), 4.06 (*dd*, *J* = 9 Hz, 7 Hz, 2H), 4.52 (*m*, 2H), 7.05 (*m*, 2H), 7.10–7.25 (*m*, 8H), 7.28 (*d*, *J* = 6 Hz, 4H), 7.53 (*d*, *J* = 9 Hz, 2H), 8.19 (*d*, *J* = 9 Hz, 2H), 8.46 (*d*, *J* = 6 Hz, 4H).

N,N'-bis-([2-(1,1-Dimethylethylsulfonylmethyl)-3-(N-oxido-4-pyridyl)-propionyl]-L-valyl)-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol (**46**). Synthesis in analogy to **6**. 2*S*-(1,1-Dimethylethylsulfonylmethyl)-3-(*N*-oxido-4-pyridyl)-propionic acid is formed from 2*S*-(1,1-dimethylethylsulfonylmethyl)-3-(4-pyridyl)-propionic acid by oxidation with an additional equivalent of oxone. MS (FAB): 1065 $(M + H)^+$.

N,N'-bis-[(3-(1,1-Dimethylethylsulfonyl)-propionyl)-L-valyl]-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol (47). Synthesis in analogy to **6**. MS (FAB): 873 $(M + Na)^+$, 851 $(M + H)^+$; ^1H NMR (270 MHz, DMSO-d_6): 0.69 (*d*, *J* = 6 Hz, 6H), 0.73 (*d*, *J* = 6 Hz, 6H), 1.33 (*s*, 18H), 1.84 (*m*, 2H), 2.54–2.59 (*m*, 6H), 2.67 (*m*, 2H), about 3.15–3.30 (*m*, 6H), 4.05 (*dd*, *J* = 7 Hz, 9 Hz, 2H), 4.47 (*m*, 2H), 4.63 (*m*, 2H), 7.06–7.21 (*m*, 10H), 7.30 (*d*, *J* = 9 Hz, 2H), 7.94 (*d*, *J* = 8 Hz, 2H).

N,N'-bis-[(2-(2-Hydroxyethylsulfonylmethyl)-3-phenylpropionyl)-L-valyl]-2S,5S-diamino-1,6-diphenylhexane-3S,4S-diol (**48**). Synthesis in analogy to **6**. MS (FAB): 1007 $(M + H)^+$.

N,N'-bis-[(2-Decylsulfonylmethyl)-3-phenylpropionyl)-L-valyl]-2S,5S-diamino-1,6-diphenylhexane-3S,4S-diol (**49**). Synthesis in analogy to **6**. MS (FAB): 1221 $(M + Na)^+$, 1199 $(M + H)^+$.

N,N'-bis-(2-[4-Pyridyl]ethylsulfonyl-L-valyl)-2S,5S-diamino-1,6-diphenylhexane-3R,4R-diol (**50**). Synthesis in analogy to **6**. MS (FAB): 836 $(M + H)^+$.

N,N'-bis-[(2-Methylsulfonylmethyl)-3-phenylpropionyl)-L-valyl]-2S,5S-diamino-1,6-diphenylhexane-3S,4S-diol (**51**). Synthesis in analogy to **6** and **34**. MS (FAB): 1069 $(M+Na)^+$, 1047 $(M+H)^+$.

Biology. HIV Protease inhibition assay

Recombinant HIV-1 protease was expressed and purified from *Escherichia coli* strain K12 as described.[12]

Inhibition of HIV protease was determined using an HPLC-test with the synthetic substrate SFNFOprQI, where Opr stands for 5-oxaproline and substitutes the proline in the natural sequence SFNFPQI (N-terminus of the protease). The Opr-containing peptide is a much better substrate than the natural one and allows the reduction of the amount of enzyme necessary for cleavage.[7] The resulting tetrapeptide fragment H-Ser-Phe-Asn-Phe-OH is easily separated and quantitated by reverse phase HPLC. The HIV protease activity was measured at 37 °C in 0.4 M sodium phosphate, pH 5.6, containing 20 mM morpholinoethanesulfonic acid, 10% (w/v) glycerol, 0.01% (v/v) Triton X 100, 0.9 mM substrate and 5 mM EDTA in a total volume of 25 µL. The protease concentration was 0.5 nM. Inhibitors were added to the assay in dimethylsulfoxide (1 µL, final DMSO concentration = 4%) The reaction was stopped after 2 h by the addition of 175 µL HPLC solvent mixture.

Assay dilution (20 µL) was analyzed using a Radial-Pak Liquid Chromatography Cartridge (Waters 8C18/5µ) by isocratic elution with a solution containing 78% (w) 0.1 M H_3PO_4, pH 2.5 with triethylamine, and 22% (w) acetonitrile at a flow rate of 1 mL min^{-1}. Peaks were detected by UV absorbance at 215 nm, retention times were 5 min for the tetrapeptide and 9 min for the substrate.

Inhibition of HIV-1 viral spread in cell culture

Stock solutions of inhibitors were prepared by dissolving 2 mg of inhibitor in 120 µL DMSO.

Virus stocks. Infectious HIV was obtained from supernatant fluids of infected peripheral blood mononuclear cells (PBL) and stored frozen in aliquots at –80 °C. HIV-1 (D34) is a particularly fast growing

HIV-1 strain of the subtype B[14] isolated from a German AIDS patient in 1985.[15b]

Cells. Peripheral blood mononuclear cells (PBL) from healthy HIV seronegative volunteers were isolated by Ficoll–Hypaque sedimentation of citrate containing blood. Cells were stimulated with phythaemagglutinine (PHA) and grown in RPMI-1640 supplemented with 20% fetal calf serum (FCS), antibiotics, HEPES and additional glutamine at 37 °C. Two days later 40 units of IL-2 (interleukin-2; Roussel Uclaf, France) were added per mL cell suspension. Stimulated cells were stored in liquid nitrogen.

Antiviral drug assay. PBL or H9 cells[15b] were cultivated for three to four days in RPMI-1640 supplemented with 20% FCS and (in the case of PBL cells) 40 IU mL^{-1} recombinant IL-2, then they were infected for a 30 min period with HIV-1 (2–4 × 10^5 TCIU/10^6 cells, TCIU: T cell infective units). The virus containing supernatant was removed, 0.5 mL of the resuspended infected cells were transferred immediately to the wells of a 24-well plate each containing 0.5 mL $well^{-1}$ of test compounds dissolved in DMSO. Dilutions of test compounds were prepared by serial dilutions of 1:5 or 1:2. The final concentration of the cells was 1–2.5 × 10^5 ml^{-1} $well^{-1}$. The samples were incubated at 37 °C for 72–96 h under 5% CO_2. Virus replication was evaluated by light microscopy for syncytia formation and/or by measurement of HIV antigen in the supernatant of the cell cultures by an antigen capture assay (Vironostika HIV, Organon Teknika).

Antigen capture assay. As antigen capture assay the ELISA assay "Vironostika HIV" (Organon Teknika, Eppelheim, Germany) was used. The main, but not exclusive, recognized antigen was the HIV p24 antigen. All assay procedures were performed according to the instructions of the manufacturer.

Cut-off values were defined by adding three standard deviations to the mean extinction values of negative controls. For the calculation of the IC_{50} values the supernatants of the corresponding cell cultures were tested in a 1:10 dilution in the antigen capture assay for the HIV-1 strain.

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