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Discovery of Novel Benzothiazolesulfonamides as Potent Inhibitors of HIV-1 Protease

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Abstract—The human immunodeficiency virus (HIV) has been shown to be the causative agent for AIDS. The HIV virus encodes for a unique aspartyl protease that is essential for the production of enzymes and proteins in the final stages of maturation. Protease inhibitors have been useful in combating the disease. The inhibitors incorporate a variety of isosteres including the hydroxyethylurea at the protease cleavage site. We have shown that the replacement of *t*-butylurea moiety by benzothiazolesulfonamide provided inhibitors with improved potency and antiviral activities. Some of the compounds have shown good oral bioavailability and half-life in rats. The synthesis of benzothiazole derivatives led us to explore other heterocycles. During the course of our studies, we also developed an efficient synthesis of benzothiazole-6-sulfonic acid via a two-step procedure starting from sulfanilamide.

Introduction

The human immunodeficiency virus type-1 (HIV-1) has been shown to be the causative agent for the disease Acquired Immune Deficiency Syndrome (AIDS). The HIV-1 virus encodes for a unique aspartyl protease, and the protease is essential for cleavage of the viral *gag* and *gag/pol* poly peptide precursors into individual enzymes and proteins during the final stages of maturation.[1] Inactivation of this enzyme has been shown to result in the production of non-infectious virons.[2] Therefore, the HIV-1 protease represents an attractive target for the design of therapeutic agents for the treatment of AIDS.[3] In an effort to combat this epidemic, many protease inhibitors have been discovered which arrest the replication of the virus. Some of the protease inhibitors have been approved for clinical use (Indinavir,[4] Nelfinavir,[5] Ritonavir,[6] Saquinavir,[7] and Amprenavir,[8a] Lopinavir[8b]), and others are at various stages of clinical trials (Tipranavir,[8c] KNI-272,[8d] Mozenavir,[8e] and Atazanavir,[8f]). The use of protease drugs in combination with other anti-viral drugs has greatly diminished mortality due to AIDS in developed countries, although in many parts of the world the spread of the disease continues unabated.

Potent inhibitors of HIV-1 protease incorporating a variety of isosteres at the cleavage site have been reported.[9] Efforts in our laboratories led to the discovery of several protease inhibitors containing the hydroxyethylurea isosteres.[10a] The *t*-butyl urea **1** (Z = carbobenzyloxy, IC_{50} = 112 nM) was one of the key inhibitors identified based on the hydroxyethylurea isoster. In order to identify new classes of compounds with better inhibitory activity and pharmacokinetic properties, we chose to modify the functional groups in the inhibitor and then vary and optimize the moieties that are attached to it. The *t*-butyl urea in **1** was replaced by a sulfonamide group, followed by optimization of moieties at P2′ and P1′ to give compound **2** (IC_{50} = 6 nM), which was shown to be a better protease inhibitor.[10b] Optimization of the phenyl group attached to the sulfonamide moiety by varying the substitutions on the

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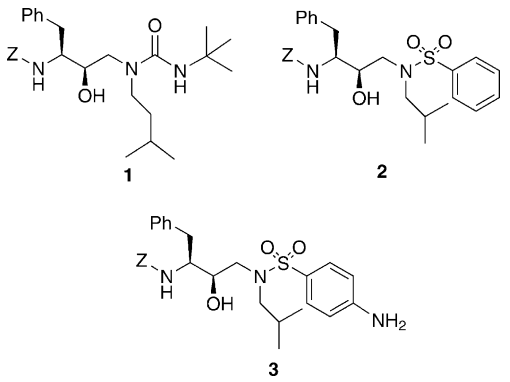


Scheme 1.

phenyl ring led to the discovery of a compound containing *p*-aminophenylsulfonamide **3** (IC_{50} = 12 nM), among other analogues (Scheme 1).

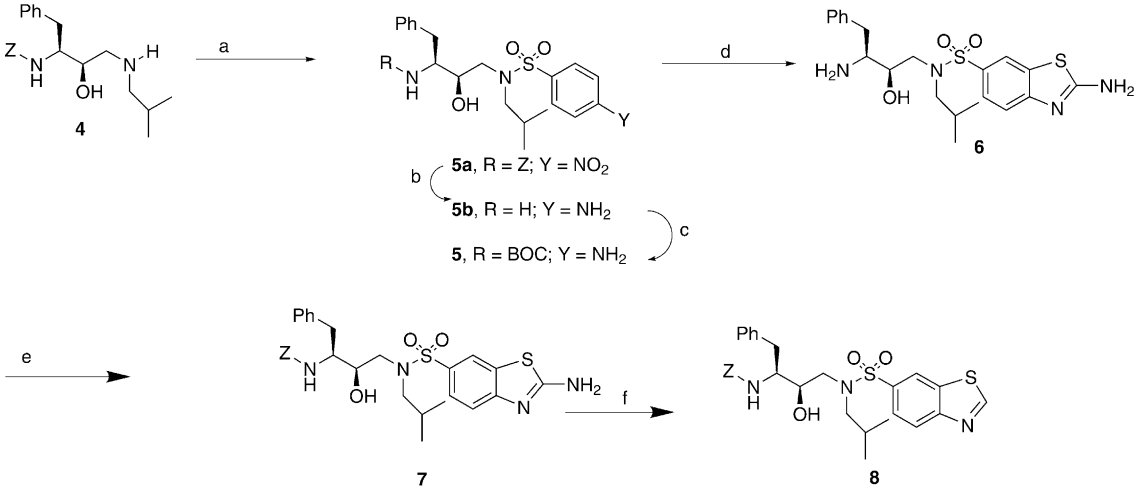
Results and Discussion

The *p*-aminophenyl group can be further modified to incorporate fused heteroaromatic sulfonamides instead of simple sulfonamides. The synthesis of benzothiazole-sulfonamide was accomplished as described in Scheme 2. *p*-Nitrophenylsulfonyl chloride was reacted with **4**[10b] to give the corresponding sulfonamide and the *p*-nitro group was reduced with Pd/C to the *p*-amino compound. The amino compound was then protected as the BOC-derivative to afford **5** in very good yield. This compound served as the key intermediate for the synthesis of benzothiazoles. The aminophenylsulfonamide **5** was then reacted with $CuSO_4$/KSCN[11] to afford **6**. The BOC-group was also removed under the reaction conditions. The sulfonamide **6**, obtained above was treated with *Z*-OSu to afford the *Z*-derivative **7**. The deamination of **7** was accomplished by treating it with isoamyl nitrite in dioxane at 85 °C to afford **8**. Both 2-amino-benzothiazole **7** (IC_{50}, 2 nM; EC_{50}, 15 nM) and the des-amino analogue **8** (IC_{50}, 3 nM) have been shown to be very potent inhibitors of the enzyme HIV-1 protease compared to **2** (6 nM).

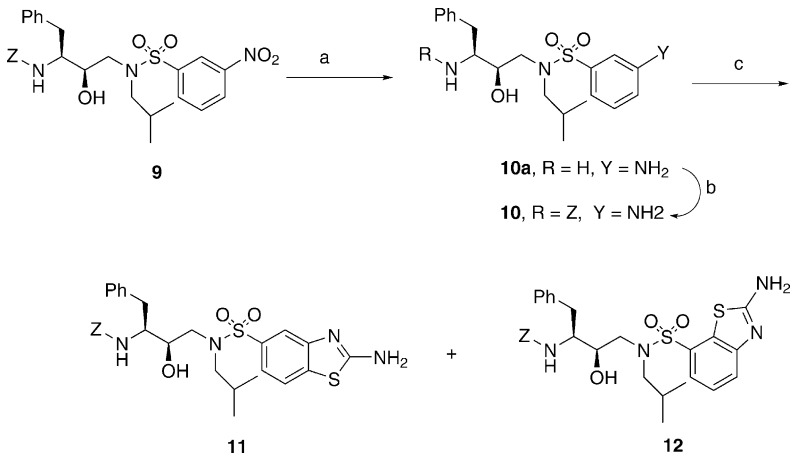
We then synthesized other isomers of benzothiazole to identify the optimal position for the sulfonamide moiety. The 3-aminobenzenesulfonamide **10**, which was synthesized as shown in Scheme 3, when subjected to the above reaction with KSCN, afforded two isomers of the 2-aminobenzothiazolesulfonamide **11** and **12**. These two isomers were easily separated by chromatography and have been shown to be not very potent (IC_{50} for **11**, 47 nM; **12**, 1000 nM) compared to **7**. Since only the benzothiazole-6-sulfonamide analogue was potent, we focused our efforts to optimize the groups (*Z*-replacement) in **7** and **8** that would fit in the P2 position.

These derivatives fall into two broad categories: amides and carbamates, both of which maintain the crucial carbonyl group for hydrogen bonding. The benzoic acids chosen for the P2 position were those containing groups in the 3-position that enhance hydrogen bond formation (the 3-hydroxy and 3-amino toluic acids). The 3-hydroxy-2-methylbenzoyl moiety has been successfully employed in the design of Nelfinavir.[5] The coupling of 3-hydroxy-2-methylbenzoic as well as 3-amino-2-methylbenzoic acids with **6** was accomplished using HOBT/EDC as shown in Scheme 4. The products have potent enzyme activity (IC_{50}'s for **22**, 2 nM; **23**, 3 nM) and antiviral activity (EC_{50}'s for **22**, 14 nM; **23**, 9 nM). However, these compounds have no significant oral bioavailability. We also synthesized simple *o*-toluamide for comparison. The activity of this compound **24** (IC_{50}, 3 nM; EC_{50}, 12 nM) is surprisingly similar to that of **22** and **23** with no improvement in oral bioavailability, indicating that the presence of either the hydroxy or the amino groups in the 3-position does not provide a significant advantage in activity in this class of compounds. The sulfone moiety of methylsulfonylpropionic acid also would enhance the hydrogen bond formation and the corresponding amide was synthesized starting from 2(*R*)-methyl-3-methylsulfonylpropionic acid. The product **25** was shown to be very potent (IC_{50}, 2 nM, EC_{50}, 84 nM), again with no improved oral bioavailability.

We next wanted to compare the activity of these compounds with the des-amino analogues. Isoamylnitrite

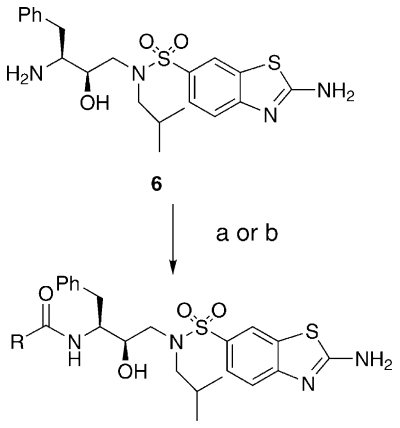


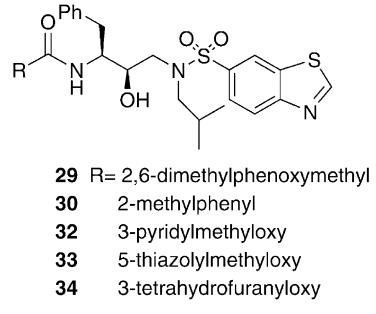
Scheme 2. Reagents and conditions: (a) *p*-nitrobenzenesulfonylchloride/NEt_3; (b) Pd/C, H_2; (c) BOC-ON; (d) $CuSO_4$/KSCN, methanol, reflux; (e) *Z*-OSu; (f) isoamylnitrite, dioxane, 85 °C.



Scheme 3. Reagents and conditions: (a) Pd/C, H_2; (b) *Z*-OSu; (c) $CuSO_4$, KSCN, MeOH, reflux.

was used for the removal of the amino group as shown in Scheme 4. Since the use of isoamylnitrite is not compatible with existing functionality in **22** and **23**, a different procedure was used for the synthesis of **36** and **37**





Scheme 4. Reagents and conditions: (a) R-COOH (**13**–**17**), EDC, HOBt; (b) R-OH (**18**–**20**), DSC, pyridine; (c) isoamylnitrite, in dioxane, reflux.

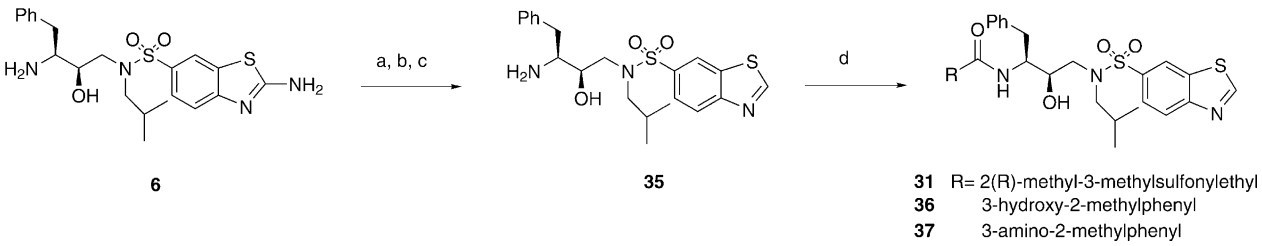
(Scheme 5). The aminobenzothiazole **6** was reacted with BOC-ON to give the BOC-protected aminobenzothiazole. The amino group at the 2-position was then removed using the technique described above, and the BOC-protective group was removed with dioxane/HCl to afford the desired des-amino compound **35** in very good yield. This was used for coupling 3-hydroxy and 3-amino-substituted toluic acids and 2(*R*)-methyl-3-methylsulfonylpropionic acid to afford **36** (IC_{50}, 2 nM; EC_{50}, 7 nM) and **37** (IC_{50}, 6 nM; EC_{50}, 21 nM) and **31** (IC_{50}, 2 nM; EC_{50}, 22 nM), respectively. Of these, only **31** showed oral bioavailability (22%). This is in sharp contrast to **21** and **29** where the des-amino compound (**29**) had no oral bioavailability compared to its 2-amino analogue (**21**) with a bioavailability of 13% (Table 1).

The P2 moieties of carbamate analogues that were synthesized have been shown to be high affinity ligands by

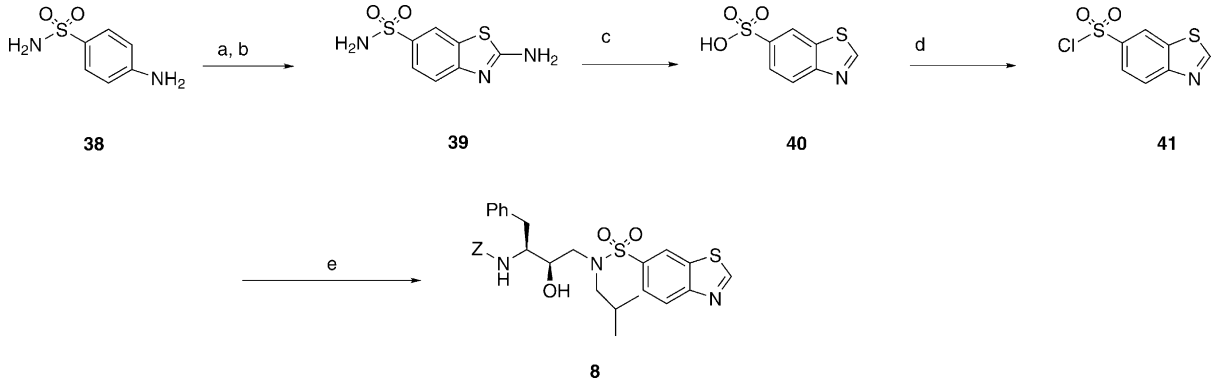
Table 1. Protease inhibitors and their IC_{50}, antiviral activity and oral bioavailability values

Compd	IC_{50} (nM)	EC_{50} (nM)	%BA in rat (@20 mpk)[b]
1	112	ND[a]	
2	6	ND	
3	12	ND	
7	2	15	
8	3	ND	
11	47	102	
12	1000	ND	
21	2	3	13
22	2	14	
23	3	9	
24	3	12	
25	2	84	
26	4	5	11
27	3	3	8
28	2	4	
29	4	42	
30	4	13	
31	2	22	22
32	4	11	28
33	5	9	20
34	4	9	5
36	2	7	
37	6	21	

[a]Not determined.
[b]Unless indicated, the compounds did not show significant oral bioavailability.



Scheme 5. Reagents and conditions: (a) BOC-ON; (b) isoamylnitrite/dioxane, 85 °C; (c) dioxane/HCl; (d) R-COOH/EDC/HOBt.



Scheme 6. Reagents and conditions: (a) NH_4SCN; (b) $Br_2/CHCl_3$; (c) isoamylnitrite, dioxane; (d) $SOCl_2$/DMF, dichloroethane; (e) **4**/*N*-methylmorpholine.

various research groups. The pyridyl, thiazolyl and tetrahydrofuranyl moieties have been successfully used in the synthesis of very potent inhibitors. The carbinols were first activated with DSC and the activated carbinols were then treated with the amine **6** to afford the desired carbamate analogues (Scheme 4). The amino group in the 2-position of benzothiazole moiety was removed using isoamyl nitrite as described above.

The new carbamate analogues synthesized are very potent inhibitors of HIV-1 protease and are potently antiviral (**26**, IC_{50}, 4 nM, EC_{50}, 5 nM; **27**, IC_{50}, 3 nM, EC_{50}, 3 nM; **28**, IC_{50}, 2 nM; EC_{50}, 4 nM). In general, the des-aminobenzothiazoles are slightly less potent compared to the 2-amino isomers (**32**, IC_{50}, 4 nM, EC_{50}, 11 nM; **33**, IC_{50}, 5 nM, EC_{50}, 9 nM; **34**, IC_{50}, 4 nM; EC_{50}, 9 nM). These carbamates, **32**, **33** and **34** also showed good oral bioavailability in rats compared to their 2-amino analogues.

During the course of this study, we also developed a two-step synthesis of benzothiazole-6-sulfonic acid starting from *p*-aminobenzenesulfonamide (**38**). A review of the literature indicated that a simple synthesis of a benzothiazole-6-sulfonic acid has not been reported in the literature. The introduction of sulfonic acid moiety on a pre-formed benzothiazole proved to be difficult as it gave intractable products or mixture of isomers. However, the synthesis of 2-aminobenzothiazolesulfonamide is described in the literature.[12] We envisioned the removal of the 2-amino group using isoamylnitrite and then converting the sulfonamide to the desired benzothiazole-6-sulfonic acid. Interestingly, when 2-aminobenzothiazole-6-sulfonamide (**39**) was treated with isoamylnitrite in DMF at 110 °C, we obtained the benzothiazole-6-sulfonic acid in very good yield (Scheme 6). The acid chloride was synthesized by treatment with thionyl chloride in dichloroethane. Treatment of the sulfonyl chloride with the amine **4**, afforded the desired sulfonamide **8** in very good yield. The product is identical in all respects to the one obtained by the route described in Scheme 3. This route provides easy access to the desired sulfonamides in fewer steps.

Conclusions

We have shown that the replacement of the urea moiety by benzothiazolesulfonamide provided inhibitors of HIV-1 protease with improved potency and antiviral activities. Certain members of the class showed good oral bioavailability in rats, most notably compounds **31**, **32**, and **33**. The synthesis of benzothiazole derivatives also led us to explore other heterocycles and the results will be reported elsewhere. During the course of our studies, we also developed a synthesis of benzothiazole-6-sulfonic acid via a two-step procedure starting from sulfanilamide **38**.

Experimental

General

Unless otherwise stated, starting materials were obtained from commercial sources and were used without further purification. All reactions were performed in

anhydrous conditions in an atmosphere of nitrogen. Nuclear magnetic resonance spectra were recorded on a Varian XL-300 spectrometer and chemical shifts are reported in ppm relative to TMS internal standard. Low resolution mass spectra were recorded on a VG40-250T instrument and the high resolution mass spectra were recorded on a Finnigan MAT 90 spectrometer operating in the FAB mode. All final compounds were analyzed by analytical hplc (gradient 5–100% acetonitrile in water containing 0.01% TFA) and peaks were monitored both at 210 and 254 nM for purity. All final compounds have been shown to be single peaks by HPLC. Details of enzyme, and antiviral assay have been provided in an earlier publication.[10]

Animal pharmacokinetic studies

Under metofane anesthesia, the femoral artery (all eight rats) and femoral vein (only four of eight rats) were isolated and canulated with PE50 tubing and secured with 3.0 silk sutures. The procedure required two catheters, with the venous line being used for infusion of compound (in the group of rats that received compound iv), and the arterial line being used for collection of blood samples. The rats were then placed in restraining cages, which allow minimal movement and allowed to recover from anesthesia for approximately 30 min. At time 0, blood samples (400 μL) were collected from arterial cannula. One group of rats (four rats per group) received compound via the oral route (18G, 3-inch curved gavage needle) at a dosing volume of 2 mL/kg (10 mg/mL, dissolved in 0.5% methyl-cellulose, 0.1% Tween 20), while the other group of rats received compound via the intravenous cannula, at a dosing volume of 2 mL/kg (10 mg/kg, dissolved in 10% EtOH, 50% PEG 400, 40% saline). The blood samples were collected from the arterial cannula at 15, 30, 60, 120, 240, and 360 min with an additional 3- min sample being collected from iv group. After each sample, the cannulas were flushed with PBS containing 10-units/mL heparin. At 6 h, the animals were terminated with excess of anesthesia or by CO_2 asphyxiation. The plasma was obtained by immediate centrifugation and kept frozen (−20 °C) until analyzed. Plasma proteins were precipitated with acetonitrile and subjected to centrifugation. The supernatant containing compound was evaporated under nitrogen and reconstituted in DMSO. To ensure complete extraction, a standard compound at various concentrations was mixed with control rat plasma and extracted. The concentration of the inhibitor present in the plasma was determined using the protease enzyme (assay described above).

3-*S*-(*N*-Benzyloxyformamido)-[2*R*-hydroxy-1-[(2-methylpropyl)(4 - nitrophenylsulfonyl)amino] - 4-phenylbutane (5a). Small portions of *p*-nitrobenzenesulfonyl chloride (3.295 g, 14.865 mmol) were added to a solution of **4** (5.0 g, 13.514 mmol) and triethylamine (4.09 g, 40.54 mmol) in dichloromethane at 0–5 °C for 30 min and at rt for 1 h. The reaction mixture was diluted with dichloromethane (200 mL), washed with citric acid (5%, 200 mL), sodium bicarbonate (200 mL, saturated), brine (200 mL), dried ($MgSO_4$) and concentrated to afford a solid. The solid was re-crystallized from hexane/ethyl acetate. The crystalline solid was filtered and dried to afford 5.7 g, (75%) of the product. ^{1}H NMR ($CDCl_3$) δ 0.86 (2d, 6H, J = 6.84 Hz), 1.94 (m, 1H), 2.8–3.2 (m, 6H), 3.6 (s, 1H), 3.9 (s, 2H), 5.05(s, 2H), 7.2–7.4 (m, 10H), 7.9, 8.3 (AB quartet, 4H). Anal. calcd for $C_{28}H_{33}N_3O_7S$: M_r 556.2118. Found: M_r 556.2119 (M + H, HRFABMS).

3-*S*-(*N*-Butyloxyformamido)-[2*R*-hydroxy-1-[(4-aminophenylsulfonyl) (2 - methylpropyl)amino]-4-phenylbutane (5). Palladium/C (6.0 g, 10%) was added to a solution of **5a** (8.0 g, 14.41 mmol) in ethyl acetate (100 mL) and the mixture was subjected to hydrogenolysis. The catalyst was filtered off and the filtrate was concentrated to afford 5.30 g (70%) of the desired product **5b** as a solid. ^{1}H NMR (CD_3OD) δ (2d, 6H, J = 6.8 Hz), 1.94 (m, 1H), 2.51 (dd, 1H, J = 9.7, 9 Hz), 2.80–3.1 (m, 5H), 3.75 (m, 1H), 6.69, 7.48 (AB quartet, 4H, J = 8.7 Hz), 7.18–7.32 (m, 5H). A mixture of (3.7 g 9.45 mmol) and BOC-ON (2.33 g, 9.45 mmol) and triethylamine (0.954 g, 9.45 mmol) in tetrahydrofuran (60 mL) was stirred for 16 h and concentrated in vacuo. The residue was dissolved in dichloromethane (200 mL), washed with sodium hydroxide (1 N, 100 mL), citric acid (5%, 100 mL), dried ($MgSO_4$), and concentrated to afford 1.18 g (94%) of the product as a white solid. ^{1}H NMR (CD_3OD) δ (0.87, 0.90, 2d, 6H, J = 6.84 Hz), 1.15 and 1.28 (2S, 9H), 1.98 (m, 1H), 2.5–3.2 (m, 6H), 3.6–3.8 (m, 2H), 6.69, 7.48 (AB quartet, 4H, J = 8.7 Hz), 7.18–7.23 (m, 5H). Anal. calcd for $C_{25}H_{37}N_3SO_5$: M_r 492.2532. Found: M_r 492.2546 (M + H, HRFABMS).

3-*S*-Amino-2*R*-hydroxy-1-[(2-aminobenzothiazol-6-sulfonyl) (2 - methylpropyl)amino]-4-phenylbutane (6). Powdered **5** (37.8 g, 76.9 mmol) was added to a mixture of anhydrous copper sulfate (151.0 g) and potassium thiocyanate (189.1 g) followed by dry methanol (1.1 L) and the resulting black-brown suspension was stirred with a mechanical stirrer and was heated at reflux for 2 h. The reaction mixture turned gray. The reaction mixture was filtered and the filtrate was diluted with water (1.6 L) and heated at reflux. Ethanol was added to the reaction mixture, cooled and filtered. The filtrate was concentrated and was diluted with water (1L) then was made basic with ammonium hydroxide. The basic reaction mixture was then extracted with ethyl acetate (5×1 L). The organic layer was successively washed with ammonium chloride (saturated, 2×500 mL), brine (500 mL), dried ($MgSO_4$) and was concentrated to afford 32.2 g (93%) of the compound as a solid. ^{1}H NMR (CD_3OD) δ 0.85, 0.88 (2d, 6H, J = 6.7 Hz), 1.96 (m, 1H), 2.54 (m, 1H), 2.89–3.15 (m, 5H), 3.38–3.44 (m, 1H), 3.72–3.77 (m, 1H), 7.18–7.32 (m, 5H), 7.50 (d, 8.5 Hz), 7.68 (dd, 1H, J = 8.5 and 2 Hz), 8.08 (d, 1H, J = 1.8 Hz). Anal. calcd for $C_{21}H_{28}N_4O_3S_2$: M_r 449.1681. Found: M_r 449.1664 (M + H, HRFABMS).

3-*S*-(*N*-Benzyloxyformamido)-2*R*-hydroxy-1-[(2-aminobenzothiazol-6-sulfonyl) (2-methylpropyl)amino]-4-phenylbutane (7). A mixture of **6** (0.229 g, 0.5094 mmol) and *Z*-OSu (0.127 g, 0.5054 mmol), and triethylamine (0.4 mL) in dimethylformamide (5 mL) was stirred at

room temperature for 18 h. The reaction mixture was concentrated and the residue was dissolved in dichloromethane (100 mL). The dichloromethane solution was washed with sodium hydroxide (1N, 100 mL), citric acid (5%, 100 mL) dried (Mg SO_4) and concentrated to afford a residue, which was recrystallized from ethyl acetate/hexane to afford 0.16 g (54%) of the product as a solid. ^{1}H NMR (CD_3OD) δ 0.85,0.89 (2d, 6H, $J=6.6$ Hz), 1.98 (m, 1H), 2.61 (m, 1H), 2.84 (m, 5H), 3.71–3.82 (m, 2H), 4.93 (q, 2H, $J=4$ Hz), 6.98 (m, 1H), 7.14–7.24 (m, 10H), 7.44 (d, 1H, $J=8.7$ Hz), 7.67 (dd, 1H, $J=8.7$ and 1.8 Hz), 8.06 (d, 1H, $J=1.6$ Hz). Anal. calcd for $C_{29}H_{34}N_4O_5S_2$: M_r 582.2049. Found: M_r 583.2026 (M + H, HRFABMS).

3-*S*-(*N*-Benzyloxyformamido)-2*R*-hydroxy-1-[(benzothiazol-6-sulfonyl) (2-methylpropyl)amino]-4-phenylbutane (8). Isoamylnitrite (70 μL) was added to a solution of **7** (0.15 g) in dioxane (3 mL) and the mixture was heated at 85 °C. After the cessation of evolution of nitrogen, the reaction mixture was concentrated and the residue was purified by chromatography (hexane–ethyl acetate 5:3) to afford 0.90 g (53%) of the product as a solid. ^{1}H NMR (CD_3OD) δ 0.84, 0.88 (2d, 6H, $J=6.6$ Hz), 1.99 (m, 1H), 2.59 (m, 1H), 2.91–3.48 (m, 5H), 3.77–3.83 (m, 2H), 4.92 (m, 2H), 7.13–7.25 (m, 10H), 7.94 (dd, 1H, $J=1.6$, 8.7 Hz), 8.16 (d, 1H, $J=8.7$ Hz), 8.59 (d, 1H, $J=1.6$ Hz), 9.41 (s, 1H). Anal. calcd for $C_{29}H_{33}N_3O_5S_2$: M_r 567.1940. Found: M_r 568.1933 (M + H, HRFABMS).

3-*S*-(*N*-Benzyloxyformamido)-2*R*-hydroxy-1-[(2-aminobenzothiazol-5-sulfonyl) (2-methylpropyl)amino]-4-phenylbutane (11) and 3-*S*-(*N*-benzyloxyformamido)-2*R*-hydroxy-1-[(2-aminobenzothiazol-7-sulfonyl) (2-methylpropyl)amino]-4-phenylbutane (12). The amine **10** (synthesized as described for **5**, starting from **4** and m-nitrobenzenesulfonyl chloride) (0.36 g, 0.685 mmol) was added to a well mixed powder of anhydrous copper sulfate (1.44 g) and potassium thiocyanate (1.80 g) followed by dry methanol (10 mL) and the resulting black-brown suspension was heated at reflux for 2 h. The reaction mixture turned gray. The reaction mixture was filtered and the filtrate was diluted with water (5 mL) and heated at reflux. Ethanol was added to the reaction mixture, cooled and filtered. The filtrate upon concentration afforded a residue which was purified by chromatography (ethyl acetate–hexane 1:1) to afford 0.18 g (45%) of the 7-isomer (**12**) as a solid. ^{1}H NMR (CD_3OD) δ 0.81 (2d, 6H, $J=7.05$ Hz), 1.96 (m, 1H), 2.58 (m, 1H), 3.07–3.3 (m, 4H), 3.58–3.81 (m, 3H), 4.94 (q, 2H, $J=3.6$ Hz), 6.87 (dd, 1H, $J=8.6$ and 2.6 Hz), 7.12–7.32 (m, 11H), 7.52 (d, 1H, 8.66 Hz). Anal. calcd for $C_{29}H_{34}N_4O_5S_2$: M_r 582.2049. Found: M_r 583.2034 (M + H, HRFABMS). Further elution of the column with (ethyl acetate–hexane 3:2) afforded 0.80 g (20%) afforded the 5-isomer (**11**) as a solid. ^{1}H NMR (CD_3OD) δ 0.87 (m, 6H), 1.96 (m, 1H), 2.58 (m, 1H), 2.89–3.45 (m, 5H), 3.68–3.89 (m, 2H), 4.92 (q, 2H, $J=3.6$ Hz), 7.46 (dd, 1H, $J=8.4$,1.7 Hz), 7.12–7.23 (m, 11H), 7.68 (d, 1H, $J=8.5$ Hz), 7.78 (d, 1H, $J=1.4$ Hz). Anal. calcd for $C_{29}H_{34}N_4O_5S_2$: M_r 582.2049. Found: M_r 583.2034 (M + H, HRFABMS).

3-*S*-{*N*-2-(2,6-Dimethylphenoxymethylcarboxamido)}-2*R*-hydroxy-1-[(2-aminobenzothiazol-6-sulfonyl) (2-methylpropyl)amino]-4-phenylbutane (21). A mixture of 2-(2,6-dimethylphenoxy)acetic acid (0.408 g, 2.27 mmol), HOBt (0.307 g, 2.27 mmol), and EDC (0.435 g, 2.27 mmol) in dimethylformamide (20 mL) was stirred at rt for 1 h. Then **6** (1.02 g, 2.27 mmol) was added and the reaction mixture was stirred for 18 h. The solvent was removed in vacuo and the residue was dissolved in dichloromethane (100 mL), washed with citric acid (5%, 100 mL), sodium bicarbonate (saturated, 100 mL), brine (100 mL), dried and concentrated. The residue obtained was purified by chromatography (20% hexane in ethyl acetate) to afford 0.520 g (38%) of the product. ^{1}H NMR (CD_3OD) δ 0.88 and 0.93 (2d, 6H, $J=6.6$ Hz), 2.06 (m, 1H), 2.13 (s, 6H), 2.75–3.53 (m, 6H), 3.89 (m, 1H), 3.94–4.52 (m, 3H), 6.88–6.99 (m, 3H), 7.15–7.29 (m, 5H), 7.45 (d, 1H, $J=8.5$ Hz), 7.70 (dd, 1H, $J=2$, 8.6 Hz), 8.09 (d, 1H, $J=2$ Hz). Anal. calcd for $C_{31}H_{38}N_4O_5S_2$: M_r 610.2362. Found: M_r 611.2367 (M + H, HRFABMS).

3-*S*–{*N*-(3-Hydroxy-2-methylphenylcarboxamido)}-[2*R*-hydroxy-1-[(2-aminobenzothiazole-6-sulfonyl)-(2-methylpropyl)amino]-4-phenylbutane (22). This compound was obtained using the procedure described above for compound **21** and replacing the acid with 2-methyl-3-hydroxybenzoic acid to afford the product. Yield: 60%. ^{1}H NMR (CD_3OD) δ 0.89, 0.94 (2d, 6H, $J=6.6$ Hz), 1.77 (s, 3H), 2.06 (m, 1H), 2.64 (m, 1H), 2.92–3.57 (m, 4H), 3.88 (m, 1H), 4.26 (m, 1H), 6.49 (dd, 1H, $J=0.6$, 7.5 Hz), 6.74 (dd, 1H, $J=0.6$, 7.5 Hz), 6.93 (t, 1H, $J=7.9$ Hz), 7.17–7.27 (m, 5H), 7.45 (d, 1H, $J=8.7$ Hz), 7.70 (dd, 1H, $J=8.6$, 2.0 Hz), 8.10 (d, 1H, $J=1.8$ Hz). Anal. calcd for $C_{29}H_{34}N_4O_5S_2$: M_r 582.2049. Found: M_r 583.2012 (M + H, HRFABMS).

3-*S*-{*N*-(3-Amino-2-methylphenylcarboxamido)} - [2*R* - hydroxy-1-[(2-aminobenzothiazole-6-sulfonyl)-(2-methylpropyl)amino]-4-phenylbutane (23). This compound was obtained employing the above procedure described for compound **21** and using 2-methyl-3-aminobenzoic acid to afford the product. Yield: 60%. ^{1}H NMR (CD_3OD) δ 0.89, 0.94 (2d, 6H, $J=6.6$ Hz), 1.71 (s, 3H), 2.01 (m, 1H), 2.63 (m, 1H), 2.92–3.16 (m, 3H), 3.54 (m, 1H), 3.88 (m, 1H), 4.27 (m, 1H), 6.38 (dd, 1H, $J=0.8$, 7.4 Hz), 6.71 (dd, 1H, $J=0.8$, 7.4 Hz), 6.89 (t, 1H, $J=7.8$ Hz), 7.16–7.28 (m, 5H), 7.45 (d, 1H, $J=8.5$ Hz), 7.70 (dd, 1H, $J=2$, 8.6 Hz), 8.10 (d, 1.8 Hz). Anal. calcd for $C_{29}H_{35}N_5O_4S_2$: M_r 581.2209. Found: M_r 582.2199 (M + H, HRFABMS).

3-*S*-{*N*-(2-Methylphenylcarboxamido)}-[2*R*-hydroxy-1-[(2-aminobenzothiazole-6-sulfonyl)-(2-methylpropyl)-amino]-4-phenylbutane (24). This compound was obtained using the above procedure described for compound **21** and replacing the acid with 2-methylbenzoic acid to afford the product. Yield: 60%. ^{1}H NMR (CD_3OD) δ 0.88, 0.94 (2d, 6H, $J=6.6$ Hz), 1.95 (s, 3H), 2.07 (m, 1H), 2.66 (m, 1H), 2.92–3.59 (m, 4H), 3.91 (m, 1H), 4.29 (m, 1H), 6.99–7.28 (m, 9H), 7.44 (d, 1H, $J=8$,5 Hz), 7.69 (dd, 1H, $J=1.8$, 8.4 Hz), 8.09 (d, 1H, $J=1.8$ Hz). Anal. calcd for

$C_{29}H_{34}N_4O_4S_2$: M_r 566.2100. Found: M_r 567.2053 (M + H, HRFABMS).

3-*S*-(*N*-5-Thiazolylmethyloxyformamido)-2*R*-hydroxy-1-[(2-aminobenzothiazole-6-sulfonyl)(2-methylpropyl)amino]-4-phenylbutane (27). Pyridine (0.198 g, 7.5 mmol) was added to a solution of thiazole-5-carbinol (0.2875 g, 2.5 mmol) in acetonitrile (12 mL) followed by DSC (0.640 g, 2.5 mmol). After 30 min, the reaction mixture became clear and the 3-*S*-amino-2*R*-hydroxy-1-[(2-aminobenzothiazole-6-sulfonyl)-(2-methylpropyl)amino]-4-phenylbutane (1.12 g, 2.5 mmol) was added and the reaction mixture was stirred at rt for 16 h. The reaction mixture was concentrated and the residue was dissolved in dichloromethane (100 mL), washed with sodium hydroxide (25 mL), brine (25 mL), dried ($MgSO_4$) and concentrated. The residue obtained was purified by chromatography (16% hexane in ethyl acetate) to afford the 0.90 g (61%) of the product. ^{1}H NMR (CD_3OD) δ 0.84, 0.88 (2d, 6H, J = 6.6 Hz), 1.97 (m, 1H), 2.53–3.40 (m, 6H), 3.71–3.83 (m, 2H), 5.14 (s, 2H), 7.08–7.16 (m, 5H), 7.45 (d, 1H, J = 8.5 Hz), 7.67 (dd, 1H, J = 1.8, 8.6 Hz), 7.74 (s, 1H), 8.07 (d, 1H, J = 1.8 Hz), 8.87 (s, 1H). Anal. calcd for $C_{26}H_{31}N_5O_5S_3$: M_r 589.1566. Found: M_r 590.1580 (M + H, HRFABMS).

3-*S*-(*N*-3-Pyridylmethyloxyformamido)-2*R*-hydroxy-1-[(2-aminobenzothiazole-6-sulfonyl) (2-methylpropyl)amino]-4-phenylbutane (26). Obtained using the procedure described for **27** above and pyridine-3-carbinol instead of thiazole-5-carbinol to afford the product. Yield: 68%. ^{1}H NMR (CD_3OD) δ 0.84, 0.89 (2d, 6H, J = 6.45 Hz), 1.98 (m, 1H), 2.59 (m, 1H), 2.84–3.45 (m, 5H), 3.71–3.85 (m, 2H), 4.98 (q, 1H, J = 13 Hz), 7.10–7.18 (m, 5H), 7.31 (t, 1H, J = 5 Hz), 7.44 (d, 1H, J = 8.5 Hz), 7.58 (d, 1H, J = 7,9 Hz), 7.67 (dd, 1H, J = 1.8, 8.4 Hz), 8.07 (dd, 1H, J = 1.8 Hz), 8.40 (s, 1H). Anal. calcd for $C_{28}H_{33}N_5O_5S_2$: M_r 583.2001. Found: M_r 584.2012 (M + H, HRFABMS).

3-*S*-(*N*-3-Tetrahydrofuranyloxyformamido)-2*R*-hydroxy-1-[(2-aminobenzothiazole-6-sulfonyl) (2-methylpropyl)amino]-4-phenylbutane (28). This compound was synthesized using the procedure above for **27** and 3-hydroxytetrahydrofuran to afford the product. Yield: 50%. ^{1}H NMR (CD_3OD) δ 0.87, 0.92 (2d, 6H, J = 6.6 Hz), 1.98–2.06 (m, 3H), 2.56 (m, 1H), 2.87–3.82 (m, 13H), 4.98 (m, 1H), 7.14–7.22 (m, 5H), 7.46 (d, 1H, 8.7 Hz), 7.68 (dd, 1H, J = 1.8, 8.4 Hz), 8.08 (d, 1H, J = 1.6 Hz). Anal. calcd for $C_{26}H_{34}N_4O_6S$: M_r 562.1998. Found: M_r 563.2014 (M + H, HRFABMS).

3-*S*-{*N*-2-(2,6-Dimethylphenoxymethylformamido)}-2*R*-hydroxy-1-[(2-benzothiazol-6-sulfonyl) (2-methylpropyl)amino]-4-phenylbutane (29). Isoamylnitrite (0.149 mL, 1.11 mmol) was added to a solution of the aminobenzothiazole (0.34 g, 0.557 mmol) in refluxing dioxane (5 mL). After the evolution of nitrogen had ceased (1 h), the reaction mixture was concentrated in vacuo and the residue was purified by chromatography (ethyl acetate–hexane, 1:1) to afford 0.21 g (64%) of the product. ^{1}H NMR (CD_3OD) δ 0.86, 0.91 (2d, 6H, J = 6.6 Hz), 2.05 (m, 1H), 2.10 (s, 6H), 2.75–4.28 (m, 11H), 6.86–6.95 (m, 3H), 7.14–7.27 (m, 5H), 7.97 (dd, 1H, J = 1.8, 8.6 Hz), 8.18 (d, 1H, J = 8.6 Hz), 8.62 (d, 1H, J = 1.6 Hz), 9.4 (s, 1H). Anal. calcd for $C_{31}H_{37}N_3O_5S_2$: M_r 595.2253. Found: M_r 596.2245 (M + H, HRFABMS).

3-*S*-{*N*-(2-Methylphenylcarboxamido)}-[2*R*-hydroxy-1-[(2-aminobenzothiazole-6-sulfonyl)-(2-methylpropyl)amino]-4-phenylbutane (30). Starting with the aminobenzothiazole **24** and using the procedure described above for **29**, the product **30** was obtained. Yield: 59%. ^{1}H NMR (CD_3OD) δ 0.88, 0.94 (2d, 6H, J = 6.6 Hz), 1.94 (s, 3H), 2.08 (m, 1H), 2.65 (m, 1H), 2.99–3.65 (m, 4H), 3.89 (m, 1H), 4.28 (m, 1H), 6.99–7.27 (m, 9H), 7.98 (dd, 1H, J = 1.8, 8.4 Hz), 8.19 (d, 1H, J = 8.5 Hz), 8.64 (d, 1H, J = 1.8 Hz) 9.44 (s, 1H). Anal. calcd for $C_{29}H_{33}N_3O_4S_2$: M_r 551.1991. Found: M_r 552.1995 (M + H, HRFABMS).

3-*S*-(*N*-5-Thiazolylmethyloxyformamido)-[2*R*-hydroxy-1-[(benzothiazole-6-sulfonyl) (2-methylpropyl)amino]-4-phenylbutane (33). Using the procedure described above for **29** and starting with the aminobenzothiazole **27**, the product was obtained. Yield: 93%. ^{1}H NMR (CD_3OD) δ 0.85, 0.89 (2d, 6H, J = 6.6 Hz), 1.99 (m, 1H), 2.56 (m, 1H), 2.92–3.45 (m, 4H), 3.67–3.82 (m, 2H), 5.15 (s, 2H), 7.09–6.17 (m, 5H), 7.75 (s, 1H), 7.95 (dd, 1H, J = 1.8, 8.6 Hz), 8.20 (d, 1H, J = 8.7 Hz), 8.61 (s, 1H, J = 1.6 Hz), 8.88 (s, 1H), 9.45 (s, 1H). Anal. calcd for $C_{26}H_{30}N_4O_5S_3$: M_r 547.1457. Found: M_r 575.1460 (M + H, HRFABMS).

3-*S*-(*N*-3-Pyridylmethyloxyformamido)-2*R*-hydroxy-1-[(benzothiazole-6-sulfonyl)(2-methylpropyl)amino]-4-phenylbutane (32). Starting with the aminobenzothiazole **26** and using the procedure described above for **29**, the product was obtained in 58% yield. ^{1}H NMR (CD_3OD) δ 0.84, 0.89 (2d, 6H, J = 0.4 Hz), 1.99 (m, 1H), 2.58 (m, 1H), 2.96–3.51 (m, 5H), 3.72–3.84 (m, 2H), 4.98 (q, 2H, J = 13 Hz), 7.08–7.18 (m, 5H), 7.31 (m, 1H), 7.59 (d, 1H, J = 7.9 Hz), 7.95 (dd, 1H, J = 6.8, 8.6 Hz), 8.18 (d, 1H, J = 8.7 Hz), 8.41 (s, 1H), 8.60 (d, 1H, J = 1.6 Hz), 9.42 (s, 1H). Anal. calcd for $C_{28}H_{32}N_4O_5S_2$: M_r 568.1892. Found: M_r 569.1894 (M + H, HRFABMS).

3-*S*-(*N*-3-Tetrahydrofuranyloxyformamido)-2*R*-hydroxy-1-[(benzothiazole-6-sulfonyl) (2-methylpropyl)amino]-4-phenylbutane (34). Starting with the aminobenzothiazole **28** and using the procedure described above for **29**, the desired product was obtained in 89% yield. ^{1}H NMR (CD_3OD) δ 0.85, 0.90, (2d, 6H, J = 6.6 Hz), 1.86–2.09 (m, 3H), 2.56 (m, 1H), 2.92–3.88 (m, 13H), 4.98 (m, 1H), 7.11–7.20 (m, 5H), 7.96 (dd, 1H, J = 1.8, 8.7 Hz), 8.19 (d, 1H, J = 8.7 Hz), 8.61 (d, 1H, J = 1.8 Hz), 9.42 (s, 1H). Anal. calcd for $C_{26}H_{33}N_3O_6S_2$: M_r 547.1889. Found: M_r 548.1869 (M + H, HRFABMS).

3-*S*-(*N*-*t*-Butyloxyformamido)-2*R*-hydroxy-1-[(2-aminobenzothiazol-6-sulfonyl) (2-methylpropyl)amino]-4-phenylbutane (42). The amino compound **6** (32.2 g, 71.63 mmol), BOC-ON (17.7 g, 71.63 mmol), and triethylamine (7.219 g, 71.63 mmol) in tetrahydrofuran (330 mL) were stirred at room temperature for 18 h. The

reaction mixture was concentrated and the residue was dissolved in dichloromethane (1 L). The dichloromethane solution was washed with sodium hydroxide (1 N, 500 mL), citric acid (5%, 500 mL) dried ($MgSO_4$) and concentrated to afford a residue, which was recrystallized from ethyl acetate–hexane to afford 30.0 g (75%) of the product as a solid. ^{1}H NMR (CD_3OD) δ 0.88, 0.92 (2d, 6H, J = 6.6 Hz), 1.28 (s, 9H), 2.04 (m, 1H), 2.56 (m, 1H), 2.88–3.43 (m, 4H, 3.60–3.76 (m, 2H), 7.14–7.23 (m, 5H), 7.46 (d. 1H, J = 8.5 Hz), 7.69 (dd, 1H, 1.8, 8.6 Hz), 8.08 (d, 1H, J = 1.8 Hz). Anal. calcd for $C_{26}H_{36}N_4O_5S_2$: M_r 549.2205. Found: M_r 549.2173.

2R-Hydroxy-1-[(benzothiazol-6-sulfonyl) (2-methylpropyl)amino]-4-phenylbutane (35). Portions of **42** (25.0 g, 45.49 mmol) were added to a solution of isoamylnitrite (12.35 mL) in dioxane (300 mL) and the mixture was heated at 85 °C. After the cessation of evolution of nitrogen, the reaction mixture was concentrated and the residue was purified by chromatography (hexane–ethyl acetate 1:1) to afford 20.5 g (84%) of the product as a solid. The crude product from the above reaction mixture (11.8 g, 22.07 mmol) was added dioxane–HCl (4 N, 40 mL) and was stirred at room temperature for 2 h and concentrated. Excess HCl was chased with toluene to afford 11.0 g (quantitative yield) of the desired product. ^{1}H NMR (CD_3OD) δ 0.83, 0.92 (2d, 6H, J = 6.6 Hz), 1.95 (m, 1H), 2.84–3.29 (m, 4H), 3.50–3.74 (m, 2H), 4.16 (m, 1H), 7.29–7.39 (m, 5H), 7.96 (dd, 1H, J = 1.8, 8.6 Hz), 8.24 (d, 1H, J = 8.7 Hz), 8.64 (d, 1H, J = 1.6 Hz), 9.50 (s, 1H). Anal. calcd for $C_{21}H_{27}N_3O_3S_2$: M_r 435.1650. Found: M_r 435.1641 (M + H, HRFABMS).

3-*S*-{*N*-(3-Hydroxy-2-methylphenylamido)}-2*R*-hydroxy-1-[(benzothiazole-6-sulfonyl)-(2-methylpropyl)amino]-4-phenylbutane (36). The procedure for the synthesis of **21** was used for the coupling of **35** and 2-methyl-3-hydroxybenzoic acid to afford the product. Yield: 81%. ^{1}H NMR (CD_3OD) δ 0.87, 0.91 (2d, 6H, J = 6.6 Hz), 1.76 (s, 3H), 2.08 (m, 1H), 2.66 (m, 1H), 2.99–3.64 (m, 5H), 3.89 (m, 1H), 4.28 (m, 1H), 6.49 (d, 1H, J = 7.3 Hz), 6.74 (d, 1H, J = 7.5 Hz), 6.92 (t, 1H, J = 7.9 Hz), 7.17–7.26 (m, 5H), 7.98 (d, 1H, J = 8.7 Hz), 8.18 (d, 1H, J = 8.7 Hz), 8.62 (s, 1H) 9.41 (s, 1H). Anal. calcd for $C_{29}H_{33}N_3O_5S_2$: M_r 568.190. Found: M_r 568.1919 (M + H, HRFABMS).

3-*S*-{*N*-(3-Amino-2-methylphenylcarboxamido)} - [2*R* - hydroxy-1-[(benzothiazole-6-sulfonyl)-(2-methylpropyl)amino]-4-phenylbutane (37). The procedure for the synthesis of **21** was used for the coupling of 35 and 2-methyl-3-aminobenzoic acid to afford the product. Yield: 60%. ^{1}H NMR (CD_3OD) δ 0.88, 0.94 (2d, 6H, J = 6.6 Hz), 1.70 (s, 3H), 2.08 (m, 1H), 2.67 (m, 1H), 2.98–3.64 (m, 5H), 3.87 (m, 1H), 4.25 (m, 1H), 6.38 (d, 1H, J = 6.9 Hz), 6.70 (d, 1H, J = 7.5 Hz), 6.88 (t, 1H, J = 7.9 Hz), 7.17–7.26 (m, 5H), 7.99 (dd, 1H, J = 7.8, 1.8 Hz), 8.21 (d, 1H, J = 8.7 Hz), 8.64 (d, 1H, J = 1.6 Hz) 9.44 (s, 1H). Anal. calcd for $C_{29}H_{34}N_4O_4S_2$: M_r 567.2099. Found: M_r 567.2127 (M + H, HRFABMS).

3-*S*-[*N*-2-{2(*R*)methyl-3-methylsulfonyl}propionyl] - 2*R* - hydroxy-1-[(2-benzothiazol-6-sulfonyl) (2-methylpropyl)amino]-4-phenylbutane. The procedure for the synthesis of **21** was used for the coupling of 35 and 2(*R*) methyl-3-sulfonyl)propionic acid to afford the product. Yield: 43%. ^{1}H NMR (CD_3OD) δ 0.85, 0.90 (2d, 6H, J = 6.6 Hz), 1.15 (d, 3H, J = 6.6 Hz), 2.03 (m, 1H), 2.44 (s, 3H), 2.65 (m, 2H), 2.81–3.51 (m, 9H), 3.82 (m, 1H), 4.06 (m, 1H), 7.14–7.25 (m, 5H), 7.97 (dd, 1H, J = 1.8, 8.6 Hz), 8.21 (d, 1H, J = 8.6 Hz), 8.63 (d, 1H, J = 1.8 Hz), 9.45 (s, 1H). Anal. calcd for $C_{26}H_{35}N_3O_6S_3$: M_r 582.1766. Found: M_r 582.1744 (M + H, HRFABMS).

Benzothiazole-6-sulfonic acid (40). A suspension of 2-amino-6-sulfonamido benzothiazole (Prepared as reported in the literature,[12] 10.0 g, 43.67 mmol) in dioxane (300 mL) was heated at reflux. Isoamylnitrite (24 mL) was added in two portions to the reaction mixture. Vigorous evolution of gas was observed (the reaction was conducted behind a blast shield as a precaution) and after 2 h, a red precipitate was deposited in the reaction vessel. The reaction mixture was filtered hot, and the solid was washed with dioxane and was dried. The solid was recrystallized from methanol-water. Only small amount of a solid was formed after 2 days. This precipitate was filtered off and the mother liquor was concentrated in vacuo to afford pale red-orange solid (8.0 g, 85%). ^{1}H NMR (CD_3OD) δ 7.87 (dd, 1H, J = 1.4, 8.4 Hz), 7.99 (d, 1H, J = 8.5 Hz), 8.41 (d, 1H, J = 1.6 Hz), 9.34 (s, 1H). Anal. calcd for $C_7H_5NO_3S_2$: M_r 215.9789. Found: M_r 215.9790 (M + H, HRFABMS).

3-*S*-(*N*-Benzyloxyformamido)-2*R*-hydroxy-1-[(2-aminobenzothiazol-6-sulfonyl) (2-methylpropyl)amino]-4-phenylbutane (8). Thionyl chloride (4 mL) was added to a suspension of the benzothiazole-6-sulfonic acid (0.60 g, 2.79 mmol) in dichloroethane (15 mL) and the reaction mixture was heated at reflux. The sulfonic acid did not dissolve in the reaction mixture. Addition of dimethylformamide (5 mL) to the reaction mixture resulted in a clear solution. After 1.5 h at reflux, the solvent was removed in vacuo and excess HCl and thionyl chloride was chased by evaporation with dichloroethane. The residue in ethyl acetate (100 mL) was added the *Z*-amino alcohol **4** (1.03 g, 2.78 mmol) followed by *N*-methylmorpholine (4 mL). After stirring at room temperature for 18 h, the reaction mixture was diluted with ethyl acetate (100 mL), washed with citric acid (5%, 100 mL), sodium bicarbonate (saturated, 100 mL), and brine (100 mL), dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (silica gel, ethyl acetate–hexane 1:1) to afford 0.340 g (23%) the product in pure form. This product was identical (^{1}H NMR, ^{13}C NMR, mass spectrum, and HPLC) to an authentic sample of **8**. ^{1}H NMR (CD_3OD) δ 0.84, 0.88 (2d, 6H, J = 6.6 Hz), 1.99 (m, 1H), 2.59 (m, 1H), 2.91–3.48 (m, 5H), 3.77–3.83 (m, 2H), 4.92 (m, 2H), 7.13–7.25 (m, 10H), 7.94 (dd, 1H, J = 1.6, 8.7 Hz), 8.16 (d, 1H, J = 8.7 Hz), 8.59 (d, 1H, J = 1.6 Hz), 9.41 (s, 1H). Anal. calcd for $C_{29}H_{33}N_3O_5S_2$: M_r 567.1940. Found: M_r 568.1933 (M + H, HRFABMS).

References and Notes

1. (a) Blundell, T. L.; Lapatto, R.; Wilderspin, A. F.; Hemmings, A. M.; Hobart, P. M.; Danley, D. E.; Whittle, P. J.

Trends Biol. Sci. **1990**, *15*, 425. (b) Debouck, C.; Metcalf, B. W. *Drug Dev. Res.* **1990**, *21*, 1.
2. Kohl, N. E.; Emini, E. A.; Schleif, W. A.; Davis, L. J.; Heimbach, J. C.; Dixon, R. A. F.; Scolnick, E. M.; Sigal, I. S. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 4686.
3. Debouck, C. *AIDS Res. Human Retroviruses* **1992**, *8*, 153.
4. Dorsey, D. D.; Levi, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schlif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Azel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *L-735, 524: J. Med. Chem.* **1994**, *34*, 3443.
5. Kaldoe, S. W.; Kalish, V. J.; Davies, II, J. F.; Shetty, B. V.; Frotz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadez, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.* **1997**, *40*, 3979.
6. Kempf, D. J.; Marsh, K. C.; Denissen, J. F.; McDonald, E.; Vasavanoda, S.; Flentge, C. A.; Green, B. E.; Fino, L.; Park, C. H.; Kong, X.-P.; Wideburg, N. E.; Saldivar, A.; Ruiz, L.; Kati, W. M.; Sham, H.; Robin, T.; Srewart, K. D.; Hsu, A.; Plattner, J. J.; Leonard, J. M.; Norbeck, D. W. *Proc. Natl. Acad. Sci.: U.S.A.* **1995**, *92*, 2484.
7. (a) Roberts, N. A.; Martin, J. A.; Kinchington, D.; Broadhurst, A. V.; Craig, J. C.; Duncan, I. B.; Galpin, S. A.; Handa, B. K.; Kay, J.; Krohn, A.; Lambert, R. W.; Merrett, J. H.; Mills, J. S.; Parkes, K. E. B.; Redshaw, S.; Ritchie, A. J.; Taylor, D. L.; Thomas, G. J.; Machin, P. J. *Science* **1990**, *248*, 358. (b) Krohn, A.; Redshaw, S.; Ritchie, A. J.; Graves, B. J.; Hatada, M. H. *J. Med. Chem.* **1991**, *34*, 3340.
8. (a) Kim, E. E.; Baker, C. T.; Dwyer, M. D.; Murcko, M. A.; Rao, B. G.; Tung, R. D.; Navia, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 1181. (b) Sham, H. L.; Kempf, D. J.; Molla, A.; Marsh, K. C.; Kumar, G. N.; Chen, C. M.; Kati, W.; Stewart, K.; Lal, R.; Hsu, A.; Betebenner, D.; Korneyeva, M.; Vasavanonda, S.; McDonald, E.; Saldivar, A.; Wideburg, N.; Chen, X.; Niu, P.; Park, C.; Jayanti, V.; Grabowski, B.; Granneman, G. R.; Sun, E.; Japour, A. J.; Norbeck, D. W. *Antimicrob. Agents Chemother.* **1998**, *42*, 3218. (c) Thaisrivongs, S.; Skulnick, H. I.; Turner, S. R.; Strohbach, J. W.; Tommasi, R. A.; Johnson, P. D.; Aristoff, P. A.; Judge, T. M.; Gammill, R. B.; Morris, J. K.; Romaines, K. A.; Chrusciel, R. A.; Hinshaw, R. R.; Chong, K.-T.; Tarpley, W. G.; Poppe, S. M.; Slade, D. E.; Lynn, J. C.; Hog, M.-M.; Tomich, P. K.; Seest, E. P.; Dolak, L. A.; Howe, W. J.; Howard, G. M.; Schwende, F. J.; Toth, L. N.; Padbury, G. E.; Wilson, G. J.; Shiou, L.; Zipp, G. L.; Wilkinson, K. F.; Rush, B. D.; Ruwart, M. J.; Koeplinger, K. A.; Zhao, Z.; Cole, S.; Zaya, R. M.; Kakuk, T. J.; Janakiraman, M. N.; Watenpaugh, K. D. *J. Med. Chem.* **1996**, *39*, 4349. (d) Mimoto, T.; Imai, J.; Kisanuki, S.; Enomoto, H.; Hattori, N.; Akaji, K.; Kiso, Y. *Kynoststin KNI-227 and –272, Chem. Pharm. Bull.* **1992**, *40*, 2251. (e) Lam, P. Y. S.; Ru, Y.; Jadhav, P. K.; Aldrich, P. E.; DeLucca, G. V.; Eyerma, C. J.; Chang, C.-H.; Emmett, G.; Holler, E. R.; Daneker, W. F.; Li, L.; Confalone, P. N.; McHugh, R. J.; Han, Q.; Li, R.; Markwalder, J. A.; Seitz, S. P.; Sharpe, T. R.; Bacheler, L. T.; Rayner, M. M.; Klabe, R. M.; Shum, L.; Winsloe, D. L.; Kornhauser, D. M.; Jackson, D. A.; Erickson-Viitanen, S.; Hodge, C. N. *J. Med. Chem.* **1996**, *39*, 3514. (f) Bold, G.; Fassler, A.; Capraro, H.-G.; Cozens, R.; Klimkait Lazdins, J.; Mestan, J.; Poncioni, B.; Rosel, J.; Stover, D.; Tintelnot-Blomley, M.; Acemoglu, F.; Beck, W.; Boss, E.; Eschbach, M.; Hurlimann, T.; Masso, E.; Roussel, S.; Ucci-Stoll, K.; Wyss, D.; Lang, M. *J. Med. Chem.* **1998**, *41*, 3387.
9. (a) Thaisrivongs, S. *Annu. Rep. Med. Chem.* **1994**, *29*, 133. Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359. b Tamamura, H.; Koh, Y.; Ueda, S.; Sasaki, Y.; Yamasaki, T.; Aoki, M.; Maeda, K.; Watai, Y.; Arikuni, H.; Otaka, A.; Mitsuya, H.; Fujii, N. *J. Med. Chem.* **2003**, *46*, 1764. c Frescos, J. N.; Bertenshaw, D. E.; Getman, D. P.; Heintz, R. M.; Mischke, B. V.; Blystone, L. W.; Bryant, M. L.; Funkes-Shippy, C.; Houseman, K. A.; Kishore, N. N.; Kocan, G. P.; Mehta, P. P. *Biorg. Med. Chem. Lett.* **1996**, *6*, 445.
10. (a) Getman, D. P.; DeCrescenzo, G. D.; Heintz, R. M.; Reed, K. L.; Talley, J. J.; Bryant, M. L.; Clare, M.; Housman, K. A.; Marr, J. J.; Mueller, R. A.; Vazquez, M. L.; Shieh, H-S.; Stallings, W. C.; Stegeman, R. A. *J. Med. Chem.* **1993**, *36*, 288. (b) Vazquez, M. L.; Bryant, M. L.; Clare, M.; DeCrescenzo, G. A.; Doherty, E. M.; Freskos, J. N.; Getman, D. P.; Houseman, K. A.; Julien, J. A.; Kocan, G. P.; Mueller, R. A.; Shieh, H.-S.; Stallings, W. C.; Stegeman, R. A.; Talley, J. J. *J. Med. Chem.* **1995**, *38*, 581.
11. Ismail, I. A.; Sharp, D. E.; Chedekal, M. R. *J. Org. Chem.* **1980**, *45*, 2243.
12. Kaufmann, H. P.; Buckmann, H. *J. Arch. Pharm.* **1941**, *279*, 194.