New Cathepsin D Inhibitors with Hydroxyethylamine Isosteres: Preparation and Characterization

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Abstract: The lysosomal aspartyl protease, cathepsin D, has been suggested to play a role in the metastatic potential of several types of cancer. Cathepsin D is secreted by malignant cells, and is believed to be involved in the breakdown of the extracellular matrix. High levels of active cathepsin D have been found in colon cancer, prostate cancer, uterine cancer and ovarian cancer. Also cathepsin D has recently been associated with the development of Alzheimer's disease. Hydroxyethyl isosteres with cyclic tertiary amine have proven to be clinically useful as inhibitors of aspartyl proteases similar to cathepsin D in activity, such as the HIV-1 aspartyl protease. In the present study twenty-eight compounds containing (hydroxyethyl)amine isosteres with cyclic tertiary amines have been synthesized. These compounds show significant activity as cathepsin D inhibitors, many with IC_{50} values in the nanomolar range. For example, the compounds that contain hydroxyethylamines where the amine is formed from N-piperazine-2-carboxylic acid methyl ester, **4y-bb**, show IC_{50} values ranging from 2.5 to 15 nM.

INTRODUCTION

Proteolytic enzymes are involved in many biological functions and deteriorative diseases [1,2]. Specific inhibitors of proteases have long been considered as potential therapeutic agents [3]. Many serious medical problems, such as cardiac disease [4], AIDS [5], Alzheimer's disease [6], malaria [7], as well as colorectal [8] and breast cancer [9], and pancreatic cancer [10], either result directly from, or are characterized by, uncontrolled protease activity. Aspartyl proteases are among the most biologically important proteolytic enzymes. Cathepsin D is an aspartyl protease similar to the HIV-1 aspartyl protease in substrate specificity [11]. Cathepsin D has emerged in recent years as a prognostic indicator in several types of carcinoma, including bladder cancer [12], colorectal cancer [13], breast cancer [14], and lung cancer [15]. Also, cathepsin D has been associated with the development of Alzheimer's disease [16]. Therefore, protease inhibitors can lead to the development of therapeutic agents for treatment of many types of carcinomas and Alzheimer's disease.

The approach we have taken in the design of cathepsin D inhibitors is similar to the development of inhibitors of the HIV-1 aspartyl protease. Inhibitors of the aspartyl HIV-1 protease that contain hydroxyethylamines have enhanced oral absorption [17]. The (R)-hydroxyethylamine insert was incorporated as a key component of many clinically used, highly potent, HIV-1 protease inhibitors. At first several compounds with hydroxyethyl amine isosteres with flexible alkyl amines lead to the development of HIV-1 aspartyl protease inhibitors with poorer bioavailability [18]. These compounds were not therapeutically useful because they suffered limited *in vivo* half-lives. However, the use of hydroxyethyl isosteres with cyclic tertiary amines provided inhibitors of the aspartyl HIV-1 protease that have enhanced oral absorption [17]. In recent years the (R)-hydroxyethylamine insert was incorporated as a key component of many clinically used, highly potent, HIV-1 protease inhibitors [18]. Hydroxyethyl amine isosteres with flexible tertiary amines have also been utilized in design of Cathepsin D inhibitors for a structure based combinatorial library [19]. Utilizing information gathered through crystallographic and magnetic resonance experiments, Kick and Roe [19] generated a combinatorial library of cathepsin D inhibitors through molecular modeling. The basic structure of cathepsin D inhibitors shows the S-hydroxyethyl amine epimer to be the more active, rather than the R-epimer preferred by the HIV-1 aspartyl protease. We have shown by molecular modeling that the phenyl group of a phenyalanine-type hydroxyethylene or hydroxyethyl amine is easily positioned in the S_1 site of the HIV-1 aspartyl protease [20]. Other studies show that a cyclic amine or amide might fit reasonably well into the $S_{2'}$ and $S_{3'}$ sites [21]. Molecular modeling (HYPERCHEM) has shown that a five or six member ring forming the tertiary amine may be able to orient the backbone of the inhibitor toward a bioactive conformation while providing more of a non-peptide functionality. Therefore, we set out to synthesize compounds that contain a peptide portion to accommodate the S_1, S_2, and S_3 subsites and a non-peptide hydroxyethyl isostere portion with a cyclic tertiary amine to accommodate the $S_{1'}$, $S_{2'}$, and $S_{3'}$ enzyme subsites. The general structure of our synthetic inhibitors is shown in Fig. (**1**).

RESULTS AND DISCUSSION

The synthetic plan of the potential cathepsin D inhibitors involved two phases: preparation of the protected hydroxyethyl amine isostere portion (Scheme **1**) and condensation

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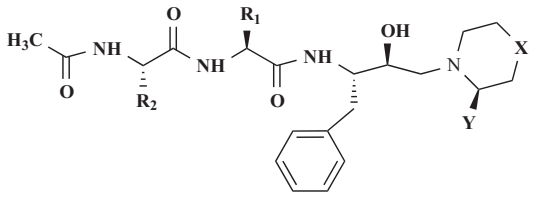

Fig. (1).

and deblocking of the peptide and non-peptide portions (Scheme **2**). The hydroxyethyl amine isosteres were prepared from a tert-butoxycarbonyl (BOC) chiral amino aminoalkyl epoxide reported earlier [17]. Similar chiral aminoalkyl epoxides (with opposite stereochemistry) have been used successfully in the preparation of several HIV-1 aspartyl protease inhibitors with hydroxyethyl amine isosteres [17,18]. The 2S, 3S epoxide is utilized to prepare HIV-1 protease inhibitors with the desired R-hydroxyethyl amine isostere [17,18]. However, since the S-hydroxyethyl amine isostere is reported to be the more active isomer for cathepsin D inhibition [19], we utilized the 2R, 3S protected amino epoxide in our synthesis (Scheme **1**). A bulky cyclic amine (morpholine, piperazine, L-proline methyl ester, N-phenyl piperazine, N-p-nitrophenylpiperazine, N-pipericoli-nate methyl ester, or N-piperazine-2-carboxylic acid methyl ester) Fig.(**2**) was used as a nucleophile in the preparation of the cyclized tertiary amines. The BOC protecting group was removed from the primary amine (N-terminus) with non-aqueous acid (4 M HCl in chloroform).

In the second phase of our synthesis, the Cbz-protected dipeptide was condensed with ethyl chloroformate and then reacted with the basified primary amine of the hydroxyethyl amine isostere portion (Scheme **2**). The Cbz protecting group of the resulting compound was then removed and replaced with an acetyl group. The synthetic inhibitors (Table **1**) were purified by sephadex HP chromatography and characterized by TLC and ^{1}H NMR.

The twenty-eight synthetic compounds were screened for their Cathepsin D inhibition by a spectrophotometric assay of hemoglobin hydrolysis (Table **2**). Modifications in the ring of the hydroxyethyl tertiary amine appear to have affected the potency of the inhibitors. Those compounds with a morpholine (**4a-d**), piperazine (4**e-h**), or L-piperazine-2-carboxylic acid methyl ester (**4y-bb**) show better Cathepsin D inhibition than the other compounds. Also, the variation in the N-terminal amino acid side appears to affect the Cathepsin D inhibition. Compounds with an alanine in the P_3 position, were somewhat less effective inhibitors than those compounds with a valine or leucine in the P_3 position. The best inhibitor of cathepsin D we found to be 3(S)-[acetyl-leucyl-phenylalanylamino]-4-phenyl-1-N-(L-piperazine-2-carboxylic acid methyl ester)-2(S)-butanol (**4aa**) with IC_{50} = 2.5 nM.

CONCLUSIONS

Our synthetic route shows a great deal of promise for the future synthesis of similar hydroxyethyl amine isosteres. Initial screening shows these compounds to be potent inhibitors of cathepsin D activity.

ACKNOWLEDGMENT

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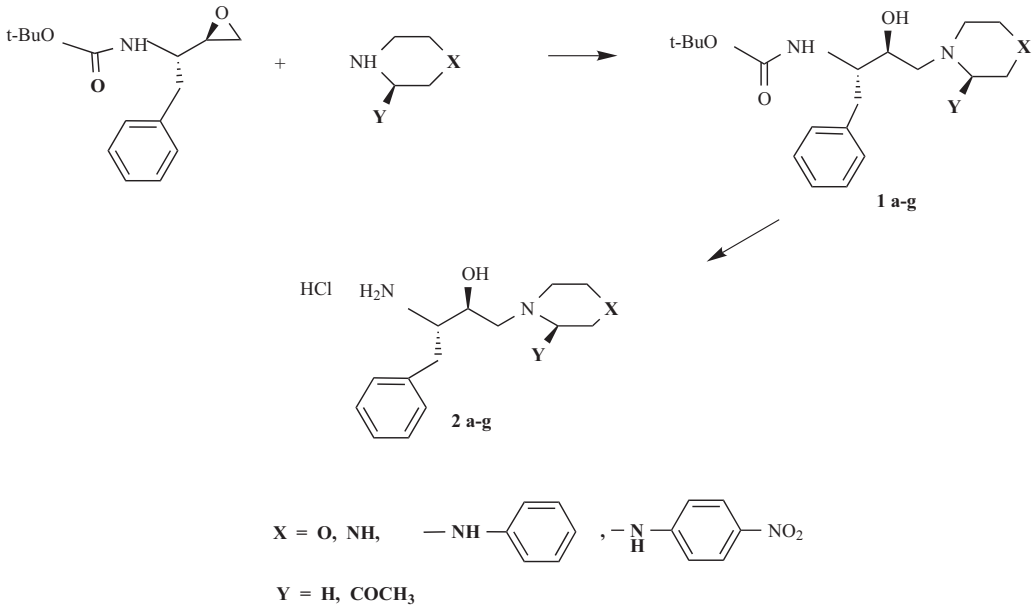
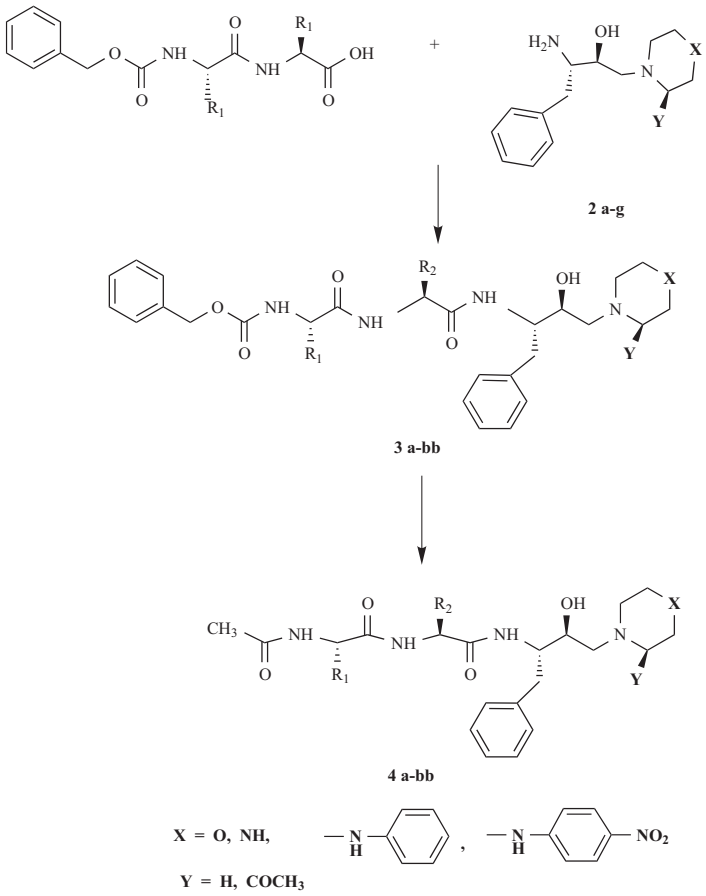


Scheme 1.



Scheme 2.

EXPERIMENTAL

Anhydrous solvents were "anhydrous grade" from Aldrich Chemical Company. Other reagents were purchased from either Aldrich or Sigma Chemical Company. All solvents were HPLC grade. The solvents described as "dry" were distilled over sodium just prior to use. Whatman PE SIL G/UV 250 µm silica gel plates were used for thin layer chromatography (TLC). Column chromatography was run on either Aldrich TLC grade silica gel 2-25µm particle size with average pore diameter 60Å, or Sigma Sephadex LH-20, lipophilic, bead size 20-100µm. ^{1}H NMR spectra were collected either on a Bruker 200 MHz AC superconducting spectrometer or on a Hitachi 60 MHz R1200 RS NMR spectrometer. ^{1}H NMR of final compounds and major intermediates were collected on a 200 MHz spectrometer, while the spectra of minor intermediates were collected on a 60 MHz NMR spectrometer. The spectral data were processed NTNMR software produced by TeleMag.

3(S)-BOC-amino-4-phenyl–1-N-morpholine-2(S)-butanol (1a)

A solution of **3a** (1.0 g, 3.1 mmol) in 100 mL dry THF was treated with 1.7 mL (20 mmol) morpholine. The solution was refluxed for 48 hrs. The mixture was then cooled to room temperature, concentrated under reduced pressure to about one half its volume, and partitioned between ethyl acetate (200 mL) and 5% aqueous sodium potassium tartarate (200 mL) containing 1.0 g NaCl. The organic layer was washed with distilled water (100 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give a white solid (0.857 g). The crude product was purified by silica gel column chromatography (2.5 cm x 60 cm length) using 60% ethyl acetate/hexanes as the mobile phase to give 0.591 g (54% yield). TLC (50% ethyl acetate/hexanes) R_f = 0.23. ^{1}H NMR ($CDCl_3$/TMS, 200MHz) δ 0.999 (9H, s), 2.376 (2H, d), 2.967 (2H, d), 3.215 (4H, t), 3.678 (4H, t), 3.892 (1H, d of t), 4.402 (1H, d of t), 4.815 (1H, m, exchangable), 5.011 (1H, m, exchangable), 7.245 (5H,s).

3(S)-BOC-amino-4-phenyl–1-N-piperazine-2(S)-butanol (1b)

A solution of 3(S)-t-butoxycarbonyl (BOC) amino-4-phenyl-2-(R)-oxirane [20] (1.0 g, 3.1 mmol) in 100 mL dry THF was treated with 0.861 g (10 mmol) piperazine. The solution was refluxed for 48 hrs. A similar reaction work-up

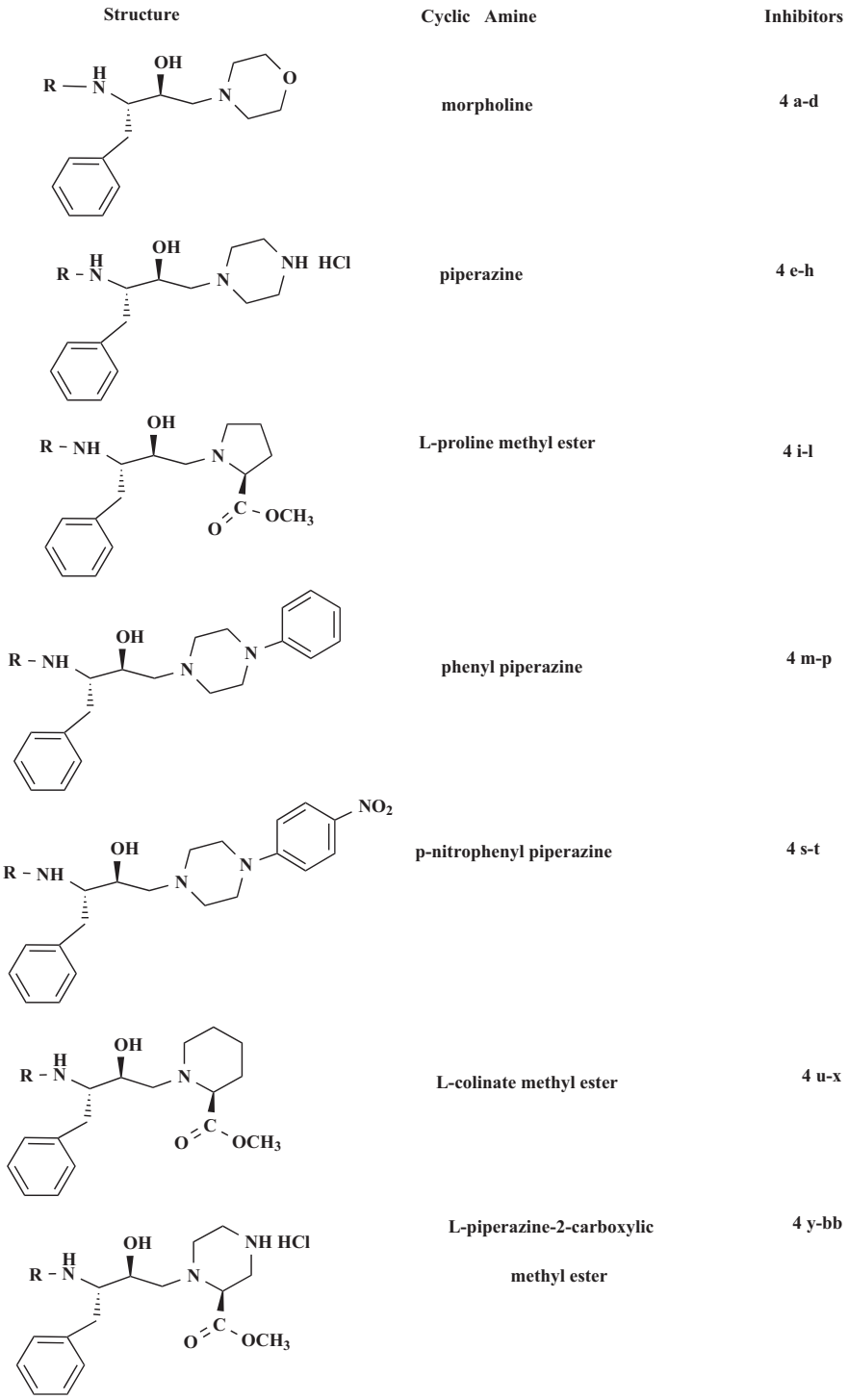


Fig. (2).

and column chromatography were used as described above for **1a** to give **1b** (0.784 g, 65%). TLC (60% ethyl acetate/ hexanes) R_f = 0.59. ^{1}H NMR ($CDCl_3$/TMS, 200MHz) δ 0.989 (9H, s), 1.653 (2H, t), 2.255 (8H, t), 2.445 (2H, d), 3.845 (1H, d of t), 4.382 (1H, m), 5.015 (1H, m, exchangable), 7.115 (5H,s).

Table 1. Synthetic Inhibitors

No.	Compound Name	Mol. Form.	M.W.
4a	3(S)-[Acetyl-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-morpholine-2(S)-butanol	$C_{28}H_{38}N_4O_5$	510.64
4b	3(S)-[Acetyl-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-morpholine-2(S)-butanol	$C_{30}H_{42}N_4O_5$	538.69
4c	3(S)-[Acetyl-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-morpholine-2(S)-butanol	$C_{31}H_{44}N_4O_5$	552.72
4d	3(S)-[Acetyl-L-leucyl-L-leucylamino]-4-phenyl-1-N-morpholine-2(S)-butanol	$C_{28}H_{46}N_4O_5$	518.70
4e	3(S)-[Acetyl-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-piperazine-2(S)-butanol Hcl	$C_{28}H_{40}N_5O_4Cl$	546.11
4f	3(S)-[Acetyl-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-piperazine-2(S)-butanol Hcl	$C_{30}H_{44}N_5O_4Cl$	574.17
4g	3(S)-[Acetyl-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-piperazine-2(S)-butanol Hcl	$C_{31}H_{46}N_5O_4Cl$	589.19
4h	3(S)-[Acetyl-L-leucyl-L-leucylamino]-4-phenyl-1-N-piperazine-2(S)-butanol Hcl	$C_{28}H_{49}N_5O_4Cl$	555.81
4i	3(S)-[Acetyl-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-(L-proline methyl ester)-2(S)-butanol	$C_{30}H_{40}N_4O_6$	552.64
4j	3(S)-[Acetyl-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-(L-proline methyl ester)-2(S)-butanol	$C_{32}H_{44}N_4O_6$	580.73
4k	3(S)-[Acetyl-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-(L-proline methyl ester)-2(S)-butanol	$C_{33}H_{46}N_4O_6$	594.75
4l	3(S)-[Acetyl-L-leucyl-L-leucylamino]-4-phenyl-1-N-(L-proline methyl ester)-2(S)-butanol	$C_{30}H_{48}N_4O_6$	560.74
4m	3(S)-[Acetyl-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-(N-phenylpiperazine)-2(S)-butanol	$C_{34}H_{43}N_5O_4$	585.75
4n	3(S)-[Acetyl-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-(N-phenylpiperazine)-2(S)-butanol	$C_{36}H_{47}N_5O_4$	613.80
4o	3(S)-[Acetyl-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-(N-phenylpiperazine)-2(S)-butanol	$C_{37}H_{49}N_5O_4$	627.83
4p	3(S)-[Acetyl-L-leucyl-L-leucylamino]-4-phenyl-1-N-(N-phenylpiperazine)-2(S)-butanol	$C_{34}H_{51}N_5O_4$	593.82
4q	3(S)-[Acetyl-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-(N-p-nitrophenylpiperazine)-2(S)-butanol	$C_{34}H_{42}N_6O_6$	630.75
4r	3(S)-[Acetyl-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-(N-p-nitrophenylpiperazine)-2(S)-butanol	$C_{36}H_{46}N_6O_6$	658.81
4s	3(S)-[Acetyl-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-(N-p-nitrophenylpiperazine)-2(S)-butanol	$C_{37}H_{48}N_6O_6$	672.83
4t	3(S)-[Acetyl-L-leucyl-L-leucylamino]-4-phenyl-1-N-(N-p-nitrophenylpiperazine)-2(S)-butanol	$C_{34}H_{50}N_6O_6$	638.82
4u	3(S)-[Acetyl-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-(L-pipecolinate methyl ester)-2(S)-butanol	$C_{31}H_{42}N_4O_6$	566.71
4v	3(S)-[Acetyl-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-(L-pipecolinate methyl ester)-2(S)-butanol	$C_{33}H_{46}N_4O_6$	594.76
4w	3(S)-[Acetyl-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-(L-pipecolinate methyl ester)-2(S)-butanol	$C_{34}H_{48}N_4O_6$	608.79
4x	3(S)-[Acetyl-L-leucyl-L-leucylamino]-4-phenyl-1-N-(L-pipecolinate methyl ester)-2(S)-butanol	$C_{31}H_{50}N_4O_6$	574.77
4y	3(S)-[Acetyl-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N(L-piperazine-2-carboxylic methyl ester)-2(S)-butanol	$C_{30}H_{42}N_5O_6Cl$	604.15
4z	3(S)-[Acetyl-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-(L-piperazine-2-carboxylic methyl ester)-2(S)-butanol	$C_{32}H_{46}N_5O_6Cl$	632.21
4aa	3(S)-[Acetyl-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-(L-piperazine-2-carboxylic methyl ester)-2(S)-butanol	$C_{33}H_{48}N_5O_6Cl$	646.24
4bb	3(S)-[Acetyl-L-leucyl-L-leucylamino]-4-phenyl-1-N-(L-piperazine-2-carboxylic methyl ester)-2(S)-butanol HC	$C_{30}H_{50}N_5O_6Cl$	612.22

3(S)-BOC-amino-4-phenyl–1-N-(L-proline methyl ester)-2(S)-butanol (1c)

A solution of 3(S)-t-butoxycarbonyl (BOC) amino-4-phenyl-2-(R)-oxirane [20] (1.0 g, 3.1 mmol) in 100 mL dry THF was treated with 1.29 g (10 mmol) L-proline methyl ester. The solution was refluxed for 48 hrs. A similar reaction work-up and column chromatography was used as described above for **1a** to give **1c** (0.503 g, 41%). TLC (15% ethyl acetate/hexanes) R_f = 0.54. ^{1}H NMR ($CDCl_3$/TMS, 200MHz) δ 0.998 (9H, s), 1.919 (4H, t), 2.220 (2H, t), 2.371 (1H, t), 2.463 (2H, d), 2.977 (2H, d), 3.612 (3H, s), 3.921 (1H, q), 4.511 (1H, q), 4.962 (1H, m, exchangable), 5.217(1H, m, exchangable), 7.133 (5H, s).

3(S)-BOC-amino-4-phenyl–1-N-(N-phenylpiperazine)-2(S)-butanol (1d)

A solution of 3(S)-t-butoxycarbonyl (BOC) amino-4-phenyl-2-(R)-oxirane [20] (1.0 g, 3.1 mmol) in 100 mL dry THF was treated with 3.25 g (20 mmol) N-phenylpiperazine. The solution was refluxed for 48 hrs. A similar reaction work-up and column chromatography was used as described above for **1a** to give **1d** (0.663 g, 50%). TLC (50% ethyl

Table 2. Inhibition of Cathepsin D hydrolysis of hemoglobin. λ = 280 nm.

Compound	IC_{50}, nM	K_i (apparent)
4a	45.4	49
4b	10.7	-----
4c	8.0	-----
4d	7.6	-----
4e	54.1	50
4f	10.0	-----
4g	6.8	-----
4h	6.2	-----
4i	95.1	96
4j	56.1	57
4k	33	34
4l	31	32
4m	128	86
4n	35	33
4o	18	17
4p	350	128
4q	55	54
4r	45	44
4s	46	45
4t	77	76
4u	106	98
4v	72	67
4w	44	23
4x	65	57
4y	15	3
4z	7.3	-----
4aa	2.5	-----
4bb	10.4	-----

acetate/hexanes) R_f = 0.45. ^{1}H NMR ($CDCl_3$/TMS, 200MHz) δ 1.003 (9H, s), 1.685 (2H, t), 2.338 (4H, t), 2.498 (2H, d), 2.691 (4 H, t), 3.892 (1H, d of t), 4.491 (1H, m), 4.925 (1H, m, exchangable), 7.135 (5H,s), 7.367 (5 H, s).

3(S)-BOC-amino-4-phenyl–1-N-(N-p-nitrophenylpiperazine)-2(S)-butanol (1e)

A solution of 3(S)-t-butoxycarbonyl (BOC) amino-4-phenyl-2-(R)-oxirane [20] (1.0 g, 3.1 mmol) in 125mL dry THF was treated with 5.18 g (25 mmol) 1-(4-nitrophenyl) piperazine. The solution was refluxed for 48 hrs. A similar reaction work-up and column chromatography was used as described above for **1a** to give **1e** (0.588 g, 66%). TLC (60% ethyl acetate/hexanes) R_f = 0.53. ^{1}H NMR ($CDCl_3$/TMS, 200MHz) δ 1.002 (9H, s), 1.639 (2H, t), 2.445 (4H, t), 2.501 (2H, d), 3.081 (4 H, t), 3.892 (1H, m), 4.531 (1H, m), 5.035 (1H, m, exchangable), 7.105 (5H,s), 7.557 (2 H, d), 8.015 (2H, d).

3(S)-BOC-amino-4-phenyl–1-N-(L-pipericolinate methyl ester)-2(S)-butanol (1f)

A solution of 3(S)-t-butoxycarbonyl (BOC) amino-4-phenyl-2-(R)-oxirane [20] (1.0 g, 3.1 mmol) in 100 mL dry THF was treated with 1.43 g (10 mmol) L-pipericolinate methyl ester. The solution was refluxed for 48 hrs. A similar reaction work-up and column chromatography was used as described above for **1a** to give **1f** (0.545 g, 43%). TLC (15% ethyl acetate/hexanes) R_f = 0.59. ^{1}H NMR ($CDCl_3$/TMS, 200MHz) δ 0.968 (9H, s), 1.423 (2H, m) 1.920 (4H, t), 2.222 (2H, t), 2.373 (1H, t), 2.465 (2H, d), 2.982 (2H, d), 3.599 (3H, s), 3.924 (1H, q), 4.509 (1H, q), 4.964 (1H, m, exchangable), 5.219(1H, m, exchangable), 7.135 (5H, s).

3(S)-BOC-amino-4-phenyl–1-N-(L-piperazine-2-carboxylic acid methyl ester)-2(S)-butanol (1g)

A solution of 3(S)-t-butoxycarbonyl (BOC) amino-4-phenyl-2-(R)-oxirane [20] (1.0 g, 3.1 mmol) in 100 mL dry THF was treated with 1.44 g (10 mmol) L-piperazinocolinate methyl ester. The solution was refluxed for 48 hrs. A similar reaction work-up and column chromatography was used as described above for **1a** to give **1g** (0.465 g, 34%). TLC (60% ethyl acetate/hexanes) R_f = 0.60. ^{1}H NMR ($CDCl_3$/TMS, 200MHz) δ 0.989 (9H, s), 1.653 (2H, t), 2.185 (2H, t), 2.235 (2H, t), 2.445 (4H, m), 2.565 (1H, t), 3.546 (3H, s), 3.847 (1H, d of t), 4.3826 (1H, m), 5.018 (1H, m, exchangable), 7.116 (5H,s).

3(S)-amino-4-phenyl–1-N-morpholine-2(S)-butanol Dihydrochloride (2a)

0.55 g of **1a** was dissolved in 50 mL cold (0 ^{0}C) 2 M HCl in chloroform. The mixture was stirred at 0 ^{0}C for 1 hour. Cold diethyl ether (250 mL) was added to induce precipitation of the product. The liquid was decanted, and the precipitant was washed twice with cold ether (100 mL). The crude solid was dissolved in 20 mL methanol and then recrystallized by the addition of 250 mL cold ether. The white solid was again washed twice with cold ether (100 mL) and dried under reduced pressure (0.51 g, 91%). TLC (15% ethanol/ethyl acetate) R_f = 0.27. ^{1}H NMR (D_2O, 60MHz) δ 2.5 (2H, d), 3.1 (2H, d), 3.3 (4H, t), 3.6 (4H, t), 3.9 (1H, m), 4.4 (1H, m), 7.0 (5H,s).

3(S)-amino-4-phenyl–1-N-piperazine-2(S)-butanol Dihydrochloride (2b)

0.50 g of **1b** was dissolved in 100 mL cold (0 ^{0}C) 4 M HCl in chloroform. The mixture was stirred at 0 ^{0}C for 1 hour. A similar reaction work-up and column chromatography was used as described above for **2a** to give **2b** (0.44 g, 95%). TLC (10% ethanol/ethyl acetate) R_f = 0.38 ^{1}H NMR (D_2O, 60MHz) δ 1.9 (2H, t), 2.9 (8H, m), 3.2 (2H, d), 3.7 (1H, m), 4.4 (1H, m), 7.1 (5H,s).

3(S)-amino-4-phenyl–1-N-(L-proline methyl ester)-2(S)-butanol Dihydrochloride (2c)

0.50 g of **1c** was dissolved in 100 mL cold (0 ^{0}C) 4 M HCl in chloroform. The mixture was stirred at 0 ^{0}C for 1 hour. A similar reaction work-up and column chromatography was used as described above for **2a** to give **2c** (0.42 g, 83%). TLC (15% ethanol/ethyl acetate) R_f = 0.43. ^{1}H NMR (D_2O, 60MHz) δ 2.1 (4H, t), 2.3 (3H, m), 2.6 (2H, d), 3.1 (2H, d), 3.6 (3H, s), 3.8 (1H, m), 4.4 (1H, m), 6.9 (5H, s).

3(S)-amino-4-phenyl–1-N-(N-phenylpiperazine)-2(S)-butanol Trihydrochloride (2d)

0.55 g of **1d** was dissolved in 100 mL cold (0 ^{0}C) 4 M HCl in chloroform. The mixture was stirred at 0 ^{0}C for 1 hour. A similar reaction work-up and column chromatography was used as described above for **2a** to give **2d** (0.43 g, 71%). TLC (10% ethanol/ethyl acetate) R_f = 0.43 ^{1}H NMR (D_2O, 60MHz) δ 2.0 (4H, t), 2.7 (8H, m), 3.0 (2H, d), 3.8 (1H, m), 4.4 (1H, m), 7.1 (5H,s).

3(S)-amino-4-phenyl–1-N-(N-p-nitrophenylpiperazine)-2(S)-butanol Trihydrochloride (2e)

0.53 g of **1e** was dissolved in 100 mL cold (0 ^{0}C) 4 M HCl in chloroform. The mixture was stirred at 0 ^{0}C for 1 hour. A similar reaction work-up and column chromatography was used as described above for **2a** to give **2e** (0.45 g, 78%). TLC (10% ethanol/ethyl acetate) R_f = 0.26 ^{1}H NMR (D_2O, 60MHz) δ 2.0 (4H, t), 2.8 (8H, m), 3.1 (2H, d), 3.8 (1H, m), 4.4 (1H, m), 7.1 (5H,s), 7.6 (2H, d), 8.1 (2H, d).

3(S)-amino-4-phenyl–1-N-(L-pipericolinate methyl ester)-2(S)-butanol Dihydrochloride (2f)

0.50 g of **1f** was dissolved in 100 mL cold (0 ^{0}C) 4 M HCl in chloroform. The mixture was stirred at 0 ^{0}C for 1 hour. A similar reaction work-up and column chromatography was used as described above for **2a** to give **2f** (0.41 g, 81%). TLC (15% ethanol/ethyl acetate) R_f = 0.43. ^{1}H NMR (D_2O, 60MHz) δ 2.0 (2H, t), 2.2 (4H, m), 2.4 (3H, d), 2.6 (2H, d), 2.8 (1H, t), 3.1 (2H, d), 3.5 (3H, s), 3.7 (1H, m), 3.9 (1H, m), 4.4 (1H, m), 7.0 (5H, s).

3(S)-amino-4-phenyl–1-N-(L-piperazine-2-carboxylic acid methyl ester)-2(S)-butanol Trihydrochloride (2g)

0.50 g of **1g** was dissolved in 100 mL cold (0 ^{0}C) 4 M HCl in chloroform. The mixture was stirred at 0 ^{0}C for 1 hour. A similar reaction work-up and column chromatography was used as described above for **2a** to give **2g** (0.39 g, 77%). TLC (15% ethanol/ethyl acetate) R_f = 0.34. ^{1}H NMR (D_2O, 60MHz) δ 2.6 (2H, d), 2.9 (7H, m), 3.2 (2H, d), 3.5 (3H, s), 3.7 (1H, m), 4.5 (1H, m), 7.1 (5H, s).

General Procedure for Coupling Cbz-dipeptide to 2a-g

A precooled solution (-15 ^{0}C) of the appropriate carbobenzoxy-dipeptide (Sigma) (0.35 mmol) in 10 mL anhydrous DMF was treated with 56 μL (0.40 mmol) triethyl amine. The mixture was allowed to react at -15 ^{0}C for 30 minutes and was then treated with 34 μL (0.35 mmol) ethyl chloroformate. The mixture was stirred under N_2 atmosphere for 1 hour at -15 ^{0}C. A precooled (0 ^{0}C) solution containing 0.32 mmole of **2a, 2b, 2c, 2d, 2e, 2f,** or **2g** in 25 mL anhydrous DMF and 125 μL (1.0 mmole) triethyl amine was then added to the mixed anhydride of the Cbz-dipeptide. The combined mixture was stirred under N_2 at 0 ^{0}C for 4 hours, allowed to warm to room temperature, and stirred overnight at room temperature. The mixture was partitioned between the layers of ethyl acetate (250 mL) and 0.01 M aqueous NaOH. The organic layer was removed and saved. The aqueous layer was extracted again with another 250 mL ethyl acetate. The organic layers were pooled, washed with distilled water (100 mL), dried over anhydrous magnesium sulfate, and evaporated under reduced pressure.

3(S)-[Cbz-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-morpholine-2(S)-butanol Hydrochloride (3a)

0.137 g (71%). TLC (20% ethanol/ethyl acetate) R_f = 0.22, ^{1}H NMR (DMSO-d_6 60 MHz) δ 2.3 (4H, t), 2.5 (5H, m), 2.7 (2H, d), 3.1 (2H, d), 3.5 (4H, t), 3.8 (1H, m), 4.6 (3H, m), 5.0 (1H, m), 5.2 (2H, s), 6.9 (5H, s), 7.1 (5H,s), 7.4 (5H, s).

3(S)-[Cbz-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-morpholine-2(S)-butanol Hydrochloride (3b)

0.122 g (60%). TLC (20% ethanol/ethyl acetate) R_f = 0.24, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.3 (6H, d), 2.3 (4H, t), 2.5 (3, m), 2.7 (2H, d), 3.1 (2H, d), 3.5 (4H, t), 3.7 (1H, m), 4.5 (3H, m), 5.0 (1H, m), 5.2 (2H, s), 6.8 (5H, s), 7.2 (5H,s), 7.4 (5H, s).

3(S)-[Cbz-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-morpholine-2(S)-butanol Hydrochloride (3c)

0.118 g (57%). TLC (20% ethanol/ethyl acetate) R_f = 0.26, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.3 (6H, d), 2.2 (4H, t), 2.5 (7, m), 2.7 (2H, d), 3.1 (2H, d), 3.5 (4H, t), 3.7 (1H, m), 4.5 (3H, m), 5.0 (1H, m), 5.4 (2H, s), 6.9 (5H, s), 7.2 (5H,s), 7.4 (5H, s).

3(S)-[Cbz-L-leucyl-L-leucylamino]-4-phenyl-1-N-morpholine-2(S)-butanol Hydrochloride (3d)

0.128 g (65%). TLC (20% ethanol/ethyl acetate) R_f = 0.34, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.3 (12H, d), 2.2 (6H, t), 2.7 (2H, m), 3.1 (2H, d), 3.5 (4H, t), 3.7 (1H, m), 4.4 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.9 (5H, s), 7.3 (5H,s).

3(S)-[Cbz-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-piperazine-2(S)-butanol Dihydrochloride (3e)

0.162 g (75%). TLC (15% ethanol/ethyl acetate) R_f = 0.19, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.9 (4H, m), 2.5 (2H, d), 2.9 (8 H, m), 3.1 (2H, d), 3.7 (1H, m), 4.6 (3H, m), 5.1 (1H, m), 5.4 (2H, s), 6.8 (5H, s), 7.1 (5H,s), 7.4 (5H, s).

3(S)-[Cbz-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-piperazine-2(S)-butanol Dihydrochloride (3f)

0.125 g (56%). TLC (15% ethanol/ethyl acetate) R_f = 0.27, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.3 (6H, d), 1.9 (4H, t), 2.5 (3, m), 2.7 (2H, d), 2.9 (8H, m), 3.2 (2H, d), 3.7 (1H, m), 4.6 (3H, m), 5.0 (1H, m), 5.4 (2H, s), 6.8 (5H, s), 7.1 (5H,s), 7.4 (5H, s).

3(S)-[Cbz-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-piperazine-2(S)-butanol Dihydrochloride (3g)

0.131 g (57%). TLC (15% ethanol/ethyl acetate) R_f = 0.34, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.3 (6H, d), 1.8 (4H,

m), 1.9 (3H, m), 2.7 (2H, d), 3.0 (8H, m), 3.2 (2H, d), 3.7 (1H, m), 4.6 (3H, m), 5.0 (1H, m), 5.4 (2H, s), 6.9 (5H, s), 7.3 (5H,s), 7.5 (5H, s).

3(S)-[Cbz-L-leucyl-L-leucyl]-4-phenyl-1-N-piperazine-2(S)-butanol Dihydrochloride (3h)

0.145 g (60%). TLC (15% ethanol/ethyl acetate) R_f = 0.43, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.4 (12H, d), 1.7 (6H, m), 1.9 (2H, d), 2.9 (8H, m), 3.1 (2H, d), 3.7 (1H, m), 4.5 (3H, m), 4.8 (1H, m), 5.3 (2H, s), 7.0 (5H, s), 7.3 (5H, s).

3(S)-[Cbz-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-(L-proline methyl ester)-2(S)-butanol Hydrochloride(3i)

0.155 g (71%). TLC (15% ethanol/ethyl acetate) R_f = 0.33, ^{1}H NMR (DMSO-d_6 60 MHz) δ 2.3 (5H, m), 3.0 (2H, m), 3.3 (1H, t), 3.5 (5H, m), 3.7 (3H, s), 3.9 (1H, m), 4.6 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.8 (5H, s), 7.1 (5H,s), 7.3 (5H, s).

3(S)-[Cbz-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-(L-proline methyl ester)-2(S)-butanol Hydrochloride(3j)

0.109 g (48%). TLC (15% ethanol/ethyl acetate) R_f = 0.47, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.3 (6H, d), 1.7 (4H, m), 2.0 (4H, m), 2.4 (3, m), 2.8 (2H, d), 3.2 (2H, d), 3.6 (3H, s), 3.8 (1H, m), 4.7 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.8 (5H, s), 7.1 (5H,s), 7.3 (5H, s).

3(S)-[Cbz-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-(L-proline methyl ester)-2(S)-butanol Hydrochloride (3k)

0.122 g (53%). TLC (15% ethanol/ethyl acetate) R_f = 0.63, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.3 (6H, d), 1.8 (6H, m), 2.0 (4H, t), 2.4 (3, m), 2.8 (2H, d), 3.3 (2H, d), 3.6 (3H, s), 3.8 (1H, m), 4.7 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.8 (5H, s), 7.2 (5H,s), 7.3 (5H, s).

3(S)-[Cbz-L-leucyl-L-leucyl]-4-phenyl-1-N-(L-proline methyl ester)-2(S)-butanol Hydrochloride (3l)

0.145 g (60%). TLC (15% ethanol/ethyl acetate) R_f = 0.71, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.4 (12H, d), 1.8 (6H, m), 2.0 (4H, t), 2.4 (3, m), 3.1 (2H, d), 3.6 (3H, s), 3.8 (1H, m), 4.7 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.9 (5H, s), 7.3 (5H, s).

3(S)-[Cbz-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-(N-phenylpiperazine)-2(S)-butanol Dihydrochloride (3m)

0.122 g (51%). TLC (18% ethanol/ethyl acetate) R_f = 0.21, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.9 (4H, m), 2.3 (3H, d), 3.0 (10H, d), 3.7 (1H, m), 4.5 (3H, m), 4.8 (1H, m), 5.4 (2H, s), 6.8 (5H, s), 7.1 (5H,s), 7.5 (5H, s), 7.9 (5H, s).

3(S)-[Cbz-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-(N-phenylpiperazine)-2(S)-butanol Dihydrochloride (3n)

0.115 g (46%). TLC (18% ethanol/ethyl acetate) R_f = 0.25, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.3 (6H, d), 2.0 (5H,mt), 3.1 (10H, m), 3.8 (1H, m), 4.7 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.9 (5H, s), 7.2 (5H,s), 7.6 (5H, s).

3(S)-[Cbz-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-(N-phenylpiperazine)-2(S)-butanol Dihydrochloride (3o)

0.112 g (44%). TLC (18% ethanol/ethyl acetate) R_f = 0.31, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.1 (6H, d), 1.5 (3H, m), 2.0 (4H, d), 3.1 (6H, m), 3.3 (4H, t), 3.8 (1H, m), 4.7 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.8 (5H, s), 7.2 (5H,s), 7.6 (5H, s).

3(S)-[Cbz-L-leucyl-L-leucylamino]-4-phenyl-1-N-(N-phenyl-piperazine)-2(S)-butanol Dihydrochloride (3p)

0.112 g (42%). TLC (18% ethanol/ethyl acetate) R_f = 0.31, ^{1}H NMR (DMSO-d_6 60 MHz) δ .3 (12H, d), 1.6 (6H, m), 2.0 (2H, d), 3.0 (6H, m), 3.3 (4H, t), 3.7 (1H, m), 4.7 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.9 (5H, s), 7.3 (5H,s), 7.6 (5H, s).

3(S)-[Cbz-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-(N-p-nitrophenyl piperazine)-2(S)-butanol Dihydrochloride (3q)

0.102 g (40%). TLC (20% ethanol/ethyl acetate) R_f = 0.26, ^{1}H NMR (DMSO-d_6 60 MHz) δ 2.0 (4H, m), 2.2 (3H, d), 3.0 (6H, d), 3.5 (4H, t), 3.7 (1H, m), 4.5 (3H, m), 4.8 (1H, m), 5.4 (2H, s), 6.8 (5H, s), 7.1 (5H,s), 7.5 (5H, s), 8.0 (2H, d), 8.4 (2H, d).

3(S)-[Cbz-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-(N-p-nitrophenyl piperazine)-2(S)-butanol Dihydrochloride (3r)

0.122 g (46%). TLC (20% ethanol/ethyl acetate) R_f = 0.29, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.3 (6H, d), 2.0 (5H,mt), 3.0 (6H, m), 3.5 (4H, t), 3.8 (1H, m), 4.7 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.9 (5H, s), 7.2 (5H,s), 7.6 (5H, s), 8.0 (2H, d), 8.4 (2H, d).

3(S)-[Cbz-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-(N-p-nitrophenyl piperazine)-2(S)-butanol Dihydrochloride (3s)

0.108 g (40%). TLC (20% ethanol/ethyl acetate) R_f = 0.33, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.1 (6H, d), 1.5 (3H, m), 2.0 (4H, d), 3.1 (6H, m), 3.4 (4H, t), 3.8 (1H, m), 4.7 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.8 (5H, s), 7.2 (5H,s), 7.5 (5H, s), 8.1 (2H, d), 8.5 (2H, d).

3(S)-[Cbz-L-leucyl-L-leucylamino]-4-phenyl-1-N-(N-p-nitrophenylpiperazine)-2(S)-butanol Dihydrochloride (3t)

0.0912 g (33%). TLC (20% ethanol/ethyl acetate) R_f = 0.35, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.3 (12H, d), 1.6 (6H, m), 2.0 (2H, d), 3.0 (6H, m), 3.5 (4H, t), 3.7 (1H, m), 4.7 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.9 (5H, s), 7.3 (5H,s), 7.6 (5H, s), 8.1 (2H, d), 8.5 (2H, d).

3(S)-[Cbz-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-(L-pipericolinate methyl ester)-2(S)-butanol Hydrochloride (3u)

0.155 g (70%). TLC (15% ethanol/ethyl acetate) R_f = 0.33, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.9 (2H, m), 2.4 (5H, m), 2.9 (2H, m), 3.1 (1H, t), 3.4 (5H, m), 3.6 (3H, s), 3.8 (1H, m), 4.6 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.8 (5H, s), 7.1 (5H,s), 7.3 (5H, s).

3(S)-[Cbz-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-(L-pipericolinate methyl ester)-2(S)-butanol Hydrochloride (3v)

0.161 g (70%). TLC (15% ethanol/ethyl acetate) R_f = 0.36, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.7 (8H, m), 2.3 (4H,

m), 2.9 (2H, m), 3.2 (1H, t), 3.4 (5H, m), 3.6 (3H, s), 3.9 (1H, m), 4.6 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.8 (5H, s), 7.1 (5H,s), 7.3 (5H, s).

3(S)-[Cbz-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-(L-pipericolinate methyl ester)-2(S)-butanol Hydrochloride (3w)

0.169 g (72%). TLC (15% ethanol/ethyl acetate) R_f = 0.41, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.6 (8H, m), 2.2 (6H, m), 3.0 (2H, m), 3.3 (1H, t), 3.5 (5H, m), 3.7 (3H, s), 4.0 (1H, m), 4.6 (3H, m), 5.0 (1H, m), 5.2 (2H, s), 6.8 (5H, s), 7.1 (5H,s), 7.3 (5H, s).

3(S)-[Cbz-L-leucyl-L-leucylamino]-4-phenyl-1-N-(L-pipericolinate methyl ester)-2(S)-butanol Hydrochloride (3x)

0.141 g (57%). TLC (15% ethanol/ethyl acetate) R_f = 0.46, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.3 (12H, m), 2.1 (3H, m), 2.4 (4H, m), 3.1 (2H, m), 3.3 (1H, t), 3.5 (3H, s), 3.8 (3H, s), 4.0 (1H, m), 4.7 (3H, m), 5.0 (1H, m), 5.2 (2H, s), 6.9 (5H, s), 7.1 (5H,s), 7.3 (5H, s).

3(S)-[Cbz-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-(L-piperazine-2-carboxylic acid methyl ester)-2(S)-butanol Dihydrochloride (3y)

0.125 g (53%). TLC (20% ethanol/ethyl acetate) R_f = 0.29, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.9 (2H, m), 2.4 (3H, d), 3.3 (9H, m), 3.6 (3H, s), 3.9 (1H, m), 4.5 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.9 (5H, s), 7.1 (5H,s), 7.3 (5H, s).

3(S)-[Cbz-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-(L-piperazine-2-carboxylic acid methyl ester)-2(S)-butanol Dihydrochloride (3z)

0.116 g (48%). TLC (20% ethanol/ethyl acetate) R_f = 0.36, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.7 (8H, m), 2.3 (4H, m), 3.2 (9H, m), 3.5 (3H, s), 3.9 (1H, m), 4.6 (3H, m), 5.0 (1H, m), 5.2 (2H, s), 6.8 (5H, s), 7.1 (5H,s), 7.3 (5H, s).

3(S)-[Cbz-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-(L-piperazine-2-carboxylic acid methyl ester)-2(S)-butanol Dihydrochloride (3aa)

0.109 g (44%). TLC (20% ethanol/ethyl acetate) R_f = 0.40, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.6 (8H, m), 2.2 (6H, m), 3.0 (2H, m), 3.3 (9H, m), 3.8 (1H, m), 3.5 (3H, s), 4.2 (1H, m), 4.6 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.9 (5H, s), 7.1 (5H,s), 7.3 (5H, s).

3(S)-[Cbz-L-leucyl-L-leucylamino]-4-phenyl-1-N-(L-piperazine-2-carboxylic acid methyl ester)-2(S)-butanol Dihydrochloride (3bb)

0.119 g (46%). TLC (20% ethanol/ethyl acetate) R_f = 0.43, ^{1}H NMR (DMSO-d_6 60 MHz) δ 1.3 (12H, m), 2.1 (3H, m), 2.4 (4H, m), 3.3 (9H, m), 3.5 (3H, s), 4.0 (1H, m), 4.8 (3H, m), 5.0 (1H, m), 5.3 (2H, s), 6.9 (5H, s), 7.1 (5H,s), 7.3 (5H, s).

General Procedure for Preparation of Synthetic Inhibitors (4a-bb)

A solution of the carbobenzoxy protected compound (**3a-bb**) (0.20 mmol) in 250 mL methanol and 1 mL 0.01 M aqueous HCl was treated with 0.050 g pre-moistened 10% Pd-C to form a slurry in a 3 neck flask. H_2 gas was bubbled (1 atm) through the rapidly stirring mixture at room temperature for 3 hours. The mixture was then filtered to remove the catalyst, and the solvent was evaporated under reduced pressure. The crude amine hydrochloride was dissolved in 15 mL dimethyl sulfoxide (DMSO) and treated with 125 μL (0.10 mole) triethyl amine. The mixture was stirred at room temperature for 30 minutes. Acetic anhydride (95 μL, 1.0 mmol) was added, and the mixture was stirred overnight at room temperature. Cold diethyl ether (250 mL) was added to precipitate the product. The liquid was decanted, and the white solid was washed three times with cold ether (200 mL). The crude product was purified by Sephadex LH-20 column chromatography (column size 5 cm dia. x 80 cm) using methanol as the mobile phase.

3(S)-[Acetyl-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-morpholine-2(S)-butanol (4a)

0.049 g (48%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.37, ^{1}H NMR (methanol-d_4, 200 MHz) δ 2.212 (3H, s), 2.307 (3H, d), 2.489 (2H, d), 2.603 (2H, d), 3.062 (2H, d), 3.200 (4H, t), 3.589 (4H, t), 3.717 (1H, m), 4.617 (3H, m), 4.988 (2H, m), 6.951 (5H, s), 7.215 (5H,s). Anal. ($C_{28}H_{38}N_4O_5$) C, H, N.

3(S)-[Acetyl-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-morpholine-2(S)-butanol (4b)

0.053 g (49%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.48, ^{1}H NMR (methanol-d_4, 200 MHz) δ 1.452 (6H, d), 1.963 (1H, m), 2.220 (3H, s), 2.490 (2H, d), 2.600 (2H, d), 3.101, (2H, d), 3.232 (4H, t), 3.591 (4H, t), 3.722 (1H, m), 4.614 (3H, m), 4.990 (3H, m), 6.960 (5H, s), 7.205 (5H,s). Anal. ($C_{30}H_{42}N_4O_5$) C, H, N.

3(S)-[Acetyl-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-morpholine-2(S)-butanol (4c)

0.048 g (43%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.54, ^{1}H NMR (methanol-d_4, 200 MHz) δ 1.299 (6H, d), 1.598 (3H, m), 2.221 (3H, s), 2.490 (2H, d), 2.596 (2H, d), 3.095 (2H, d), 3.227 (4H, t), 3.590 (4H, t), 3.720 (1H, m), 4.613 (3H, m), 4.994 (2H, m), 6.964 (5H, s), 7.216 (5H,s). Anal. ($C_{31}H_{44}N_4O_5$) C, H, N.

3(S)-[Acetyl-L-leucyl-L-leucylamino]-4-phenyl-1-N-morpholine-2(S)-butanol (4c)

0.061 g (59%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.71, ^{1}H NMR (methanol-d_4, 200 MHz) δ 1.198 (12H, d), 1.601 (6H, m), 2.231 (3H, s), 2.494 (2H, d), 3.089 (2H, d), 3.312 (4H, t), 3.592 (4H, t), 3.723 (1H, m), 4.615 (3H, m), 4.996 (2H, m), 7.209 (5H,s). Anal.($C_{28}H_{46}N_4O_5$) C, H, N.

3(S)-[Acetyl-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-piperazine-2(S)-butanol Hydrochloride (4e)

0.056 g (51%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.46, ^{1}H NMR (methanol-d_4, 200 MHz) δ 2.279 (3H, s), 2.301 (3H, d), 2.462 (4H, m), 2.692 (8H, t), 3.189 (2H, d), 3.716 (1H, m), 4.610 (3H, m), 5.081 (3H, m), 6.949 (5H, s), 7.210 (5H, s). Anal. ($C_{28}H_{40}N_5O_4Cl$) C, H, N.

3(S)-[Acetyl-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-piperazine-2(S)-butanol Hydrochloride (4f)

0.049 g (43%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.51, ^{1}H NMR (methanol-d_4, 200 MHz) δ 1.489 (6H, d),

1.989 (1H, m), 2.266 (3H, s), 2.458 (4H, m), 2.689 (8H, t), 3.099 (2H, d), 3.720 (1H, m), 4.613 (3H, m), 4.999 (3H, m), 6.959 (5H, s), 7.203 (5H,s). Anal. ($C_{30}H_{44}N_5O_4Cl$) C, H, N.

3(S)-[Acetyl-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-piperazine-2(S)-butanol Hydrochloride (4g)

0.046 g (39%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.66, ^{1}H NMR (methanol-d_4, 200 MHz) δ 1.300 (6H, d), 1.609 (3H, m), 2.199 (3H, s), 2.459 (4H, m), 2.701 (8H, t), 3.102 (2H, d), 3.721 (1H, m), 4.614 (3H, m), 4.993 (3H, m), 6.960 (5H, s), 7.213 (5H,s). Anal. ($C_{31}H_{46}N_5O_4Cl$) C, H, N.

3(S)-[Acetyl-L-leucyl-L-leucyl]-4-phenyl-1-N-piperazine-2(S)-butanol Hydrochloride (4h)

0.049 g (44%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.71, ^{1}H NMR (methanol-d_4, 200 MHz) δ 1.208 (12H, d), 1.604 (6H, m), 2.201 (3H, s), 2.461 (4H, m), 2.651 (8H, t), 3.109 (2H, d), 3.724 (1H, m), 4.634 (3H, m), 5.013 (3H, m), 6.977 (5H, s), 7.243 (5H,s). Anal. ($C_{28}H_{48}N_5O_4Cl$) C, H, N.

3(S)-[Acetyl-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-(L-proline methyl ester)-2(S)-butanol (4i)

0.062 g (56%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.45, ^{1}H NMR (methanol-d_4, 200 MHz) δ 2.235 (3H, s), 2.292 (3H, d), 2.348 (4H, m), 2.459 (4H, d), 2.633 (2H, t), 2.815 (1H, t), 3.101 (2H, d), 3.511 (3H, s), 3.709 (1H, m), 4.621 (3H, m), 5.015 (3H, m), 7.010 (5H, s), 7.248 (5H,s). Anal. ($C_{30}H_{40}N_4O_6$) C, H, N.

3(S)-[Acetyl-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-(L-proline methyl ester)-2(S)-butanol (4j)

0.055 g (47%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.56, ^{1}H NMR (methanol-d_4, 200 MHz) δ 1.451 (6H, d), 1.962 (1H, m), 2.220 (3H, s) 2.308 (4H, m), 2.451 (4H, m), 2.601 (2H, t), 2.801 (1H, t) 3.102 (2H, d), 3.521 (3H, s), 3.723 (1H, m), 4.657 (3H, m), 4.997 (2H, m), 6.981 (5H, s), 7.303 (5H,s). Anal. ($C_{32}H_{44}N_4O_6$) C, H, N.

3(S)-[Acetyl-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-(L-proline methyl ester)-2(S)-butanol (4k)

0.061 g (51%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.63, ^{1}H NMR (methanol-d_4, 200 MHz) δ 1.300 (6H, d), 1.589 (3H, m), 2.221 (3H, s) 2.463 (4H, d), 2.613 (2H, t), 2.891 (1H, t), 3.118 (2H, d), 3.605 (3H, s), 3.727 (1H, m), 4.617 (3H, m), 4.999 (2H, m), 6.978 (5H, s), 7.201 (5H,s). Anal. ($C_{33}H_{46}N_4O_6$) C, H, N.

3(S)-[Acetyl-L-leucyl-L-leucylamino]-4-phenyl-1-N-(L-proline methyl ester)-2(S)-butanol (4l)

0.048 g (43%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.69, ^{1}H NMR (methanol-d_4 200 MHz) δ 1.120 (12H, d), 1.605 (6H, m), 2.219 (3H, s) 2.365 (4H, m), 2.499 (2H, d), 2.601 (2H, t), 2.811 (1H, t), 3.120 (2H, d), 3.605 (3H, s), 3.727 (1H, m), 4.617 (3H, m), 5.011 (2H, m), 7.201 (5H,s). Anal. ($C_{30}H_{48}N_4O_6$) C, H, N.

3(S)-[Acetyl-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-(N-phenylpiperazine)-2(S)-butanol (4m)

0.061 g (52%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.58, ^{1}H NMR (methanol-d_4 200 MHz) δ 2.255 (3H, s), 2.315 (3H, d), 2.465 (4H, d), 2.689 (4H, t), 2.899 (4H, t), 3.186 (2H, d), 3.715 (1H, m), 4.615 (3H, m), 4.998 (3H, m), 6.999 (5H, s), 7.242 (5H,s), 7.855 (3H, m), 8.045 (2H, d). Anal. ($C_{34}H_{43}N_5O_4$) C, H, N.

3(S)-[Acetyl-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-(N-phenylpiperazine)-2(S)-butanol (4n)

0.074 g (60%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.63, ^{1}H NMR (methanol-d_4 200 MHz) δ 1.552 (6H, d), 2.009 (1H, m), 2.296 (3H, s), 2.366 (4H, t), 2.546 (4H, d), 2.690 (4H, t), 3.180 (2H, d), 3.722 (1H, m), 4.625 (3H, m), 4.999 (3H, m), 6.989 (5H, s), 7.301 (5H,s), 7.856 (3H, m), 8.066 (2H, d). Anal. ($C_{36}H_{47}N_5O_4$) C, H, N.

3(S)-[Acetyl-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-(N-phenylpiperazine)-2(S)-butanol (4o)

0.078 g (62%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.69, ^{1}H NMR (methanol-d_4 200 MHz) δ 1.552 (6H, d), 2.009 (1H, m), 2.296 (3H, s), 2.366 (4H, t), 2.546 (4H, d), 2.690 (4H, t), 3.180 (2H, d), 3.722 (1H, m), 4.625 (3H, m), 4.999 (3H, m), 6.989 (5H, s), 7.301 (5H,s), 7.856 (3H, m), 8.066 (2H, d). Anal. ($C_{36}H_{47}N_5O_4$) C, H, N.

3(S)-[Acetyl-L-leucyl-L-leucyl]-4-phenyl-1-N-(N-phenylpiperazine)-2(S)-butanol (4p)

0.069 g (58%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.72, ^{1}H NMR (methanol-d_4 200 MHz) δ 1.453 (12H, d), 1.545 (6H, m), 2.288 (3H, s), 2.466 (2H, t), 2.589 (4H, t), 2.710 (4H, t), 3.178 (2H, d), 3.712 (1H, m), 4.585 (3H, m), 5.039 (4H, m), 7.301 (5H, s), 7.854 (3H, m), 8.067 (2H, d). Anal. ($C_{33}H_{49}N_5O_4$) C, H, N.

3(S)-[Acetyl-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-(N-p-nitrophenyl piperazine)-2(S)-butanol (4q)

0.045 g (36%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.42, ^{1}H NMR (methanol-d_4 200 MHz) δ 2.256 (3H, s), 2.313 (3H, d), 2.466 (4H, d), 2.696 (4H, t), 3.099 (4H, t), 3.188 (2H, d), 3.716 (1H, m), 4.617 (3H, m), 4.999 (3H, m), 7.009 (5H, s), 7.243 (5H, s), 8.204 (2H, d), 8.615 (2H, d). Anal. ($C_{34}H_{42}N_6O_6$) C, H, N.

3(S)-[Acetyl-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-(N-p-nitrophenylpiperazine)-2(S)-butanol (4r)

0.055 g (42%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.43, ^{1}H NMR (methanol-d_4 200 MHz) δ 1.553 (6H, d), 2.008 (1H, m), 2.297 (3H, s), 2.546 (4H, d), 2.721 (4H, t), 3.100 (4H, t), 3.203 (2H, d), 3.722 (1H, m), 4.625 (3H, m), 4.999 (3H, m), 6.989 (5H, s), 7.281 (5H,s), 8.206 (2H, d), 8.626 (2H, d). Anal. ($C_{36}H_{46}N_6O_6$) C, H, N.

3(S)-[Acetyl-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-(N-p-nitrophenyl piperazine)-2(S)-butanol (4s)

0.056 g (42%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.45, ^{1}H NMR (methanol-d_4 200 MHz) δ 1.554 (6H, d), 2.010 (1H, m), 2.297 (3H, s), 2.547 (4H, d), 2.699 (4H, t), 3.106 (4H, t), 3.214 (2H, d), 3.724 (1H, m), 4.625 (3H, m), 4.999 (3H, m), 6.999 (5H, s), 7.302 (5H,s), 8.219 (2H, d), 8.646 (2H, d). Anal. ($C_{37}H_{48}N_6O_6$) C, H, N.

3(S)-[Acetyl-L-leucyl-L-leucyl]-4-phenyl-1-N-(N-p-nitrophenylpiperazine)-2(S)-butanol (4t)

0.039 g (31%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.54, ^{1}H NMR (methanol-d_4 200 MHz) δ 1.306 (12H,

d), 1.615 (6H, m), 2.302 (3H, s), 2.552 (4H, d), 2.718 (4H, t), 3.099 (4H, t), 3.221 (2H, d), 3.724 (1H, m), 4.634 (3H, m), 5.013 (3H, m), 7.012 (5H, s), 7.313 (5H,s), 8.220 (2H, d), 8.627 (2H, d). Anal. ($C_{34}H_{50}N_6O_6$) C, H, N.

3(S)-[Acetyl-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-(L-pipericolinate methyl ester)-2(S)-butanol (4u)

0.052 g (46%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.52, ^{1}H NMR (methanol-d_4, 200 MHz) δ 2.230 (3H, s), 2.289 (3H, d), 2.344 (6H, m), 2.469 (4H, d), 2.634 (2H, t), 2.833 (1H, t), 3.101 (2H, d), 3.545 (3H, s), 3.709 (1H, m), 4.621 (3H, m), 5.015 (3H, m), 7.012 (5H, s), 7.249 (5H,s). Anal. ($C_{31}H_{42}N_4O_6$) C, H, N.

3(S)-[Acetyl-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-(L-pipericolinate methyl ester)-2(S)-butanol (4v)

0.065 g (55%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.61, ^{1}H NMR (methanol-d_4, 200 MHz) δ 1.449 (6H, d), 1.965 (1H, m), 2.221 (3H, s) 2.284 (6H, m), 2.453 (4H, m), 2.622 (2H, t), 2.802 (1H, t) 3.110 (2H, d), 3.527 (3H, s), 3.725 (1H, m), 4.659 (3H, m), 5.017 (2H, m), 6.993 (5H, s), 7.302 (5H,s). Anal. ($C_{33}H_{46}N_4O_6$) C, H, N.

3(S)-[Acetyl-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-(L-pipericolinate methyl ester)-2(S)-butanol (4w)

0.048 g (39%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.68, ^{1}H NMR (methanol-d_4, 200 MHz) δ 1.302 (6H, d), 1.591 (3H, m), 2.222 (3H, s) 2.365 (6H, d), 2.613 (2H, t), 2.893 (1H, t), 3.120 (2H, d), 3.607 (3H, s), 3.729 (1H, m), 4.619 (3H, m), 5.019 (2H, m), 6.981 (5H, s), 7.205 (5H,s). Anal. ($C_{34}H_{48}N_4O_6$) C, H, N.

3(S)-[Acetyl-L-leucyl-L-leucylamino]-4-phenyl-1-N-(L-pipericolinate methyl ester)-2(S)-butanol (4x)

0.048 g (42%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.69, ^{1}H NMR (methanol-d_4 200 MHz) δ 1.119 (12H, d), 1.601 (6H, m), 2.220 (3H, s) 2.359 (6H, m), 2.498 (2H, d), 2.600 (2H, t), 2.813 (1H, t), 3.119 (2H, d), 3.603 (3H, s), 3.729 (1H, m), 4.618 (3H, m), 5.009 (2H, m), 7.202 (5H,s). Anal. ($C_{33}H_{50}N_4O_6$) C, H, N.

3(S)-[Acetyl-L-alanyl-L-phenylalanylamino]-4-phenyl-1-N-(L-piperazine-2-carboxylic acid methyl ester)-2(S)-butanol hydrochloride (4y)

0.042 g (35%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.36, ^{1}H NMR (methanol-d_4, 200 MHz) δ 2.223 (3H, s), 2.293 (3H, d), 2.445 (4H, d), 2.703 (7H, m), 3.101 (2H, d), 3.545 (3H, s), 3.709 (1H, m), 4.621 (3H, m), 5.034 (3H, m), 5.211 (1H, m), 7.010 (5H, s), 7.255 (5H,s). Anal. ($C_{30}H_{42}N_5O_6Cl$) C, H, N.

3(S)-[Acetyl-L-valyl-L-phenylalanylamino]-4-phenyl-1-N-(L-piperazin-2-carboxylic acid methyl ester)-2(S)-butanol hydrochloride (4z)

0.035 g (28%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.33, ^{1}H NMR (methanol-d_4, 200 MHz) δ 1.451 (6H, d), 1.945 (1H, m), 2.223 (3H, s), 2.456 (4H, m), 2.705 (7H, m), 3.110 (2H, d), 3.522 (3H, s), 3.719 (1H, m), 4.653 (3H, m), 5.009 (2H, m), 5.299 (2H, m), 6.998 (5H, s), 7.301 (5H,s). Anal. ($C_{32}H_{46}N_5O_6Cl$) C, H, N.

3(S)-[Acetyl-L-leucyl-L-phenylalanylamino]-4-phenyl-1-N-(L-piperazine-2-carboxylic acid methyl ester)-2(S)-butanol hydrochloride(4aa)

0.038 g (29%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.39, ^{1}H NMR (methanol-d_4, 200 MHz) δ 1.309 (6H, d), 1.596 (3H, m), 2.219 (3H, s), 2.705 (7H, m), 3.121 (2H, d), 3.597 (3H, s), 3.715 (1H, m), 4.611 (3H, m), 5.021 (2H, m), 7.081 (5H, s), 7.215 (5H,s). Anal. ($C_{33}H_{48}N_5O_6Cl$) C, H, N.

3(S)-[Acetyl-L-leucyl-L-leucylamino]-4-phenyl-1-N-(L-piperazine-2-carboxylic acid methyl ester)-2(S)-butanol hydrochloride(4bb)

0.031 g (25%). TLC (1-butanol/H_2O/acetic acid, 15/2/1) R_f = 0.45, ^{1}H NMR (methanol-d_4 200 MHz) δ 1.109 (12H, d), 1.559 (6H, m), 2.218 (3H, s), 2.499 (2H, d), 2.743 (7H, m), 3.113 (2H, d), 3.583 (3H, s), 3.716 (1H, m), 4.618 (3H, m), 5.010 (2H, m), 5.216 (2H, m), 7.214 (5H,s). Anal. ($C_{30}H_{50}N_5O_6Cl$) C, H, N.

CATHEPSIN D ASSAY

The potency of compounds **4a-bb** was measured as inhibitors of the cathepsin D hydrolysis of human hemoglobin (Sigma), and the results are presented in **Table 2**. Inhibition of cathepsin D was measured by the following method: 225 µL of the inhibitor of appropriate concentration in sodium formate-formic acid buffer (0.50 M, pH 3.2) and 250 µL of a 0.5% hemoglobin solution were mixed and incubated at 45 ^{0}C for 20 minutes. Human cathepsin D (Sigma), 25 µL of a 1.0 µg/mL, was added and mixed, for a total enzyme concentration of 1.1 x 10^{-9} M. The mixture was incubated at 45 ^{0}C for 1.5 hours. The reaction was quenched by the addition of 1.0 mL cold 0.3 M trichloroacetic acid. The solution was mixed thoroughly and then chilled in ice for 30 min to allow separation of precipitated protein. The mixture was centrifuged and warmed to 25 ^{0}C. The liquid was decanted into a quartz cuvette and the absorbance measured at 280 nm. The absorbance of a blank containing no enzyme was subtracted from the reading. The inhibition of the enzyme activity was measured four times at five or more inhibitor concentrations. The average absorbance of each inhibitor concentration was utilized in the calculations of the IC_{50} values. All absorbances were within #0.002 standard deviations from the mean for a given inhibitor concentration. The standard error for the linear regression plots was in each case less than 3%. A plot of percent inhibition versus the log of the inhibitor concentration provided a value for the 50% inhibition concentration (IC_{50}). All plots were linear through the 50% inhibition value and have slopes ranging from 22 to 40. The apparent inhibition constants, $K_{i\ (app)}$, were calculated as $K_{i\ (app)} = IC_{50} - 0.5[E_0]$, where $[E_0]$ is the enzyme concentration [22, 23].

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