Exhibit 9 – Part 1 of 7

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(54) **Retroviral protease inhibiting compounds.**

(57) A retroviral protease inhibiting compound of the formula
A - X - B
or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein X is a linking group;
A is
(1) substituted amino,
(2) substituted carbonyl,
(3) functionalized imino,

(4) functionalized alkyl,
(5) functionalized acyl,
(6) functionalized heterocyclic or
(7) functionalized (heterocyclic)alkyl; and B is
(1) substituted carbonyl independently defined as herein,
(2) substituted amino independently defined as herein,
(3) functionalized imino independently defined as herein,
(4) functionalized alkyl independently defined as herein,
(5) functionalized acyl independently defined as herein,
(6) functionalized heterocyclic independently defined as herein or
(7) functionalized (heterocyclic)alkyl independently defined as herein.

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RETROVIRAL PROTEASE INHIBITING COMPOUNDS

This is a continuation-in-part of U.S. Patent application Serial No. 456,124, filed December 22, 1989, which is a continuation-in-part of U.S. Patent application Serial No. 405,604, filed September 8, 1989, which is a continuation-in-part of U.S. Patent application Serial No. 355,945, filed May 23, 1989.

Technical Field

This invention was made with Government support under contract number AI27220-01 awarded by the National Institute of Allergy and Infectious Diseases. The Government has certain rights in this invention.

The present invention relates to novel compounds and a composition and method for inhibiting retroviral proteases and in particular for inhibiting human immunodeficiency virus (HIV) protease, a composition and method for treating a retroviral infection and in particular an HIV infection, processes for making such compounds and synthetic intermediates employed in these processes.

Background Art

Retroviruses are those viruses which utilize a ribonucleic acid (RNA) intermediate and a RNA-dependent deoxyribonucleic acid (DNA) polymerase, reverse transcriptase, during their life cycle. Retroviruses include, but are not limited to, the RNA viruses of the Retroviridae family, and also the DNA viruses of the Hepadnavirus and Caulimovirus families. Retroviruses cause a variety of disease states in man, animals and plants. Some of the more important retroviruses from a pathological standpoint include human immunodeficiency viruses (HIV-1 and HIV-2), which cause acquired immune deficiency syndrome (AIDS) in man, hepatitis B virus, which causes hepatitis and hepatic carcinomas in man, human T-cell lymphotrophic viruses I, II, IV and V, which cause human acute cell leukemia, and bovine and feline leukemia viruses which cause leukemia in domestic animals.

Proteases are enzymes which cleave proteins at specific peptide bonds. Many biological functions are controlled or mediated by proteases and their complementary protease inhibitors. For example, the protease renin cleaves the peptide angiotensinogen to produce the peptide angiotensin I. Angiotensin I is further cleaved by the protease angiotensin converting enzyme (ACE) to form the hypotensive peptide angiotensin II. Inhibitors of renin and ACE are known to reduce high blood pressure in vivo. An inhibitor of a retroviral protease should provide a therapeutic agent for diseases caused by the retrovirus.

The genomes of retroviruses encode a protease that is responsible for the proteolytic processing of one or more polyprotein precursors such as the pol and gag gene products. See Wellink, Arch. Virol. 98 1 (1988). Retroviral proteases most commonly process the gag precursor into core proteins, and also process the pol precursor into reverse transciptase and retroviral protease. In addition, retroviral proteases are sequence specific. See Pearl, Nature 328 482 (1987).

The correct processing of the precursor polyproteins by the retroviral protease is necessary for the assembly of infectious virions. It has been shown that in vitro mutagenesis that produces protease-defective virus leads to the production of immature core forms which lack infectivity. See Crawford, J. Virol. 53 899 (1985); Katoh, et al., Virology 145 280 (1985). Therefore, retroviral protease inhibition provides an attractive target for antiviral therapy. See Mitsuya, Nature 325 775 (1987).

Current treatments for viral diseases usually involve administration of compounds that inhibit viral DNA synthesis. Current treatments for AIDS (Dagani, Chem. Eng. News, November 23, 1987 pp. 41-49) involve administration of compounds such as 2',3'-dideoxycytidine, trisodium phosphonoformate, ammonium 21-tungsto-9-antimoniate, 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, 3'-azido-3'-deoxythymidine, and adriamycin that inhibit viral DNA synthesis; compounds such as AL-721 and polymannoacetate which may prevent HIV from penetrating the host cell; and compounds which treat the opportunistic infections caused by the immunosuppression resulting from HIV infection. None of the current AIDS treatments have proven to be totally effective in treating and/or reversing the disease. In addition, many of the compounds currently used to treat AIDS cause adverse side effects including low platelet count, renal toxicity and bone marrow cytopenia.

Inhibitors of HIV protease are disclosed by Moore, Biochem. Biophys. Res. Commun., 159 420 (1989); Billich, J. Biol. Chem., 263 1790S (1988); Richards, FEBS Lett., 247 113 (1989); Miller, Science 246 1149 (1989); Meek, Nature 343 90 (1990); McQuade, Science 247 454 (1990); Sigal, et al., European Patent

Application No. EP0337714, published October 18, 1989; Kempf, et al., PCT Patent Application No. WO89/10752, published November 16, 1989; Molling, et al., European Patent Application No. EP354522, published February 14, 1990; Sigal, et al., European Patent Application No. EP357332, published March 7, 1990; Handa, et al., European Patent Application No. EP346847, published December 20, 1989; Desolms, et al, European Patent Application No. EP356223, published February 28, 1990; Schirlin. et al., European Patent Application No. EP362002, published April 4, 1990; Dreyer, et al., PCT Patent Application No. WO90/00399, published January 25, 1990; and Hanko, et al., European Patent Application No. EP361341, published April 4, 1990.

U.S. Patent No. 4,652,552 discloses methyl ketone derivatives of tetrapeptides as inhibitors of viral proteases. U.S. Patent No. 4,644,055 discloses halomethylketone derivatives of peptides as inhibitors of viral proteases.

None of the references mentioned above disclose or suggest the invention claimed herein.

The compounds (A-X-B) shown in Table 1 are disclosed in the following list of references. None of these references disclose or suggest the use of these compounds as inhibitors of retroviral protease or as antiviral agents.

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28. T. Hosokawa, et al., Bull. Chem. Soc. Jpn., 58 194 (1985).
29. G. Olah, et al., Synthesis, 221 (1980). (In the table "Ph" represents phenyl).

TABLE 1

A	X	B
$PhOCH_2-$	$-C(O)-$	$PhSCH_2-$
$PhS(O)_2CH_2-$	$-C(O)-$	$PhCH_2CH_2-$
$PhCH_2CH_2-$	$-C(O)-$	$PhSCH_2-$
$PhS(O)_2CH_2-$	$-C(O)-$	$PhS(O)_2CH_2-$
$PhOCH_2-$	$-C(O)-$	$PhOCH_2-$
$PhS(O)CH_2-$	$-C(O)-$	$PhCH_2CH_2-$
$PhSCH_2-$	$-C(O)-$	$PhSCH_2-$
$PhCH_2CH_2-$	$-C(O)-$	$PhCH_2CH_2-$
$PhCH_2CH_2-$	$-CH(OH)-$	$PhSCH_2-$
$PhOCH_2-$	$-CH(OH)-$	$PhOCH_2-$
$PhS(O)_2CH_2-$	$-CH(OH)-$	$PhS(O)_2CH_2-$
$PhCH_2CH_2-$	$-CH(NH_2)-$	$PhCH_2CH_2-$
$PhNHCH_2-$	$-CH(OH)-$	$PhOCH_2-$
$PhNHCH_2-$	$-CH(OH)-$	$PhNHCH_2-$
$PhCH_2CH_2-$	$-CH(OH)-$	$PhCH_2CH_2-$
$PhCH_2CH_2-$	$-CH(OH)-$	$PhSCH_2-$
$PhOCH_2-$	$-CH(OH)-$	$PhSCH_2-$
$PhNHCH_2-$	$-CH(OH)-$	$PhSCH_2-$
$PhSCH_2-$	$-CH(OH)-$	$PhSCH_2-$
$PhCH_2CH_2-$	$-N(OH)-$	$PhCH_2CH_2-$
$PhSCH_2-$	$-N(OH)-$	$PhSCH_2-$
$PhCH_2CH_2-$	$-P(OH)(H)-$	$PhCH_2CH_2-$
$PhS(O)_2CH_2-$	$-N(OH)-$	$PhS(O)_2CH_2-$
$PhNHCH_2-$	$-P(O)(OH)-$	$PhNHCH_2-$
$PhOCH_2-$		$PhOCH_2-$
$PhCH_2CH_2-$	$-S(O)_2-$	$PhCH_2CH_2-$
$PhS(O)_2CH_2-$	$-S(O)_2-$	$PhS(O)_2CH_2-$
$PhSCH_2-$	$-P(O)(OH)-$	$PhSCH_2-$
$PhOCH_2-$	$-P(O)(OH)-$	$PhOCH_2-$
$PhCH_2CH_2-$	$-P(O)(OH)-$	$PhCH_2CH_2-$
$PhNHCH_2-$	$-P(O)(OH)-$	$PhNHCH_2-$
$PhCH_2CH_2-$	$-S(O)-$	$PhCH_2CH_2-$
$PhCH_2CH_2-$	$-C(=N-OH)-$	$PhCH_2CH_2-$

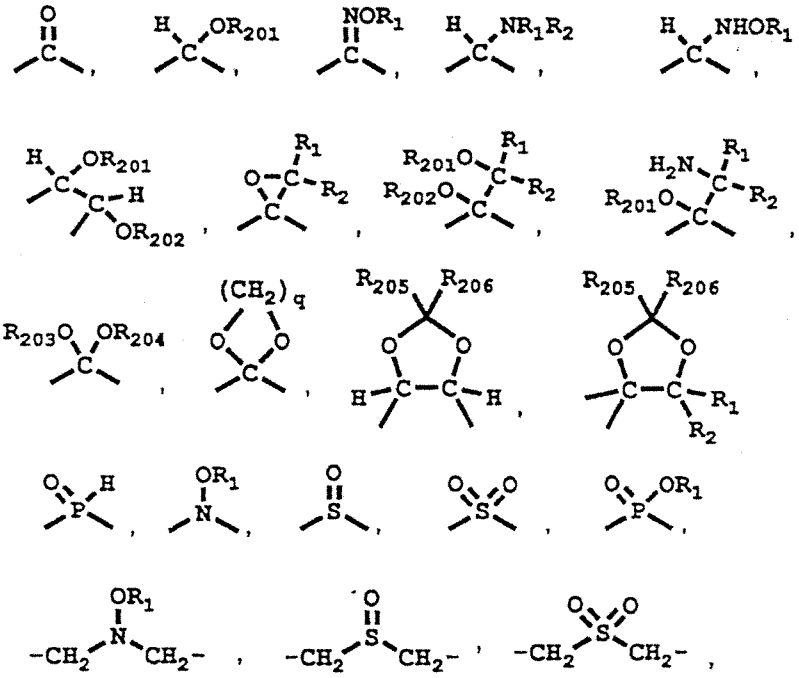
Disclosure of the Invention

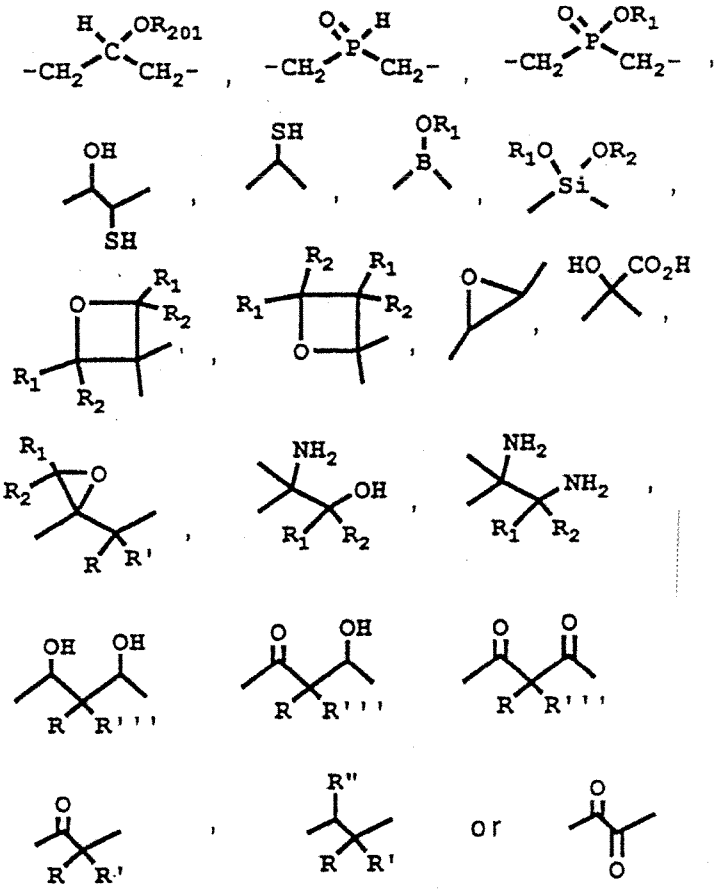
In accordance with the present invention, there are retroviral protease inhibiting compounds of the formula:

A - X - B (I)

or a pharmaceutically acceptable salt, prodrug or ester thereof.

X is





wherein R_1 and R_2 are independently selected from
- (1) hydrogen,
- (2) loweralkyl,
- (3) hydroxyalkyl and
- (4) alkoxyalkyl; and

R_{201} and R_{202} are independently selected from
- (1) hydrogen,
- (2) alkoxyalkyl,
- (3) thioalkoxyalkyl and
- (4) alkoxyalkoxyalkyl; R_{203} is loweralkyl;

R_{204} is loweralkyl;

R_{205} and R_{206} are independently selected from
- (1) hydrogen
- (2) loweralkyl
- (3) alkoxyalkyl; R is hydrogen or halogen;

R' is hydrogen, halogen, loweralkyl, $-NH_2$, -NH(loweralkyl) or $-OR_{206}$ wherein R_{206} is defined as above;

R'' is $-NH_2$, -NH(loweralkyl) or $-OR_{206}$ wherein R_{206} is independently defined as above;

R''' is halogen; and

q is 2 or 3.

A is
- (1) substituted amino,
- (2) substituted carbonyl,
- (3) functionalized imino,
- (4) functionalized alkyl,
- (5) functionalized acyl,

(6) functionalized heterocyclic or
(7) functionalized (heterocyclic)alkyl.

B is:
(1) substituted carbonyl independently defined as herein,
(2) substituted amino independently defined as herein,
(3) functionalized imino independently defined as herein,
(4) functionalized alkyl independently defined as herein,
(5) functionalized acyl independently defined as herein,
(6) functionalized heterocyclic independently defined as herein or
(7) functionalized (heterocyclic)alkyl independently defined as herein.

The term "substituted amino" as used herein includes $-NR_{300}CH(R_3)C(O)-L-R_4$ wherein R_{300} is hydrogen or loweralkyl, L is absent or represents a peptide chain containing 1-4 amino acids wherein R_4 is bonded to the carboxy terminus of the peptide chain and R_4 is hydroxy, alkoxy or functionalized amino and "substituted amino" also includes $-N(R_{207})(R_3)$ wherein R_3 and R_{207} are independently selected from
(i) loweralkyl,
(ii) aryl,
(iii) thioalkoxyalkyl
(iv) (aryl)alkyl,
(v) cycloalkyl,
(vi) cycloalkylalkyl,
(vii) hydroxyalkyl,
(viii) alkoxyalkyl,
(ix) aryloxyalkyl,
(x) haloalkyl,
(xi) carboxyalkyl,
(xii) alkoxycarbonylalkyl,
(xiii) aminoalkyl,
(xiv) (N-protected)aminoalkyl,
(xv) alkylaminoalkyl,
(xvi) ((N-protected)(alkyl)amino)alkyl,
(xvii) dialkylaminoalkyl,
(xviii) guanidinoalkyl,
(xix) loweralkenyl,
(xx) heterocyclic,
(xxi) (heterocyclic)alkyl,
(xxii) hydrogen,
(xxiii) arylthioalkyl,
(xxiv) arylsulfonylalkyl,
(xxv) (heterocyclic)thioalkyl,
(xxvi) (heterocyclic)sulfonylalkyl,
(xxvii) (heterocyclic)oxyalkyl,
(xxviii) arylalkoxyalkyl,
(xxix) arylthioalkoxyalkyl,
(xxx) arylalkylsulfonylalkyl,
(xxxi) (heterocyclic)alkoxyalkyl,
(xxxii) (heterocyclic)thioalkoxyalkyl,
(xxxiii) (heterocyclic)alkylsulfonylalkyl,
(xxxiv) cycloalkyloxyalkyl,
(xxxv) cycloalkylthioalkyl,
(xxxvi) cyloalkylsulfonylalkyl,
(xxxvii) cycloalkylalkoxyalkyl,
(xxxviii cycloalkylthioalkoxyalkyl,
(xxxiv) cycloalkylalkylsulfonylalkyl,
(xl) aminocarbonyl,
(xli) alkylaminocarbonyl,
(xlii) dialkylaminocarbonyl,
(xliii) aroylalkyl,
(xliv) (heterocyclic)carbonylalkyl,

(xlv) polyhydroxyalkyl,
(xlvi) aminocarbonylalkyl,
(xlvii) alkylaminocarbonylalkyl and
(xlviii) dialkylaminocarbonylalkyl; with the proviso that R_3 and R_{207} are not both hydrogen.

The term "substituted carbonyl" as used herein includes $-C(O)(R_3)$ wherein R_3 is independently defined as above.

The term "functionalized imino" as used herein includes $-C(=NOR_1)(R_3)$ wherein R_1 is independently defined as above and R_3 is independently defined as above, or $-C(=NNR_1R_2)(R_3)$ wherein R_1 and R_2 are independently defined as above and R_3 is independently defined as above.

The term "functionalized alkyl" as used herein includes:

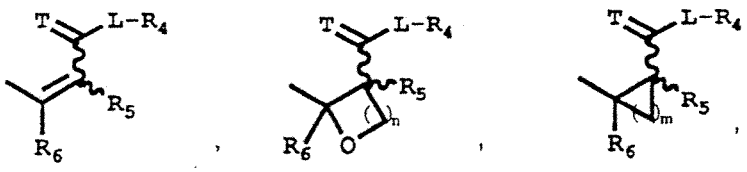
(1) $-CH(Z)((CH_2R_{500})_d-R_3)$ wherein R_3 is independently defined as above; d is 0 or 1;

R_{500} is
(i) -S-,
(ii) -O-,
(iii) -NH-,
(iv) -N(loweralkyl)-,
(v) -S(O)-,
(vi) $-S(O)_2-$ or
(vii) $-CH_2-$; and

Z is
(i) hydrogen,
(ii) fluoro,
(iii) azido,
(iv) $-CH(G)(R_9)$ wherein R_9 is hydrogen, loweralkyl, aryl, arylalkyl, heterocyclic or (heterocyclic)alkyl; and G is (a) functionalized carbonyl, (b) functionalized sulfonyl, (c) functionalized phosphonyl, (d) loweralkyl substituted with functionalized carbonyl, functionalized sulfonyl or functionalized phosphonyl, (e) -J-H or (f) $-J-R_3$ wherein R_3 is independently defined as above and J is absent or represents a peptide chain containing 1-4 amino acids wherein H or R_3 is bonded to the amino terminus of the peptide chain,
(v) $-N(G)(R_9)$ wherein R_9 and G are defined as above,
(vi) -OG wherein G is defined as above;
(vii) -SG wherein G is defined as above; or
(viii) heterocyclic;

(2) $-CF(Z)(R_3)$ wherein R_3 and Z are defined as above,
(3) $-CH(Z)(OR_3)$ wherein R_3 and Z are defined as above,
(4) $-CH(Z)(NR_3R_9)$ wherein R_3, R_9 and Z are defined as above,
(5) $-CH(Z)(SR_3)$ wherein R_3 and Z are defined as above,
(6) $-CH(Z)(S(O)R_3)$ wherein R_3 and Z are defined as above or
(7) $-CH(Z)(S(O)_2R_3)$ wherein R_3 and Z are defined as above.

The term "functionalized acyl" as used herein includes:



wherein L is absent or represents a peptide chain containing 1-4 amino acids wherein R_4 is bonded to the carboxy terminus of the peptide chain,
T is O or S;

R_4 is
(1) hydroxy,
(2) alkoxy or
(3) functionalized amino, R_5 and R_6 are independently selected from
(1) hydrogen,
(2) loweralkyl,
(3) aryl,
(4) heterocyclic,
(5) arylalkyl and
(6) (heterocyclic)alkyl, R_7 is
(1) hydrogen,
(2) fluoro,
(3) loweralkyl,
(4) hydroxyalkyl,
(5) alkoxyalkyl,
(6) aryl,
(7) heterocyclic,
(8) arylalkyl or
(9) (heterocyclic)alkyl, R_8 is
(1) hydrogen or
(2) fluoro; ff is 1 or 2;
n is 0-3; and
m is 1-4.

The term "functionalized carbonyl" as used herein includes:

(1) R_{501}-$(CH(R_3))_i$-$(C(T))_a$-$(CH(R_3))_b$-$(E)_c$-$(CH(R_3))_g$-C-(T)-W- wherein W is absent or represents a peptide chain containing 1-3 amino acids wherein R_{501}-$(C(T))_a$-$(CH(R_3))_b$-$(E)_c$-$(CH(R_3))_g$-C(T)- is bonded to the amino terminus of the peptide chain; T is independently O or S; R_3 at each occurrence is independently defined as above; E is O, S or $N(R_3)$ wherein R_3 is independently defined as above; a is 0-1; b is 0-3; c is 0-1; g is 0-3; i is 0-3; and

R_{501} is
(a) R_{17}-$(R_{800})_h$- wherein R_{800} is $N(R_{17})$, O or S and h is 0 or 1,
(b) $(R_{17})_2N$-O- or
(c) $R_{17}S(O)_2N(R_3)$-
wherein R_3 is independently defined as above and at each occurrence R_{17} is independently selected from:
(i) hydrogen,
(ii) loweralkyl,
(iii) cycloalkyl,
(iv) aryl,
(v) arylalkyl,
(vi) (aryl)alkoxyalkyl
(vii) (aryl)alkoxyalkyl,
(viii) aminoalkyl,
(ix) N-protected-aminoalkyl,
(x) alkylaminoalkyl,
(xi) (N-protected)(alkyl)aminoalkyl,
(xii) dialkylaminoalkyl,
(xiii) carboxyalkoxyalkyl,
(xiv) (alkoxycarbonyl)alkoxyalkyl,
(xv) carboxyalkyl,
(xvi) alkoxycarbonylalkyl,
(xvii) (amino)carboxyalkyl,
(xviii) ((N-protected)amino)carboxyalkyl,
(xix) (alkylamino)carboxyalkyl,
(xx) ((N-protected)alkylamino)carboxyalkyl,
(xxi) (dialkylamino)carboxyalkyl,
(xxii) (amino)alkoxycarbonylalkyl,
(xxiii) ((N-protected)amino)alkoxycarbonylalkyl,
(xxiv) (alkylamino)alkoxycarbonylalkyl,

(xxv) ((N-protected)alkylamino)alkoxycarbonylalkyl,
(xxvi) (dialkylamino)alkoxycarbonylalkyl,
(xxviix) aminocycloalkyl,
(xxviii) alkoxyalkyl,
(xxix) (polyalkoxy)alkyl,
(xxx) heterocyclic,
(xxxi) (heterocyclic)alkyl,
(xxxii) N-protecting group,
(xxxiii) (hydroxyamino)alkyl,
(xxxiv) (alkoxyamino)alkyl,
(xxxv) cycloalkylalkyl,
(xxxvi) loweralkenyl,
(xxxvii) hydroxyalkyl,
(xxxviii) dihydroxyalkyl,
(xxxix) (alkoxy)(alkyl)aminoalkyl,
(xl) alkylaminocycloalkyl,
(xli) dialkylaminocycloalkyl and
(xlii) polyhydroxyalkyl;

and

(2) R_{501}-$(CH(R_3))_f$-$(S(O)_t)_a$-$(CH(R_3))_b$-$(E)_c$-$(CH(R_3))_g$-C(T)-W- wherein W is absent or represents a peptide chain containing 1-3 amino acids wherein R_{501}-$(S(O)_t)_a$-$(CH(R_3))_b$-$(E)_c$-$(CH(R_3))_g$-C(T)- is bonded to the amino terminus of the peptide chain; T is independently O or S; R_3 at each occurrence is independently defined as above; E is O, S or N(R_3) wherein R_3 is independently defined as above; a is 0-1; b is 0-3; c is 0-1; f is 1 or 2; g is 0-3; i is 0-3; and R_{501} is defined as above.

The term "functionalized sulfonyl" as used herein includes:

(1) R_{501}-$(CH(R_3))_f$-$(C(T))_a$-$(CH(R_3))_b$-$(E)_c$-$(CH(R_3))_g$-$S(O)_f$-W- wherein W is absent or represents a peptide chain containing 1-3 amino acids wherein R_{501}-$(C(T))_a$-$(CH(R_3))_b$-$(E)_c$-$(CH(R_3))_g$-$S(O)_f$- is bonded to the amino terminus of the peptide chain; T is independently O or S; R_3 at each occurrence is independently defined as above; E is O, S or N(R_3) wherein R_3 is independently defined as above; a is 0-1; b is 0-3; c is 0-1; f is 1 or 2; g is 0-3; i is 0-3; and R_{501} is defined as above; and

(2) R_{501}-$(CH(R_3))_f$-$(S(O)_t)_a$-$(CH(R_3))_b$-$(E)_c$-$(CH(R_3))_g$-$S(O)_f$-W- wherein W is absent or represents a peptide chain containing 1-3 amino acids wherein R_{501}-$(S(O)_t)_a$-$(CH(R_3))_b$-$(E)_c$-$(CH(R_3))_g$-$S(O)_f$- is bonded to the amino terminus of the peptide chain; R_3 at each occurrence is independently defined as above; E is O, S or N(R_3) wherein R_3 is independently defined as above; a is 0-1; b is 0-3; c is 0-1; f at each occurrence is 1 or 2; g is 0-3; i is 0-3; and R_{501} is defined as above.

The term "functionalized phosphonyl" as used herein includes:

(1) R_{501} $(CH(R_3))_f$-$(C(T))_a$-$(CH(R_3))_b$-$(E)_c$-$(CH(R_3))_g$-P(=E)-W- wherein W is absent or represents a peptide chain containing 1-3 amino acids wherein R_{501}-$(C(T))_a$-$(CH(R_3))_b$-$(E)_c$-$(CH(R_3))_g$-$S(O)_f$- is bonded to the amino terminus of the peptide chain; T is independently O or S; R_3 at each occurrence is independently defined as above; E at each occurrence is independently O, S or N(R_3) wherein R_3 is independently defined as above; a is 0-1; b is 0-3; c is 0-1; g is 0-3; i is 0-3; and R_{501} is defined as above; and

(2) R_{501}-$(CH(R_3))_f$-$(S(O)_t)_a$-$(CH(R_3))_b$-$(E)_c$-$(CH(R_3))_g$-P(=E)-W- wherein W is absent or represents a peptide chain containing 1-3 amino acids wherein R_{501}-$(S(O)_t)_a$-$(CH(R_3))_b$-$(E)_c$-$(CH(R_3))_g$-$S(O)_f$- is bonded to the amino terminus of the peptide chain; R_3 at each occurrence is independently defined as above; E at each occurrence is independently O, S or N(R_3) wherein R_3 is independently defined as above; a is 0-1; b is 0-3; c is 0-1; f at each occurrence is 1 or 2; g is 0-3; i is 0-3; and R_{501} is defined as above.

The term "a peptide chain of 1-3 amino acids" as used herein includes -$(N(R_{208})$-$CH(R_3)$-$C(O))_u$- wherein at each occurrence R_3 is independently defined as above, u is 1-3, and at each occurrence R_{208} is hydrogen or loweralkyl, or R_3 and R_{208} taken together is -$(CH_2)_v$- wherein v is 3-5.

The term "functionalized amino" as used herein includes:

-$NR_{15}R_{16}$ wherein R_{15} and R_{16} are independently selected from hydrogen, loweralkyl, hydroxyalkyl, alkoxyalkyl, dihydroxyalkyl, haloalkyl, aminoalkyl, alkylaminoalkyl, aryl, arylalkyl, (heterocyclic)alkyl, heterocyclic, dialkylaminoalkyl, (N-protected)aminoalkyl, (N-protected)alkylaminoalkyl, cyanoalkyl, hydroxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, (amino)carboxyalkyl, ((N-protected)amino)carboxyalkyl, (alkylamino)carboxyalkyl, ((N-protected)alkylamino)carboxyalkyl, (dialkylamino)carboxyalkyl, (amino)-alkoxycarbonylalkyl, ((N-protected)amino)alkoxycarbonylalkyl, (alkylamino)alkoxycarbonylalkyl, ((N-protected)alkylamino)alkoxycarbonylalkyl and (dialkylamino)alkoxycarbonylalkyl.

The term "functionalized heterocyclic" as used herein refers to a heterocyclic group indepedently

defined as herein which is substituted with a functional group G wherein G is independently defined as herein.

The term "functionalized (heterocyclic)alkyl" as used herein refers to a (heterocyclic)alkyl group independently defined as herein in which the heterocyclic group is substituted with a functional group G wherein G is independently defined as herein.

The chiral centers of the compounds of the invention may be racemic or asymmetric. Racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention are included in the present invention. The terms "S" and "R" configuration are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13 - 30.

The terms "Ala", "Asn", "Gly", "Ile", "Leu", "Lys", "Phe", "Pro", "Ser", and "Val" as used herein refer to alanine, asparagine, glycine, isoleucine, leucine, lysine, phenylalanine, proline, serine and valine, respectively. In general, the amino acid abbreviations used herein follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature for amino acids and peptides (Eur. J. Biochem. 1984, 158, 9-31).

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect nitrogen atoms against undesirable reactions during synthetic procedures or to prevent the attack of exopeptidases on the final compounds or to increase the solubility of the final compounds and includes but is not limited to acyl, acetyl, pivaloyl, t-butylacetyl, t-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz) or benzoyl groups or an L- or D- aminoacyl residue, which may itself be N-protected similarly.

The term "loweralkyl" as used herein refers to straight or branched chain alkyl radicals containing from 1 to 6 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "alkylene" as used herein refers to a straight or branched chain carbon diradical containing from 1 to 6 carbon atoms including, but not limited to, $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH_2CH_2-$ and the like.

The term "loweralkenyl" as used herein refers to a loweralkyl radical which contains at least one carbon-carbon double bond including, but not limited to, propenyl, butenyl and the like. Alkenyl groups can be unsubstituted or substituted with one or more substituents independently selected from loweralkyl, haloalkyl, cycloalkyl, aryl, heterocyclic, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, carboalkoxy and carboxamide.

The term "aryl" as used herein refers to a monocyclic or bicyclic carbocyclic ring system having one or more aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl and the like. Aryl groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, carboalkoxy and carboxamide. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "arylalkyl" as used herein refers to an aryl group appended to a loweralkyl radical including, but not limited to, benzyl, 4-hydroxybenzyl, 1-naphthylmethyl and the like.

The term "aminoalkyl" as used herein refers to $-NH_2$ appended to a loweralkyl radical.

The term "cyanoalkyl" as used herein refers to -CN appended to a loweralkyl radical.

The term "hydroxyalkyl" as used herein refers to -OH appended to a loweralkyl radical.

The term "dihydroxyalkyl" as used herein refers to a loweralkyl radical disubstituted with -OH groups.

The term "polyhydroxyalkyl" as used herein refers to a loweralkyl radical substituted with more than two -OH groups.

The term "hydroxyaminoalkyl" as used herein refers to a hydroxyamino group (-NHOH) appended to a loweralkyl radical.

The term "alkoxyaminoalkyl" as used herein refers to $-NHR_{250}$ (wherein R_{250} is an alkoxy group) appended to a loweralkyl radical.

The term "(alkoxy)(alkyl)aminoalkyl" as used herein refers to $(R_{270})(R_{271})N-$ wherein R_{270} is alkoxy and R_{271} is loweralkyl appended to a loweralkyl radical.

The term "alkylamino" as used herein refers to a loweralkyl radical appended to an NH radical.

The term "hydroxyalkylamino" as used herein refers to a hydroxyalkyl group appended to an NH radical.

The term "dihydroxyalkylamino" as used herein refers to a dihydroxyalkyl group appended to an NH radical.

The term "(hydroxyamino)alkylamino" as used herein refers to $-NHR_{251}$ wherein R_{251} is a hydroxyaminoalkyl group.

The term "(alkoxyamino)alkylamino" as used herein refers to $-NHR_{252}$ wherein R_{252} is an alkoxyaminoalkyl group.

The term "((hydroxyamino)alkyl)(alkyl)amino" as used herein refers to $-NR_{253}R_{254}$ wherein R_{253} is a hydroxyaminoalkyl group and R_{254} is a loweralkyl group.

The term "((alkoxyamino)alkyl)(alkyl)amino" as used herein refers to $-NR_{255}R_{256}$ wherein R_{255} is an alkoxyaminoalkyl group and R_{256} is a loweralkyl group.

The term "(N-protected)aminoalkylamino" as used herein refers to an N-protected amino group which is appended to a loweralkyl group which in turn is appended to an -NH radical.

The term "cycloalkyl" as used herein refers to an aliphatic ring having 3 to 7 carbon atoms including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl and the like. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, carboalkoxy and carboxamide.

The term "cycloalkylalkyl" as used herein refers to a cycloalkyl group appended to a loweralkyl radical, including but not limited to cyclohexylmethyl.

The term "alkylaminocycloalkyl" as used herein refers to an alkylamino group appended to a cycloalkyl radical.

The term "dialkylaminocycloalkyl" as used herein refers to a dialkylamino group appended to a cycloalkyl radical.

The terms "alkoxy" and "thioalkoxy" as used herein refer to $R_{18}O-$ and $R_{18}S-$, respectively, wherein R_{18} is a loweralkyl group or benzyl.

The term "(hydroxyamino)alkoxy" as used herein refers to $R_{257}O-$ wherein R_{257} is a hydroxyaminoalkyl group.

The term "(alkoxyamino)alkoxy" as used herein refers to $R_{258}O-$ wherein R_{258} is an alkoxyaminoalkyl group.

The term "alkoxyalkyl" as used herein refers to an alkoxy group appended to a loweralkyl radical.

The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group appended to a loweralkyl radical.

The term "alkoxyalkoxyalkyl" as used herein refers to an alkoxy group appended to an alkoxy group which is in turn appended to a loweralkyl radical including, but not limited to, methoxyethoxymethyl and the like.

The term "guanidinoalkyl" as used herein refers to a guanidino group ($-NHC(=NH)NH_2$) appended to a loweralkyl radical.

The term "alkenyloxy" as used herein refers to $R_{19}O-$wherein R_{19} is a loweralkenyl group.

The term "hydroxyalkoxy" as used herein refers to -OH appended to an alkoxy radical.

The term "dihydroxyalkoxy" as used herein refers to an alkoxy radical which is disubstituted with -OH groups.

The term "arylalkoxy" as used herein refers $R_{90}O-$wherein R_{90} is a arylalkyl group as defined above.

The term "(heterocyclic)alkoxy" as used herein refers to $R_{301}O-$ wherein R_{301} is a (heterocyclic)alkyl group.

The term "arylalkoxyalkyl" as used herein refers to a arylalkoxy group as defined above appended to a loweralkyl radical.

The term "aryloxyalkyl" as used herein refers to a $R_{220}O-$ group appended to a loweralkyl radical, wherein R_{220} is an aryl group.

The term "dialkylamino" as used herein refers to $-NR_{20}R_{21}$ wherein R_{20} and R_{21} are independently selected from loweralkyl groups.

The term "(hydroxyalkyl)(alkyl)amino" as used herein refers to $-NR_{22}R_{23}$ wherein R_{22} is hydroxyalkyl and R_{23} is loweralkyl.

The term "N-protected aminoalkyl" as used herein refers to $-NHR_{24}$ appended to a loweralkyl group, wherein R_{24} is an N-protecting group.

The term "alkylaminoalkyl" as used herein refers to NHR_{25} appended to a loweralkyl radical, wherein R_{25} is a loweralkyl group.

The term "(N-protected)(alkyl)aminoalkyl" as used herein refers to $-NR_{24}R_{25}$, which is appended to a loweralkyl radical, wherein R_{24} and R_{25} are as defined above.

The term "dialkylaminoalkyl" as used herein refers to $-NR_{26}R_{27}$ which is appended to a loweralkyl radical wherein R_{26} and R_{27} are independently selected from loweralkyl.

The term "azidoalkyl" as used herein refers to a $-N_3$ group appended to a loweralkyl radical.

The term "carboxyalkyl" as used herein refers to a carboxylic acid group (-COOH) appended to a loweralkyl radical.

The term "alkoxycarbonylalkyl" as used herein refers to a $R_{28}C(O)-$ group appended to a loweralkyl radical, wherein R_{28} is an alkoxy group .

The term "carboxyalkoxyalkyl" as used herein refers to a carboxylic acid group (-COOH) appended to an alkoxy group which is appended to a loweralkyl radical.

The term "alkoxycarbonylalkoxyalkyl" as used herein refers to an alkoxycarbonyl group ($R_{30}C(O)$- wherein R_{30} is an alkoxy group) appended to an alkoxy group which is appended to a loweralkyl radical.

The term "(amino)carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxylic acid group (-COOH) and an amino group ($-NH_2$).

The term "((N-protected)amino)carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxylic acid group (-COOH) and $-NHR_{31}$ wherein R_{31} is an N-protecting group.

The term "(alkylamino)carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxylic acid group (-COOH) and an alkylamino group.

The term "((N-protected)alkylamino)carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxylic acid group (-COOH) and an $-NR_{31}R_{32}$ wherein R_{31} is as defined above and R_{32} is a loweralkyl group.

The term "(dialkylamino)carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxylic acid group (-COOH) and $-NR_{32}R_{32}$ wherein R_{32} is as defined above.

The term "(amino)alkoxycarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxycarbonyl group as defined above and an amino group ($-NH_2$).

The term "((N-protected)amino)alkoxycarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxycarbonyl group as defined above and $-NHR_{31}$ wherein R_{31} is as defined above.

The term "(alkylamino)alkoxycarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxycarbonyl group as defined above and an alkylamino group as defined above.

The term "((N-protected)alkylamino)alkoxycarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxycarbonyl group as defined above and $-NR_{31}R_{32}$ wherein R_{31} and R_{32} are as defined above.

The term "(dialkylamino)alkoxycarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkoxycarbonyl group as defined above and $-NR_{32}R_{32}$ wherein R_{32} is as defined above.

The term "carboxyalkylamino" as used herein refers to $-NHR_{33}$ wherein R_{33} is a carboxyalkyl group.

The term "alkoxycarbonylalkylamino" as used herein refers to $-NHR_{34}$ wherein R_{34} is an alkoxycarbonylakyl group.

The term "(amino)carboxyalkylamino" as used herein refers to $-NHR_{35}$ wherein R_{35} is an (amino)carboxyalkyl group.

The term "((N-protected)amino)carboxyalkylamino" as used herein refers to $-NHR_{36}$ wherein R_{36} is an [(N-protected)amino]carboxyalkyl group.

The term"(alkylamino)carboxyalkylamino" as used herein refers to $-NHR_{37}$ wherein R_{37} is an (alkylamino)carboxyalkyl group.

The term "((N-protected)alkylamino)carboxyalkylamino" as used herein refers to $-NHR_{38}$ wherein R_{38} is an ((N-protected)alkylamino)carboxyalkyl group.

The term "(dialkylamino)carboxyalkylamino" as used herein refers to $-NHR_{39}$ wherein R_{39} is a (dialkylamino)carboxyalkyl group.

The term "(amino)alkoxycarbonylalkylamino" as used herein refers to $-NHR_{40}$ wherein R_{40} is an (amino)alkoxycarbonylalkyl group.

The term "((N-protected)amino)alkoxycarbonylalkylamino" as used herein refers to $-NHR_{41}$ wherein R_{41} is an ((N-protected)amino)alkoxycarbonylalkyl group.

The term "(alkylamino)alkoxycarbonylalkylamino" as used herein refers to $-NHR_{42}$ wherein R_{42} is an (alkylamino)alkoxycarbonylalkyl group.

The term "((N-protected)alkylamino)alkoxycarbonylalkylamino" as used herein refers to $-NHR_{43}$ wherein R_{43} is an ((N-protected)alkylamino)alkoxycarbonylalkyl group.

The term "(dialkylamino)alkoxycarbonylalkylamino" as used herein refers to $-NHR_{44}$ wherein R_{44} is a (dialkylamino)alkoxycarbonylalkyl group.

The term "aminocycloalkyl" as used herein refers to an NH_2 appended to a cycloalkyl radical.

The term "((alkoxy)alkoxy)alkyl" as used herein refers to an alkoxy group appended to an alkoxy group which is appended to a loweralkyl radical.

The term "polyalkoxyalkyl" as used herein refers to a polyalkoxy residue appended to a loweralkyl radical.

The term "polyalkoxy" as used herein refers to $-OR_{45}$ wherein R_{45} is a straight or branched chain containing 1-5, $C_{n'}$-O-$C_{n''}$ linkages wherein n' and n'' are independently selected from 1 to 3, including but not limited to methoxyethoxymethoxy, methoxymethoxy and the like.

The term "(arylalkyl)amino" as used herein refers to $R_{100}NH$- wherein R_{100} is an arylalkyl group as

defined above.

The term "(arylalkyl)(alkyl)amino" as used herein refers to $R_{104}R_{105}N$- wherein R_{104} is an arylalkyl group as defined above and R_{105} is a loweralkyl group.

The term "(heterocyclic)alkylamino" as used herein refers to $R_{900}NH$- wherein R_{900} is a (heterocyclic)-alkyl group.

The term "((heterocyclic)alkyl)(alkyl)amino" as used herein refers to $R_{900}R_{901}N$- wherein R_{900} is a (heterocyclic)alkyl group and R_{901} is a loweralkyl group.

The term "dialkylaminoalkyl(alkyl)amino" as used herein refers to $-NR_{49}R_{50}$ wherein R_{49} is a dialkylamino residue appended to a loweralkyl residue and R_{50} is a loweralkyl residue.

The term "alkylaminoalkylamino" as used herein refers to $-NHR_{50a}$ wherein R_{50a} is an alkylaminoalkyl group as previously defined.

The term "dialkylaminoalkylamino" as used herein refers to $-NHR_{50b}$ wherein R_{50b} is a dialkylaminoalkyl group as previously defined.

The term "aminoalkylamino" as used herein refers to $-NHR_{51}$ wherein R_{51} is an aminoalkyl residue.

The term "(dihydroxyalkyl)(alkyl)amino" as used herein refers to a loweralkyl group which is disubstituted with -OH radicals, appended to an amino group, which amino group also has appended another loweralkyl group, including but not limited to N-(2,3-dihydroxypropyl)-N-(methyl)amine.

The term "di-(hydroxyalkyl)amino" as used herein refers to $-NR_{52}R_{53}$ wherein R_{52} and R_{53} are hydroxyalkyl residues.

The term "alkoxyalkyl(alkyl)amino" as used herein refers to $-NR_{54}R_{55}$ wherein R_{54} is an alkoxyalkyl group and R_{55} is a loweralkyl group.

The term "di-(alkoxyalkyl)amino" as used herein refers to $-NR_{56}R_{57}$ wherein R_{56} and R_{57} are alkoxyalkyl groups.

The term "di-(polyalkoxyalkyl)amino" as used herein refers to $-NR_{58}R_{59}$ wherein R_{58} and R_{59} are polyalkoxy residues appended to loweralkyl residues.

The term "((polyalkoxy)alkyl))(alkyl)amino" as used herein refers to $-NR_{60}R_{61}$ wherein R_{60} is a polyalkoxy residue appended to a loweralkyl residue and R_{61} is a loweralkyl residue.

The term "halo" or "halogen" as used herein refers to -Cl, -Br, -I or -F.

The term "haloalkyl" as used herein refers to a loweralkyl radical in which one or more of the hydrogen atoms are replaced by halogen including, but not limited to, chloromethyl, trifluoromethyl, 1-chloro-2-fluoroethyl and the like.

The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group appended to a loweralkyl radical.

The term "alkylsulfonyl" as used herein refers to $R_{62}SO_2$ wherein R_{62} is loweralkyl group.

The term "arylthioalkyl" as used herein refers to R_{505}-S-R_{506}- wherein R_{505} is an aryl group and R_{506} is an alkylene group.

The term "arylsulfonylalkyl" as used herein refers to R_{507}-S(O)$_2$-R_{508}- wherein R_{507} is any aryl group and R_{508} is an alkylene group.

The term "(heterocyclic)oxyalkyl" as used herein refers to R_{509}-O-R_{510}- wherein R_{509} is an aryl group and R_{510} is an alkylene group.

The term "(heterocyclic)thioalkyl" as used herein refers to R_{511}-S-R_{512}- wherein R_{511} is an aryl group and R_{512} is an alkylene group.

The term "(heterocyclic)sulfonylalkyl" as used herein refers to R_{513}-S(O)$_2$-R_{514}- wherein R_{513} is an aryl group and R_{514} is an alkylene group.

The "arylalkoxyalkyl" as used herein refers to R_{515}-O-R_{516}- wherein R_{515} is an arylalkyl group and R_{516} is an alkylene group.

The "arylthioalkoxyalkyl" as used herein refers to R_{517}-S-R_{518}- wherein R_{517} is an arylalkyl group and R_{518} is an alkylene group.

The "arylalkylsulfonylalkyl" as used herein refers to R_{519}-S(O)$_2$-R_{520}- wherein R_{519} is an arylalkyl group and R_{520} is an alkylene group.

The term "(heterocyclic)alkoxyalkyl" as used herein refers to R_{521}-O-R_{522}- wherein R_{521} is a (heterocyclic)alkyl group and R_{522} is an alkylene group.

The term "(heterocyclic)thioalkoxyalkyl" as used herein refers to R_{523}-S-R_{524}- wherein R_{523} is a (heterocyclic)alkyl group and R_{524} is an alkylene group.

The term "(heterocyclic)alkylsulfonylalkyl" as used herein refers to R_{525}-S(O)$_2$-R_{526}- wherein R_{525} is a (heterocyclic)alkyl group and R_{526} is an alkylene group.

The term "cycloalkyloxyalkyl" as used herein refers to R_{527}-O-R_{528}- wherein R_{527} is a cycloalkyl group and R_{528} is an alkylene group.

The term "cycloalkylthioalkyl" as used herein refers to R_{529}-S-R_{530}- wherein R_{529} is a cycloalkyl group

and R_{530} is an alkylene group.

The term "cycloalkylsulfonylalkyl" as used herein refers to R_{531}-$S(O)_2$-R_{532}- wherein R_{531} is a cycloalkyl group and R_{532} is an alkylene group.

The term "cycloalkylalkoxyalkyl" as used herein refers to R_{533}-O-R_{534}- wherein R_{533} is a cycloalkylalkyl group and R_{534} is an alkylene group.

The term "cycloalkylthioalkoxyalkyl" as used herein refers to R_{535}-S-R_{536}- wherein R_{535} is a cycloalkylalkyl group and R_{536} is an alkylene group.

The term "cycloalkylalkylsulfonylalkyl" as used herein refers to R_{537}-$S(O)_2$-R_{538}- wherein R_{537} is a cycloalkylalkyl group and R_{538} is an alkylene group.

The term "aminocarbonyl" as used herein refers to -$C(O)NH_2$.

The term "aminocarbonylalkyl" as used herein refers to an aminocarbonyl group appended to a loweralkyl radical.

The term "alkylaminocarbonyl" as used herein refers to -$C(O)NHR_{539}$ wherein R_{539} is loweralkyl.

The term "alkylaminocarbonylalkyl" as used herein refers to an alkylaminocarbonyl group appended to a loweralkyl radical.

The term "dialkylaminocarbonyl" as used herein refers to -$C(O)NR_{540}R_{541}$ wherein R_{540} and R_{541} are independently selected from loweralkyl.

The term "dialkylaminocarbonylalkyl" as used herein refers to a dialkylaminocarbonyl group appended to a loweralkyl group.

The term "aroylalkyl" as used herein refers to R_{542}-C(O)-R_{543}- wherein R_{542} is an aryl group and R_{543} is an alkylene group.

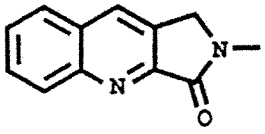
The term "(heterocyclic)carbonylalkyl" as used herein refers to R_{544}-C(O)-R_{545}- wherein R_{544} is a heterocyclic group and R_{545} is an alkylene group.

The term "arylamino" as used herein refers to R_{546}NH-wherein R_{546} is an aryl group.

The term "(heterocyclic)amino" as used herein refers to R_{547}NH- wherein R_{547} is a heterocyclic group.

The term "heterocyclic ring" or "heterocyclic" as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from oxygen, nitrogen and sulfur; or a 5- or 6-membered ring containing one, two or three nitrogen atoms; one nitrogen and one sulfur atom; or one nitrogen and one oxygen atom. The 5-membered ring has 0-2 double bonds and the 6-membered ring has 0-3 double bonds. The nitrogen and sulfur heteroatoms can be optionally oxidized. The nitrogen heteroatoms can be optionally quaternized. The term "heterocyclic" also includes bicyclic groups in which any of the above heterocyclic rings is fused to a benzene ring or or a cyclohexane ring or another heterocyclic ring. Heterocyclics include: pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl and benzothienyl.

Heterocyclics also include: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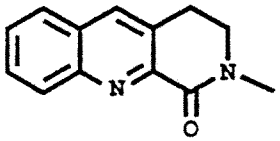
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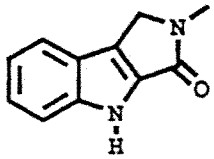
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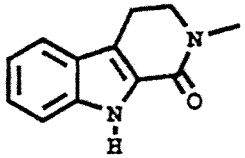
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Heterocyclics can be unsubstituted or monosubstituted or disubstituted with substituents independently selected from hydroxy, halo, oxo (=O), alkylimino (R*N= wherein R* is a loweralkyl group), amino, alkylamino, dialkylamino, alkoxy, polyalkoxy, haloalkyl, cycloalkyl, -COOH, -SO_3H and loweralkyl. In addition, nitrogen containing heterocycles can be N-protected.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group appended to a loweralkyl radical, including but not limited to imidazolylmethyl, thiazolylmethyl, pyridylmethyl and morpholinylmethyl.

The term "heterocyclic carbonyloxy" as used herein refers to $R_{304}C(O)O$- wherein R_{304} is a heterocyclic group.

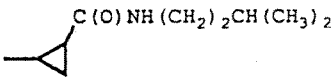
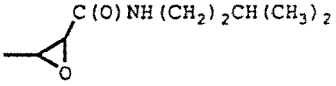
The term "heterocyclic carbonylamino" as used herein refers to $R_{305}C(O)NH$- wherein R_{305} is a heterocyclic group.

In the compounds of the present invention, the A, X and B components may have asymmetric centers and occur as racemates, racemic mixtures, mixtures of diastereomers and as individual diastereomers, with all isomeric forms being included in the invention.

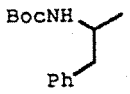
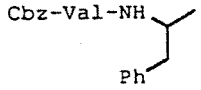
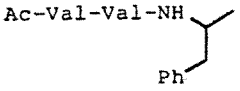
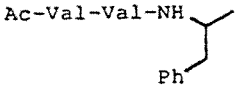
When any variable (i.e., R_1, R_2, R_3, etc.) occurs more than one time in any constituent or in a compound of Formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Representative compounds of the invention include those represented in Table 2. (In the table "Ph" represents phenyl and p-C7H7 represents 4-methylphenyl).

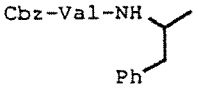
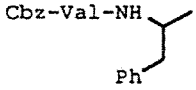
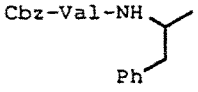
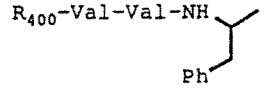
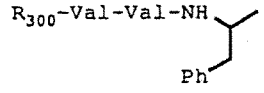
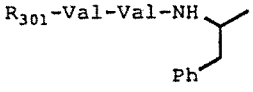
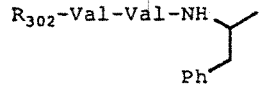
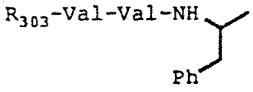
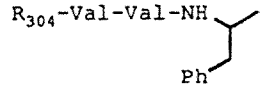
TABLE 2

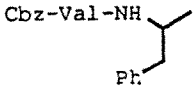
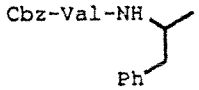
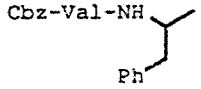
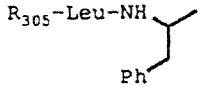
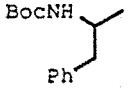
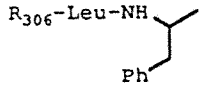
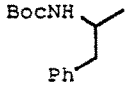
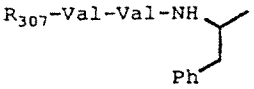
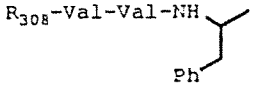
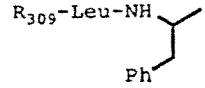
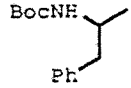
Compound of Example	A	X	B
1B	$PhCH_2CH_2$-	-S(O)$_2$-	$PhCH_2CH_2$-
2	$PhCH_2CH_2$-	-S(O)-	$PhCH_2CH_2$-
3B	$PhCH_2CH_2$-	-CH(OH)-	$PhCH_2CH_2$-
3A	$PhCH_2CH_2$-	-C(O)-	$PhCH_2CH_2$-
4	$PhOCH_2$-	-CH(OH)-	$PhOCH_2$-
5	$PhOCH_2$-	-C(O)-	$PhOCH_2$-
6G	$PhCH_2CH_2$-	-CH(OH)-	-CH=CHC(O)NH-$(CH_2)_2CH(CH_3)_2$
7B	$PhCH_2CH_2$-	-CH(OH)-	
8B	$PhCH_2CH_2$-	-CH(OH)-	
9	$PhCH_2CH_2$-	-P(O)H-	$PhCH_2CH_2$-
10C	$PhCH_2CH(NHBoc)$-	-CH(OH)-	$PhCH_2CH(N_3)$-
11	$PhCH_2CH(NHBoc)$-	-CH(OH)-	$PhCH_2CH(NH_2)$-
12	$PhCH_2CH(NH_2)$-	-CH(OH)-	$PhCH_2CH(NH_2)$-
13	$PhCH_2CH(NHSO_2Me)$-	-CH(OH)-	$PhCH_2CH(NHSO_2Me)$-
14	$PhNHCH_2$-	-CH(OH)-	$PhNHCH_2$-
15	$PhSCH_2$-	-CH(OH)-	$PhSCH_2$-
16B	$PhCH_2CH_2$-		$PhCH_2CH_2$-

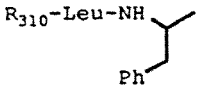
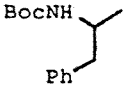
17B	$PhCH_2CH(NHBoc)-$	$-CH(OH)CH(OH)-$	$PhCH_2CH-(N(CH_2Ph)Cbz)-$
18	$PhCH_2CH(NHBoc)-$	$-CH(OH)CH(OH)-$	$PhCH_2CH(NHCH_2Ph)-$
19	$PhCH_2CH(NH_2)-$	$-CH(OH)CH(OH)-$	$PhCH_2CH(NHCH_2Ph)-$
20	$PhCH_2CH_2-$	$-C(OH)(CH_2OH)-$	$PhCH_2CH_2-$
21B	$PhOCH_2-$		$PhOCH_2-$
22	$PhCH_2CH(NHBoc)-$	$-CH(OH)-$	$PhCH_2CH(CH_2C(O)-NHCH_2CH_2CH(CH_3)_2)-$
23B	$PhCH_2C(O)-$	$-CH(OH)CH(OH)-$	$PhCH_2C(O)-$
24	$PhCH_2CH(OH)-$	$-CH(OH)CH(OH)-$	$PhCH_2CH(OH)-$
25B	$PhCH_2C(=NOH)-$	$-CH(OH)CH(OH)-$	$PhCH_2C(=NOH)-$
26	$PhCH_2C(=NOMe)-$	$-CH(OH)CH(OH)-$	$PhCH_2C(=NOMe)-$
27	$PhCH_2C(=NNH_2)-$	$-CH(OH)CH(OH)-$	$PhCH_2C(=NNH_2)-$
28	$PhCH_2CH(CH_2CH_3)-$	$-S(O)-$	$PhCH_2CH(CH_2CH_3)-$
29B	$PhCH_2CH(F)-$	$-S(O)-$	$PhCH_2CH_2-$
30B	$PhCH_2CH_2-$	$-N(OH)-$	$PhCH_2CH_2-$
31	$PhCH_2CH_2-$	$-C(=NOH)-$	$PhCH_2CH_2-$
32	$PhCH_2CH_2-$	$-CH(NH_2)-$	$PhCH_2CH_2-$
33	$PhCH_2CH_2-$	$-CH(NH(OH))-$	$PhCH_2CH_2-$
34C	$PhCH_2CH(F)-$	$-C(O)-$	$PhCH_2CH_2-$
35	$PhCH_2CH(NHC(O)Me)-$	$-CH(OH)-$	$PhCH_2CH(NHC(O)Me)-$
36G	$PhCH_2CH(NH_2)-$	$-CH(OH)-$	$-CH=CHC(O)NH-CH_2CH_2CH(CH_3)_2$
37	$PhCH_2CH(NHC(O)Me)-$	$-CH(OH)-$	$-CH=CHC(O)NH-CH_2CH_2CH(CH_3)_2$
38	$PhCH_2CH(NHSO_2NMe_2)-$	$-CH(OH)-$	$PhCH_2CH(NHSO_2NMe_2)-$
39	$PhCH_2CH(NHC(O)NH_2)-$	$-CH(OH)-$	$PhCH_2CH(NHC(O)NH_2)-$

40	$PhCH_2CH_2-$	$-P(O)(OH)-$	$PhCH_2CH_2-$
41B	$PhCH_2CH_2-$	$-C(OH)(CH_2NH_2)-$	$PhCH_2CH_2-$
42	$(CH_3)_2CHCH_2CH_2-$	$-CH(OH)-$	$(CH_3)_2CHCH_2CH_2-$
43C	$PhCH_2CF_2-$	$-C(O)-$	$PhCH_2CH_2-$
44	$PhCH_2CH_2-$	$-CH(OH)-$	$CH_3CH_2OC(O)CF_2-$
45	$PhCH_2CH_2-$	$-CH(OH)-$	$HOC(O)CF_2-$
46	$PhCH_2CH_2-$	$-CH(OH)-$	$(CH_3)_2CHCH_2CH_2NHC(O)CF_2-$
47	$PhCH_2CH_2-$	$-C(O)-$	$(CH_3)_2CHCH_2CH_2NHC(O)CF_2-$
48	$PhCH_2CH(NHC(O)-C(CH_3)_2CH_2C(O)OCH_2Ph)-$	$-CH(OH)-$	$PhCH_2CH(NHC(O)-C(CH_3)_2CH_2C(O)OCH_2Ph)-$
49	$PhCH_2CH(NHC(O)-C(CH_3)_2CH_2COOH)-$	$-CH(OH)-$	$PhCH_2CH(NHC(O)-C(CH_3)_2CH_2COOH)-$
50	$4-NO_2-C_6H_4OCH_2-$	$-CH(OH)-$	$4-NO_2-C_6H_4OCH_2-$
51	$PhCH_2CH_2-$	$-CH(OCH_2OCH_3)-$	$PhCH_2CH_2-$
52B	$PhCH_2CH_2CH_2-$	$-C(O)-$	$PhCH_2CH_2CH_2-$
53	$PhCH_2CH_2CH_2-$	$-CH(OH)-$	$PhCH_2CH_2CH_2-$
54B	$PhCH_2CH_2-$	$-CH(OH)-$	$-CH=CHC(O)-Val-Val-NH_2$
55		$-CH(OH)-$	
56		$-CH(OH)-$	
57		$-CH(OH)-$	
58		$-CH(OH)-$	

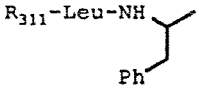
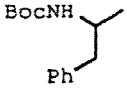
59	Ac-Val-Val-NH, Ph	-CH(OH)-	Ac-Val-Val-NH, Ph
60	Ac-Val-Val-NH, Ph	-C(O)-	Ac-Val-Val-NH, Ph
61E	N_3, Ph		Cbz-Val-NH, Ph
62	$PhCH_2NH$, Ph	-CH(OH)CH(OH)-	Ac-Val-Val-NH, Ph
63	N_3, Ph	-C(OH)(CH_2OH)-	Cbz-Val-NH, Ph
64C	Cbz-Val-O, Ph	-CH(OH)CH(OH)-	Cbz-Val-O, Ph
65	BocNH, Ph	-CH(OH)-	Cbz-Leu-Asn-NH, Ph
66	BocNH, Ph	-CH(OH)-	Cbz-Asn-NH, Ph
67	H_2N, Ph	-CH(OH)-	Cbz-Asn-NH, Ph
68	Cbz-Asn-NH, Ph	-CH(OH)-	Cbz-Asn-NH, Ph

69		-CH(OH)-	
70		-CH(OH)-	
71D		-CH(OH)-	 (R_{400} = $CH_3OC(O)-(CH_2)_4-C(O)-$)
72		-CH(OH)-	 (R_{300} = $CH_3OC(O)-(CH_2)_4-C(O)-$)
73C	 (R_{301} = $CbzNH(CH_2)_5C(O)-$)	-CH(OH)-	 (R_{302} = $CH_3OC(O)-(CH_2)_4-C(O)-$)
74	 (R_{303} = $CbzNH(CH_2)_4C(O)-$)	-CH(OH)-	 (R_{304} = $HOC(O)-(CH_2)_4-C(O)-$)

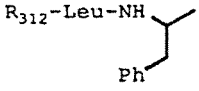
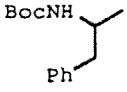
75	$PhOCH_2-$	$-CH(OH)-$		
76	$PhSCH_2-$	$-CH(OH)-$		
77	$PhSO_2CH_2-$	$-CH(OH)-$		
78D		$-CH(OH)-$		
(R_{305} = $CbzNHC(CH_3)_2CH_2C(O)-$)				
79C		$-CH(OH)-$		
(R_{306} = 3,4-dihydroxypyrrolidinyl-carbonyl)				
80		$-CH(OH)-$		
(R_{307} = $H_2N(CH_2)_4C(O)-$)			(R_{308} = $HO_2C(CH_2)_4C(O)-$)	
81	$PhSCH_2-$	$-CH(OCH_2OCH_3)-$	$PhSCH_2-$	
82	$PhOCH_2-$	$-CH(OCH_2OCH_3)-$	$PhOCH_2-$	
83C		$-CH(OH)-$		
(R_{309} = thiomorpholinyl-carbonyl)				

84C  -CH(OH)- 

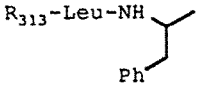
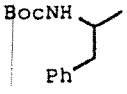
(R_{310} = sulfonylmorpholinyl-carbonyl)

85C  -CH(OH)- 

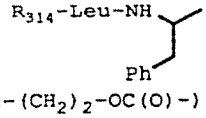
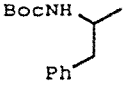
(R_{311} = $(CH_3)_2N(CH_2)_2N(CH_3)C(O)-$)

86E  -CH(OH)- 

(R_{312} = $HOCH_2CH(OH)CH_2N(CH_3)C(O)-$)

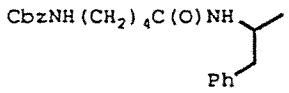
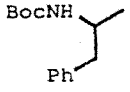
87C  -CH(OH)- 

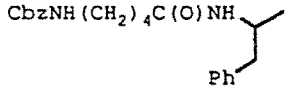
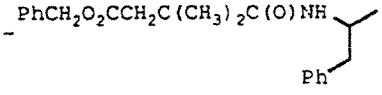
(R_{313} = Cbz-piperidin-4-yl-carbonyl)

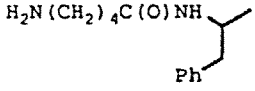
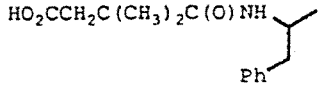
88D  -CH(OH)- 

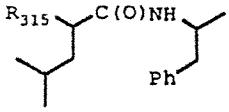
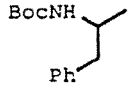
(R_{314} = $HOCH_2-(CH_2)_2-OC(O)-$)

89B	$(4-(CH_3)_2CH)C_6H_4CH_2CH_2-$	-CH(OH)-	$(4-(CH_3)_2CH)C_6H_4CH_2CH_2-$
90B	$4-HOC_6H_4CH_2CH_2-$	-CH(OH)-	$4-HOC_6H_4CH_2CH_2-$
91B	$(1-naphthyl)CH_2CH_2-$	-CH(OH)-	$(1-naphthyl)CH_2CH_2-$
92B	$4-CH_3OC_6H_4CH_2CH_2-$	-CH(OH)-	$4-CH_3OC_6H_4CH_2CH_2-$
93B	$4-BrC_6H_4CH_2CH_2-$	-CH(OH)-	$4-BrC_6H_4CH_2CH_2-$
94B	$PhCH_2CH_2-$	-(H·Ala-O)CH-	$PhCH_2CH_2-$
95B	$PhCH_2CH_2-$	-(H·Gly-O)CH-	$PhCH_2CH_2-$
96B	$PhCH_2CH_2-$	-(H·Lys-O)CH-	$PhCH_2CH_2-$

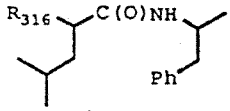
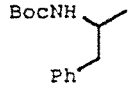
97  -CH(OH)- 

98  -CH(OH)- 

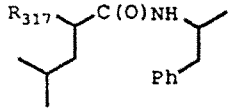
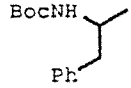
99  -CH(OH)- 

100G  -CH(OH)- 

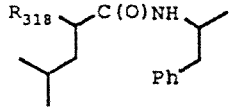
(R_{315} = 4-morpholinylC(O)CH_2-)

101C  -CH(OH)- 

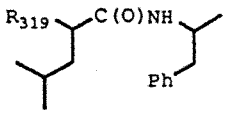
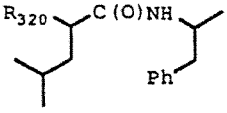
(R_{316} = 4-morpholinylC(O)O-)

102C  -CH(OH)- 

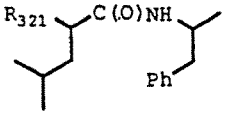
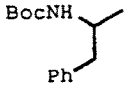
(R_{317} = $PhCH_2NHC(O)CH_2$-)

103  -CH(OH)- 

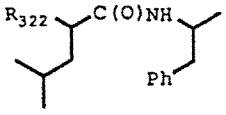
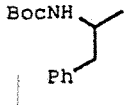
(R_{318} = $PhCH_2NHC(O)CH_2$-)

104  -CH(OH)- 

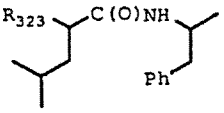
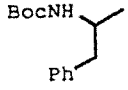
(R_{319} = $PhCH_2NHC(O)CH_2$-) (R_{320} = $PhCH_2NHC(O)CH_2$-)

105C  -CH(OH)- 

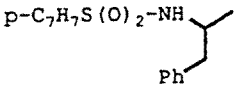
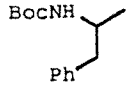
(R_{321} = $PhCH_2NHC(O)NHCH_2$-)

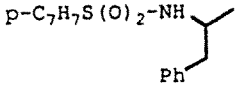
106C  -CH(OH)- 

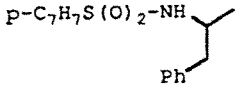
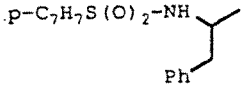
(R_{322} = $CH_3CH_2OC(O)NHCH_2$-)

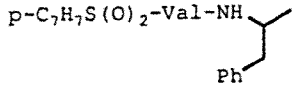
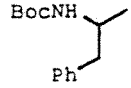
107F  -CH(OH)- 

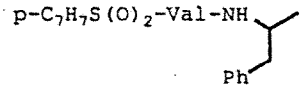
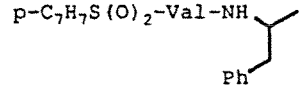
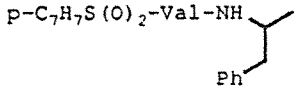
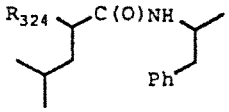
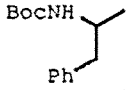
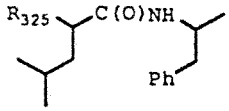
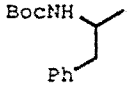
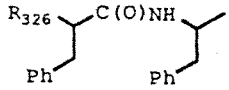
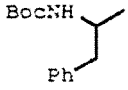
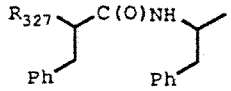
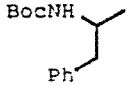
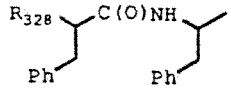
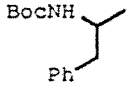
(R_{323} = $CH_3OCH_2CH_2OCH_2OCH_2CH_2N(CH_3)C(O)CH_2$-)

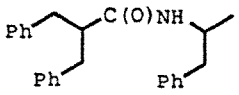
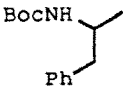
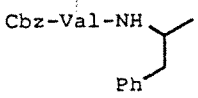
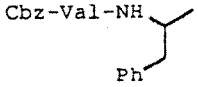
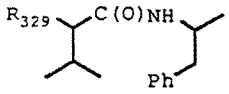
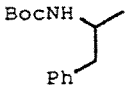
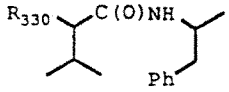
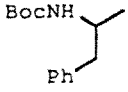
108  -CH(OH)- 

109  -CH(OH)- 

110  -CH(OH)- 

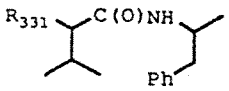
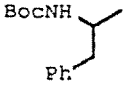
111  -CH(OH)- 

112		-CH(OH)-	
113		-CH(OH)-	
114D	 (R_{324} = $CbzNH(CH_2)_3NH$-)	-CH(OH)-	
115	 (R_{325} = $H_2N(CH_2)_3NH$-)	-CH(OH)-	
116D	 (R_{326} = $CH_3ON(CH_3)CH_2$-)	-CH(OH)-	
117C	 (R_{327} = 1-pyrazolyl-CH_2-)	-CH(OH)-	
118D	 (R_{328} = $(CH_3)_3CS(O)_2CH_2$-)	-CH(OH)-	

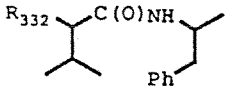
119		-CH(OH)-		
120	(4-$(CH_3)_2$CH)$C_6H_4CH_2CH_2$-	-CH(OCH_2OCH_3)-	(4-$(CH_3)_2$CH)$C_6H_4CH_2CH_2$-	
121	(1-naphthyl)CH_2CH_2-	-CH(OCH_2OCH_3)-	(1-naphthyl)CH_2CH_2-	
122	4-$CH_3OC_6H_4CH_2CH_2$-	-CH(OCH_2OCH_3)-	4-$CH_3OC_6H_4CH_2CH_2$-	
123	4-$BrC_6H_4CH_2CH_2$-	-CH(OCH_2OCH_3)-	4-$BrC_6H_4CH_2CH_2$-	
124	$PhCH_2CH_2$-	-CH(OCH_2SCH_3)-	$PhCH_2CH_2$-	
125	$PhCH_2CH_2$-	-CH($OCH_2OCH_2CH_2OCH_3$)-	$PhCH_2CH_2$-	
126C	$PhCH_2CHF$-	-CH(OH)-	$PhCH_2CH(N_3)$-	
127	$PhCH_2CHF$-	-CH(OH)-	$PhCH_2CH(NH_2)$-	
128	$PhCH_2CHF$	-CH(OH)-		
129	$PhCH_2CHF$	-C(O)-		
130F		-CH(OH)-		
131C		-CH(OH)-		

(R_{329} = 4-methylpiperizinyl-$S(O)_2CH_2$-)

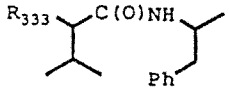
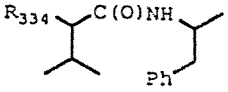
(R_{330} = 4-morpholinyl-$S(O)_2CH_2$-)

132C  -CH(OH)- 

(R_{331} = $PhCH_2NHS(O)_2CH_2$-)

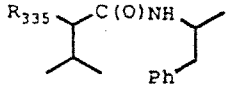
133  -CH(OH)- 

(R_{332} = 4-methylpiperizinyl-$S(O)_2CH_2$-)

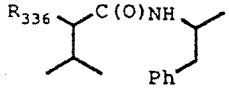
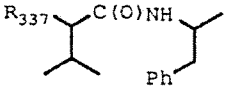
134  -CH(OH)- 

(R_{333} = 4-methylpiperizinyl-$S(O)_2CH_2$-)

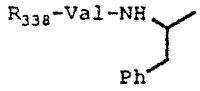
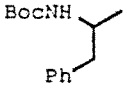
(R_{334} = 4-methylpiperizinyl-$S(O)_2CH_2$-)

135  -CH(OH)- 

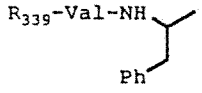
(R_{335} = $PhCH_2NHS(O)_2CH_2$-)

136  -CH(OH)- 

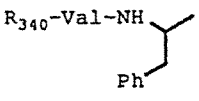
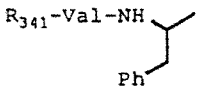
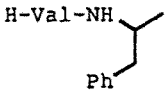
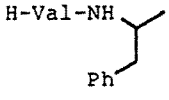
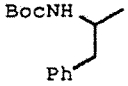
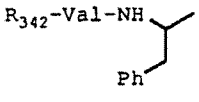
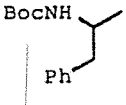
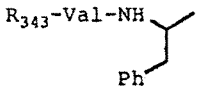
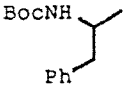
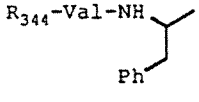
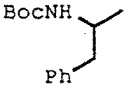
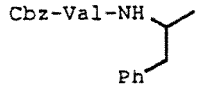
(R_{336} = $PhCH_2NHS(O)_2CH_2$-) (R_{337} = $PhCH_2NHS(O)_2CH_2$-)

137C  -CH(OH)- 

(R_{338} = 4-methylpiperizinyl-$S(O)_2$-)

138  -CH(OH)- 

(R_{339} = 4-methylpiperizinyl-$S(O)_2$-)

139		-CH(OH)-	
	(R_{340} = 4-methylpiperizinyl-S(O)$_2$-)		(R_{341} = 4-methylpiperizinyl-S(O)$_2$-)
140		-CH(OH)-	
141		-CH(OH)CH(OH)-	
142C		-CH(OH)-	
	(R_{342} = $PhCH_2CH_2C(O)$-)		
143	$PhCH_2CH_2$-	-N(OCH_2OCH_3)-	$PhCH_2CH_2$-
144C		-CH(OH)-	
	(R_{343} = $PhCH_2NHC(O)$-)		
145C		-CH(OH)-	
	(R_{344} = $PhCH_2CH_2CH_2$-)		
146		-CH(OCH_2OCH_3)-