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(54) **INHIBITEURS DE LA CALPAINE DESTINES AU TRAITEMENT DE MALADIES NEURODEGENERATIVES**

(54) **CALPAIN INHIBITORS FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES**

(57) L'invention concerne de nouveaux analogues d'acides aminés, et un de leurs sels pharmacologiquement acceptable, de formule (I): $Z\text{-}A_3\text{-}A_2\text{-}A_1\text{-}Q$, dans laquelle Z représente H ou un groupe de protection; A_3 et A_2 représentent indépendemment valine, leucine, alanine, isoleucine, phénylalnine, tyrosine, glycine, 2-arylglycine, toutes éventuellement protégées, et présentant une stéréochimie D ou L ou une liaison chimique; A_1 représente valine, leucine, isoleucine, alanine, phénylalnine, tyrosine, 2-phényl-glycine, 2-phénéthyl-glycine, 2-aryl-glycine, toutes éventuellement protégées; Q représente H, CH_2OCOL, CH_2OL, CH_2SL, CH_2X, $NHNHCOCH_2OCOL$, $NHNHCOCH_2OL$, $NHNHCOCH_2SL$, où L représente aryle ou hétéroaryle éventuellement substitués; et X représente Cl, Br ou F.

(57) Novel amino acid analogs are provided having the formula (I): $Z\text{-}A_3\text{-}A_2\text{-}A_1\text{-}Q$, wherein Z is H or a protecting group; A_3 and A_2 are independently an optionally protected valine, leucine, alanine, isoleucine, phenylalnine, tyrosine, glycine, 2-arylglycine having either D or L stereochemistry or a chemical bond; A_1 is an optionally protected valine, leucine, isoleucine, alanine, phenylalnine, tyrosine, 2-phenyl-glycine, 2-phenethyl-glycine, 2-aryl-glycine; Q is H, CH_2OCOL, CH_2OL, CH_2SL, CH_2X, $NHNHCOCH_2OCOL$, $NHNHCOCH_2OL$, $NHNHCOCH_2SL$, wherein L is an optionally substituted aryl or optionally substituted hereroaryl; and X is Cl, Br or F, and a pharmaceutically acceptable salt thereof.

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(54) Title: CALPAIN INHIBITORS FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

(57) Abstract

Novel amino acid analogs are provided having the formula (I): Z-A_3-A_2-A_1-Q, wherein Z is H or a protecting group; A_3 and A_2 are independently an optionally protected valine, leucine, alanine, isoleucine, phenylalnine, tyrosine, glycine, 2-arylglycine having either D or L stereochemistry or a chemical bond; A_1 is an optionally protected valine, leucine, isoleucine, alanine, phenylalnine, tyrosine, 2-phenyl-glycine, 2-phenethyl-glycine, 2-aryl-glycine; Q is H, CH_2OCOL, CH_2OL, CH_2SL, CH_2X, $NHNHCOCH_2OCOL$, $NHNHCOCH_2OL$, $NHNHCOCH_2SL$, wherein L is an optionally substituted aryl or optionally substituted hereroaryl; and X is CI, Br or F, and a pharmaceutically acceptable salt thereof.

CALPAIN INHIBITORS FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to a series of novel amino acid analogs which exhibit selective inhibition of Calpain I, to compositions containing the novel amino acid analogs and methods for therapeutic use. The Calpain I inhibitors described in this invention comprise novel amino acid derivatives which possess particular utility in treatment of neurodegenerative diseases.

Reported Developments

Calpain is a cytosolic protease enzyme found in all mammalian tissue and cell types. There are two forms of the enzyme with different sensitivities to calcium; the high-sensitivity form, calpain I, is activated by a low calcium concentration (2-75 μM), and the low-sensitivity form, calpain II, is activated by a higher calcium concentration (200-800 μM). Although calpain II is the prominant form, calpain I is concentrated in synapses and neuronal cell bodies and is thought to be involved in the phenomenon of long-term synaptic potentiation.

The location of active calpain explain how calpain can promote: (1) down-regulation of membrane-associated active protein kinase C; (2) formation of a calpain-activated soluble kinase; and (3) reorganization of the cytoskeleton (Melloni, E., and Pontremoli, S. (1989), The Calpains, Trends Neurosci. 12, 438-44). Inactivation of the kinase results in repression of superoxide anion production, a process correlated to the protein kinase C-mediated phosphorylation of membrane proteins. Formation of a soluble, fully active kinase, operating in association with active calpain, results in selective modification in the organization of the cytoskeletal proteins,

which is correlated with the extracellular discharge of granule contents. These conclusions have been reached by specific and direct inhibition of the proteinases, which results in: (1) a significant increase in superoxide anion production; (2) a marked decrease in the down-regulation of protein kinase C activity; (3) reduced formation of calpain-activated protein kinase; (4) decreased phosphorylation and phosphorylation-mediated proteolytic degradation of cytoskeletal proteins; and (5) inhibition of granule exocytosis.

In addition, studies of (Lee, K. S., Frank, S., Vanderklish, P., Arai, A., and Lynch, G. (1991), Inhibition of Proteolysis Protects Hippocampal Neurons from Ischemia, Proc. Nat. Acad. Sci. USA, 88, 7233) suggest that the inhibition of calpain may protect from various ischemia induced-neurodegeneration, essential hypertension, and benefits CNS disorders, and stroke.

A wide variety of apeptidylz analogs are reported to inhibit the action of proteases (Mehdi, Shujaath, Cell-Penetrating Inhibitors of Calpain, TIPS, 16, 150 April 1991). These peptidyl analogs include: epoxisuccinates (E-64), leupeptin (CH_3CO-Leu-Leu-ArgH),and ketopeptides. However, these inhibitors suffer from some of the following disadvantages:

weak enzyme specificity,
lack of inhibitory potency,
inhibit wide variety of proteases in addition to calpain I, and
multi-inhibition of various enzymes limits their therapeutic applicability.

A limited number of peptidyl methyl ketone analogs constitute a well-known class of compounds having enzymatic (papain, cathepsin B) inhibition activity. These analogs, however, are essentially devoid of potency and selectivity in inhibiting calpain I.

In spite of various known calpain inhibitors, no effective therapy has yet been developed for the majority of ischemia-induced neurodegenerative diseases, CNS disorders, and stroke. Consequently, there is a need for therapeutic agents effective in the treatment and prevention of these diseases.

SUMMARY OF THE INVENTION

Novel amino acid analogs are provided having the formula (I)

$$Z—A_3—A_2—A_1—Q \qquad (I)$$

wherein

Z is H or a protecting group;

A_3 and A_2 are independently an optionally protected valine, leucine, alanine, isoleucine, phenylalnine, tyrosine, glycine, 2-arylglycine having either D or L stereochemistry or a chemical bond;

A_1 is an optionally protected valine, leucine, isoleucine, alanine, phenylalanine, tyrosine, 2-phenyl-glycine, 2-phenethyl-glycine, 2-aryl-glycine;

Q is H, CH_2OCOL, CH_2OL, CH_2SL, CH_2X, $NHNHCOCH_2OCOL$, $NHNHCOCH_2OL$, $NHNHCOCH_2SL$, wherein

L is an optionally substituted aryl or optionally substituted heteroaryl; and

X is Cl, Br or F, and a pharmaceutically acceptable salt thereof.

As used herein the following terms shall be understood to have the following meanings, unless otherwise indicated.

"Alkyl" means a saturated or an unsaturated aliphatic hydrocarbon which may be either straight- or branched-chain. Preferred groups have no more than about 12 carbon atoms and may be methyl, ethyl and structural isomers of propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl.

"Lower alkyl" means an alkyl group as above, having 1 to 7 carbon atoms. Suitable lower alkyl groups are methyl, ethyl, n-propyl, isopropyl, butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, and n-heptyl.

"Aryl" means phenyl and substituted phenyl.

"Substituted phenyl" means a phenyl group in which one or more of the hydrogens has been replaced by the the same or different substituents including halo, lower alkyl, nitro, amino, acylamino, hydroxyl, lower alkoxy, aryl, heteroaryl, lower alkoxy, alkylsulfonyl, trifluoromethyl, morpholinoethoxy, morpholino-sulfonyl, and carbobenzoxy-methylsulfamoyl.

"Heteroaryl" means pyridyl, pyrimidyl, tetrazolyl or thiadiazolyl.

"Substituted heteroaryl" means a heteroaryl group in which one or more of the hydrogens has been replaced by the same or different substituents including halo, lower alkyl, nitro, amino, acylamino, hydroxyl, lower alkoxy, aryl, heteroaryl, lower alkoxy, alkylsulfonyl, trifluoromethyl, morpholinoethoxy, morpholiho-sulfonyl, and carbobenzoxymethylsulfamoyl.

A "protecting group" is a radical attached to an oxygen, sulfur, or nitrogen atom, respectively, which radical serves to protect the oxygen, sulfur, or nitrogen functionally against undesired reaction. Such protecting groups are well known in the art, many are described in "The Peptides", E. Gross and J. Meienhofer, Eds. Vol. 3 Academic Press, NY (1981).

The N-protecting groups can be N-acyl, N-alkoxycarbonyl, N-arylmethoxycarbonyl and N-arylsulfonyl protecting groups.

Suitable O-protecting groups include benzyl, tert-butyl, methyl, tosyl ad carbobenzoxy groups.

S-protecting groups include methyl, tert-butyl, benzyl and carbobenzoxy groups.

Pharmaceutically acceptable salts include both acid and base addition salts. Pharmaceutically acceptable acid addition salt refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid,

nitric acid, phosphoric acid, and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyrubic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, and p-toluenesulfonic acid and the like. Pharmaceutically acceptable base addition salts include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically accceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occuring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procain, hydrabamine, choline, betaine, ethylendiamine, glucosamine, methylglucamine, theobromine, purines, peperiziner, piperidine, polyamine resins and the like. Particularly preferred organic non-toxic bases are isopropylamine, diethylamine, ethanol-amine, dicyclohexylamine, choline and caffeine.

This invention also contemplates pharmaceutically acceptable acid-addition salts of the compounds of Formula I. It is well known in the pharmacological arts that nontoxic addition salts of pharmacologically active amine compounds do not differ in activities from their free base. All stereoisomers as well as optical isomers related to the novel calpain inhibitory amino acid analogs described herein are also considered to be within the scope of this invention.

The amino acid analogs of the present invention are selective calpain inhibitors. More particularly, the amino acid analogs of the present invention bind at the active site of the proteolytic enzyme, specifically calpain I.

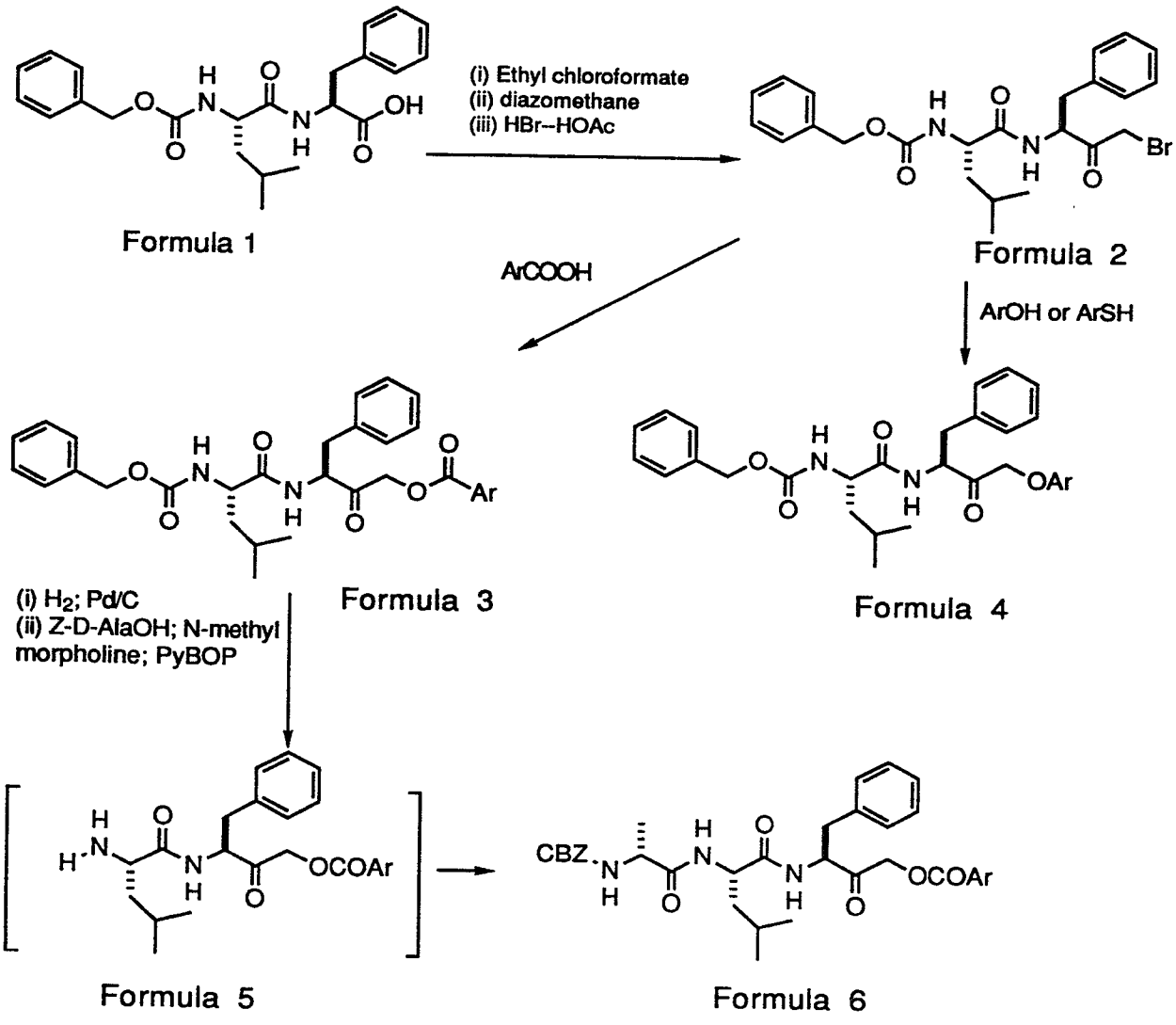
The present invention further provides pharmaceutical compositions comprised of the above-described novel amino acid analog inhibitors and

method of treating ischemia-induced neurodegenerative diseases, stroke, myocardial infarction, CNS disorders, and immunological diseases involving interleukin 1.

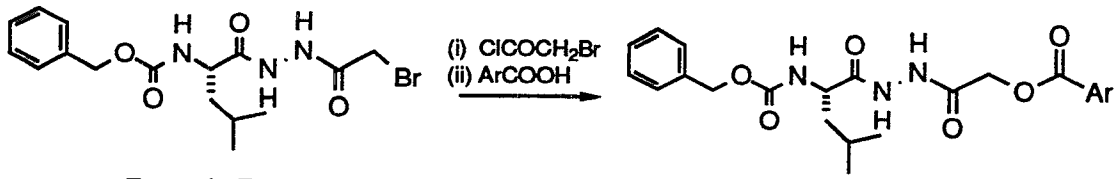
DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are prepared by the general synthetic methods described in Schemes 1, 2 and 3.

Scheme 1

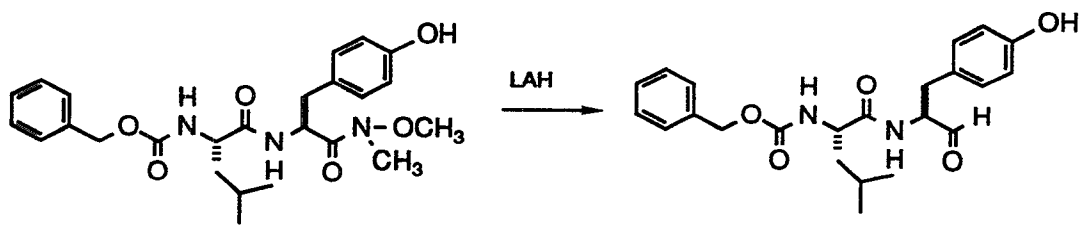


Scheme 2



Formula 7 Formula 8

Scheme 3



Formula 9 Formula 10

The first step of this procedure involves the synthesis of N-protected dipeptidic bromomethyl ketone (formula 2). Methods for the preparation of various dipeptides (formula 1) are well established in the art. The N-protected dipeptide (formula 1), which in some cases is commercially available, is then converted to the corresponding bromoketone (formula 2) by way of hydrobromination or hydrohalogenation of a diazomethyl ketone intermediate. A displacement reaction of the bromomethyl or chloromethyl ketone by an aromatic carboxylic acid or alcohol (or thiol) then yields the desired arylcarboxymethyl ketone (formula 3) or aryloxy (or aryl-thio)methyl ketone (formula 4) of the invention.

The N-protected dipeptidic arylcarboxymethyl ketone (formula 3) is deprotected by conventional hydrogenolysis and the resulting free amino

dipeptide analog (formula 5) is readily converted to the corresponding tripeptidic arycarboxymethyl ketone (formula 6) under standard peptide coupling conditions as shown in Scheme 1.

The preparation of various amino acid N-arylcarboxyacetyl-hydrazides (for example formula 8) involves the synthesis of amino acid bromoacetyl hydrazide by reacting the corresponding amino acid hydrazide (formula 7) with a haloacyl halide. The resulting haloacyl-hydrazide is then readily converted to the arylcarboxyacetyl-hydrazide (formula 8) or aryloxyacetyl-hydrazide by coupling with arylcarboxylic acid or aryl alcohol respectively (Scheme 2).

The peptidic aldehydes (for example formula 10) of this invention are readily prepared by synthesizing the corresponding peptidic N-methoxy-N-methylamide analogs (for example formula 9) via standard synthesis followed by LAH reduction of the above amides.

The following examples will further illustrate the compounds of the present invention.

Example 1

N-Benzyloxycarbonyl-D-alanyl-L-leucyl-L-phenylalanine 2,6-difluorophenyl carboxymethyl ketone

(a) N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine bromomethyl ketone

N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine (10.16 g, 24.63 mmol) was dissolved in dry THF (100 mL) under nitrogen. The solution was cooled to -15°C, N-methylmorpholine (2.98 mL 22.1 mmol) was added followed by dropwise addition of isobutyl chloroformate (3.35 mL, 25.86 mmol) over a 5 min period. A solution of dried diazomethane in ether (50 mmol in 100 mL ether dried over Na_2SO_4; from Diazald-Aldrich) was poured into the

reaction mixture. The reaction mixture (-15°C) was allowed to slowly warm to 0°C after 1 hr, and then held 1 hr at room temperature.

The reaction mixture was cooled to 0°C, 47 mL of 50% HBr/AcOH added with stirring at 0°C, and the resulting mixture was transferred to a separatory funnel with 500 mL of water. The aqueous phase was extracted with ethyl acetate (3x) and the organic layer was washed successively with water, 0.3N $KHSO_4$, saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield a white solid which was recrystallized from dichloromethane/hexane to afford 10.35 g (86%) of N-benzyloxycarbonyl-L-leucyl-L-phenylalanine bromomethyl ketone.

(b) N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-difluoro-phenylcarboxymethyl ketone

2,6-Difluorobenzoic acid (65 mg. 0.41 mmol) was added to a solution of N-benzyloxycarbonyl-L-leucyl-L-phenylalanine bromo-methyl ketone (200 mg, 0.41 mmol) and potassium fluoride in dry DMF under nitrogen. The reaction mixture was poured into ether and the organic layer was washed successively with water, 5% $NaHCO_3$, water, and brine. The ether solution was dried over $MgSO_4$ and concentrated to afford a solid product which was recrystallized from ether/hexane to yield 165 mg (70%) of N-benzyloxycarbonyl-L leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone, m.p. 108-9°C.

(c) L-Leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone

To a mixture of N-benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone (670 mg, 1.18 mmol) in anhydrous ethanol under nitrogen was added 10% palladium on carbon (67 mg), and the mixture was cooled to O°C. The nitrogen atmosphere was then replaced with hydrogen gas by equalizing with hydrogen supplied from a balloon.

When the atmosphere was exchanged for hydrogen, 6N HCl solution (0.39 mL) was added and the solution was allowed to stir for 1.5 hr at room temperature. The reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to afford the hydrochloride salt of L-leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone.

(d) N-Benzyloxycarbonyl-D-alanyl-L-leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone

To a mixture of L-leucyl-L-phenylalanine 2,6-difluorophenacyloxymethyl ketone hydrochloride (180 mg, 0.394 mmol; azeotroped with toluene), benzyoxycarbonyl-D-alanine (97 mg, 0.43 mmol), benzotriazol-1-yloxy-tripyrrolidinophosphonium hexafluoro-phosphate (225 mg, 0.43 mmol) was added under nitrogen 5 mL of dichloromethane, and the resulting mixture was cooled to 0°C. N-Methylmorpholine (117 mg, 1.06 mmol) was added to the above mixture and the resulting reaction mixture was stirred for 30 min at 0°C, and then stirred at room temperature overnight. The mixture was poured into water, extracted with ethyl acetate, and the organic layer was washed successively with 0.3N $KHSO_4$, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* and the residue was purified by chromatography eluting with 30-50% ethyl acetate/hexane to afford 111 mg (45%) of N-benzyloxycarbonyl-D-alanyl-L-leucyl-L-phenylalanine 2,6-difluorophenacyloxymethyl ketone, m.p. 171-2°C.

Employing the synthetic procedure described in Scheme 1 and Example 1 the following additional calpain inhibitors were synthesized.

Example 2

Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichloro-3-[(2-morpholino)-ethoxy]phenylcarboxymethyl ketone

Example 3

Benzyloxycarbonyl-L-leucyl-L-tyrosine 2,6-dichlorophenylcarboxymethyl ketone

Example 4

Benzyloxycarbonyl-L-prolyl-L-leucyl-L-phenylalanine 2,6-dichlorophenylcarboxymethyl ketone

Example 5

Benzyloxycarbonyl-L-leucyl-glycine 2,6-dichloro-3-(morpholinosulfonyl)phenylcarboxymethyl ketone

Example 6

Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichloro-3-(morpholinosulfonyl)phenylcarboxymethyl ketone

Example 7

Benzyloxycarbonyl-glycyl-L-leucyl-L-phenylalanine 2,6-difluoro-phenylcarboxymethyl ketone

Example 8

Benzyloxycarbonyl-L-leucyl-L-tyrosine 2,6-dichloro-3-(morpholino-sulfonyl)phenylcarboxymethyl ketone

Example 9

Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dichloro-3-(morpholino-sulfonyl)phenylcarboxymethyl ketone

Example 10

Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichlorophenyl-carboxymethyl ketone

Example 11

Benzyloxycarbonyl-L-valyl-L-phenylalanine 2,6-dichlorophenyl-carboxymethyl ketone

Example 12

Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-difluorophenyl-carboxymethyl ketone

Example 13

Tert-Butyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-difluorophenyl-carboxymethyl ketone

Example 14

Benzyloxycarbonyl-L-leucyl-L-tyrosine 2,6-difluorophenylcarboxymethyl ketone

Example 15

Benzyloxycarbonyl-L-leucyl-L-glycine 2,6-dichlorophenylcarboxymethyl ketone

Example 16

Benzyloxycarbonyl-L-leucyl-L-glycine 3,6-dichloro-2-acetamido-phenylcarboxymethyl ketone

Example 17

p-Toluenesulfonyl-L-leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone

Example 18

Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dimethylphenylcarboxymethyl ketone

Example 19

Benzyloxycarbonyl-L-leucyl-L-glycine 2-acetamido-6-chlorophenyl-carboxymethyl ketone

Example 20

Benzyloxycarbonyl-L-leucyl-L-alanine 2-acetamido-6-chlorophenyl-carboxymethyl ketone

Example 21

Benzyloxycarbonyl-L-N-methylleucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone

Example 22

Benzyloxycarbonyl-L-N-methylleucyl-L-phenylalanine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone

Example 23

Benzyloxycarbonyl-L-valyl-L-phenylalanine 2-acetamido-6-chlorophenylcarboxymethyl ketone

Example 24

Benzyloxycarbonyl-L-N-methylleucyl-L-phenylalanine 2,6-dichloro-3-(morpholinosulfonyl)phenylcarboxymethyl ketone

Example 25

Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichloro-3-(carbobenzoxymethylsulfamoyl)phenylcarboxymethyl ketone

Example 26

Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dichloro-3-(carbobenzoxymethylsulfamoyl)phenylcarboxymethyl ketone

Example 27

Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone

Example 28

Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dimethoxyphenylcarboxymethyl ketone

Example 29

Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-chlorophenylcarboxymethyl ketone

Example 30

Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-acetamido-6-chlorophenylcarboxymethyl ketone

Example 31

Benzyloxycarbonyl-L-leucyl-L-glycine 2-acetamido-3,6-dichlorophenyl-carboxymethyl ketone

Example 32

Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-pyridylcarboxymethyl ketone

Example 33

Benzyloxycarbonyl-L-leucyl-L-glycine 2,6-fluorophenylcarboxymethyl ketone

Example 34

Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-difluorophenylcarboxymethyl ketone

Example 35

Benzyloxycarbonyl-L-valyl-L-alanine 2,6-bistrifluoromethylphenyl-carboxymethyl ketone

Example 36

p-Nitrobenzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-difluorophenyl-carboxymethyl ketone

Example 37

Benzyloxycarbonyl-L-leucyl-L-phenylalanine 1-naphthylcarboxymethyl ketone

Example 38

Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichloro-3-benzyloxyphenylcarboxymethyl ketone

Example 39

N-Benzyloxycarbonyl-L-leucyl-N-(2,6-dichlorophenylcarboxyacetyl)hydrazide

To a solution of N-benzyloxycarbonyl-L-leucyl-N-(bromoacetyl) hydrazide (50 mg, 0.12 mmol) and 2,6-dichlorobenzoic acid (29 mg, 0.15 mmol) in dry DMF (5 mL) was added potassium fluoride (18 mg) in one portion. The resulting mixture was poured into water, extracted with ether, and the organic layer was washed successively with water, 5% $NaHCO_3$, water, and brine. The organic layer was dried over $MgSO_4$ and concentrated to afford 56 mg (88%) of N-benzyloxycarbonyl-L-leucyl-N-(2,6-dichlorophenylcarboxyacetyl) hydrazide, m.p. 103-5°C.

Employing the synthetic procedure described in Example 39, the following compounds were made.

Example 40

N-Benzyloxycarbonyl-L-leucyl-N-methyl, N-(2-acetamido-6-chlorophenycarboxy-acetyl)hydrazide

Example 41

N-Benzyloxycarbonyl-L-leucyl-N-(2-acetamido-6-chlorophenylcarboxy-acetyl)hydrazide

Example 42

Benzyloxycarbonyl-L-leucyl-L-tyrosine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone

Example 43

Methoxycarbonyl-D-alanyl-L-leucyl-L-phenylalanine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone

Example 44

Benzyloxycarbonyl-D-alanyl-L-leucyl-L-tyrosine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone

Example 45

Benzyloxycarbonyl-L-valyl-L-phenylalanine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone

Example 46

Benzyloxycarbonyl-L-valyl-glycine 2,6-dichloro-3-(carbobenzoxy-methylsulfamoyl)phenylcarboxymethyl ketone

Example 47

Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dichloro-3-[2-(morpholino)-ethoxy]phenylcarboxymethyl ketone

Example 48

Benzyloxycarbonyl-L-leucyl-glycine 2,6-dichloro-3-[2-(morpholino)-ethoxy]phenylcarboxymethyl ketone

Example 49

Methoxycarbonyl-D-alanyl-L-leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone

Example 50

Benzyloxycarbonyl-L-alanyl-L-glycine 2,6-dichloro-3-(carbobenzoxy-methylsulfamoyl)phenylcarboxymethyl ketone

Example 51

Benzyloxycarbonyl-glycyl-L-phenylalanine 2,6-dichloro-3-(carbobenzoxymethylsulfamoyl)phenylcarboxymethyl ketone

Example 52

Benzyloxycarbonyl-L-valyl-glycine 2,6-dichlorophenylcarboxymethyl ketone

Example 53

Benzyloxycarbonyl-glycyl-L-phenylalanine 2,6-dichlorophenylcarboxymethyl ketone

Example 54

Benzyloxycarbonyl-L-phenylalanyl-L-alanine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone

Example 55

Benzyloxycarbonyl-L-phenylalanyl-glycine 2,6-dichlorophenylcarboxymethyl ketone

Example 56

Benzyloxycarbonyl-D-alanyl-L-leucyl-glycine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone

Example 57

Benzyloxycarbonyl-L-leucyl-glycine 2,6-dichlorophenylcarboxymethyl ketone

Example 58

Benzyloxycarbonyl-L-phenylalanyl-glycine 2,6-dichlorophenylcarboxymethyl ketone

Example 59

Benzyloxycarbonyl-L-alanyl-glycine 2,6-dichlorophenylcarboxymethyl ketone

Example 60

Benzyloxycarbonyl-L-phenylalanyl-L-alanine 2,6-bistrifluoromethylphenylcarboxymethyl ketone

Example 61

N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichlorophenoxymethyl ketone

To a solution of benzyloxycarbonyl-L-leucyl-L-phenylalanine bromomethyl ketone (100 mg, 0.204 mmol), 2,6-dichlorophenol 34 mg, 0.204 mmol) and K_2CO_3 (29 mg, 0.204 mmol) in 8 mL of DMF was added tetra-n-butyl-ammonium iodide (8 mg) and the resulting mixture was stirred overnight at room temperature. The mixture was diluted with ethyl acetate, washed with water and brine, and the organic layer was dried over Na_2SO_4. The solvent was concentrated in vacuo to afford 80 mg of N-benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichlorophenoxymethyl ketone, as a white solid, m.p. 102-4°C.

Employing the synthetic procedure described in Example 61 and Scheme 1 the following additional calpain inhibitors were synthesized.

Example 62

N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-[1-(3-pyridyl)tetrazolyl]thiomethyl ketone

Example 63

N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-[(4-morpholinoethyl)-tetrazolyl]thiomethyl ketone

Example 64

N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-[(5-methylthio)tetrazolyl]thiomethyl ketone

Example 65

N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-[(5-methylthio)tetrazolyl]thiomethyl ketone

Example 66

N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-difluorophenylthiomethyl ketone

Example 67

N-Benzyloxycarbonyl-L-valyl-L-phenylalanine 2,6-difluorophenoxymethyl ketone

Example 68

N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-pyrimidylthiomethyl ketone

Example 69

N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-(1-phenyl)-tetrazolylthiomethyl ketone

To a solution of benzyloxycarbonyl-L-leucyl-L-phenylalanine bromomethyl ketone (150 mg, 0.306 mmol) and 2-mercapto-phenyl-tetrazole (57.2 mg, 0.32 mmol) in 2 mL of DMF was added K_2CO_3 (42.3 mg, 0.306 mmol) at room temperature and the resulting reaction mixture was stirred overnight. The mixture was poured into 50 mL of water and then extracted with ethyl acetate. The organic layer was washed with 0.3N $KHSO_4$, 5% $NaHCO_3$, water, and brine and dried over Na_2SO_4. The solvent was concentrated *in vacuo* to afford 168 mg (94%) of N-benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-(1-phenyl)-tetrazolylthio-methyl ketone, as a white solid, m.p. 183-4°C.

Example 70

Benzyloxycarbonyl-L-leucyl-L-tyrosinal

Benzyloxycarbonyl-L-leucyl-L-tyrosyl-N-(methoxy),N-methyl amide (0.182 mmol) was dissoved in 4 mL of ether/THF (1:1) under nitrogen and the solution was cooled to 0°C. LAH ether solution (0.182 mmol) was added by syringe to the reaction mixture with stirring. The reaction mixture was quenched with 0.3N $KHSO_4$ (0.6 mL) and the mixture was transferred into a separatory funnel containing 50 mL of water and 50 mL of ether/ethyl acetate (1:1). The aqueous layer was extracted with ether/ethyl acetate and the combined organic layer was washed with 0.3N $KHSO_4$, water, and brine. The organic solution was dried over Na_2SO_4 and concentrated in vacuo to afford 53 mg (70.6%) of benzyloxycarbonyl-L-leucyl-L-tyrosinal, m.p. 57-60°C.

Employing the synthetic procedure described in Scheme 1, Scheme 2 and Scheme 3 the following additional calpain inhibitors were prepared.

Example 71

Benzyloxycarbonyl-L-valyl-L-tyrosinal

Example 72

Benzyloxycarbonyl-L-leucyl-L-O-methyl-tyrosinal

Example 73

Benzyloxycarbonyl-L-leucyl-L-phenylalaninal

Example 74

Benzyloxycarbonyl-L-isoleucyl-L-tyrosinal

Example 75

Benzyloxycarbonyl-L-valyl-DL-2-(2-naphthylmethyl)glycinal

Example 76

Benzyloxycarbonyl-L-isoleucyl-L-phenylalaninal

Example 77

Benzyloxycarbonyl-L-valyl-DL-2-(phenethyl)glycinal

Example 78

Benzyloxycarbonyl-L-2-neopentyl-glycyl-L-phenylalaninal

Example 79

Benzyloxycarbonyl-L-valyl-DL-2-(1-naphthylmethyl)glycinal

Example 80

Benzyloxycarbonyl-L-2-phenylglycyl-L-phenylalaninal

Example 81

Benzyloxycarbonyl-L-alanyl-L-phenylalaninal

Example 82

Benzyloxycarbonyl-L-2-phenethylglycyl-L-phenylalaninal

Example 83

Benzyloxycarbonyl-L-phenylalanyl-L-phenylalaninal

Example 84

Benzyloxycarbonyl-L-2-tert-butylglycyl-L-phenylalaninal

Example 85

Benzyloxycarbonyl-L-2-(1-naphthymethyl)glycyl-DL-phenylalaninal

Example 86

Benzyloxycarbonyl-L-leucyl-N-chloroacetyl-hydrazide

Example 87

Benzyloxycarbonyl-L-leucyl-N-bromoacetyl-hydrazide

Example 88

Benzyloxycarbonyl-L-leucine chloromethyl ketone

Example 89

Benzyloxycarbonyl-L-leucyl-L-leucyl-L-phenylalanine chloromethyl ketone

Example 90

Benzyloxycarbonyl-L-leucyl-L-alanine chloromethyl ketone

Example 91

Benzyloxycarbonyl-L-leucyl-L-phenylalanine chloromethyl ketone

Example 92

Benzyloxycarbonyl-glycyl-L-leucyl-L-tyrosine chloromethyl ketone

Example 93

Benzyloxycarbonyl-L-leucyl-L-phenylalanine chloromethyl ketone

Example 94

Benzyloxycarbonyl-L-leucyl-glycine chloromethyl ketone

Example 95

Benzyloxycarbonyl-L-leucyl-L-alanine bromomethyl ketone

Example 96

Benzyloxycarbonyl-L-valyl-L-phenylalanine bromomethyl ketone

Example 97

Benzyloxycarbonyl-L-leucyl-L-leucine bromomethyl ketone

Example 98

Benzyloxycarbonyl-L-asparagyl-L-phenylalanine chloromethyl ketone

Example 99

Benzyloxycarbonyl-L-leucyl-L-phenylalanine bromomethyl ketone

Example 100

Benzyloxycarbonyl-L-phenylalanyl-L-alanine chloromethyl ketone

Example 101

Benzyloxycarbonyl-glycyl-L-phenylalanine bromomethyl ketone

Example 102

Benzyloxycarbonyl-L-valyl-glycine bromomethyl ketone

Example 103

Benzyloxycarbonyl-L-leucine chloromethyl ketone

Example 104

Benzyloxycarbonyl-L-phenylalanyl-L-alanine bromomethyl ketone

Example 105

Benzyloxycarbonyl-L-alanyl-glycine bromomethyl ketone

Example 106

Benzyloxycarbonyl-L-2-(2-naphthylmethyl) glycine chloromethyl ketone

Example 107

Benzyloxycarbonyl-L-phenylalanyl-glycine chloromethyl ketone

Example 108

Benzyloxycarbonyl-L-phenylalanyl-L-phenylalanine chloromethyl ketone

Example 109

Benzyloxycarbonyl-L-leucyl-N-(bromoacyl) hydrazide

Example 110

Benzyloxycarbonyl-L-leucyl-L-tyrosine bromomethyl ketone

Compounds of the present invention were tested for calpain I inhibition activity using the following assay method.

Calpain I InhibitionAssay

Isolation of Human erythrocyte Calpain I

Human red blood cells were obtained from the Northeastern New York Chapter of the American Red Cross. The isolation of calpain from human

erythrocytes was similar to that described by Wang et al. (1988). One unit of in-dated packed red cells was diluted with an equal volume of diluting/wash solution and centrifuged. The supernatant was removed and the procedure was repeated. The washed cells were pooled, lysed with 700 mL of lysing solution and centrifuged to remove cell debris. The membrane-free hemolysate was added to 500 mL DEAE-sephacel and the slurry was stirred gently at 4°C for 1 hour.

Batch elution was done using DEAE-sephacel wash solution to remove a large amount of unwanted protein, most of which was hemoglobin. The slurry was poured into a column connected in tandem to a phenyl-sepharose CL-4B column. Material eluted from the DEAE-sephacel was applied directly to the phenyl-sepharose CL-4B. The phenyl-sepharose CL-4B column was washed first with 75 mM NaCl and then with no salt. Calpain begins to disassociate from the DEAE-sephacel with the 75 mM NaCl but the majority should adhere to the column until the salt is removed. Fractions were collected (20 mL), assayed for caseinolytic activity with and without calpastatin and pooled accordingly. The pooled fractions were concentrated using an Amicon stirred cell equipped with a YK-10 membrane. Calpain was stored at 4°C with 10 mM EDTA and 5 mM 2-mercaptoethanol and is stable for at least 6 months.

Assay Procedure

The tritated assay is a modification of that described by Gopalakrishna, R. and Barsky, S.H., Anal. Biochem., 148, 413,1985. All reagents, compound 25 ul, HEPES buffer 25 ul, $CaCl_2$ 50 ul, enzyme 50 ul, and ^{3}H-acetyl Casein, were combined in 1 mL polystyrene titer plates. The plates were preincubated at 25°C for 5 min with gentle shaking prior to the addition of substrate. The incubation was continued for an additional 2 hours and was terminated with the addition of 0.5 mL ice cold 5% TCA. Unlabled casein was added, samples were centrifuged and 0.5 mL of the supernatant was counted in 5 mL of Ready Protein liquid scintillation cocktail for 2 min. This assay measures ^{3}H-acetyl Casein degradation as an endpoint for calpain activity.

Representative assay results are shown in the following tables.

Table 1

Acyloxyketone Calpain I Inhibitors

$Z\text{-}A_3\text{-}A_2\text{-}A_1\text{-}CH_2\text{-}O\text{-}CO\text{-}Q$

Ex.	Z	A_3	A_2	A_1	Q	IC_{50}/uM
1	CBZ	D-Ala	L-Leu	L-Phe	2,6-difluoropheny	.046
2	CBZ	-	L-Leu	L-Phe	2,6-dichloro-3-[2-(morpholino) ethoxy]phenyl	0.14
3	CBZ	-	L-Leu	L-Tyr	2,6-dichlorophenyl	0.22
4	CBZ	L-Pro	L-Leu	L-Phe	2,6-fluorophenyl	0.08
5	CBZ	-	L-Leu	Gly	2,6-dichloro-3-(morpholinosulfonyl)phenyl	0.11
6	CBZ	-	L-Leu	L-Phe	2,6-dichloro-3-(morpholinosulfonyl)phenyl	0.17
7	CBZ	Gly	L-Leu	L-Phe	2,6-difluorophenyl	0.04
8	CBZ	-	L-Leu	L-Tyr	2,6-dichloro-3 (morpholinosulfonyl)phenyl	0.17
9	CBZ	-	L-Leu	L-Ala	2,6-dichloro-3-(morpholinosulfonyl)phenyl	0.43
10	CBZ	-	L-Leu	L-Phe	2,6-dichlorophenyl	0.33
11	CBZ	-	L-Val	L-Phe	2,6-dichlorophenyl	0.55
12	CBZ	-	L-Leu	L-Phe	2,6-difluorophenyl	0.16
13	CtBu	-	L-Leu	L-Phe	2,6-difluorophenyl	0.42
14	CBZ	-	L-Leu	L-Tyr	2,6-difluorophenyl	0.40
15	CBZ	-	L-Leu	Gly	2,6-dichlorophenyl	0.29
16	CBZ	-	L-Leu	Gly	3,6-dichloro-2-acetamidophenyl	>10
17	Tos	-	L-Leu	L-Phe	2,6-difluorophenyl	0.16
18	CME	-	L-Leu	L-Phe	2,6-dimethylphenyl	0.63
19	CBZ	-	L-Leu	Gly	2-acetamido-6-chlorophenyl	0.78
20	CBZ	-	L-Leu	L-Ala	2-acetamido-6-chlorophenyl	0.36

Table 2

Aryloxyketone Calpain I Inhibitors

Ex.	Z	A_3	A2	Q	IC_{50}/uM
61	CBZ	L-Leu	L-Phe	2,6-dichlorophenoxy	2.3
62	CBZ	L-Leu	L-Phe	2-[1-(3-pyridyl)tetrazoyl] thio	0.53
63	CBZ	L-Leu	L-Phe	2-[(4-morpholinoethyl) tetrazolyl]thio	3.8
64	CBZ	L-Leu	L-Phe	2-[(5-methylthio)thiadiazoyl] thio	2.0
65	CBZ	L-Leu	L-Phe	2,6-difluorophenoxy	>10
66	CBZ	L-Leu	L-Phe	2,6-dichlorophenylthio	>10
67	CBZ	L-Val	L-Phe	2,6-difluorophenoxy	>10
68	CBZ	L-Leu	L-Phe	2-pyrimidylthio	>10
69	CBZ	L-Leu	L-Phe	2-(1-phenyltetrazoyl)thio	>10

Table 3

Peptide Aldehyde Calpain I Inhibitors

$Z\text{-}A_2\text{-}A_1\text{-}H$

Ex.	Z	A_2	A1	IC_{50}/uM
70	CBZ	L-Leu	L-Tyrosinal	0.02
71	CBZ	L-Val	L-Tyrosinal	0.026
72	CBZ	L-Val	L-Tyrosinal(O-methyl)	0.03
73	CBZ	L-Leu	L-Phenylalaninal	0.037
74	CBZ	L-Ile	L-Tyrosinal	0.053
75	CB Z	L-Val	DL-2-(2-Naphthy methyl)glycinal	0.07
76	CBZ	L-Ile	L-Phenylalaninal	0.08
77	CBZ	L-Val	DL-2-(Phenethyl)glycinal	0.10
78	CBZ	L-2-(Neopentyl) Glycyl	L-Phenylalaninal	0.10

Table 3(contd.)

Peptide Aldehyde Calpain I Inhibitors

$Z\text{-}A_2\text{-}A_1\text{-}H$

Ex.	Z	A_2	A1	IC_{50}/uM
79	CBZ	L-Val	DL-2-(1-Naphthyl-methyl)glycinal	0.11
80	CBZ	2-Phenylglycyl	L-Phenylalaninal	0.11
81	CBZ	L-Ala	L-Phenylalaninal	0.17
82	CBZ	L-2-(Phenethyl) Glycyl	L-Phenylalaninal	0.27
83	CBZ	L-Phe	L-Phenylalaninal	0.41

Table 4

Haloketone Calpain I Inhibitors

$CBZ\text{-}A_2\text{-}A_1\text{-}CH_2X$

Ex.	A_3	A_2	A1	X	IC_{50}/uM
86	-	-	L-Leu-NHNHCO	Cl	2.2
87	-	-	L-Leu-NHNHCO	Br	6.8
88	-	-	L-Leu	Cl	>10
89	L-Leu	L-Leu	L-Phe	Cl	>10
90	-	L-Leu	L-Ala	Cl	>10
91		L-Leu	L-Phe	Cl	43.3
92	Gly	L-Leu	L-Phe	Cl	6.6
93	-	L-Leu	L-Tyr	Cl	40
94	-	L-Leu	L-Phe	Cl	>10
95	-	L-Leu	L-Ala	Br	>10
96	-	L-Val	L-Phe	Br	>10
97	-	L-Leu	L-Leu	Br	>10
98	-	L-Asp(NH_2)	L-Phe	Cl	>10
99	-	L-Leu	L-Phe	Br	9.1

The present invention includes a calpain inhibitor of this invention formulated into compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants or vehicles which are collectively referred to herein as carriers, for parenteral injection or oral administration, in solid or liquid form, for rectal or topical administration, or the like.

The compositions can be administered to humans and animals either orally, rectally, parenterally (intravenous, intramuscularly or subcutaneously), intracisternally, intravaginally, intraperitoneally, locally (powders, ointments or drops), or as a buccal or nasal spray.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol and silicic acid, (b) binders, as for example, carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose and acacia, (c) humectants, as for example, glylcerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate or mixtures thereof. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, ground-nut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers or propellants as may be required. Opthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

Actual dosage levels of the active ingredient in the compositions of the present invention may be varied so as to obtain an amount of active ingredient that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, on the route of administration, on the desired duration of treatment and other factors.

The total daily dose of the compounds of this invention administered to a host in single or divided doses may be in amounts, for example, of from about 0.5 mg to about 10 mg per kilogram of body weight. Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the body weight, general health, sex, diet, time and route of administration, rates of absorption and excretion, combination with other drugs and the severity of the particular disease being treated.

WHAT IS CLAIMED IS:

1. A compound of the formula (I)

$$Z–A_3–A_2–A_1–Q \qquad (I)$$

wherein

Z is H or a protecting group;

A_3 and A_2 are independently an optionally protected valine, leucine, alanine, isoleucine, phenylalnine, tyrosine, glycine, 2-arylglycine having either D or L stereochemistry or a chemical bond;

A_1 is an optionally protected valine, leucine, isoleucine, alanine, phenylalnine, tyrosine, 2-phenyl-glycine, 2-phenethyl-glycine, 2-aryl-glycine;

Q is H, CH_2OCOL, CH_2OL, CH_2SL, CH_2X, $NHNHCOCH_2OCOL$, $NHNHCOCH_2OL$, $NHNHCOCH_2SL$, wherein

L is an optionally substituted aryl or optionally substituted heteroaryl; and

X is Cl, Br or F, or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein L is substituted aryl selected from the group consisting of phenyl or naphthyl optionally substituted by 1 to 3 substituents selected from the group consisting of lower alkyl, lower alkoxy, halo, acetyl, acetamido, hydroxy, phenyl, morpholino-lower alkyloxy, morphorino lower alkyl, benzyl, benzyloxy, nitro, amino, loweralkylamino, morpholinosulfonyl, morpholinosulfamoyl, benzyloxycarbonyl-methylsulfamoyl, acetylamino or trifluoromethyl.

3. The compound of claim 1 wherein L is substituted heteroaryl selected from the group consisting of thiazole, furan, thiadiazole, thiophen, tetrazole, pyridyl, pyrimidyl, triazole optionally substituted by 1 to 3 substituents selected from the group consisting of lower alkyl, lower alkoxy, halo, acetyl, acetamido, hydroxy, morpholino-lower alkyloxy, morphorino lower alkyl, benzyl, benzyloxy, nitro, amino,

loweralkylamino, morpholinosulfonyl, morpholinosulfamoyl, benzyloxycarbonyl-methylsulfamoyl, acetylamino, phenyl or trofluoromethyl.

4. The compound of claim 1 selected from the group consisting of: N-Benzyloxycarbonyl-D-alanyl-L-leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichloro3-[(2-morpholino) ethoxy]phenyl-carboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-tyrosine 2,6-dichlorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-prolyl-L-leucyl-L-phenylalanine 2,6-dichlorophenyl-carboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-glycine 2,6-dichloro-3-(morpholinosulfonyl) phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichloro-3-(morpholinosulfonyl)phenyl carboxymethyl ketone, Benzyloxycarbonyl-glycyl-L-leucyl-L-phenylalanine 2,6-difluoro-phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-tyrosine 2,6-dichloro-3-(morpholinosulfonyl)phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dichloro-3-(morpholinosulfonyl)phenylcarboxymethyl ketone and Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichlorophenylcarboxymethyl ketone.

5. The compound of claim 1 selected from the group consisting of: Benzyloxycarbonyl-L-valyl-L-phenylalanine 2,6-dichlorophenyl-carboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone, Tert-Butyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-difluorophenyl-carboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-tyrosine 2,6-difluorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-glycine 2,6-dichlorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-glycine 3,6-dichloro-2-acetamido-phenylcarboxymethyl ketone, p-Toluenesulfonyl-L-leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-

phenylalanine 2,6-dimethylphenyl carboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-glycine 2-acetamido-6-chlorophenylcarboxymethyl ketone and Benzyloxycarbonyl-L-leucyl-L-glycine 2-acetamido-6-chlorophenyl-carboxymethyl ketone.

6. The compound of claim 1 selected from the group consisting of: Benzyloxycarbonyl-L-N-methylleucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-N-methylleucyl-L-phenylalanine 2,6-dichloro-3-[2-(morpholino) ethoxy]phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-valyl-L-phenylalanine 2-acetamido-6-chlorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-N-methylleucyl-L-phenylalanine 2,6-dichloro-3-(morpholinosulfonyl)phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichloro-3-(carbobenzoxymethylsulfamoyl)phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dichloro-3-(carbobenzoxymethylsulfamoyl)phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dimethoxyphenyl carboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dichlorophenylcarboxymethyl ketone and Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-acetamido-6-chlorophenylcarboxymethyl ketone.

7. The compound of claim 1 selected from the group consisting of: Benzyloxycarbonyl-L-leucyl-L-glycine 2-acetamido-3,6-dichlorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-pyridylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-glycine 2,6-fluorophenylcarboxy-methyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-difluorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-valyl-L-alanine 2,6-bistrifluoromethylphenylcarboxymethyl ketone, p-Nitrobenzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-

phenylalanine 1-naphthylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichloro-3-benzyloxyphenylcarboxymethyl ketone, N-Benzyloxycarbonyl-L-leucyl-N-(2,6-dichlorophenylcarboxyacetyl)hydrazide and N-Benzyloxycarbonyl-L-leucyl-N-methyl, N-(2-acetamido-6-chlorophenylcarboxy-acetyl)hydrazide.

8. The compound of claim 1 selected from the group consisting of: N-Benzyloxycarbonyl-L-leucyl-N-(2-acetamido-6-chlorophenyl-carboxy-acetyl)hydrazide, Benzyloxycarbonyl-L-leucyl-L-tyrosine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone, Methoxycarbonyl-D-alanyl-L-leucyl-L-phenylalanine 2,6-dichloro-3-[2-(morpholino)-ethoxy]phenylcarboxymethyl ketone, Benzyloxycarbonyl-D-alanyl-L-leucyl-L-tyrosine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-valyl-L-phenylalanine 2,6-dichloro-3-[2-(morpholino)-ethoxy]phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-valyl-glycine 2,6-dichloro-3-(carbobenzoxy-methylsulfamoyl)phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenyl-carboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-glycine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone, Methoxycarbonyl-D-alanyl-L-leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone and Benzyloxycarbonyl-L-alanyl-L-glycine 2,6-dichloro-3-(carbobenzoxymethylsulfamoyl)-phenylcarboxymethyl ketone.

9. The compound of claim 1 selected from the group consisting of: Benzyloxycarbonyl-glycyl-L-phenylalanine 2,6-dichloro-3-(carbobenzoxymethylsulfamoyl)phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-valyl-glycine 2,6-dichlorophenyl-carboxymethyl ketone, Benzyloxycarbonyl-glycyl-L-phenylalanine 2,6-dichlorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-phenylalanyl-L-alanine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone, Benzyloxycarbonyl-

L-phenylalanyl-glycine 2,6-dichlorophenyl-carboxymethyl ketone, Benzyloxycarbonyl-D-alanyl-L-leucyl-glycine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenyl-carboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-glycine 2,6-dichlorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-phenylalanyl-glycine 2,6-dichlorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-alanyl-glycine 2,6-dichlorophenyl carboxymethyl ketone and Benzyloxycarbonyl-L-phenylalanyl-L-alanine 2,6-bistrifluoromethylphenylcarboxymethyl ketone.

10. The compound of claim 1 selected from the group consisting of: N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichlorophenoxymethyl ketone, N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-[1-(3-pyridyl)tetrazolyl]thiomethyl ketone, N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-[(4-morpholinoethyl)tetrazolyl]thiomethyl ketone, N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-[(5-methylthio)tetrazolyl]thiomethyl ketone, N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-[(5-methylthio)tetrazolyl]thiomethyl ketone, N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-difluorophenylthiomethyl ketone, N-Benzyloxycarbonyl-L-valyl-L-phenylalanine 2,6-difluorophenoxymethyl ketone, N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-pyrimidylthiomethyl ketone, N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-(1-phenyl)tetrazolylthiomethyl ketone and Benzyloxycarbonyl-L-leucyl-L-tyrosinal.

11. The compound of claim 1 selected from the group consisting of: Benzyloxycarbonyl-L-valyl-L-tyrosinal, Benzyloxycarbonyl-L-leucyl-L-O-methyl-tyrosinal, Benzyloxycarbonyl-L-leucyl-L-phenylalaninal, Benzyloxycarbonyl-L-isoleucyl-L-tyrosinal, Benzyloxycarbonyl-L-valyl-DL-2-(2-naphthylmethyl)glycinal, Benzyloxycarbonyl-L-isoleucyl-L-phenylalaninal, Benzyloxycarbonyl-L-valyl-DL-2-(phenethyl)glycinal, Benzyloxycarbonyl-L-2-neopentyl-glycyl-L-

phenylalaninal, Benzyloxycarbonyl-L-valyl-DL-2-(1-naphthylmethyl)glycinal and Benzyloxycarbonyl-L-2-phenylglycyl-L-phenylalaninal.

12. The compound of claim 1 selected from the group consisting of: Benzyloxycarbonyl-L-alanyl-L-phenylalaninal, Benzyloxycarbonyl-L-2-phenethylglycyl-L-phenylalaninal, Benzyloxycarbonyl-L-phenylalanyl-L-phenylalaninal, Benzyloxycarbonyl-L-2-tert-butylglycyl-L-phenylalaninal, Benzyloxycarbonyl-L-2-(1-naphthymethyl)glycyl-DL-phenylalaninal, Benzyloxycarbonyl-L-leucyl-N-chloroacetyl-hydrazide, Benzyloxycarbonyl-L-leucyl-N-bromoacetyl-hydrazide, Benzyloxycarbonyl-L-leucine chloromethyl ketone, Benzyloxycarbonyl-L-leucyl-L-leucyl-L-phenylalanine chloromethyl ketone and Benzyloxycarbonyl-L-leucyl-L-alanine chloromethyl ketone.

13. The compound of claim 1 selected from the group consisting of: Benzyloxycarbonyl-L-leucyl-L-phenylalanine chloromethyl ketone, Benzyloxycarbonyl-glycyl-L-leucyl-L-tyrosine chloromethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine chloromethyl ketone, Benzyloxycarbonyl-L-leucyl-glycine chloromethyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine bromomethyl ketone, Benzyloxycarbonyl-L-valyl-L-phenylalanine bromomethyl ketone, Benzyloxycarbonyl-L-leucyl-L-leucine bromomethyl ketone, Benzyloxycarbonyl-L-asparagyl-L-phenylalanine chloromethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine bromomethyl ketone and Benzyloxycarbonyl-L-phenylalanyl-L-alanine chloromethyl ketone.

14. The compound of claim 1 selected from the group consisting of: Benzyloxycarbonyl-glycyl-L-phenylalanine bromomethyl ketone, Benzyloxycarbonyl-L-valyl-glycine bromomethyl ketone, Benzyloxycarbonyl-L-leucine chloromethyl ketone, Benzyloxycarbonyl-L-phenylalanyl-L-alanine bromomethyl ketone, Benzyloxycarbonyl-L-alanyl-glycine bromomethyl ketone,

Benzyloxycarbonyl-L-2-(2-naphthylmethyl)glycine chloromethyl ketone, Benzyloxycarbonyl-L-phenylalanyl-glycine chloromethyl ketone, Benzyloxycarbonyl-L-phenylalanyl-L-phenylalanine chloromethyl ketone, Benzyloxycarbonyl-L-leucyl-N-(bromoacyl) hydrazide and Benzyloxycarbonyl-L-leucyl-L-tyrosine bromomethyl ketone.

15. A pharmaceutical composition for the treatment or inhibition of neurodegenerative disease in a mammal comprising an effective amount of a compound of the formula (I)

$$Z—A_3—A_2—A_1—Q \qquad (I)$$

wherein

Z is H or a protecting group;

A_3 and A_2 are independently an optionally protected valine, leucine, alanine, isoleucine, phenylalnine, tyrosine, glycine, 2-arylglycine having either D or L stereochemistry or a chemical bond;

A_1 is an optionally protected valine, leucine, isoleucine, alanine, phenylalnine, tyrosine, 2-phenyl-glycine, 2-phenethyl-glycine, 2-aryl-glycine;

Q is H, CH_2OCOL, CH_2OL, CH_2SL, CH_2X, $NHNHCOCH_2OCOL$, $NHNHCOCH_2OL$, $NHNHCOCH_2SL$, wherein

L is an optionally substituted aryl or optionally substituted heteroaryl; and

X is Cl, Br or F, in a pharmaceutically acceptable vehicle.

16. The pharmaceutical composition of claim 15 wherein L is substituted aryl selected from the group consisting of phenyl or naphthyl optionally substituted by 1 to 3 substituents selected from the group consisting of lower alkyl, lower alkoxy, halo, acetyl, acetamido, hydroxy, phenyl, morpholino-lower alkyloxy, morpholino lower alkyl, benzyl, benzyloxy, nitro, amino, loweralkylamino, morpholinosulfonyl,

morpholinosulfamoyl, benzyloxycarbonylmethylsulfamoyl, acetylamino or trifluoromethyl.

17. The pharmaceutical composition of claim 15 wherein L is substituted heteroaryl selected from the group consisting of thiazole, furan, thiadiazole, thiophen, tetrazole, pyridyl, pyrimidyl, triazole optionally substituted by 1 to 3 substituents selected from the group consisting of lower alkyl, lower alkoxy, halo, acetyl, acetamido, hydroxy, morpholino-lower alkyloxy, morpholino lower alkyl, benzyl, benzyloxy, nitro, amino, loweralkylamino, morpholinosulfonyl, morpholinosulfamoyl, benzyloxycarbonylmethylsulfamoyl, acetylamino, phenyl or trifluoromethyl.

18. The pharmaceutical composition of claim 15 wherein said compound is selected from the group consisting of: N-Benzyloxycarbonyl-D-alanyl-L-leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichloro-3-[(2-morpholino) ethoxy]phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-tyrosine 2,6-dichlorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-prolyl-L-leucyl-L-phenylalanine 2,6-dichlorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-glycine 2,6-dichloro-3-(morpholinosulfonyl) phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichloro-3-(morpholinosulfonyl)phenyl carboxymethyl ketone, Benzyloxycarbonyl-glycyl-L-leucyl-L-phenylalanine 2,6-difluoro-phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-tyrosine 2,6-dichloro-3-(morpholinosulfonyl)phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dichloro-3-(morpholinosulfonyl)phenylcarboxymethyl ketone and Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichlorophenyl carboxymethyl ketone.

19. The pharmaceutical composition of claim 15 wherein said compound is selected from the group consisting of: Benzyloxycarbonyl-L-valyl-L-phenylalanine 2,6-dichlorophenyl-carboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone, Tert-Butyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-difluorophenyl-carboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-tyrosine 2,6-difluorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-glycine 2,6-dichlorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-glycine 3,6-dichloro-2-acetamido-phenylcarboxymethyl ketone, p-Toluenesulfonyl-L-leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dimethylphenyl -carboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-glycine 2-acetamido-6-chlorophenylcarboxymethyl ketone and Benzyloxycarbonyl-L-leucyl-L-glycine 2-acetamido-6-chlorophenyl-carboxymethyl ketone.

20. The pharmaceutical composition of claim 15 wherein said compound is selected from the group consisting of: Benzyloxycarbonyl-L-N-methylleucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-N-methylleucyl-L-phenylalanine 2,6-dichloro-3-[2-(morpholino) ethoxy]phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-valyl-L-phenylalanine 2-acetamido-6-chlorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-N-methylleucyl-L-phenylalanine 2,6-dichloro-3-(morphorinosulfonyl)phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichloro-3-(carbobenzoxymethylsulfamoyl)phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dichloro-3-(carbobenzoxymethylsulfamoyl)phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dimethoxyphenyl- carboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-chlorophenylcarboxymethyl

ketone and Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-acetamido-6-chlorophenylcarboxymethyl ketone.

21. The pharmaceutical composition of claim 15 wherein said compound is selected from the group consisting of: Benzyloxycarbonyl-L-leucyl-L-glycine 2-acetamido-3,6-dichlorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-pyridylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-glycine 2,6-fluorophenylcarboxy-methyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-difluorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-valyl-L-alanine 2,6-bistrifluoromethylphenylcarboxymethyl ketone, p-Nitrobenzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine 1-naphthylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichloro-3-benzyloxyphenylcarboxymethyl ketone, N-Benzyloxycarbonyl-L-leucyl-N-(2,6-dichlorophenylcarboxyacetyl)hydrazide and N-Benzyloxycarbonyl-L-leucyl-N-methyl-N-(2-acetamido-6-chlorophenylcarboxy-acetyl)hydrazide.

22. The pharmaceutical composition of claim 15 wherein said compound is selected from the group consisting of: Benzyloxycarbonyl-L-leucyl-N-(2-acetamido-6-chlorophenyl-carboxy-acetyl)hydrazide, Benzyloxycarbonyl-L-leucyl-L-tyrosine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone, Methoxycarbonyl-D-alanyl-L-leucyl-L-phenylalanine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone, Benzyloxycarbonyl-D-alanyl-L-leucyl-L-tyrosine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-valyl-L-phenylalanine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-valyl-glycine 2,6-dichloro-3-(carbobenzoxy-methylsulfamoyl)phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine 2,6-dichloro-3-[2-

(morpholino)ethoxy]phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-glycine 2,6-dichloro-3-[2-(morpholino)-ethoxy]phenylcarboxymethyl ketone, Methoxycarbonyl-D-alanyl-L-leucyl-L-phenylalanine 2,6-difluorophenylcarboxymethyl ketone and Benzyloxycarbonyl-L-alanyl-L-glycine 2,6-dichloro-3-(carbobenzoxymethylsulfamoyl)phenylcarboxymethyl ketone.

23. The pharmaceutical composition of claim 15 wherein said compound is selected from the group consisting of: Benzyloxycarbonyl-glycyl-L-phenylalanine 2,6-dichloro-3-(carbobenzoxymethylsulfamoyl)phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-valyl-glycine 2,6-dichlorophenyl-carboxymethyl ketone, Benzyloxycarbonyl-glycyl-L-phenylalanine 2,6-dichlorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-phenylalanyl-L-alanine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenylcarboxymethyl ketone, Benzyloxycarbonyl-L-phenylalanyl-glycine 2,6-dichlorophenyl-carboxymethyl ketone, Benzyloxycarbonyl-D-alanyl-L-leucyl-glycine 2,6-dichloro-3-[2-(morpholino)ethoxy]phenyl-carboxymethyl ketone, Benzyloxycarbonyl-L-leucyl-glycine 2,6-dichlorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-phenylalanyl-glycine 2,6-dichlorophenylcarboxymethyl ketone, Benzyloxycarbonyl-L-alanyl-glycine 2,6-dichlorophenyl-carboxymethyl ketone and Benzyloxycarbonyl-L-phenylalanyl-L-alanine 2,6-bistrifluoromethylphenylcarboxymethyl ketone.

24. The pharmaceutical composition of claim 15 wherein said compound is selected from the group consisting of: N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-dichlorophenoxymethyl ketone, N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-[1-(3-pyridyl)tetrazolyl]thiomethyl ketone, N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-[(4-morpholinoethyl)tetrazolyl]thiomethyl ketone, N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-[(5-methylthio)tetrazolyl]thiomethyl ketone, N-Benzyloxycarbonyl-L-

leucyl-L-phenylalanine 2-[(5-methylthio)tetrazolyl]thiomethyl ketone, N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2,6-difluorophenylthiomethyl ketone, N-Benzyloxycarbonyl-L-valyl-L-phenylalanine 2,6-difluorophenoxymethyl ketone, N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-pyrimidylthiomethyl ketone, N-Benzyloxycarbonyl-L-leucyl-L-phenylalanine 2-(1-phenyl)tetrazolylthiomethyl ketone and Benzyloxycarbonyl-L-leucyl-L-tyrosinal.

25. The pharmaceutical composition of claim 15 wherein said compound is selected from the group consisting of: Benzyloxycarbonyl-L-valyl-L-tyrosinal, Benzyloxycarbonyl-L-leucyl-L-O-methyl-tyrosinal, Benzyloxycarbonyl-L-leucyl-L-phenylalaninal, Benzyloxycarbonyl-L-isoleucyl-L-tyrosinal, Benzyloxycarbonyl-L-valyl-DL-2-(2-naphthylmethyl)glycinal, Benzyloxycarbonyl-L-isoleucyl-L-phenylalaninal, Benzyloxycarbonyl-L-valyl-DL-2-(phenethyl)glycinal, Benzyloxycarbonyl-L-2-neopentylglycyl-L-phenylalaninal, Benzyloxycarbonyl-L-valyl-DL-2-(1-naphthylmethyl)glycinal and Benzyloxycarbonyl-L-2-phenylglycyl-L-phenylalaninal.

26. The pharmaceutical composition of claim 15 wherein said compound is selected from the group consisting of: Benzyloxycarbonyl-L-alanyl-L-phenylalaninal, Benzyloxycarbonyl-L-2-phenethylglycyl-L-phenylalaninal, Benzyloxycarbonyl-L-phenylalanyl-L-phenylalaninal, Benzyloxycarbonyl-L-2-tert-butylglycyl-L-phenylalaninal, Benzyloxycarbonyl-L-2-(1-naphthylmethyl)glycyl-DL-phenylalaninal, Benzyloxycarbonyl-L-leucyl-N-chloroacetyl-hydrazide, Benzyloxycarbonyl-L-leucyl-N-bromoacetyl-hydrazide, Benzyloxycarbonyl-L-leucine chloromethyl ketone, Benzyloxycarbonyl-L-leucyl-L-leucyl-L-phenylalanine chloromethyl ketone and Benzyloxycarbonyl-L-leucyl-L-alanine chloromethyl ketone.

27. The pharmaceutical composition of claim 15 wherein said compound is selected from the group consisting of: Benzyloxycarbonyl-L-

leucyl-L-phenylalanine chloromethyl ketone, Benzyloxycarbonyl-glycyl-L-leucyl-L-tyrosine chloromethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine chloromethyl ketone, Benzyloxycarbonyl-L-leucyl-glycine chloromethyl ketone, Benzyloxycarbonyl-L-leucyl-L-alanine bromomethyl ketone, Benzyloxycarbonyl-L-valyl-L-phenylalanine bromomethyl ketone, Benzyloxycarbonyl-L-leucyl-L-leucine bromomethyl ketone, Benzyloxycarbonyl-L-asparagyl-L-phenylalanine chloromethyl ketone, Benzyloxycarbonyl-L-leucyl-L-phenylalanine bromomethyl ketone and Benzyloxycarbonyl-L-phenylalanyl-L-alanine chloromethyl ketone.

28. The pharmaceutical composition of claim 15 wherein said compound is selected from the group consisting of: Benzyloxycarbonyl-glycyl-L-phenylalanine bromomethyl ketone, Benzyloxycarbonyl-L-valyl-glycine bromomethyl ketone, Benzyloxycarbonyl-L-leucine chloromethyl ketone,
Benzyloxycarbonyl-L-phenylalanyl-L-alanine bromomethyl ketone, Benzyloxycarbonyl-L-alanyl-glycine bromomethyl ketone, Benzyloxycarbonyl-L-2-(2-naphthylmethyl)glycine chloromethyl ketone, Benzyloxycarbonyl-L-phenylalanyl-glycine chloromethyl ketone, Benzyloxycarbonyl-L-phenylalanyl-L-phenylalanine chloromethyl ketone, Benzyloxycarbonyl-L-leucyl-N-(bromoacyl) hydrazide and Benzyloxycarbonyl-L-leucyl-L-tyrosine bromomethyl ketone.

29. A method of treating or inhibiting a neurodegenerative disease in a mammal comprising the administration to said mammal an effective amount of a composition according to claim 15.

30. A method of treating or inhibiting a neurodegenerative disease in a mammal comprising the administration to said mammal an effective amount of a composition according to claim 16.

31. A method of treating or inhibiting a neurodegenerative disease in a mammal comprising the administration to said mammal an effective amount of a composition according to claim 17.

32. A method of treating or inhibiting a neurodegenerative disease in a mammal comprising the administration to said mammal an effective amount of a composition according to claim 18.

33. A method of treating or inhibiting a neurodegenerative disease in a mammal comprising the administration to said mammal an effective amount of a composition according to claim 19.

34. A method of treating or inhibiting a neurodegenerative disease in a mammal comprising the administration to said mammal an effective amount of a composition according to claim 20.

35. A method of treating or inhibiting a neurodegenerative disease in a mammal comprising the administration to said mammal an effective amount of a composition according to claim 21.

36. A method of treating or inhibiting a neurodegenerative disease in a mammal comprising the administration to said mammal an effective amount of a composition according to claim 22.

37. A method of treating or inhibiting a neurodegenerative disease in a mammal comprising the administration to said mammal an effective amount of a composition according to claim 23.

38. A method of treating or inhibiting a neurodegenerative disease in a mammal comprising the administration to said mammal an effective amount of a composition according to claim 24.

39. A method of treating or inhibiting a neurodegenerative disease in a mammal comprising the administration to said mammal an effective amount of a composition according to claim 25.

40. A method of treating or inhibiting a neurodegenerative disease in a mammal comprising the administration to said mammal an effective amount of a composition according to claim 26.

41. A method of treating or inhibiting a neurodegenerative disease in a mammal comprising the administration to said mammal an effective amount of a composition according to claim 27.

42. A method of treating or inhibiting a neurodegenerative disease in a mammal comprising the administration to said mammal an effective amount of a composition according to claim 28.