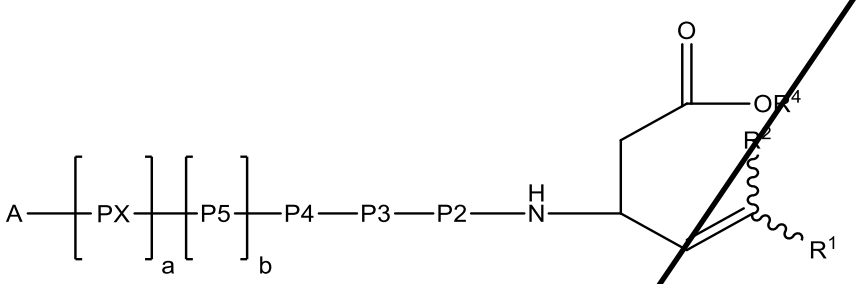
CLAIMS

1. A compound of Formula I:



I

wherein

a is 0 or 1;

b is 0 or 1 provided that when b is 0, a is 0;

A is

1) H,

2) C_1-C_6 alkyl,

3) aryl,

4) heteroaryl,

5) heterocyclyl,

6) R^3-C(O)-,

7) R^3-OC(O)-;

8) R^3-C(O)O-, or

9) R^3-$S(O)_2$-;

P2, P3, P4, P5, when present, and PX, when present, are any (D) or (L) amino acid residue;

the line "–" when located between P2, P3, P4, P5 or PX represents a peptide bond or a peptidomimetic bond;

the wavy line represents either cis or trans orientation of R^1 and R^2;

R^1 is

1) aryl,

2) heteroaryl,

3) heterocyclyl,

4) C_2-C_6 alkene-$\mathbf{R^{20}}$,

5) SO_2R^5,

6) SO_3R^5,

7) SOR^5,

8) $SONHR^5$,

9) SO_2NHR^5,

10) CN,

11) CO_2R^5,

12) COR^5,

13) PO_3R^5,

14) $PO(OR^5)_2$, or

15) $PO(OR^5)$,

wherein the aryl, the heteroaryl, or the heterocyclyl are optionally substituted with one or more R^{30}**;**

R^2 is

1) $\mathbf{R^1}$;or

2) H,

3) halogen,

4) haloalkyl,

5) C_1 –C_6 alkyl,

6) C_2-C_6 alkene,

7) C_3-C_7 cycloalkyl,

8) OR^9;

9) $OCOR^6$,

10) OCO_2R^6,

11) NR^7R^8,

12) $NHSO_2R^6$,

13) $NHCOR^6$,

14) aryl,

15) heteroaryl, or

16) heterocyclyl;

R^3 is

1) C_1-C_6 alkyl,

2) aryl,

3) heteroaryl, or

4) heterocyclyl;

R^4 is

1) H, or

2) C_1–C_6 alkyl;

R^5 is

1) H,

2) C_1-C_6 alkyl,

3) C_2-C_6 alkene,

4) C_3-C_7 cycloalkyl,

5) aryl,

6) heteroaryl,

7) heterocyclyl, or

8) any optionally protected (D) or (L) amino acid residue;

R^6 is

1) any (D) or (L) amino acid residue,

2) C_1-C_6 alkyl,

3) C_3-C_7 cycloalkyl,

4) aryl,

5) heteroaryl, or

6) heterocyclyl,

in which the alkyl or the cycloalkyl are optionally substituted with one or more **R^{10}** substituents; and in which the aryl, heteroaryl or heterocyclyl are optionally substituted with one or more **R^{20}** substituents;

R^7 and R^8 are independently selected from:

1) H,

2) C_1–C_6 alkyl,

3) C_3–C_7 cycloalkyl,

4) haloalkyl,

5) aryl,

6) heteroaryl, or

7) heterocyclyl,

wherein the alkyl and the cycloalkyl are optionally substituted with one or more R^{10} substituents, and the aryl, the heteroaryl and the heterocyclyl are optionally substituted with one or more R^{20} substituents;

R^9 is

1) H,

2) C_1-C_6 alkyl,

3) C_3-C_7 cycloalkyl,

4) aryl,

5) heteroaryl, or

6) heterocyclyl,

in which the alkyl or the cycloalkyl are optionally substituted with one or more $\mathbf{R^{10}}$ substituents; and in which the aryl, heteroaryl or heterocyclyl are optionally substituted with one or more $\mathbf{R^{20}}$ substituents;

R^{10} is independently selected from:

1) halogen,

2) C_1–C_6 alkyl,

3) C_3–C_7 cycloalkyl,

4) haloalkyl,

5) aryl,

6) heteroaryl,

7) heterocyclyl,

8) OR^9,

9) $S(O)_mR^9$,

10) NR^7R^8 ,

11) COR^9,

12) $C(O)OR^9$,

13) $OC(O)R^9$,

14) $SC(O)R^9$,

15) $CONR^7R^8$, or

16) $S(O)_2NR^7R^8$;

R^{20} is independently selected from:

1) halogen,

2) NO_2,

3) CN,

4) C_1-C_6 alkyl,

5) haloalkyl,

6) C_3-C_7 cycloalkyl,

7) OR^7,

8) NR^7R^8,

9) SR^7,

10) aryl,

11) heteroaryl,

12) heterocyclyl,

13) SO_2R^5,

14) SO_3R^5,

15) SOR^5,

16) $SONHR^5$,

17)SO_2NHR^5,

18) PO_3R^5,

19) $PO(OR^5)_2$,

20) $PO(OR^5)$,

21) COR^7,

22) CO_2R^7,

23) $S(O)_mR^7$,

24) $CONR^7R^8$, or

25) $S(O)_2NR^7R^8$,

wherein the alkyl and the cycloalkyl are optionally substituted with one or more R^6 substituents; and wherein the aryl, •the heteroaryl, or the heterocyclyl are optionally substituted with one or more R^{30};

R^{30} is

1) NO_2,

2) C_2-C_6 alkene-$\mathbf{R^{20}}$,

3) SO_2R^5,

4) SOR^5,

5) $SONHR^5$,

6) SO_2NHR^5,

7) CN,

8) CO_2R^5,

9) COR^5,

10) PO_3R^5,

11) $PO(OR^5)_2$, or

12) $PO(OR^5)$;

or a prodrug, or a pharmaceutically acceptable salt, or the compound is labeled with a detectable label or an affinity tag thereof.

2. The compound, according to claim 1, in which A is H.

3. The compound, according to claim 1, in which A is $PhCH_2OC(O)$-

4. The compound according to claim 1, in which R^4 is H or CH_3.

5. The compound, according to claim 1, in which R^4 is H.

6. The compound, according to claim 1, in which a and b are both 0.

7. The compound, according to claim 1, in which a is 0 and b is 1.

8. The compound, according to claim 1, in which R^1 is in the trans configuration.

9. The compound, according to claim 1, R^1 is

1) SO_2R^5,

2) SO_3R^5; or

3) SOR^5,

wherein R^5 is C_1-C_6 alkyl, aryl, or heterocylyl.

10. The compound, according to claim 1, in which R^2 is

1) H,

2) halogen,

3) haloalkyl,

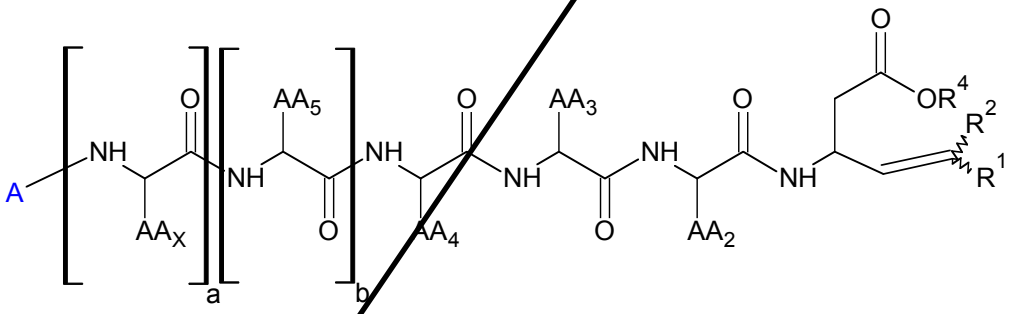
4) C_1 –C_6 alkyl, or

5) C_3-C_7 cycloalkyl.

11. The compound, according to claim 10, in which R^2 is H or Cl.

12. The compound, according to claim 11, in which R^2 is Cl.

13. A compound of Formula IA



IA

wherein

a is 0 or 1;

b is 0 or 1 provided that when b is 0, a is 0;

A is

1) H,

2) C_1-C_6 alkyl,

3) aryl,

4) heteroaryl,

5) heterocyclyl,

6) R^3-OC(O)-;

7) R^3-C(O)O-, or

8) R^3-$S(O)_2$-;

AA_2 is the (R) or (S) amino acid side chain of Val, Leu, Pro, Met, Ala, Thr, His, Ser, or Lys;

AA_3 is the (R) or (S) amino acid side chain of Trp, Tyr, Ala, Asp, Gln, Glu, Phe, Ser, Thr, Val, Tyr, Gly, Leu, His, or Ile; or AA_3 is phenylglycine, indanylglycine, or Ala-(2'-quinolyl);

AA_4 is the (R) or (S) amino acid side chain of Asp, Ile, Leu, Glu, Ala, Val, Tyr, Trp, Phe, or Pro;

AA_5, when present, is the (R) or (S) amino acid side chain of Val or Leu;

AA_X, when present, is the (R) or (S) amino acid side chain of any D or L amino acid residue;

the wavy line represents either cis or trans orientation of R^1 and R^2;

R^1 is

1) aryl,

2) heteroaryl,

3) heterocyclyl,

4) C_2-C_6 alkene-$\mathbf{R^{20}}$,

5) SO_2R^5,

6) SO_3R^5,

7) SOR^5,

8) $SONHR^5$,

9) SO_2NHR^5,

10) CN,

11) CO_2R^5,

12) COR^5,

13) PO_3R^5,

14) $PO(OR^5)_2$, or

15) $PO(OR^5)$,

wherein the aryl, the heteroaryl, or the heterocyclyl are optionally substituted with one or more R^{30};

R^2 is

1) R^1;or

2) H,

3) halogen,

4) haloalkyl,

5) C_1 –C_6 alkyl,

6) C_2-C_6 alkene,

7) C_3-C_7 cycloalkyl,

8) OR^9;

9) $OCOR^6$,

10) OCO_2R^6,

11) NR^7R^8,

12) $NHSO_2R^6$,

13) $NHCOR^6$,

14) aryl,

15) heteroaryl, or

16) heterocyclyl;

R^3 is

1) C_1-C_6 alkyl,

2) aryl,

3) heteroaryl, or

4) heterocyclyl;

R^4 is

1) H, or

2) C_1–C_6 alkyl;

R^5 is

1) H,

2) C_1-C_6 alkyl,

3) C_2-C_6 alkene,

4) C_3-C_7 cycloalkyl,

5) aryl,

6) heteroaryl,

7) heterocyclyl, or

8) any optionally protected (D) or (L) amino acid residue;

R^6 is

1) any (D) or (L) amino acid residue,

2) C_1-C_6 alkyl,

3) C_3-C_7 cycloalkyl,

4) aryl,

5) heteroaryl, or

6) heterocyclyl,

in which the alkyl or the cycloalkyl are optionally substituted with one or more $\mathbf{R^{10}}$ substituents; and in which the aryl, heteroaryl or heterocyclyl are optionally substituted with one or more $\mathbf{R^{20}}$ substituents;

R^7 and R^8 are independently selected from:

1) H,

2) C_1–C_6 alkyl,

3) C_3–C_7 cycloalkyl,

4) haloalkyl,

5) aryl,

6) heteroaryl, or

7) heterocyclyl,

wherein the alkyl and the cycloalkyl are optionally substituted with one or more R^{10} substituents, and the aryl, the heteroaryl and the heterocyclyl are optionally substituted with one or more R^{20} substituents;

R^9 is

1) H,

2) C_1-C_6 alkyl,

3) C_3-C_7 cycloalkyl,

4) aryl,

5) heteroaryl, or

6) heterocyclyl,

in which the alkyl or the cycloalkyl are optionally substituted with one or more $\mathbf{R^{10}}$ substituents; and in which the aryl, heteroaryl or heterocyclyl are optionally substituted with one or more $\mathbf{R^{20}}$ substituents;

R^{10} is independently selected from:

1) halogen,

2) C_1–C_6 alkyl,

3) C_3–C_7 cycloalkyl,

4) haloalkyl,

5) aryl,

6) heteroaryl,

7) heterocyclyl,

8) OR^9,

9) $S(O)_mR^9$,

10) NR^7R^8 ,

11) COR^9,

12) $C(O)OR^9$,

13) $OC(O)R^9$,

14) $SC(O)R^9$,

15) $CONR^7R^8$, or

16) $S(O)_2NR^7R^8$;

R^{20} is independently selected from:

1) halogen,

2) NO_2,

3) CN,

4) C_1-C_6 alkyl,

5) haloalkyl,

6) C_3-C_7 cycloalkyl,

7) OR^7,

8) NR^7R^8,

9) SR^7,

10) aryl,

11) heteroaryl,

12) heterocyclyl,

13) SO_2R^5,

14) SO_3R^5,

15) SOR^5,

16) $SONHR^5$,

17) SO_2NHR^5,

18) PO_3R^5,

19) $PO(OR^5)_2$,

20) $PO(OR^5)$,

21) COR^7,

22) CO_2R^7,

23) $S(O)_mR^7$,

24) $CONR^7R^8$, or

25) $S(O)_2NR^7R^8$,

wherein the alkyl and the cycloalkyl are optionally substituted with one or more R^6 substituents; and wherein the aryl, the heteroaryl, or the heterocyclyl are optionally substituted with one or more R^{30}**;**

R^{30} is

1) NO_2,

2) C_2-C_6 alkene-$\mathbf{R^{20}}$,

3) SO_2R^5,

4) SOR^5,

5) $SONHR^5$,

6) SO_2NHR^5,

7) CN,

8) CO_2R^5,

9) COR^5,

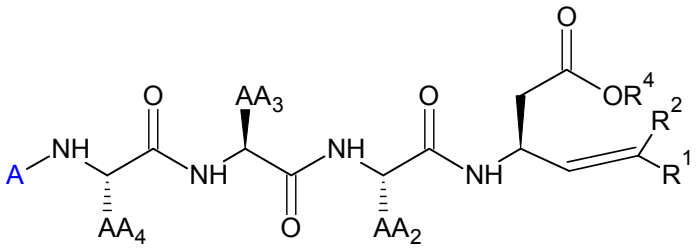
10) PO_3R^5,

11) $PO(OR^5)_2$, or

12) $PO(OR^5)$;

or a prodrug, or a pharmaceutically acceptable salt, or the compound is labeled with a detectable label or an affinity tag thereof.

14. The compound, according to claim 13, includes compounds of Formula IIA



IIA

wherein

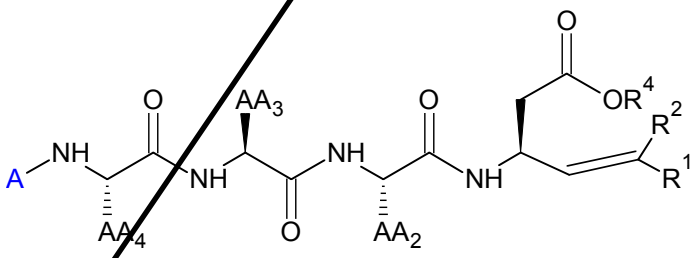
AA_2 is the amino acid side chain of Val, Leu, Pro, Met, Ala, Thr, His, Ser, or Lys;

AA_3 is the amino acid side chain of Trp, Tyr, Ala, Asp, Gln, Phe, Ser, Thr, Val, Tyr, Gly, Leu; or AA_3 is phenylglycine, indanylglycine, or Ala-(2'-quinolyl);

AA_4 is the amino acid side chain of Asp;

and wherein A, R^1, R^2 and R^4 are as defined in claim 13.

15. The compound, according to claim 13, includes compounds of Formula IIA



IIA

wherein

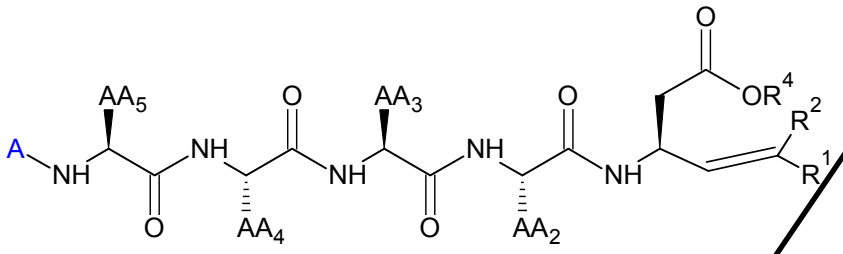
AA_2 is the amino acid side chain of Thr, His, Val, Trp, Ile, or Ala

AA_3 is the amino acid side chain of Glu or AA_3 is Ala-(2'-quinolyl);

AA_4 is the amino acid side chain of Ile, Leu, Glu, Asp, Ala, Pro or Val;

and wherein A, R^1, R^2 and R^4 are as defined in claim 13.

16. The compound, according to claim 13, includes compounds of Formula IIIA



IIIA

wherein

AA_2 is the amino acid side chain of Ala, Ser, Lys or Val;

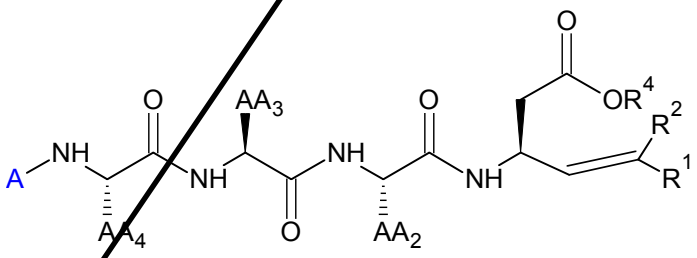
AA_3 is the amino acid side chain of Val, Glu, Thr, or Gln;

AA_4 is the amino acid side chain of Asp, or Leu;

AA_5 is the amino acid side chain of Val or Leu;

and wherein A, R^1, R^2 and R^4 are as defined in claim 13.

17. The compound, according to claim 13, includes compounds of Formula IIA



IIA

wherein

AA_2 is the amino acid side chain of Val, Ala, Thr, or His;

AA_3 is the amino acid side chain of Glu, Gln, Asp, Ala, Gly, Thr, Val, Trp; or AA_3 is phenylglycine or indanylglycine;

AA_4 is the amino acid side chain of Tyr, Trp, Phe, or Asp;

and wherein A, R^1, R^2 and R^4 are as defined in claim 13.

18. A compound, according to claims 1 or 13, selected from the group consisting of: compound #48, compound #51, compound #53, compound #57, compound #55, compound #59, and compound #88.

19. An Intermediate compound selected from the group consisting of: compound #4, compound #12, compound #16, and compound #20.

20. A pharmaceutical composition for preventing and/or treating a caspase-related disease in a subject in need thereof, comprising an effective amount of a compound according to any one of claims 1-18.

21. A method for preventing and/or treating a caspase-related disease in a subject in need thereof, comprising administering to said subject an effective amount of a compound according to any one of claims 1-18.

22. Use of a compound according to any one of claims 1-18 for the manufacture of a medication for preventing and/or treating of caspase-related diseases in a subject in need thereof.

23. Use of a compound according to any one of claims 1-18 for preventing and/or treating of caspase-related diseases in a subject in need thereof.

24. The method, according to claim 21, in which the caspase-related disease is selected from the group consisting of apoptosis mediated diseases, IL-1 mediated diseases, inflammatory diseases, autoimmune diseases, autoinflammatory diseases, proliferative diseases, infectious diseases, degenerative diseases, retinal disorders, inflammatory peritonitis, osteoarthritis, pancreatitis, asthma, respiratory distress syndrome, rheumatoid arthritis, systemic lupus erythematous, scleroderma, Grave's disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, hepatitis, inflammatory bowel disease, crohn's disease, psoriasis, dermatitis, Graft vs host disease, organ transplant rejection, osteoporosis, leukemias and related disorders, multiple myeloma-related diseases, metastatic melanomas, Kaposi's sarcoma, sepsis, septic shock, Alzheimer's disease, Parkinson's disease, Huntington's disease, cerebral ischemia, epilepsy, myocardial ischemia, acute and chronic heart disease, myocardial infarction, congestive heart failure, atherosclerosis, spinal muscular atrophy, amyotrophic lateral sclerosis, multiple sclerosis, HIV-related encephalitis, aging, neurological damage due to stroke, ulcerative colitis, traumatic brain injury, spinal cord injury, hepatitis-B, hepatitis-C, hepatitis-G, liver-related diseases, renal disease, and HIV infection.

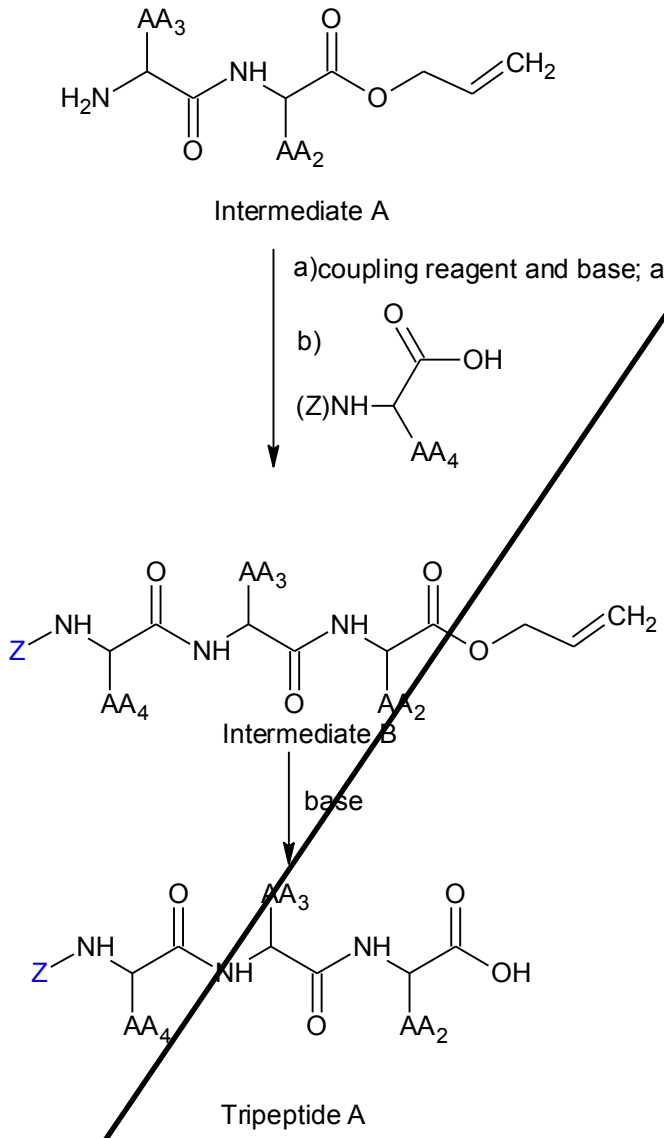
25. The use, according to any one of claims 21-23, in which the caspase-related disease is selected from the group consisting of apoptosis mediated diseases, IL-1 mediated diseases, inflammatory diseases, autoimmune diseases, autoinflammatory diseases, proliferative diseases, infectious diseases, degenerative diseases, retinal disorders, inflammatory peritonitis, osteoarthritis, pancreatitis, asthma, respiratory distress syndrome, rheumatoid arthritis, systemic lupus erythematous, scleroderma, Grave's disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, hepatitis, inflammatory bowel disease, crohn's disease, psoriasis, dermatitis, Graft vs host disease, organ transplant rejection, osteoporosis, leukemias and related disorders, multiple myeloma-related diseases, metastatic melanomas, Kaposi's sarcoma, sepsis, septic shock, Alzheimer's disease, Parkinson's disease, Huntington's disease, cerebral ischemia, epilepsy, myocardial ischemia, acute and chronic heart disease, myocardial infarction, congestive heart failure, atherosclerosis, spinal muscular atrophy, amyotrophic lateral sclerosis, multiple sclerosis, HIV-related encephalitis, aging, neurological damage due to stroke, ulcerative colitis, traumatic brain injury, spinal cord injury, hepatitis-B, hepatitis-C, hepatitis-G, liver-related diseases, renal disease, and HIV infection.

26. A method of treating excessive apoptosis affected by caspase activity in a cell or a tissue, the method comprising: contacting the cell or tissue with an effective amount of one or more compounds according to any one of claims 1-18, so as to treat the excessive apoptosis.

27. A process for synthesizing tripeptide A, the process comprising:

a) coupling intermediate A with a protected amino acid (Z)NHCHAA_2-OH to produce allyl intermediate B, and

b) removing the allyl group from intermdediate B to produce tripeptide A, according to the scheme:



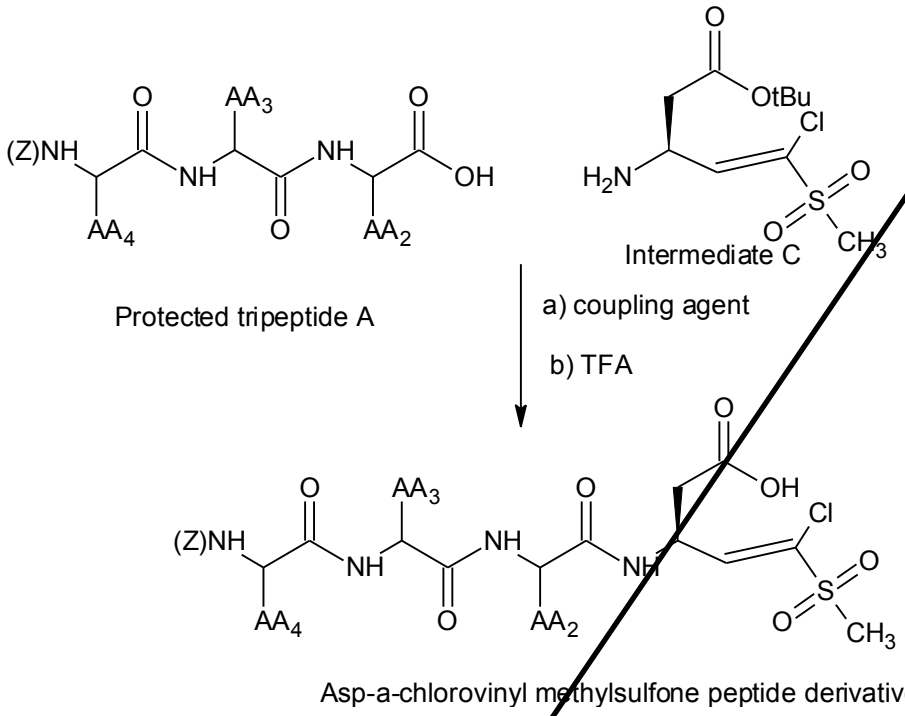
wherein AA_2, AA_3 and AA_4 are any (D) or (L) amino acid residue side chains; and Z is an amino protecting group.

28. The process, according to claim 27, in which the base is tetrakis morpholine.

29. A process for synthesizing Asp-a-chlorovinyl methylsulfone peptide derivatives, the process comprising:

a) coupling protected tripeptide A and intermediate C in the prescence of a coupling agent; and

b) removing the tert-butyl ester so as to produce the Asp-a-chlorovinyl methylsulfone peptide derivatives, according to the scheme:

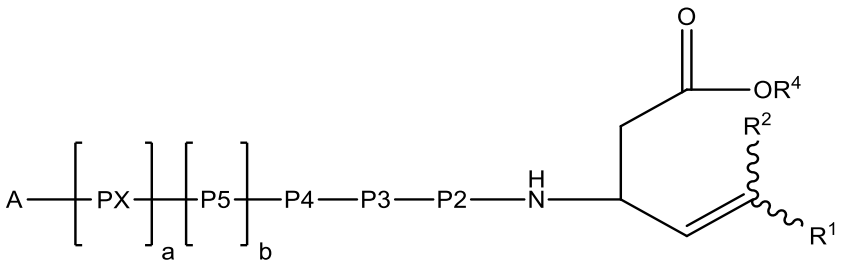


wherein AA_2, AA_3 and AA_4 are any (D) or (L) amino acid residue side chains; and Z is an amino protecting group.

30. The compound, according to claims 1 or 13, in which the pharmaceutically acceptable salt is one that allows the compound to penetrate cells.

CLAIMS

1. A compound of Formula I:



I

in which

a is 0 or 1;

b is 0 or 1 provided that when b is 0, a is 0;

A is

1) H,

2) C_1-C_6 alkyl,

3) aryl,

4) heteroaryl,

5) heterocyclyl,

6) R^3-OC(O)-;

7) R^3-C(O)O-;

8) R^3-$S(O)_2$-; or

9) $PhCH_2OC(O)$-

P2, P3, P4, and, when present, P5 and PX, are any (D) or (L) amino acid residue;

the line "–" when located between P2, P3, P4, P5 or PX represents a peptide bond or a peptidomimetic bond, in which the peptidomimetic bond is preferably selected from the group consisting of CH_2-NH, CO-CH_2, azapeptide and retro-inverso bonds;

the wavy line represents either cis or trans orientation of R^1 and R^2;

R^1 is

1) aryl,

2) heteroaryl,

3) heterocyclyl,

4) C_2-C_6 alkene-$\mathbf{R^{20}}$,

5) SO_2R^5,

6) SO_3R^5,

7) SOR^5,

8) $SONHR^5$,

9) SO_2NHR^5,

10) CN,

11) CO_2R^5,

12) COR^5,

13) PO_3R^5,

14) $PO(OR^5)_2$, or

15) $PO(OR^5)$,

in which the aryl, the heteroaryl, or the heterocyclyl are optionally substituted with one or more R^{30}**;**

R^2 is

1) $\mathbf{R^1}$;or

2) H,

3) halogen,

4) haloalkyl,

5) C_1 –C_6 alkyl,

6) C_2-C_6 alkene,

7) C_3-C_7 cycloalkyl,

8) OR^9;

9) $OCOR^6$,

10) OCO_2R^6,

11) NR^7R^8,

12) $NHSO_2R^6$,

13) $NHCOR^6$,

14) aryl,

15) heteroaryl, or

16) heterocyclyl;

R^3 is

1) C_1-C_6 alkyl,

2) aryl,

3) heteroaryl, or

4) heterocyclyl;

R^4 is

1) H, or

2) C_1–C_6 alkyl;

R^5 is

1) H,

2) C_1-C_6 alkyl,

3) C_2-C_6 alkene,

4) C_3-C_7 cycloalkyl,

5) aryl,

6) heteroaryl,

7) heterocyclyl, or

8) any optionally protected (D) or (L) amino acid residue;

R^6 is

1) any (D) or (L) amino acid residue,

2) C_1-C_6 alkyl,

3) C_3-C_7 cycloalkyl,

4) aryl,

5) heteroaryl, or

6) heterocyclyl,

in which the alkyl or the cycloalkyl are optionally substituted with one or more **R^{10}** substituents; and in which the aryl, heteroaryl or heterocyclyl are optionally substituted with one or more **R^{20}** substituents;

R^7 and R^8 are independently selected from:

1) H,

2) C_1–C_6 alkyl,

3) C_3–C_7 cycloalkyl,

4) haloalkyl,

5) aryl,

6) heteroaryl, or

7) heterocyclyl,

in which the alkyl and the cycloalkyl are optionally substituted with one or more R^{10} substituents, and the aryl, the heteroaryl and the heterocyclyl are optionally substituted with one or more R^{20} substituents;

R^9 is

1) H,

2) C_1-C_6 alkyl,

3) C_3-C_7 cycloalkyl,

4) aryl,

5) heteroaryl, or

6) heterocyclyl,

in which the alkyl or the cycloalkyl are optionally substituted with one or more **R^{10}** substituents; and in which the aryl, heteroaryl or heterocyclyl are optionally substituted with one or more **R^{20}** substituents;

R^{10} is independently selected from:

1) halogen,

2) C_1–C_6 alkyl,

3) C_3–C_7 cycloalkyl,

4) haloalkyl,

5) aryl,

6) heteroaryl,

7) heterocyclyl,

8) OR^9,

9) $S(O)_mR^9$,

10) NR^7R^8 ,

11) COR^9,

12) $C(O)OR^9$,

13) $OC(O)R^9$,

14) $SC(O)R^9$,

15) $CONR^7R^8$, or

16) $S(O)_2NR^7R^8$;

R^{20} is independently selected from:

1) halogen,

2) NO_2,

3) CN,

4) C_1-C_6 alkyl,

5) haloalkyl,

6) C_3-C_7 cycloalkyl,

7) OR^7,

8) NR^7R^8,

9) SR^7,

10) aryl,

11) heteroaryl,

12) heterocyclyl,

13) SO_2R^5,

14) SO_3R^5,

15) SOR^5,

16) $SONHR^5$,

17) SO_2NHR^5,

18) PO_3R^5,

19) $PO(OR^5)_2$,

20) $PO(OR^5)$,

21) COR^7,

22) CO_2R^7,

23) $S(O)_mR^7$,

24) $CONR^7R^8$, or

25) $S(O)_2NR^7R^8$,

in which the alkyl and the cycloalkyl are optionally substituted with one or more R^6 substituents; and in which the aryl, the heteroaryl, or the heterocyclyl are optionally substituted with one or more R^{30};

R^{30} is

1) NO_2,

2) C_2-C_6 alkene-$\mathbf{R^{20}}$,

3) SO_2R^5,

4) SOR^5,

5) $SONHR^5$,

6) SO_2NHR^5,

7) CN,

8) CO_2R^5,

9) COR^5,

10) PO_3R^5,

11) $PO(OR^5)_2$, or

12) $PO(OR^5)$;

or a pharmaceutically acceptable salt, or the compound is labeled with a detectable label.

2. A compound according to Claim 1, in which A is H or A is $PhCH_2OC(O)$-.

3. A compound according to Claim 1, in which R^4 is H, CH_3 or CH_3CH_2.

4. A compound according to Claim 1, in which a and b are both 0; or a is 0 and b is 1.

5. A compound according to Claim 1, in which R^1 is in the trans configuration.

6. A compound according to Claim 1, in which R^1 is

1) SO_2R^5,

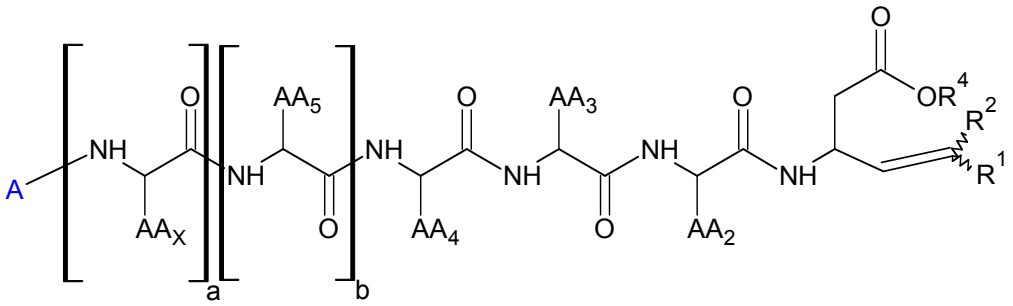
2) SO_3R^5; or

3) SOR^5,

in which R^5 is C_1-C_6 alkyl, aryl, or heterocylyl.

7. A compound according to Claim 1, in which R^2 is H or Cl.

8. A compound of Formula IA



IA

in which

a is 0 or 1;

b is 0 or 1 provided that when b is 0, a is 0;

A is

1) H,

2) C_1-C_6 alkyl,

3) aryl,

4) heteroaryl,

5) heterocyclyl,

6) R^3-OC(O)-;

7) R^3-C(O)O-;

8) R^3-$S(O)_2$-; or

9) $PhCH_2OC(O)$-

AA_2 is the (R) or (S) amino acid side chain of Val, Leu, Pro, Met, Ala, Thr, His, Ser, Lys or Ile;

AA_3 is the (R) or (S) amino acid side chain of Trp, Tyr, Ala, Asp, Gln, Glu, Phe, Ser, Thr, Val, Tyr, Gly, Leu, His, or Ile; or AA_3 is phenylglycine, indanylglycine, or Ala-(2'-quinolyl);

AA_4 is the (R) or (S) amino acid side chain of Asp, Ile, Leu, Glu, Ala, Val, Tyr, Trp, Phe, or Pro;

AA_5, when present, is the (R) or (S) amino acid side chain of Val or Leu;

AA_X, when present, is the (R) or (S) amino acid side chain of any D or L amino acid residue;

the wavy line represents either cis or trans orientation of R^1 and R^2;

R^1 is

1) aryl,

2) heteroaryl,

3) heterocyclyl,

4) C_2-C_6 alkene-$\mathbf{R^{20}}$,

5) SO_2R^5,

6) SO_3R^5,

7) SOR^5,

8) $SONHR^5$,

9) SO_2NHR^5,

10) CN,

11) CO_2R^5,

12) COR^5,

13) PO_3R^5,

14) $PO(OR^5)_2$, or

15) $PO(OR^5)$,

in which the aryl, the heteroaryl, or the heterocyclyl are optionally substituted with one or more R^{30};

R^2 is

1) R^1;or

2) H,

3) halogen,

4) haloalkyl,

5) C_1 –C_6 alkyl,

6) C_2-C_6 alkene,

7) C_3-C_7 cycloalkyl,

8) OR^9;

9) $OCOR^6$,

10) OCO_2R^6,

11) NR^7R^8,

12) $NHSO_2R^6$,

13) $NHCOR^6$,

14) aryl,

15) heteroaryl, or

16) heterocyclyl;

R^3 is

1) C_1-C_6 alkyl,

2) aryl,

3) heteroaryl, or

4) heterocyclyl;

R^4 is

1) H, or

2) C_1–C_6 alkyl;

R^5 is

1) H,

2) C_1-C_6 alkyl,

3) C_2-C_6 alkene,

4) C_3-C_7 cycloalkyl,

5) aryl,

6) heteroaryl,

7) heterocyclyl, or

8) any optionally protected (D) or (L) amino acid residue;

R^6 is

1) any (D) or (L) amino acid residue,

2) C_1-C_6 alkyl,

3) C_3-C_7 cycloalkyl,

4) aryl,

5) heteroaryl, or

6) heterocyclyl,

in which the alkyl or the cycloalkyl are optionally substituted with one or more $\mathbf{R^{10}}$ substituents; and in which the aryl, heteroaryl or heterocyclyl are optionally substituted with one or more $\mathbf{R^{20}}$ substituents;

R^7 and R^8 are independently selected from:

1) H,

2) C_1–C_6 alkyl,

3) C_3–C_7 cycloalkyl,

4) haloalkyl,

5) aryl,

6) heteroaryl, or

7) heterocyclyl,

in which the alkyl and the cycloalkyl are optionally substituted with one or more R^{10} substituents, and the aryl, the heteroaryl and the heterocyclyl are optionally substituted with one or more R^{20} substituents;

R^9 is

1) H,

2) C_1-C_6 alkyl,

3) C_3-C_7 cycloalkyl,

4) aryl,

5) heteroaryl, or

6) heterocyclyl,

in which the alkyl or the cycloalkyl are optionally substituted with one or more **R^{10}** substituents; and in which the aryl, heteroaryl or heterocyclyl are optionally substituted with one or more **R^{20}** substituents;

R^{10} is independently selected from:

1) halogen,

2) C_1–C_6 alkyl,

3) C_3–C_7 cycloalkyl,

4) haloalkyl,

5) aryl,

6) heteroaryl,

7) heterocyclyl,

8) OR^9,

9) $S(O)_mR^9$,

10) NR^7R^8 ,

11) COR^9,

12) $C(O)OR^9$,

13) $OC(O)R^9$,

14) $SC(O)R^9$,

15) $CONR^7R^8$, or

16) $S(O)_2NR^7R^8$;

R^{20} is independently selected from:

1) halogen,

2) NO_2,

3) CN,

4) C_1-C_6 alkyl,

5) haloalkyl,

6) C_3-C_7 cycloalkyl,

7) OR^7,

8) NR^7R^8,

9) SR^7,

10) aryl,

11) heteroaryl,

12) heterocyclyl,

13) SO_2R^5,

14) SO_3R^5,

15) SOR^5,

16) $SONHR^5$,

17) SO_2NHR^5,

18) PO_3R^5,

19) $PO(OR^5)_2$,

20) $PO(OR^5)$,

21) COR^7,

22) CO_2R^7,

23) $S(O)_mR^7$,

24) $CONR^7R^8$, or

25) $S(O)_2NR^7R^8$,

in which the alkyl and the cycloalkyl are optionally substituted with one or more R^6 substituents; and in which the aryl, the heteroaryl, or the heterocyclyl are optionally substituted with one or more R^{30}**;**

R^{30} is

1) NO_2,

2) C_2-C_6 alkene-$\mathbf{R^{20}}$,

3) SO_2R^5,

4) SOR^5,

5) $SONHR^5$,

6) SO_2NHR^5,

7) CN,

8) CO_2R^5,

9) COR^5,

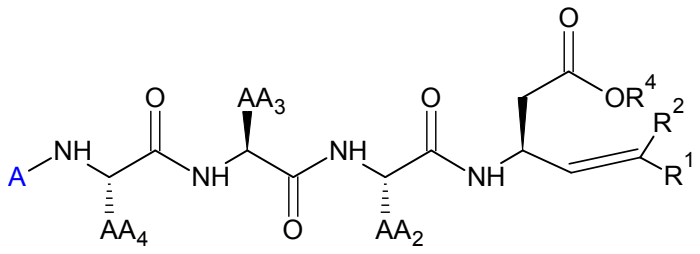
10) PO_3R^5,

11) $PO(OR^5)_2$, or

12) $PO(OR^5)$;

or a pharmaceutically acceptable salt, or the compound is labeled with a detectable label.

9. A compound according to Claim 8, which includes compounds of Formula IIA



IIA

in which

AA_2 is the amino acid side chain of Val, Leu, Pro, Met, Ala, Thr, His, Ser, Lys or Ile;

AA_3 is the amino acid side chain of Trp, Tyr, Ala, Asp, Gln, Phe, Ser, Thr, Val, Tyr, Gly, Leu; or AA_3 is phenylglycine, indanylglycine, or Ala-(2'-quinolyl);

AA_4 is the amino acid side chain of Asp or Trp; or

in which

AA_2 is the amino acid side chain of Thr, His, Val, Trp, Ile or Ala;

AA_3 is the amino acid side chain of Glu or AA_3 is Ala-(2'-quinolyl);

AA_4 is the amino acid side chain of Ile, Leu, Glu, Asp, Ala, Pro or Val; or

in which

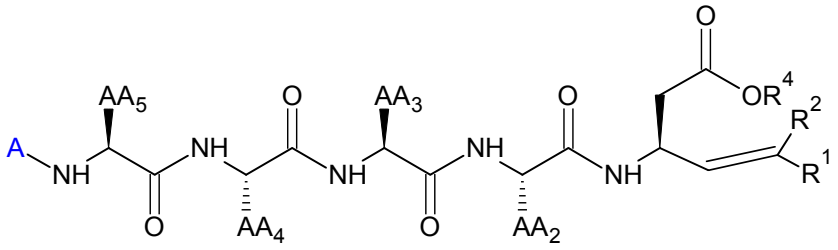
AA_2 is the amino acid side chain of Val, Ala, Thr or His;

AA_3 is the amino acid side chain of Glu, Gln, Asp, Ala, Gly, Thr, Val, Trp; or AA_3 is phenylglycine or indanylglycine;

AA_4 is the amino acid side chain of Tyr, Trp, Phe or Asp;

and in which A, R^1, R^2 and R^4 are as defined in Claim 8.

10. A compound according to Claim 8, which includes compounds of Formula IIIA



IIIA

in which

AA_2 is the amino acid side chain of Ala, Ser, Lys or Val;

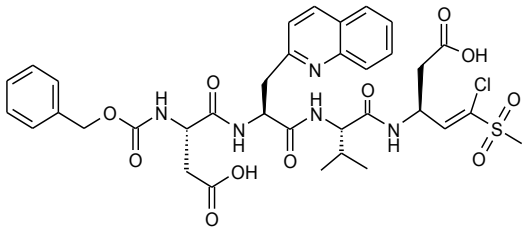
AA_3 is the amino acid side chain of Val, Glu, Thr, or Gln;

AA_4 is the amino acid side chain of Asp, or Leu;

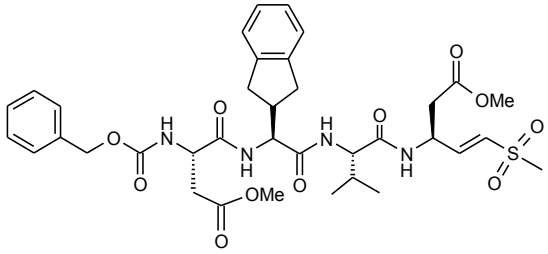
AA_5 is the amino acid side chain of Val or Leu;

and in which A, R^1, R^2 and R^4 are as defined in Claim 8.

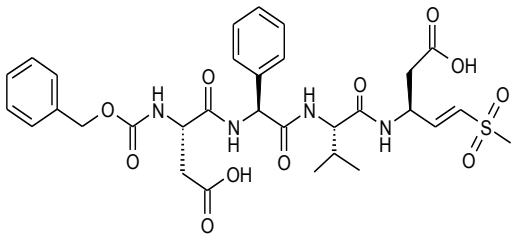
11. A compound according to Claim 1 or 8, in which the compound is selected from the group consisting of:



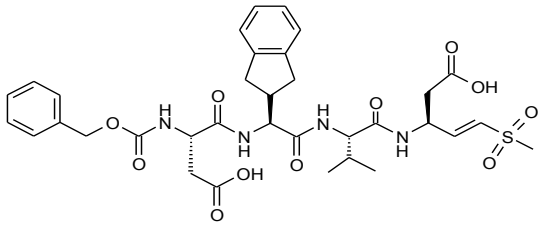
compound #48



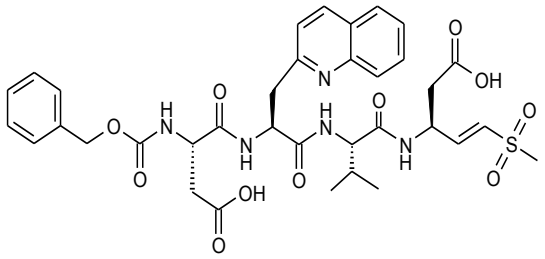
compound #51



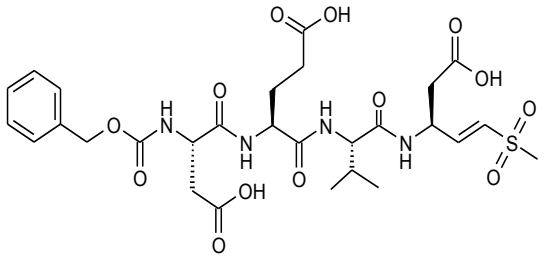
compound #53



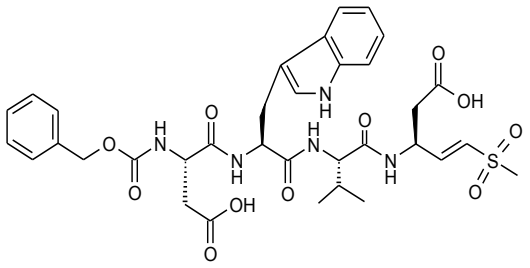
compound #57



compound #55



compound #59; and



compound #88.

12. A compound according to any preceding claim, in which the detectable label comprises a radioisotope.

13. A pharmaceutical composition for preventing and/or treating a caspase-related disease in a subject in need thereof, comprising an effective amount of a compound according to any of Claims 1 to 12.

14. Use of a compound according to any of Claims 1 to 12 for the manufacture of a medication for preventing and/or treating of caspase-related diseases in a subject in need thereof.

15. Use according to Claim 14, in which the caspase-related disease is selected from the group consisting of apoptosis mediated diseases, IL-1 mediated diseases, inflammatory diseases, autoimmune diseases, autoinflammatory diseases, proliferative diseases, infectious diseases, degenerative diseases, retinal disorders, inflammatory peritonitis, osteoarthritis, pancreatitis, asthma, respiratory distress syndrome, rheumatoid arthritis, systemic lupus erythematous, scleroderma, Grave's disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, hepatitis, inflammatory bowel

disease, crohn's disease, psoriasis, dermatitis, Graft vs host disease, organ transplant rejection, osteoporosis, leukemias and related disorders, multiple myeloma-related diseases, metastatic melanomas, Kaposi's sarcoma, sepsis, septic shock, Alzheimer's disease, Parkinson's disease, Huntington's disease, cerebral ischemia, epilepsy, myocardial ischemia, acute and chronic heart disease, myocardial infarction, congestive heart failure, atherosclerosis, spinal muscular atrophy, amyotrophic lateral sclerosis, multiple sclerosis, HIV-related encephalitis, aging, neurological damage due to stroke, ulcerative colitis, traumatic brain injury, spinal cord injury, hepatitis-B, hepatitis-C, hepatitis-G, liver-related diseases, renal disease, and HIV infection.

16. Use of a compound according to any of Claims 1 to 12 for the manufacture of a medicament for treating excessive apoptosis affected by caspase activity in a cell or a tissue.

17. A compound according to any of Claims 1 to 12, in which the pharmaceutically acceptable salt is one that allows the compound to penetrate cells.