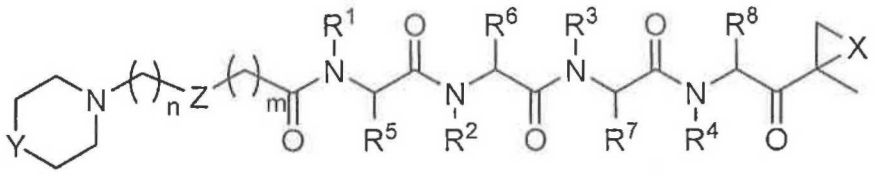
Claims:

1. Use of a compound having a structure of formula I or a pharmaceutically acceptable salt thereof,



I

wherein

X is O, NH, or N-alkyl;

Y is NH, N-alkyl, O, or $C(R^9)_2$;

Z is O or $C(R^9)_2$;

R^1, R^2, R^3, and R^4 are all hydrogen;

each R^5, R^6, R^7, R^8, and R^9 is independently selected from hydrogen, C_{1-6}alkyl, C_{1-6} hydroxyalkyl, C_{1-6}alkoxyalkyl, aryl, and C_{1-6}aralkyl, each of which is optionally substituted with a group selected from alkyl, amide, amine, carboxylic acid or a pharmaceutically acceptable salt thereof, carboxyl ester, thiol, and thioether;

m is an integer from 0 to 2; and

n is an integer from 0 to 2, preferably 0 or 1,

in the manufacture of a medicament for treating inflammation, neurodegenerative disease, muscle-wasting disease, cancer, chronic infectious disease, hyperproliferative condition, muscle disuse, immune-related condition, or parasitic infection; inhibiting or reducing HIV infection; affecting the level of viral gene expression in a subject; or altering the variety of antigenic peptides produced by the proteasome in an organism.

2. The use of claim 1, wherein X is O.

3. The use of claim 2, wherein R^5, R^6, R^7, and R^8 are independently selected from C_{1-6}alkyl, C_{1-6}hydroxyalkyl, and C_{1-6}aralkyl; and R^9 is hydrogen.

4. The use of claim 3, wherein R^5 and R^7 are independently C_{1-6}aralkyl and R^6 and R^8 are independently C_{1-6}alkyl.

5. The use of claim 4, wherein R^1, R^2, R^3, and R^4 are all hydrogen.

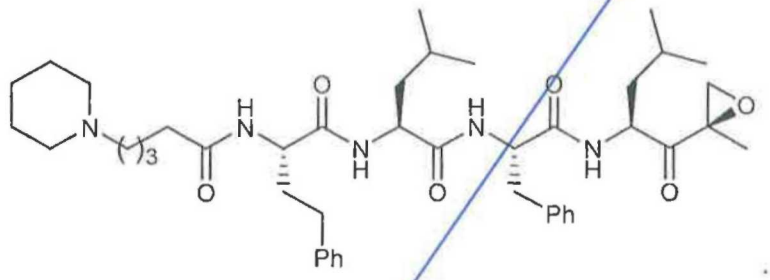
6. The use of claim 5, wherein Y is selected from N-alkyl, O, and CH_2.

7. The use of claim 6, wherein Z is CH_2, and m and n are both 0.

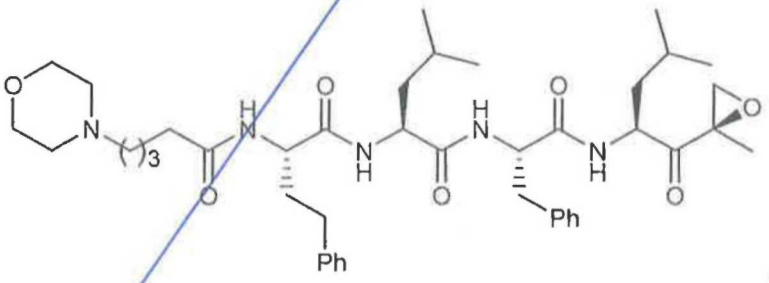
8. The use of claim 6, wherein Z is CH_2, m is 0, and n is 2.

9. The use of claim 6, wherein Z is O, m is 1, and n is 2.

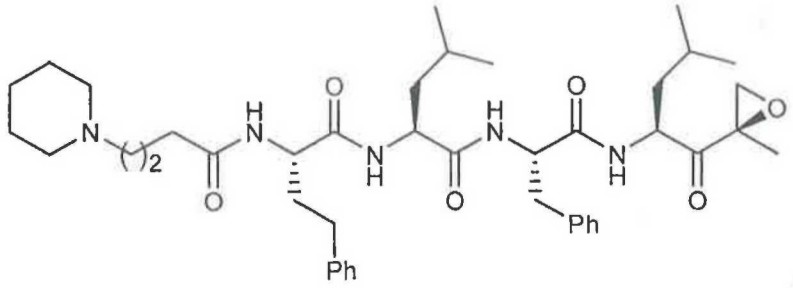
10. The use of claim 1, wherein the compound has the structure



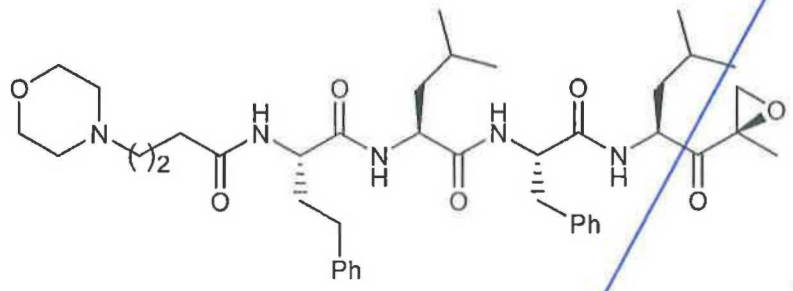
11. The use of claim 1, wherein the compound has the structure



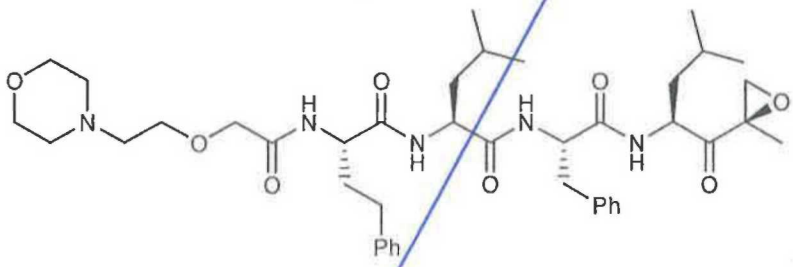
12. The use of claim 1, wherein the compound has the structure



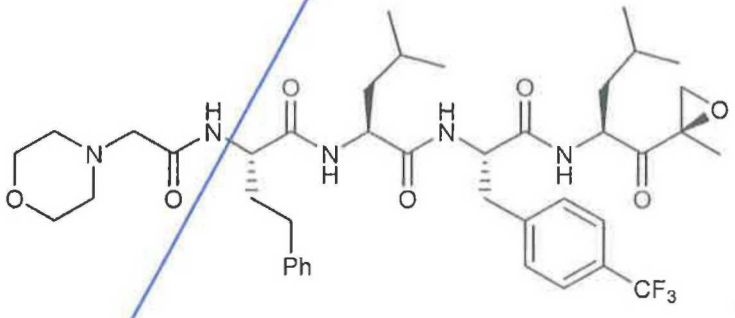
13. The use of claim 1, wherein the compound has the structure



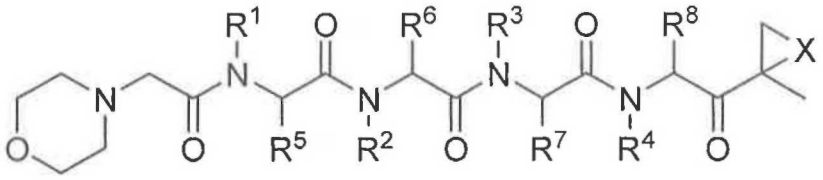
14. The use of claim 1, wherein the compound has the structure



15. The use of claim 1, wherein the compound has the structure



16. Use of a compound having a structure of formula III or a pharmaceutically acceptable salt thereof,



III

wherein

X is selected from O, NH, and N-alkyl;

R^1, R^2, R^3, and R^4 are all hydrogen; and

R^5, R^6, R^7, and R^8 are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6} hydroxyalkyl, C_{1-6}alkoxyalkyl, aryl, and C_{1-6}aralkyl, each of which is optionally substituted with a group selected from amide, amine, carboxylic acid or a pharmaceutically acceptable salt thereof, carboxyl ester, thiol, and thioether,

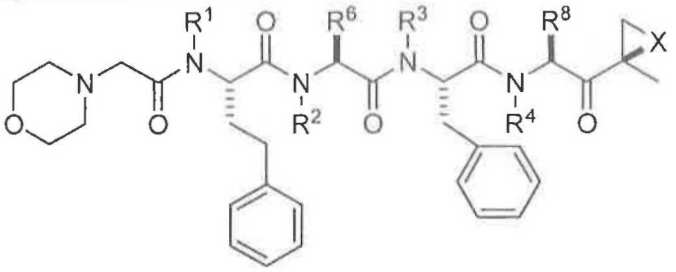
in the manufacture of a medicament for treating inflammation, neurodegenerative disease, muscle-wasting disease, cancer, chronic infectious disease, hyperproliferative condition, muscle disuse, immune-related condition, or parasitic infection; inhibiting or reducing HIV infection; affecting the level of viral gene expression in a subject; or altering the variety of antigenic peptides produced by the proteasome in an organism.

17. The use of claim 16, wherein X is O.

18. The use of claim 17, wherein R^5, R^6, R^7, and R^8 are independently selected from C_{1-6} alkyl, C_{1-6} hydroxyalkyl, and C_{1-6}aralkyl.

19. The use of claim 18, wherein R^5 and R^7 are independently C_{1-6}aralkyl and R^6 and R^8 are independently C_{1-6}alkyl.

20. Use of a compound having a structure of formula IV or a pharmaceutically acceptable salt thereof,



IV

wherein

X is O, NH, or N-alkyl;

R^1, R^2, R^3, and R^4 are all hydrogen; and

R^6 and R^8 are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}hydroxyalkyl, C_{1-6}alkoxyalkyl, aryl, and C_{1-6}aralkyl, each of which is optionally substituted with a group selected from amide, amine, carboxylic acid or a pharmaceutically acceptable salt thereof, carboxyl ester, thiol, and thioether,

in the manufacture of a medicament for treating inflammation, neurodegenerative disease, muscle-wasting disease, cancer, chronic infectious disease, hyperproliferative condition, muscle disuse, immune-related condition, or parasitic infection; inhibiting or reducing HIV infection; affecting the level of viral gene expression in a subject; or altering the variety of antigenic peptides produced by the proteasome in an organism.

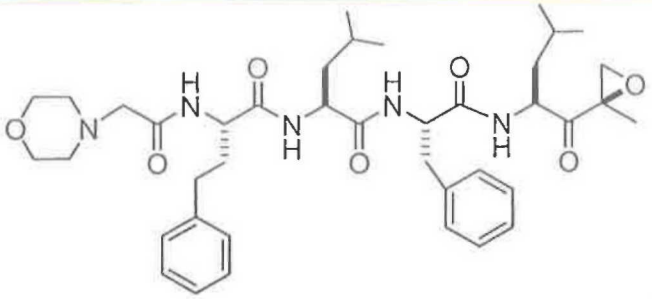
21. The use of claim 20, wherein X is O.

22. The use of claim 21, wherein R^6 and R^8 are independently selected from C_{1-6}alkyl, C_{1-6}hydroxyalkyl, and C_{1-6}aralkyl.

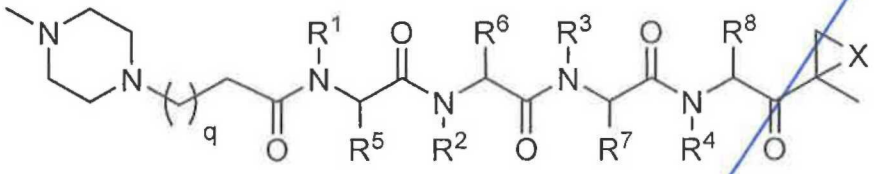
23. The use of claim 22, wherein R^6 and R^8 are independently C_{1-6}alkyl.

24. The use of claim 23, wherein R^6 and R^8 are both isobutyl.

25. The use of claim 20, wherein the compound has the structure



26. Use of a compound having a structure of formula V or a pharmaceutically acceptable salt thereof,



V

where X is O, NH, or N-alkyl;

R^1, R^2, R^3, and R^4 are all hydrogen;

R^5, R^6, R^7, and R^8 are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}hydroxyalkyl, C_{1-6}alkoxyalkyl, aryl, and C_{1-6}aralkyl, each of which is optionally substituted with a group selected from amide, amine, carboxylic acid or a pharmaceutically acceptable salt thereof, carboxyl ester, thiol, and thioether; and

q is an integer from 0 to 3,

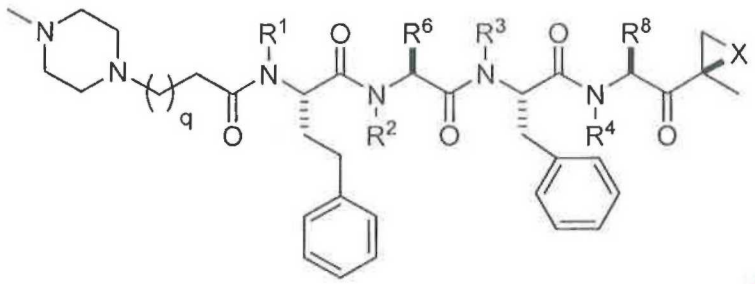
in the manufacture of a medicament for treating inflammation, neurodegenerative disease, muscle-wasting disease, cancer, chronic infectious disease, hyperproliferative condition, muscle disuse, immune-related condition, or parasitic infection; inhibiting or reducing HIV infection; affecting the level of viral gene expression in a subject; or altering the variety of antigenic peptides produced by the proteasome in an organism.

27. The use of claim 26, wherein X is O.

28. The use of claim 27, wherein R^5, R^6, R^7, and R^8 are independently selected from C_{1-6} alkyl, C_{1-6}hydroxyalkyl, and C_{1-6}aralkyl.

29. The use of claim 28, wherein R^5 and R^7 are independently C_{1-6}aralkyl and R^6 and R^8 are independently C_{1-6}alkyl.

30. Use of a compound having a structure of formula VI or a pharmaceutically acceptable salt thereof,



VI

wherein

X is O, NH, or N-alkyl;

R^1, R^2, R^3, and R^4 are all hydrogen;

R^6 and R^8 are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}hydroxyalkyl, C_{1-6}alkoxyalkyl, aryl, and C_{1-6}aralkyl, each of which is optionally substituted with a group selected from amide, amine, carboxylic acid or a pharmaceutically acceptable salt thereof, carboxyl ester, thiol, and thioether; and

q is an integer from 0 to 3,

in the manufacture of a medicament for treating inflammation, neurodegenerative disease, muscle-wasting disease, cancer, chronic infectious disease, hyperproliferative condition, muscle disuse, immune-related condition, or parasitic infection; inhibiting or reducing HIV infection; affecting the level of viral gene expression in a subject; or altering the variety of antigenic peptides produced by the proteasome in an organism.

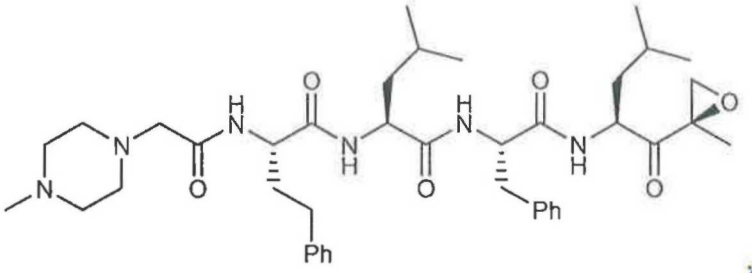
31. The use of claim 30, wherein X is O.

32. The use of claim 31, wherein R^6 and R^8 are independently selected from C_{1-6}alkyl, C_{1-6}hydroxyalkyl, and C_{1-6}aralkyl.

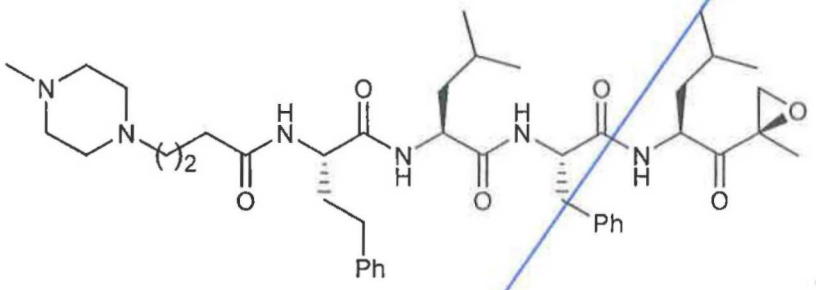
33. The use of claim 32, wherein R^6 and R^8 are independently C_{1-6}alkyl.

34. The use of claim 33, wherein R^6 and R^8 are both isobutyl.

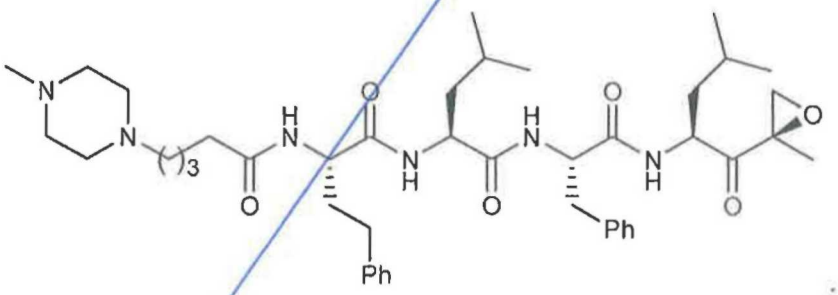
35. The use of claim 30, wherein the compound has the structure



36. The use of claim 30, wherein the compound has the structure

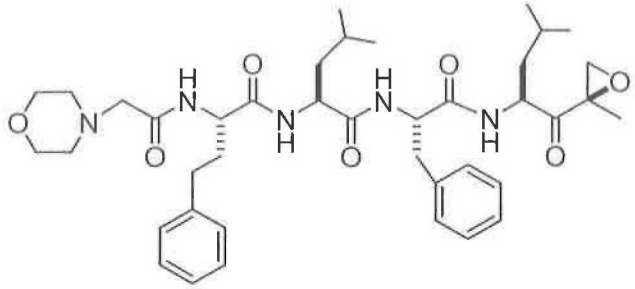


37. The use of claim 30, wherein the compound has the structure



Claims:

1. Use of a compound having a structure:



or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for (a) the treatment of inflammation, neurodegenerative disease, muscle-wasting disease, cancer, chronic infectious disease, hyperproliferative condition, muscle disuse, immune-related condition, or parasitic infection in a subject, (b) inhibiting or reducing HIV infection or affecting the level of viral gene expression in a subject, or (c) altering the variety of antigenic peptides produced by the proteasome in an organism.

2. The use of claim 1, wherein the subject suffers from cancer.

3. The use of claim 1, wherein the subject suffers from a neurodegenerative disease.

4. The use of claim 1, wherein the subject suffers from inflammation.

5. The use of claim 1, wherein the subject suffers from a muscle-wasting disease or muscle disuse.

6. The use of claim 1, wherein the subject suffers from a chronic infectious disease.

7. The use of claim 1, wherein the subject suffers from a hyperproliferative condition.

8. The use of claim 1, wherein the subject suffers from an immune-related condition.

9. The use of claim 1, wherein the subject suffers from a parasitic infection.

COMPOUNDS FOR PROTEASOME ENZYME INHIBITION

ABSTRACT

Peptide-based compounds including heteroatom-containing, three-membered rings efficiently and selectively inhibit specific activities of N-terminal nucleophile (Ntn) hydrolases. The activities of those Ntn having multiple activities can be differentially inhibited by the compounds described. For example, the chymotrypsin-like activity of the 20S proteasome may be selectively inhibited with the inventive compounds. The peptide-based compounds include an epoxide or aziridine, and functionalization at the N-terminus. Among other therapeutic utilities, the peptide-based compounds are expected to display anti-inflammatory properties and inhibition of cell proliferation.