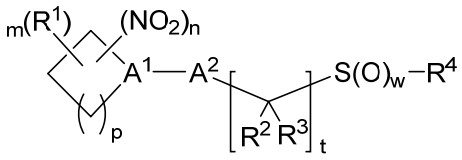
[0005] Accordingly, there is a need for new treatment regimes to treat these and other cancers. The present invention fulfills this need and provides other related advantages.

SUMMARY

[0006] The present disclosure provides sulfoxyalkyl organonitro and related compounds, compositions containing such compounds, and methods for using such compounds and compositions to treat medical disorders, such as a neurodegenerative disorder, autoimmune disease, infection, or cancer in a patient. Various aspects and embodiments of the present disclosure are described in further detail below.

[0006a] In one aspect of the present disclosure, there is provided a compound of Formula I or II, wherein Formula I is represented by:



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

A^1 is N or -C(R^5)-;

A^2 is -C(O)- or -($C(R^6)_2$)$_x$C(O)($C(R^6)_2$)$_x$-;

R^1 is C_1-C_5alkyl;

R^2 and R^3 each represent independently for each occurrence hydrogen or C_1-C_5alkyl; or R^2 and R^3 are taken together with the carbon atom to which they are attached to form a carbocyclic ring;

R^4 is C_1-C_5alkyl substituted with one X^1 group and one X^2 group; wherein X^1 is -N(R^7)(R^8), -N(R^7)C(O)$_k$-C_1-C_5alkyl, -N(R^7)C(O)$_k$-C_3-C_7cycloalkyl, -N(R^7)C(O)$_k$-aryl, -N(R^7)C(O)$_k$-aralkyl, or -N(R^7)C(O)-(C_1-C_5alkylene)-C(H)[N(R^7)(R^8)]-CO_2R^9; and X^2 is -CO_2R^{10} or -C(O)N(R^7)-(C_1-C_5alkylene)-CO_2R^{10};

R^5 is hydrogen or C_1-C_5alkyl;

R^6 represents independently for each occurrence C_1-C_6alkyl, C_1-C_5haloalkyl, aryl, or aralkyl;

R^7 and R^8 each represent independently for each occurrence hydrogen or C_1-C_5alkyl; or R^7 and R^8 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered heterocyclic ring;

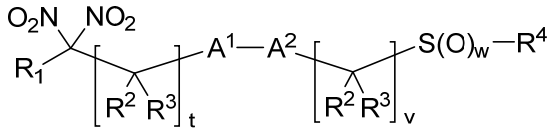
R^9 and R^{10} each represent independently hydrogen, C_1-C_5alkyl, C_3-C_7cycloalkyl, aryl, or aralkyl;

k and w are independently 1 or 2;

n, p, and t are independently 1, 2, or 3; and

m and x each represent independently for each occurrence 0, 1, 2, 3, or 4;

Formula II is represented by:



(II)

or a pharmaceutically acceptable salt or solvate thereof: wherein:

A^1 is -$N(R^5)$- or -$C(R^2)(R^3)$-;

A^2 is -C(O)- or –$(C(R^6)_2)_xC(O)(C(R^6)_2)_x$-;

R^1 is C_1-C_5alkyl or C_3-C_7cycloalkyl;

R^2 and R^3 each represent independently for each occurrence hydrogen or C_1-C_5alkyl; or R^2 and R^3 are taken together with the carbon atom to which they are attached to form a carbocyclic ring;

R^4 is C_1-C_5alkyl substituted with one X^1 group and one X^2 group; wherein X^1 is -$N(R^7)(R^8)$, -$N(R^7)C(O)_k$-C_1-C_5alkyl, -$N(R^7)C(O)_k$-C_3-C_7cycloalkyl, -$N(R^7)C(O)_k$-aryl, -$N(R^7)C(O)_k$-aralkyl, or -$N(R^7)$C(O)-(C_1-C_5alkylene)-C(H)[$N(R^7)(R^8)$]-CO_2R^9; and X^2 is -CO_2R^{10} or -C(O)$N(R^7)$-(C_1-C_5alkylene)-CO_2R^{10};

R^5 is hydrogen or C_1-C_5alkyl;

R^6 represents independently for each occurrence C_1-C_5alkyl, C_1-C_5haloalkyl, aryl, or aralkyl;

R^7 and R^8 each represent independently for each occurrence hydrogen or C_1-C_5alkyl; or R^7 and R^8 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered heterocyclic ring;

R^9 and R^{10} each represent independently hydrogen, C_1-C_5alkyl, C_3-C_7cycloalkyl, aryl, or aralkyl;

k and w are independently 1 or 2;

t and v are independently 1, 2, or 3; and

x represents independently for each occurrence 0, 1, 2, 3, or 4.

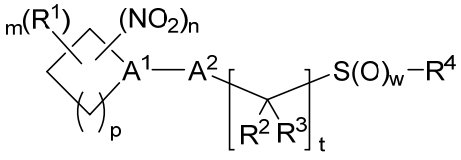
[0006b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable carrier.

[0006c] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating cancer in a patient.

[0006d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating a disorder selected from the group consisting of a neurodegenerative disorder, autoimmune disease, an infection, a storage disease, and a metabolic injury disease.

[0006e] In a further aspect of the present disclosure, there is provided a compound disclosed herein for use in treating cancer, or a disorder selected from the group consisting of a neurodegenerative disorder, autoimmune disease, an infection, a storage disease, and a metabolic injury disease.

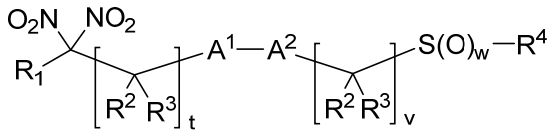
[0007] The present disclosure also provides a family of sulfoxyalkyl organonitro compounds embraced by Formula I:



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein the variables are as defined in the detailed description. In certain embodiments, the compounds are provided in the form of an isolated compound of Formula I.

[0008] The present disclosure also provides a family of sulfoxyalkyl organonitro compounds embraced by Formula II:



(II)

or a pharmaceutically acceptable salt or solvate thereof, wherein the variables are as defined in the detailed description. In certain embodiments, the compounds are provided in the form of an isolated compound of Formula II.

[0009] The present disclosure further provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a sulfoxyalkyl organonitro or related compound described herein, such as a compound of Formula I or II.

[0010] The present disclosure also provides a method of treating cancer in a patient. The method comprises administering to a patient in need thereof a therapeutically effective amount of a sulfoxyalkyl organonitro or related compound described herein, such as a compound of Formula I or II, to treat the cancer.

[0011] The present disclosure further provides a method of treating a disorder selected from the group consisting of a neurodegenerative disorder, autoimmune disease, an infection, a storage disease, and a metabolic injury disease. The method comprises administering to a patient in need thereof a therapeutically effective amount of a sulfoxyalkyl organonitro or related compound described herein, such as a compound of Formula I or II, to treat the disorder.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The invention provides sulfoxyalkyl organonitro and related compounds, compositions containing such compounds, and methods for using such compounds and compositions to treat medical disorders, such as a neurodegenerative disorder, autoimmune disease, infection, or cancer in a patient. The practice of the present invention employs, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, cell biology, and biochemistry. Such techniques are explained in the literature, such as in "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992); "Current protocols in molecular biology" (F.M. Ausubel *et al.*, eds., 1987, and periodic updates); and "Current protocols in immunology" (J.E. Coligan *et al.*, eds., 1991), each of which is herein incorporated by reference in its entirety. Various aspects of the invention are set forth below in sections; however, aspects of the invention described in one particular section are not to be limited to any particular section.

I. DEFINITIONS

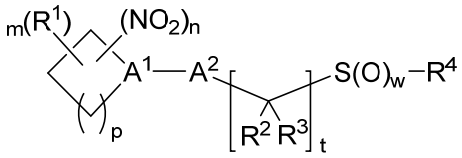
[0013] To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

[0014] The terms "a" and "an" as used herein mean "one or more" and include the plural unless the context is inappropriate.

[0015] The term "alkyl" as used herein refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-12, 1-10, or 1-6 carbon atoms, referred to herein as C_1-C_{12}alkyl, C_1-C_{10}alkyl, and C_1-C_6alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-

Claims:

1. A compound of Formula I or II, wherein Formula I is represented by:



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

A^1 is N or -C(R^5)-;

A^2 is -C(O)- or -($C(R^6)_2)_xC(O)(C(R^6)_2)_x$-;

R^1 is C_1-C_5alkyl;

R^2 and R^3 each represent independently for each occurrence hydrogen or C_1-C_5alkyl; or R^2 and R^3 are taken together with the carbon atom to which they are attached to form a carbocyclic ring;

R^4 is C_1-C_5alkyl substituted with one X^1 group and one X^2 group; wherein X^1 is -N(R^7)(R^8), -N(R^7)C(O)$_k$-C_1-C_5alkyl, -N(R^7)C(O)$_k$-C_3-C_7cycloalkyl, -N(R^7)C(O)$_k$-aryl, -N(R^7)C(O)$_k$-aralkyl, or -N(R^7)C(O)-(C_1-C_5alkylene)-C(H)[N(R^7)(R^8)]-CO_2R^9; and X^2 is -CO_2R^{10} or -C(O)N(R^7)-(C_1-C_5alkylene)-CO_2R^{10};

R^5 is hydrogen or C_1-C_5alkyl;

R^6 represents independently for each occurrence C_1-C_6alkyl, C_1-C_5haloalkyl, aryl, or aralkyl;

R^7 and R^8 each represent independently for each occurrence hydrogen or C_1-C_5alkyl; or R^7 and R^8 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered heterocyclic ring;

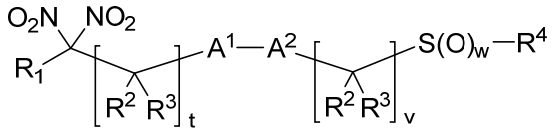
R^9 and R^{10} each represent independently hydrogen, C_1-C_5alkyl, C_3-C_7cycloalkyl, aryl, or aralkyl;

k and w are independently 1 or 2;

n, p, and t are independently 1, 2, or 3; and

m and x each represent independently for each occurrence 0, 1, 2, 3, or 4;

Formula II is represented by:



(II)

or a pharmaceutically acceptable salt or solvate thereof: wherein:

A^1 is -$N(R^5)$- or -$C(R^2)(R^3)$-;

A^2 is -C(O)- or –$(C(R^6)_2)_xC(O)(C(R^6)_2)_x$-;

R^1 is C_1-C_5alkyl or C_3-C_7cycloalkyl;

R^2 and R^3 each represent independently for each occurrence hydrogen or C_1-C_5alkyl; or R^2 and R^3 are taken together with the carbon atom to which they are attached to form a carbocyclic ring;

R^4 is C_1-C_5alkyl substituted with one X^1 group and one X^2 group; wherein X^1 is -$N(R^7)(R^8)$, -$N(R^7)C(O)_k$-C_1-C_5alkyl, -$N(R^7)C(O)_k$-C_3-C_7cycloalkyl, -$N(R^7)C(O)_k$-aryl, -$N(R^7)C(O)_k$-aralkyl, or -$N(R^7)$C(O)-(C_1-C_5alkylene)-C(H)[$N(R^7)(R^8)$]-CO_2R^9; and X^2 is -CO_2R^{10} or -C(O)$N(R^7)$-(C_1-C_5alkylene)-CO_2R^{10};

R^5 is hydrogen or C_1-C_5alkyl;

R^6 represents independently for each occurrence C_1-C_5alkyl, C_1-C_5haloalkyl, aryl, or aralkyl;

R^7 and R^8 each represent independently for each occurrence hydrogen or C_1-C_5alkyl; or R^7 and R^8 are taken together with the nitrogen atom to which they are attached to form a 3-7 membered heterocyclic ring;

R^9 and R^{10} each represent independently hydrogen, C_1-C_5alkyl, C_3-C_7cycloalkyl, aryl, or aralkyl;

k and w are independently 1 or 2;

t and v are independently 1, 2, or 3; and

x represents independently for each occurrence 0, 1, 2, 3, or 4.

2. The compound of claim 1, wherein the organonitro compound is a compound of Formula I.

3. The compound of claim 2, wherein A^1 is N.

4. The compound of claim 2 or 3, wherein A^2 is -C(O)-.

5. The compound of any one of claims 2-4, wherein R^2 and R^3 are hydrogen.

6. The compound of any one of claims 2-5, wherein m is 0.

7. The compound of any one of claims 2-6, wherein n is 2.

8. The compound of any one of claims 2-7, wherein t is 1.

9. The compound of any one of claims 2-8, wherein p is 1.

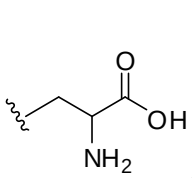
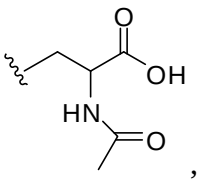
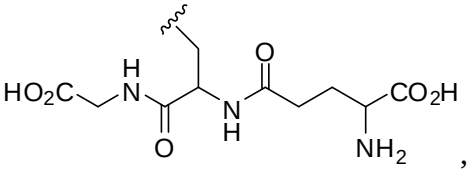
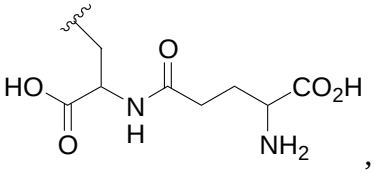
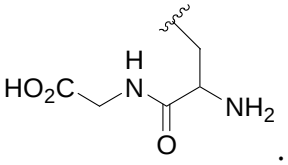
10. The compound of any one of claims 2-9, wherein R^4 is $-CH_2C(H)(X^1)X^2$.

11. The compound of any one of claims 2-10, wherein k is 1.

12. The compound of any one of claims 2-10, wherein k is 2.

13. The compound of any one of claims 2-10, wherein X^1 is $-N(R^7)(R^8)$, $-N(R^7)C(O)-C_1-C_5$alkyl, or $-N(R^7)C(O)-(C_1-C_5$alkylene$)-C(H)[N(R^7)(R^8)]CO_2R^9$.

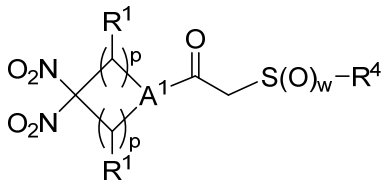
14. The compound of any one of claims 2-10, wherein X^1 is $-NH_2$, $-N(H)C(O)CH_3$, or $-N(H)C(O)CH_2CH_2C(H)(NH_2)-CO_2H$; and X^2 is $-CO_2H$, $-CO_2Me$, or $-C(O)N(H)CH_2CO_2H$.

15. The compound of any one of claims 2-9, wherein R^4 is , , , , or .

16. The compound of any one of claims 1-15, wherein w is 1.

17. The compound of any one of claims 1-15, wherein w is 2.

18. The compound of claim 1, wherein the compound is a compound of Formula I-A:



(I-A)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

A^1 is N or C(H);

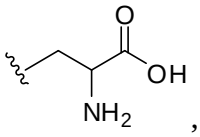
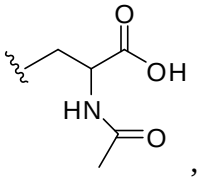
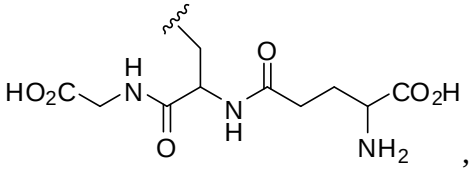
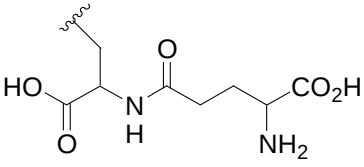
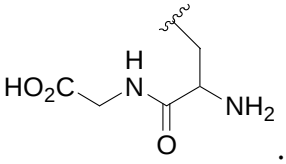
R^1 represents independently for each occurrence hydrogen or methyl;

R^4 is C_1-C_5alkyl substituted with one X^1 group and one X^2 group; wherein X^1 is $-NH_2$, $-N(H)C(O)-C_1-C_5$alkyl, or $-N(H)C(O)-(C_1-C_5$alkylene$)-C(H)(NH_2)-CO_2H$; and X^2 is $-CO_2H$, $-CO_2-C_1-C_5$alkyl, or $-C(O)N(H)CH_2CO_2H$;

p represents independently for each occurrence 1 or 2; and

w is 1 or 2.

19. The compound of claim 18, wherein A^1 is N.

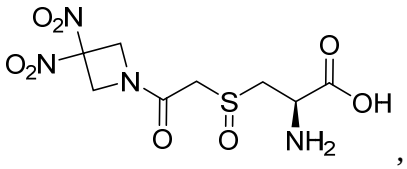
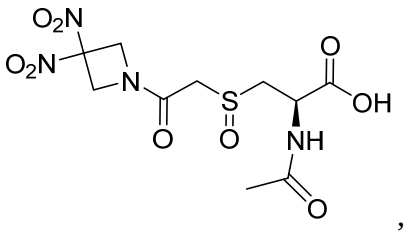
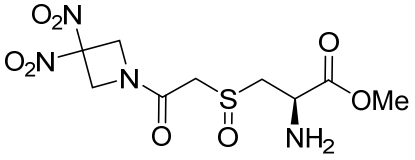
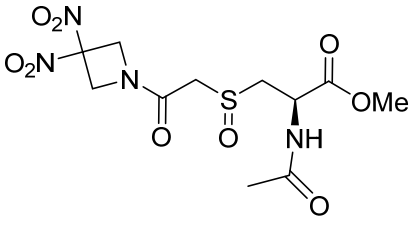
20. The compound of claim 18 or 19, wherein R^4 is , , , , or .

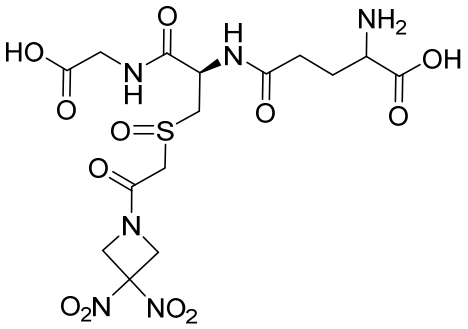
21. The compound of any one of claims 18-20, wherein p is 1.

22. The compound of any one of claims 18-20, wherein w is 1.

23. The compound of any one of claims 18-20, wherein w is 2.

24. The compound of claim 1, wherein the compound is one of the following:

, , , ,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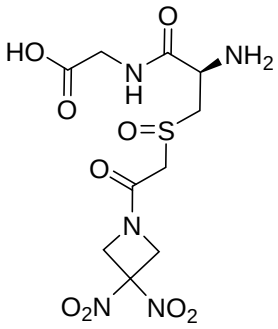
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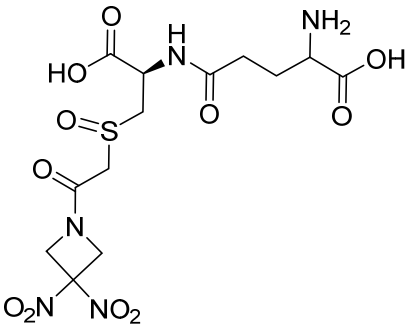
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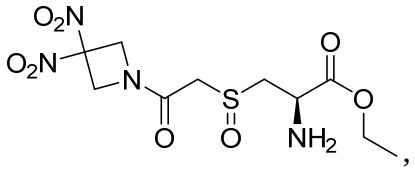
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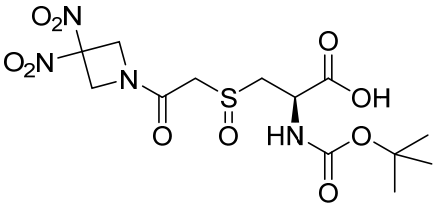
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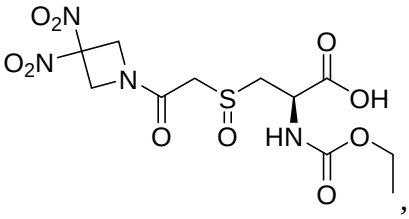
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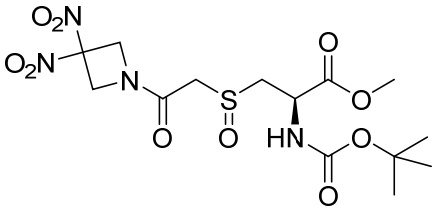
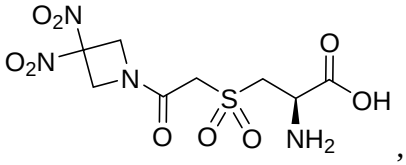

, or a pharmaceutically acceptable salt thereof.

25. The compound of claim 1, wherein the compound is one of the following: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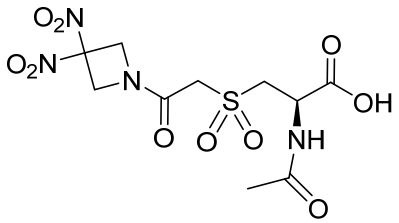
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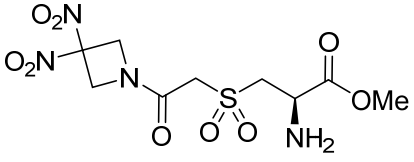
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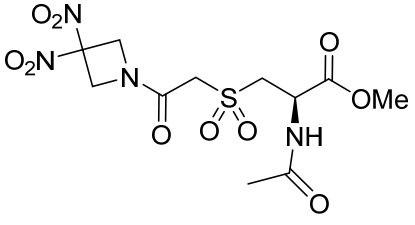
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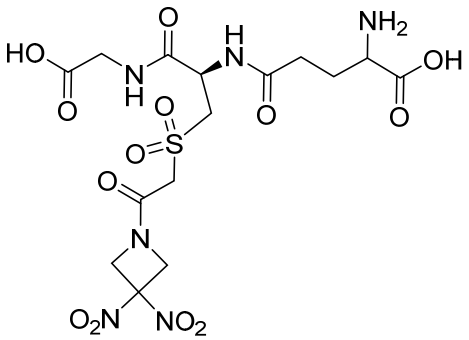
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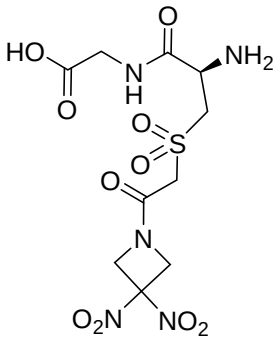
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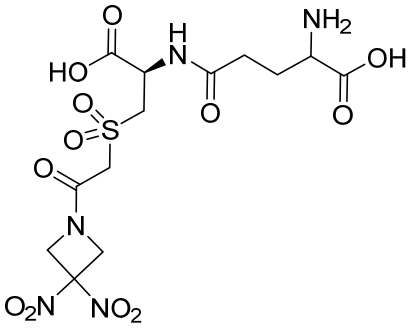
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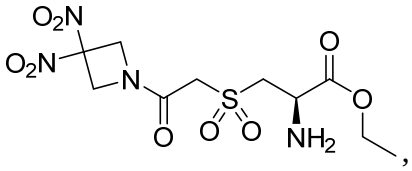
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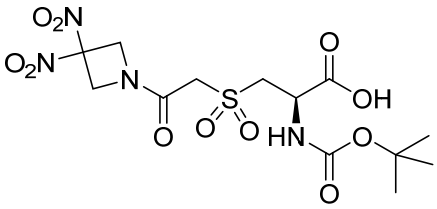
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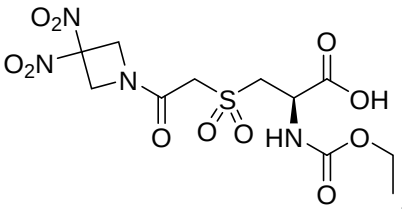
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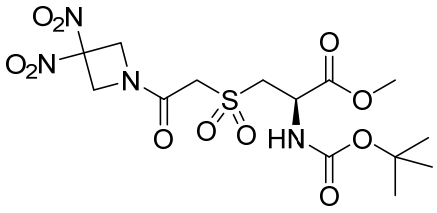

, or a pharmaceutically acceptable salt thereof.

26. The compound of claim 1, wherein the compound is a compound of Formula II.

27. The compound of claim 26, wherein A^1 is N.

28. The compound of claim 26 or 27, wherein A^2 is -C(O)-.

29. The compound of any one of claims 26-28, wherein R^1 is methyl.

30. The compound of any one of claims 26-29, wherein t and v are independently 1 or 2.

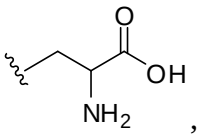
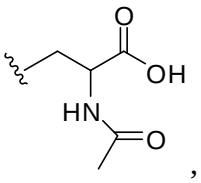
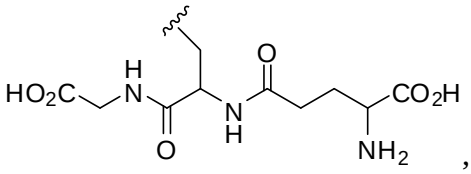
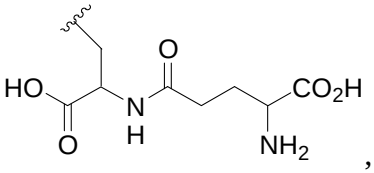
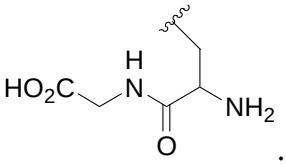
31. The compound of any one of claims 26-30, wherein R^4 is $-CH_2C(H)(X^1)X^2$.

32. The compound of any one of claims 26-31, wherein k is 1.

33. The compound of any one of claims 26-31, wherein k is 2.

34. The compound of any one of claims 26-31, wherein X^1 is $-N(R^7)(R^8)$, $-N(R^7)C(O)-C_1-C_5$alkyl, or $-N(R^7)C(O)-(C_1-C_5$alkylene$)-C(H)[N(R^7)(R^8)]CO_2R^9$.

35. The compound of any one of claims 26-31, wherein X^1 is $-NH_2$, $-N(H)C(O)CH_2$, or $-N(H)C(O)CH_2CH_2C(H)(NH_2)-CO_2H$; and X^2 is $-CO_2H$, $-CO_2Me$, or $-C(O)N(H)CH_2CO_2H$.

36. The compound of any one of claims 26-31, wherein R^4 is , , , , or .

37. The compound of any one of claims 26-36, wherein w is 1.

38. The compound of any one of claims 26-36, wherein w is 2.

39. A pharmaceutical composition comprising a compound of any one of claims 1-38 and a pharmaceutically acceptable carrier.

40. Use of a compound of any one of claims 1-38 in the manufacture of a medicament for treating cancer in a patient.

41. Use of a compound of any one of claims 1-38 in the manufacture of a medicament for treating a disorder selected from the group consisting of a neurodegenerative disorder, autoimmune disease, an infection, a storage disease, and a metabolic injury disease.

42. A compound of any one of claims 1-38 for use in treating cancer, or a disorder selected from the group consisting of a neurodegenerative disorder, autoimmune disease, an infection, a storage disease, and a metabolic injury disease.