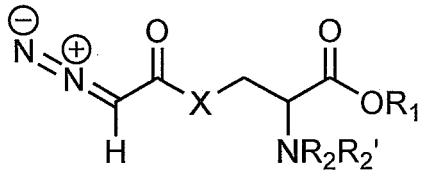
clinical studies. However, the occurrence of severe toxicity (e.g., dose limiting GI toxicities, such as oral mucosistis, gastric bleeding, nausea and vomiting, abdominal pain, leukopenia, thrombocytopenia, and the like) when administering such glutamine antagonists at therapeutic dose levels has hampered their clinical development.

Prior attempts to mitigate the severe toxicity associated with glutamine antagonists, such as DON, have been unsuccessful. For example, dividing daily dosing and administering of DON every four to six hours apparently doubled DON's toxicity potential (MgGill, et al., 1957). In another example, development of a treatment involving DON dosed with glutaminase to decrease plasma glutamine so that the DON dose could be reduced was halted after publication of a clinical trial.

SUMMARY

The presently disclosed subject matter provides prodrugs of glutamine antagonists, and pharmaceutically acceptable salts and esters thereof. Disclosed is a prodrug of a glutamine antagonist, or a pharmaceutically acceptable salt or ester thereof, the prodrug having a structure of formula (I):

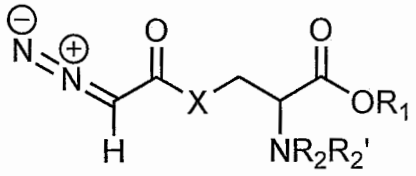


(I);

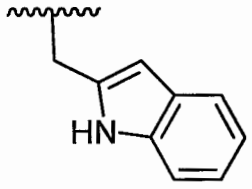
wherein: X is selected from the group consisting of a bond, –O–, and $–(CH_2)_n–$, wherein n is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; R_1 is selected from the group consisting of H and a first prodrug-forming moiety capable of forming a salt or an ester; and R_2 is H or a second prodrug-forming moiety capable of forming an amide linkage, a carbamate linkage, a phosphoramidate linkage or a phosphorodiamidate linkage with the nitrogen adjacent to R_2; R_2' is selected from the group consisting of H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, or R_2 and R_2' together form a ring structure comprising –C(=O)–G–C(=O)–, wherein G is selected from the group consisting of C_1-C_8 alkylene, C_1-C_8 heteroalkylene, C_5-C_8 cycloalkylene, C_6-C_{12} arylene, C_5-C_{14} heteroarylene, bivalent C_4-C_{10} heterocycle, each of which can be optionally substituted; or R_1 and R_2' together form a 4-to 6-membered heterocylic ring comprising the oxygen atom adjacent to R_1 and the nitrogen atom adjacent to R_2';

provided that the compound has at least one prodrug-forming moiety selected from the group consisting of the first and the second prodrug-forming moieties.

In one aspect, the present invention provides A compound having formula (I):



(I); or a pharmaceutically acceptable salt thereof, wherein: X is selected from the group consisting of a bond, –O–, and $–(CH_2)_n–$, wherein n is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; R_1 is selected from the group consisting of H, a C_{1-6} straight-chain alkyl, a substituted C_{1-6} straight-chain alkyl, a C_{1-6} branched alkyl, and a substituted C_{1-6} branched alkyl; R_2 is selected from the group consisting of amino acid, N-substituted amino acid, and $-C(=O)-O-(CR_3R_4)_m-O-C(=O)-R_{10}$; R_2' is selected from the group consisting of H, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl; each R_3 and R_4 are independently H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, aryl, substituted aryl, $-(CR_3R_4)_m-NR_5R_6$,



or ; m is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; R_5 and R_6 are independently H or alkyl; and R_{10} is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, monosaccharide, acylated monosaccharide, aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

Also disclosed is a pharmaceutical composition comprising a compound of formula (I), and a pharmaceutically acceptable carrier, diluent, or excipient.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

Also disclosed is a method for treating a disease or a condition, the method comprising administering to a subject in need of treatment thereof, a compound of formula (I), or a pharmaceutical composition thereof, in an amount effective for treating the disease

or condition. Also disclosed is the use of a compound of formula (I), or a pharmaceutical composition thereof, for treating a disease or condition. In some examples, the disease or condition is selected from the group consisting of an infection, cancer, an autoimmune disease, an inflammatory disease, and a neurodegenerative or neurological disease.

In yet another aspect, the present invention provides use of a compound described herein, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament to treat cancer in a subject.

In yet another aspect, the present invention provides a compound as described herein or a pharmaceutical composition as described herein for use in therapy.

Also disclosed is a compound of formula (I), or a pharmaceutically composition thereof, for use as a medicament.

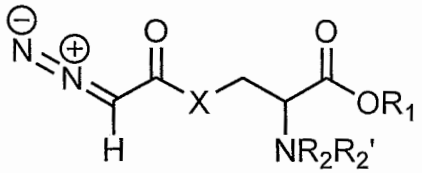
Also disclosed is a compound of formula (I), or a pharmaceutically composition thereof, for use in the treatment of a disease or condition, preferably the disease or condition is selected from the group consisting of an infection, cancer, an autoimmune disease, an inflammatory disease, and a neurodegenerative or neurological disease.

Also disclosed is a compound of formula (I) or a pharmaceutically composition thereof, for use in the treatment of the excess and/or aberrant glutamine activity.

Certain aspects of the presently disclosed subject matter having been stated hereinabove, which are addressed in whole or in part by the presently disclosed subject matter, other aspects will become evident as the description proceeds when taken in connection with the accompanying Examples and Figures as best described herein below.

THAT WHICH IS CLAIMED:

1. A compound having formula (I):



(I);

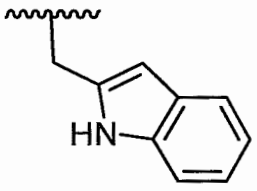
or a pharmaceutically acceptable salt thereof, wherein:

X is selected from the group consisting of a bond, –O–, and $-(CH_2)_n-$, wherein n is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8;

R_1 is selected from the group consisting of H, a C_{1-6} straight-chain alkyl, a substituted C_{1-6} straight-chain alkyl, a C_{1-6} branched alkyl, and a substituted C_{1-6} branched alkyl;

R_2 is selected from the group consisting of amino acid, N-substituted amino acid, and $-C(=O)-O-(CR_3R_4)_m-O-C(=O)-R_{10}$;

R_2' is selected from the group consisting of H, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl;

each R_3 and R_4 are independently H, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, aryl, substituted aryl, $-(CR_3R_4)_m-NR_5R_6$, or ;

m is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8;

R_5 and R_6 are independently H or alkyl; and

R_{10} is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, monosaccharide, acylated monosaccharide, aryl, substituted aryl, heteroaryl, and substituted heteroaryl.

2. The compound of claim 1, wherein X is $-CH_2-$ or -O-.

3. The compound of claim 1, wherein R_1 is selected from the group consisting of methyl, ethyl, and isopropyl.

4. The compound of claim 1, wherein:

R_2 is selected from the group consisting -C(=O)-Y-$(CR_3R_4)_m$-NR_5R_6, and -C(=O)-O-$(CR_3R_4)_m$-O-C(=O)-R_{10},

Y is –O– or a bond;

m is an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, and 8;

each R_3 and R_4 is independently H, C_1-C_6 alkyl or substituted C_1-C_6 alkyl, aryl or substituted aryl and;

R_{10} is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl.

5. The compound of claim 4, wherein R_2 is -C(=O)-Y-$(CR_3R_4)_m$-NR_5R_6;

wherein:

Y is a bond;

m is 1; and

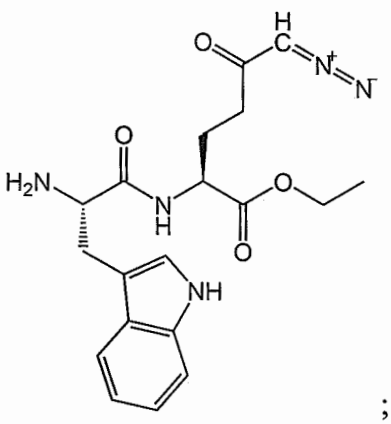
R_5 and R_6 are each H.

6. The compound of claim 1, wherein R_2 is an amino acid.

7. The compound of claim 1, wherein R_2 is a N-acyl amino acid.

8. The compound of claims 6 or 7, wherein the amino acid is tryptophan.

9. The compound of claim 1 selected from the group consisting of:



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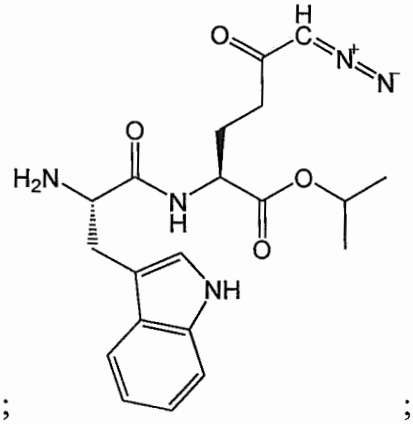

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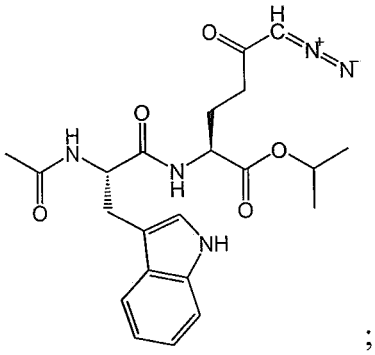
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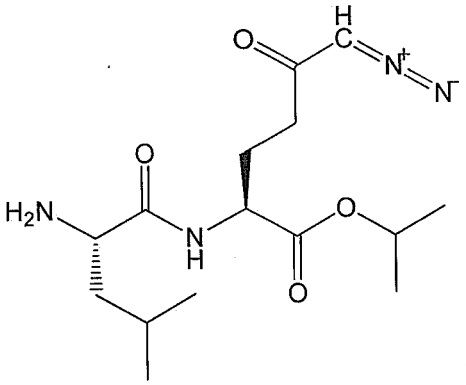
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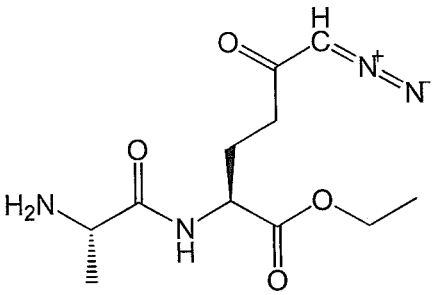
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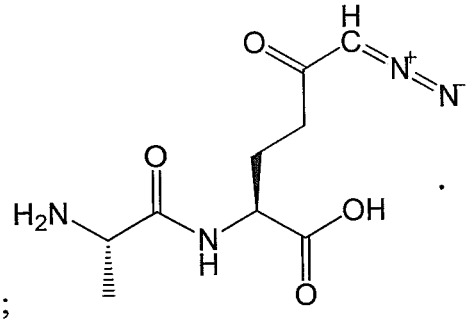
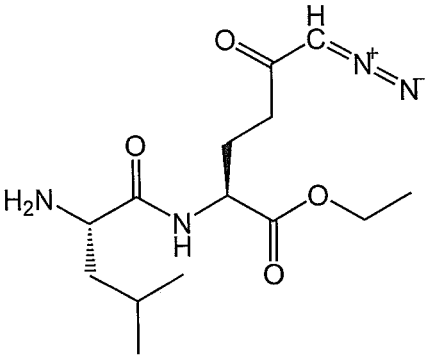

· Et_3N ;.

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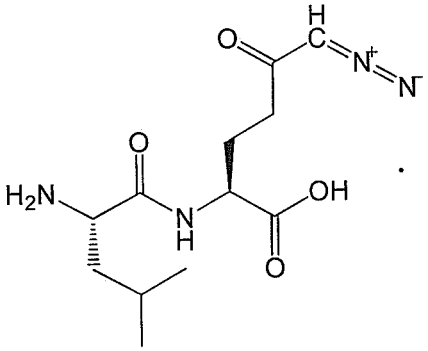
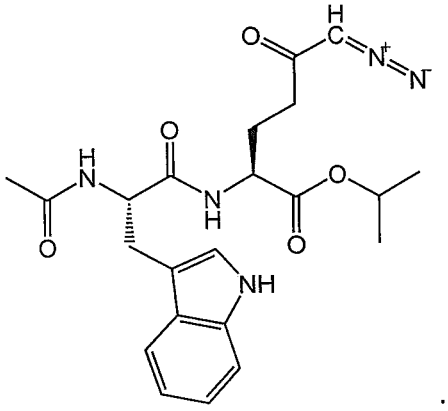

· Et_3N
; and .

10. The compound of claim 9 which is: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11. The compound of claim 4, wherein R_2 is $-C(=O)-O-(CR_3R_4)_m-O-C(=O)-R_{10}$; wherein:

(i) m is 1;

R_3 is H; and

R_4 is methyl, iPr, or aryl;

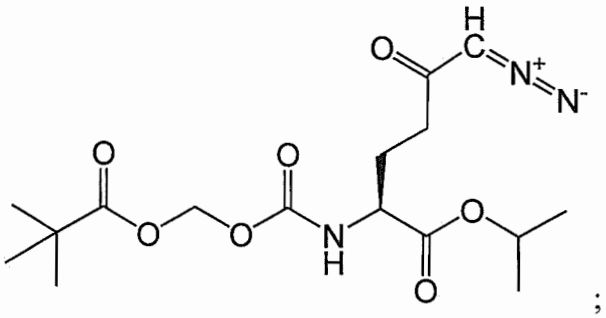
(ii) m is 1;

R_3 and R_4 are each H; or

(iii) m is 1;

R_3 and R_4 are each methyl.

12. The compound of claim 11 selected from the group consisting of:



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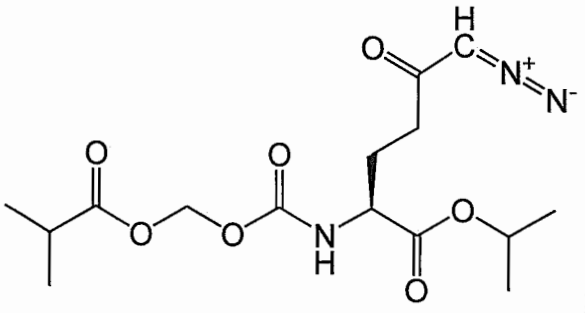

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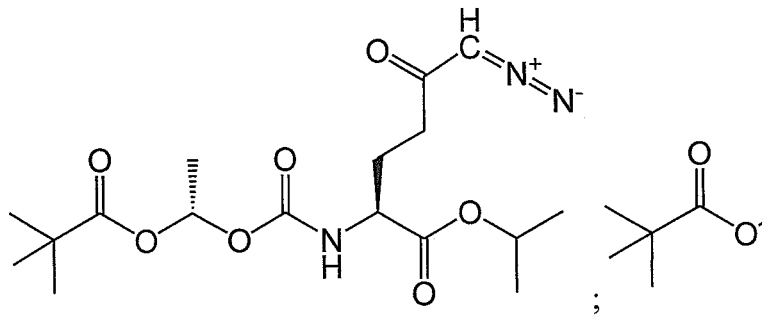
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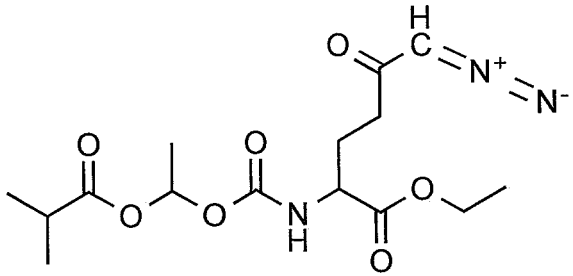
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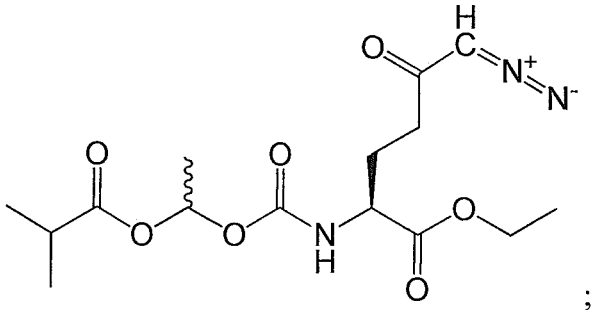
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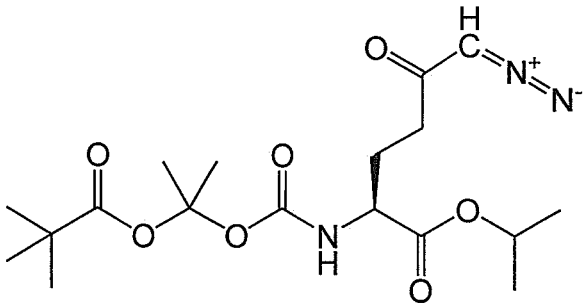
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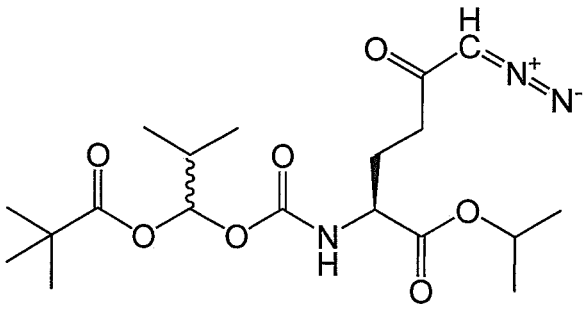
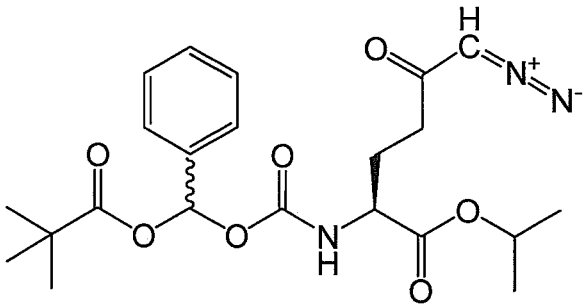

; and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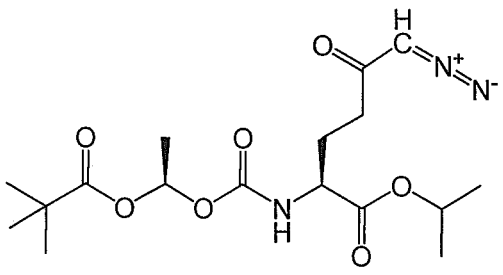
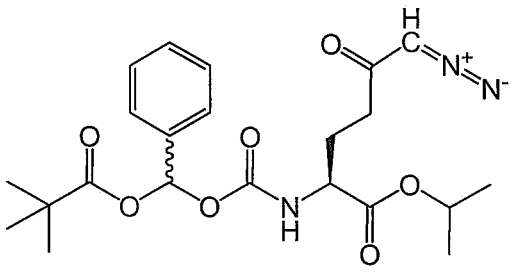
13. The compound of claim 12 selected from the group consisting of:


and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14. A pharmaceutical composition comprising a compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

15. Use of a compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament to treat cancer in a subject.

16. A compound of any one of claims 1-13 or a pharmaceutical composition of claim 14 for use in therapy.