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United States Patent
Zhao

(10) **Number:** **US 10,131,682 C1**(45) **Certificate Issued:** **Jan. 4, 2021**

(54) **HYDROPHILIC LINKERS AND THEIR USES
 FOR CONJUGATION OF DRUGS TO A CELL
 BINDING MOLECULES**

C07D 207/46 (2006.01)*C07D 401/12* (2006.01)*A61K 31/10* (2006.01)*A61K 31/454* (2006.01)*C07F 9/58* (2006.01)

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(52) **U.S. Cl.**

CPC *C07F 9/572* (2013.01); *A61K 31/10*
 (2013.01); *A61K 31/454* (2013.01); *A61K*
31/662 (2013.01); *A61K 47/6889* (2017.08);
C07D 207/46 (2013.01); *C07D 401/12*
 (2013.01); *C07F 9/58* (2013.01)

Reexamination Request:

No. 90/014,390, Oct. 16, 2019

(58) **Field of Classification Search**

None

See application file for complete search history.

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§ 371 (c)(1),

(2) Date: **Mar. 27, 2015**PCT Pub. No.: **WO2014/080251**PCT Pub. Date: **May 30, 2014**

(56)

References Cited

To view the complete listing of prior art documents cited during the proceeding for Reexamination Control Number 90/014,390, please refer to the USPTO's public Patent Application Information Retrieval (PAIR) system under the Display References tab.

Primary Examiner — Dwayne C. Jones(51) **Int. Cl.***C07F 9/572* (2006.01)*A61K 47/68* (2017.01)*A61K 31/662* (2006.01)

(57)

ABSTRACT

Cell binding agent-drug conjugates comprising hydrophilic linkers, and methods of using such linkers and conjugates are provided.

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EX PARTE

REEXAMINATION CERTIFICATE

THE PATENT IS HEREBY AMENDED AS
INDICATED BELOW.

Matter enclosed in heavy brackets [] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

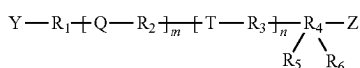
AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims 1, 3, 18 and 20 are determined to be patentable as amended.

Claims 2, 4-17, 19 and 21, dependent on an amended claim, are determined to be patentable.

New claims 22-34 are added and determined to be patentable.

1. A hydrophilic linker of formula (I)



wherein:

Y represents a functional group that enables reaction of the hydrophilic linker with a cell-binding agent;
Q and T are either $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

m and n are [integer] integers from 0 to 5, but not 0 at the same time; provided that when $m=1$, $n=0$, Q is not $-P(=O)(OM)-$; when $n=1$, $m=0$, T is not $-P(=O)(OM)-$; and when Q or T is $-S(O_2)-$, m and n are not 0[.];

Z represents a functional group that enables linkage of the hydrophilic linker to a cytotoxic drug via a disulfide, thioether, thioester, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof, *provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, R_2 is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof,*

or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4), *provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, R_2 is a straight or*

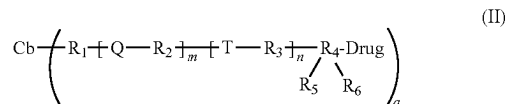
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branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, R_1 , R_3 or R_4 ;

R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt.

3. A cell-binding agent-drug conjugate of formula (II):



wherein:

Cb represents a cell-binding agent;

Drug represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

q is an integer from 1 to 20; Q and T are either $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

m and n are [integer] integers from 0 to 5, but not 0 at the same time; provided that when $m=1$, $n=0$, Q is not $-P(=O)(OM)-$; when $n=1$, $m=0$, T is not $-P(=O)(OM)-$; and when Q or T is $-S(O)-$, m and n are not 0[.];

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof, *provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, R_2 is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof,*

or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4), *provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, R_2 is a straight or branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, R_1 , R_3 or R_4 ;*
 R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy

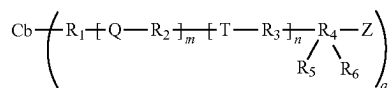
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unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;
M is H, or Na, or K, or $\text{N}^+\text{R}_1\text{R}_2\text{R}_3$ or a pharmaceutical salt,

provided that:

when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, and when (i) Q is $-\text{S}(\text{O}_2)-$, m is 1, and n is 0, or (ii) T is $-\text{S}(\text{O}_2)-$, n is 1 and m is 0, R_1 is not a chain of three atoms selected from the group consisting of C and S.

18. A compound of formula (III):



wherein:

Cb represents a cell-binding agent;

Q and T are either $-\text{P}(=\text{O})(\text{OM})-$, or $-\text{S}(\text{O}_2)-$, or $-\text{S}(\text{O})-$;

m and n are [integer] integers from 0 to 5, but not 0 at the same time; provided that when $m=1$, $n=0$, Q is not $-\text{P}(=\text{O})(\text{OM})-$; and when $n=1$, $m=0$, T is not $-\text{P}(=\text{O})(\text{OM})-$;

q is an integer from 1 to 20;

Z represents a functional group that enables linkage of the compound to a cytotoxic drug via a disulfide, thioether, thioester, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cyclo-heteroalkane, heteroaromatic, alkoxime or amide bond;

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, R_2 is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 1-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

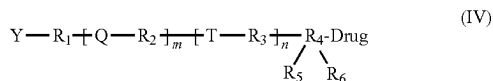
or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4), provided that when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, R_2 is a straight or branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, R_1 , R_3 or R_4 ;

R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

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M is H, or Na, or K, or $\text{N}^+\text{R}_1\text{R}_2\text{R}_3$ or a pharmaceutical salt.

20. A compound of formula (IV):



wherein:

Y represents a functional group that enables reaction of the compound with a cell-binding agent;

Q and T are either $-\text{P}(=\text{O})(\text{OM})-$, or $-\text{S}(\text{O}_2)-$, or $-\text{S}(\text{O})-$;

m and n are [integer] integers from 0 to 5, but not 0 at the same time; provided that when $m=1$, $n=0$, Q is not $-\text{P}(=\text{O})(\text{OM})-$; and when $n=1$, $m=0$, T is not $-\text{P}(=\text{O})(\text{OM})-$;

"Drug" represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, R_2 is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4), provided that when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, R_2 is a straight or branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, R_1 , R_3 or R_4 ;

R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

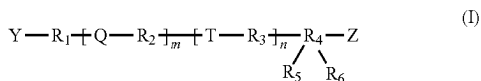
M is H, or Na, or K, or $\text{N}^+\text{R}_1\text{R}_2\text{R}_3$ or a pharmaceutical salt,

provided that:

when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, and when (i) Q is $-\text{S}(\text{O}_2)-$, m is 1, and n is 0, or (ii) T is $-\text{S}(\text{O}_2)-$, n is 1 and m is 0, Y is an N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl ester, pyridyldisulfide, nitro-

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hydridyl disulfide, maleimide, haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine.
 22. A hydrophilic linker of formula (I)



wherein:

Y represents a functional group that enables reaction of the hydrophilic linker with a cell-binding agent
 Q and T are either $-(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

m and n are integers from 0 to 5, but not 0 at the same time; provided that when $m=1$, $n=0$, Q is not $-P(=O)(OM)-$; when $n=1$, $m=0$, T is not $-P(=O)(OM)-$; and when Q or T is $-S(O_2)-$, m and n are not 0;

Z represents a functional group that enables linkage of the hydrophilic linker to a cytotoxic drug via a disulfide, thioether, thioester, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof.

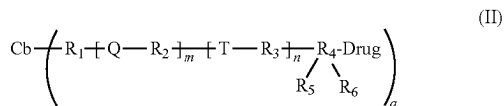
or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4),

R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt and

wherein the hydrophilic linker comprises at least one $-P(=O)(OM)-$.

23. A cell-binding agent-drug conjugate of formula (II):



wherein:

Cb represents a cell-binding agent;

Drug represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

q is an integer from 1 to 20; Q and T are either $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

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m and n are integers from 0 to 5, but not 0 at the same time; provided that when $m=1$, $n=0$, Q is not $-P(=O)(OM)-$; when $n=1$, $m=0$, T is not $-P(=O)(OM)-$; and when Q or T is $-S(O)-$, m and n are not 0;

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof.

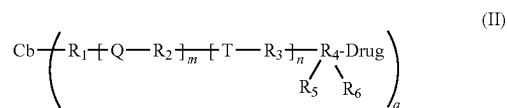
or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4),

R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt, and

wherein the conjugate comprises at least one $-P(=O)(OM)-$.

24. A cell-binding agent-drug conjugate of formula (II):



wherein:

Cb represents a cell-binding agent;

Drug represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

q is an integer from 1 to 20; Q and T are either $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

m and n are integers from 1 to 5;

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, R_2 is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof.

or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a

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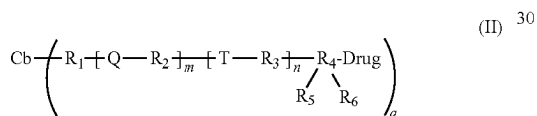
conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4), provided that when Q and T are each independently $-S(O)-$ or $-S(O)-$, R_2 is a straight or branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, R_1 , R_3 or R_4 , provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$,

R_5 and R_6 are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt.

25. The cell-binding agent-drug conjugate of claim 24, wherein when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$; and each of remaining R_1 , R_2 , R_3 and R_4 comprises an alkyl or $(OCH_2CH_2)_p$.

26. A cell-binding agent-drug conjugate of formula (II):



wherein:

Cb represents a cell-binding agent;

Drug represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

q is an integer from 1 to 20; Q and T are either $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

m and n are integers from 1 to 5;

R_1 , R_2 , R_3 , and R_4 are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, R_2 is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof,

or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4), provided that when Q and T are each independently $-S(O_2)-$ or $-(O)-$, R_2 is a straight or

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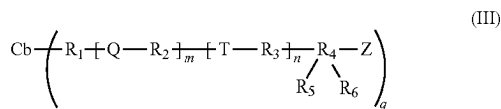
branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, R_1 , R_3 or R_4 ;

R_5 and R_6 are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt,

provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, m is 1 and n is 1, R_2 is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof, or R_2 is a branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, R_3 or R_4 .

27. A compound of formula (III):



wherein:

Cb represents a cell-binding agent

Q and T are either $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

m and n are integers from 0 to 5, but not 0 at the same time; provided that when $m=1$, $n=0$, Q is not $-P(=O)(OM)-$; and when $n=1$, $m=0$, T is not $-P(=O)(OM)-$;

q is an integer from 1 to 20;

Z represents a functional group that enables linkage of the compound to a cytotoxic drug via a disulfide, thioether, thioester, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

R_1 , R_2 , R_3 , and R_4 are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof,

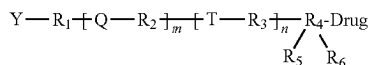
or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4), R_5 and R_6 are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or

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polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $\text{N}^+\text{R}_1\text{R}_2\text{R}_3$ or a pharmaceutical salt, and wherein the conjugate comprises at least one $-\text{P}(=\text{O})(\text{OM})-$.

28. A compound of formula (IV):



wherein:

Y represents a functional group that enables reaction of the compound with a cell-binding agent;

Q and T are either $-\text{P}(=\text{O})(\text{OM})-$, or $-\text{S}(\text{O}_2)-$, or $-\text{S}(\text{O})-$;

m and n are integers from 0 to 5, but not 0 at the same time; provided that when $m=1$, $n=0$, Q is not $-\text{P}(=\text{O})(\text{OM})-$; and when $n=1$, $m=0$, T is not $-\text{P}(=\text{O})(\text{OM})-$;

"Drug" represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

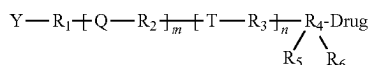
or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4),

R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $\text{N}^+\text{R}_1\text{R}_2\text{R}_3$ or a pharmaceutical salt, and

wherein the conjugate comprises at least one $-\text{P}(=\text{O})(\text{OM})-$.

29. A compound of formula (IV):



wherein:

Y represents a functional group that enables reaction of the compound with a cell-binding agent;

Q and T are either $-\text{P}(=\text{O})(\text{OM})-$, or $-\text{S}(\text{O}_2)-$, or $-\text{S}(\text{O})-$;

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m and n are integers from 0 to 5, but not 0 at the same time; provided that when $m=1$, $n=0$, Q is not $-\text{P}(=\text{O})(\text{OM})-$; and when $n=1$, $m=0$, T is not $-\text{P}(=\text{O})(\text{OM})-$;

"Drug" represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, R_2 is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof,

or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4), provided that when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, R_2 is a straight or branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, R_1 , R_3 or R_4 ;

R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

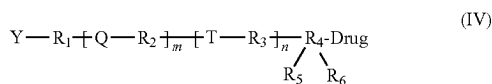
M is H, or Na, or K, or $\text{N}^+\text{R}_1\text{R}_2\text{R}_3$ or a pharmaceutical salt,

provided that:

when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, m is 1 and n is 1, R_2 is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof, or R_2 is a branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, R_3 or R_4 ; and

when (i) Q is $-\text{S}(\text{O}_2)-$, m is 1, and n is 0, or (ii) T is $-\text{S}(\text{O}_2)-$, n is 1 and m is 0, Y is an N -hydroxysuccinimide (NHS) ester, p -nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl ester, pyridyldisulfide, nitro-pyridyldisulfide, maleimide, haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine.

30. A compound of formula (IV):



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wherein:

Y represents a functional group that enables reaction of the compound with a cell-binding agent;

Q and *T* are either $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

m and *n* are integers from 1 to 5;

"Drug" represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkox-
ime or amide bond;

*R*₁, *R*₂, *R*₃, and *R*₄, are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein *p* is an integer from 1 to about 1000, or combination thereof, provided that when *Q* and *T* are each independently $-S(O_2)-$ or $-S(O)-$, *R*₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein *p* is an integer from 1 to about 1000, or combination thereof;

or *R*₁, *R*₂, *R*₃ and *R*₄ are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (*R*₁, *R*₂, *R*₃ and *R*₄), provided that when *Q* and *T* are each independently $-S(O_2)-$ or $-S(O)-$, *R*₂ is a straight or branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, *R*₁, *R*₃ or *R*₄;

*R*₅ and *R*₆, are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear,

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branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein *p* is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt,

provided that when *Q* and *T* are each independently $-S(O_2)-$ or $-S(O)-$, *m* is 1 and *n* is 1, *R*₂ is absent, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein *p* is an integer from 1 to about 1000, or combination thereof, or *R*₂ is a branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, *R*₃ or *R*₄.

31. The compound of claim 30, wherein when *Q* and *T* are each independently $-S(O_2)-$ or $-S(O)-$, at least one of *R*₁, *R*₂, *R*₃ and *R*₄ comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$.

32. The compound of claim 31, wherein when *Q* and *T* are each independently $-S(O_2)-$ or $-S(O)-$, at least one of *R*₁, *R*₂, *R*₃ and *R*₄ comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$; and each of remaining *R*₁, *R*₂, *R*₃ and *R*₄ comprises an alkyl or $(OCH_2CH_2)_p$.

33. The conjugate of claim 3, wherein when *Q* and *T* are each independently $-S(O_2)-$ or $-S(O)-$, at least one of *R*₁, *R*₂, *R*₃ and *R*₄ comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$; and each of remaining *R*₁, *R*₂, *R*₃ and *R*₄ comprises an alkyl or $(OCH_2CH_2)_p$.

34. The compound of claim 20, wherein when *Q* and *T* are each independently $-S(O_2)-$ or $-S(O)-$, at least one of *R*₁, *R*₂, *R*₃ and *R*₄ comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$; and each of remaining *R*₁, *R*₂, *R*₃ and *R*₄ comprises an alkyl or $(OCH_2CH_2)_p$.

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