[0005] The central role of STING in controlling anticancer immune responses was exemplified by observations that spontaneous and radiation-induced adaptive anticancer immunity was reduced in the absence of STING, illustrating the potential of STING-targeting for cancer immunotherapy.

[0006] Bioorthogonal conjugation or click reactions are selective and orthogonal (non-interacting with) functionalities found in biological systems, and have found use in various applications in the fields of chemistry, chemical biology, molecular diagnostics, and medicine, where they can be used to facilitate the selective manipulation of molecules, cells, particles and surfaces, and the tagging and tracking of biomolecules *in vitro* and *in vivo*. These reactions include the Staudinger ligation, the azide-cyclooctyne cycloaddition, and the inverse-electron-demand Diels-Alder reaction.

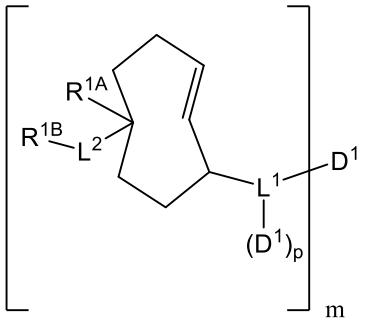
[0007] WO2017/044983 describes anti-tumor effects of a trans-cyclooctene conjugate of doxorubicin through release of doxorubicin at a tumor site by bioorthogonal reaction with a tetrazine-functionalized alginate implanted at the tumor site.

SUMMARY

[0008] The present disclosure provides trans-cyclooctene derivatives for delivering payload molecules in a subject using bioorthogonal chemistry. The disclosure also provides methods of producing the compositions, as well as methods of using the same.

[0008a] In another aspect, there is provided a use of a pharmaceutical combination in the manufacture of a medicament for the treatment of a tumor, the combination comprising:

(a) a compound of formula (II-A'), or a pharmaceutically acceptable salt, or composition thereof;



(II-A')

wherein

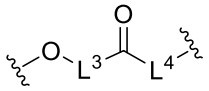
R^{1A} is $C_{1\text{-}4}$alkyl;

R^{1B} is OH, $–N(R^{1c})CHR^{1e}CO_2H$, or $–N(R^{1c})–C_{1\text{-}6}$alkylene$–CO_2H$;

R^{1c} is hydrogen;

$R^{1e}–$ is $C_{1\text{-}4}$alkylene$–CO_2H$;

D^1, at each occurrence, is independently an anticancer agent payload;

L^1 is ;

L^2 is –C(O)–;

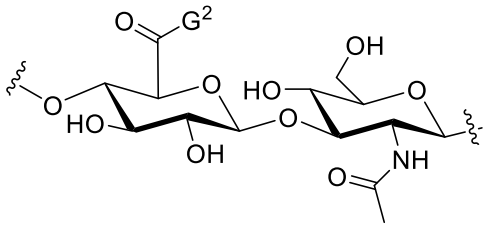
L^3 is a bond;

L^4 is a bond;

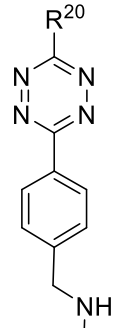
m is 1, 2, or 3; and

p is 0;

b) a therapeutic support composition that is a substituted hyaluronic acid comprising units of formula (II):



(II)



wherein G^2 is tetrazine-containing group ; and R^{20} is $C_{1\text{-}4}$alkyl and

(c) one or more immunomodulatory agents, wherein the immunomodulatory agent(s) are selected from the group consisting of a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist.

[0008b] In another aspect, there is provided a use of:

a) the compound of formula (II-A'), as defined above, or a pharmaceutically acceptable salt or composition thereof;

b) one or more immunomodulatory agents, wherein the immunomodulatory agent(s) are selected from the group consisting of a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist, or a pharmaceutically acceptable salt or composition thereof;

c) a substituted hyaluronic acid, as defined above; and

d) instructions for use;

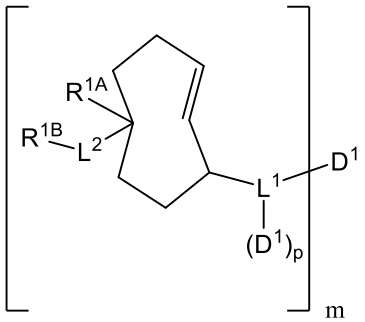
in the manufacture of a kit for the treatment of a tumor.

[0009] In one example, the disclosure provides compounds of formula (I), or a pharmaceutically acceptable salt thereof,

CLAIMS

1. Use of a pharmaceutical combination in the manufacture of a medicament for the treatment of a tumor, the combination comprising:

(a) a compound of formula (II-A'), or a pharmaceutically acceptable salt, or composition thereof;



(II-A')

wherein

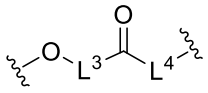
R^{1A} is $C_{1\text{-}4}$alkyl;

R^{1B} is OH, $–N(R^{1c})CHR^{1e}CO_2H$, or $–N(R^{1c})–C_{1\text{-}6}$alkylene$–CO_2H$;

R^{1c} is hydrogen;

$R^{1e}–$ is $C_{1\text{-}4}$alkylene$–CO_2H$;

D^1, at each occurrence, is independently an anticancer agent payload;

L^1 is ;

L^2 is –C(O)–;

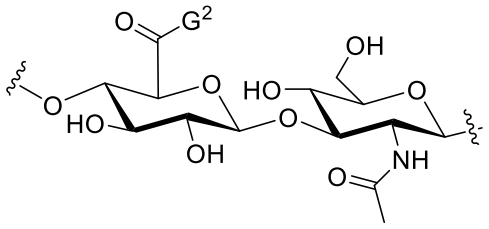
L^3 is a bond;

L^4 is a bond;

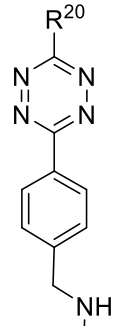
m is 1, 2, or 3; and

p is 0;

b) a therapeutic support composition that is a substituted hyaluronic acid comprising units of formula (II):



(II)



wherein G^2 is tetrazine-containing group ; and R^{20} is $C_{1\text{-}4}$alkyl and

(c) one or more immunomodulatory agents, wherein the immunomodulatory agent(s) are selected from the group consisting of a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist.

2. The use of claim 1, wherein the tumor is of a cancer selected from the group consisting of melanoma, renal cancer, prostate cancer, ovarian cancer, breast cancer, glioma, lung cancer, soft tissue carcinoma, soft tissue sarcoma, osteosarcoma, rhabdomyosarcoma, colon cancer and pancreatic cancer.

3. The use of claim 1 or 2, wherein the immunomodulatory agent is a toll-like receptor (TLR) agonist.

4. The use of claim 3, wherein the TLR agonist is a TLR9 agonist.

5. The use of claim 1 or 2, wherein the immunomodulatory agent is a stimulator of interferon genes (STING) agonist.

6. The use of any of claims 1-5, wherein:
R^{1A} is CH_3; and
R^{1e} is $–CH_2CO_2H$.

7. The use of claim 6, wherein R^{1B} is OH.

8. The use of claim 6, wherein R^{1B} is $–N(R^{1c})CH_2CO_2H$.

9. The use of claim 6, wherein R^{1B} is $–N(R^{1c})CHR^{1e}CO_2H$.

10. The use of any of claims 1-9, wherein m is 1.

11. The use of any of claims 1-10, wherein D^1 is paclitaxel, doxorubicin, docetaxel, SN38, auristatin, or monomethyl auristatin E.

12. The use of claim 11, wherein D^1 is doxorubicin.

13. The use of any of claims 1-12, wherein the tetrazine-containing group is incorporated into the hyaluronic acid from 10% to 50%, as measured by the % of carboxylic acids being linked or conjugated to the tetrazine-containing group.

14. Use of:
a) the compound of formula (II-A'), as defined in claim 1, or a pharmaceutically acceptable salt or composition thereof;
b) one or more immunomodulatory agents, wherein the immunomodulatory agent(s) are selected from the group consisting of a toll-like receptor (TLR) agonist and a stimulator of interferon genes (STING) agonist, or a pharmaceutically acceptable salt or composition thereof;
c) a substituted hyaluronic acid, as defined in claim 1; and
d) instructions for use;
in the manufacture of a kit for the treatment of a tumor.