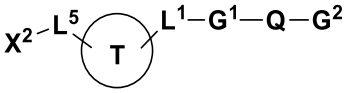
SUMMARY

[0008] There is therefore a need for selective treatment strategies for cancer that are (i) selective (tumor specific); (ii) overcome the obstacle of poor permeability across biologic membranes; (iii) are substantially stable against endo- and exonucleases without significant alteration of their pharmacokinetics and targeting properties; and (iv) allows for the development of a patient specific theragnostic agent. The compounds disclosed herein include all of these features, such that they are selective for cancer cells, are quickly bound to or are internalized into those cells and are quickly localized into the appropriate compartment(s) in the cell where the compounds can exact their greatest therapeutic effect in a patient specific fashion.

[0008a] In a first aspect of the present disclosure, there is provided a compound of the Formula (V):



(V)

or a pharmaceutically acceptable salt, polymorph, solvate or clathrate thereof, wherein:

X^2 is a chelating agent, an imaging agent, a diagnostic agent or a therapeutic agent;

L^1 is a linker group;

L^5 is a linker group or a bond, wherein L^1 and L^5 can be the same or different, optionally wherein L^1 and/or L^5 has a chain length of from 1 to 40 atoms;

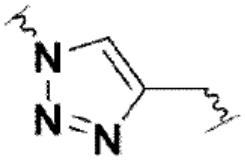
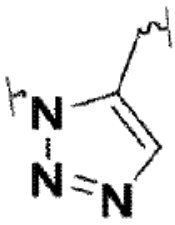
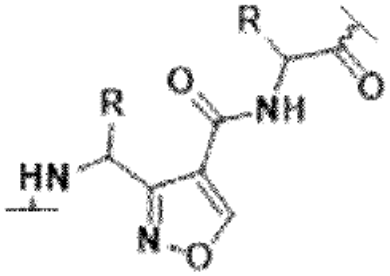
T is a click-chemistry-derived core;

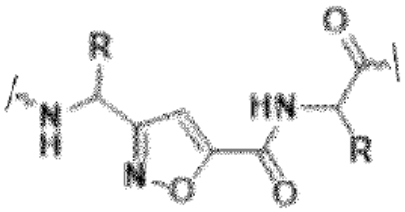
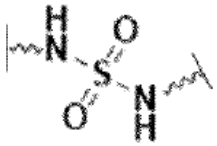
G^1 is a forward primer binding site;

Q is a randomized single-stranded DNA; and

G^2 is a reverse primer binding site,

wherein the click-chemistry-derived core is (i) an azole, (ii) an oxazole, (iii) a heterocycle derivable from electrocyclization chemistry, or (iv) selected from one of the following formula:

(a)  , (b)  , (c)  ,

(d)  , (e)  , or (f)  .

[0008b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising one or more compounds as disclosed herein and a pharmaceutically acceptable carrier or excipient.

[0008c] In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or the composition as disclosed herein, in the manufacture of a medicament for treating cancer in a subject in need of such treatment, optionally wherein the cancer is selected from all possible cancers, including prostate cancer, breast cancer, pancreatic cancer, thyroid cancer, bone cancer, glioblastoma and neuroendocrine tumors; or optionally wherein the compound or composition is to be administered in combination with at least one anticancer agent.

[0008d] In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or the composition as disclosed herein, for use in therapy.

DESCRIPTION

[0009] Reference will now be made in detail to certain embodiments of the disclosed subject matter. While the disclosed subject matter will be described in conjunction with the enumerated claims, it will be understood that the exemplified subject matter is not intended to limit the claims to the disclosed subject matter.

[0010] The instant disclosure relates to compounds of the Formula (I):

$$A—L^1—G^1—Q—G^2$$

(I)

wherein

A comprises at least one avidin-type molecule, each avidin-type molecule comprising one to four monomer units;

L^1 is a linker group;

G^1 is a forward primer binding site;

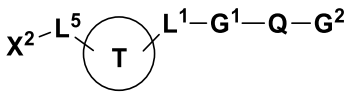
Q is a randomized single-stranded DNA; and

G^2 is a reverse primer binding site.

[0011] As used herein, the term “avidin-type molecule” includes species that engage in an interaction with biotin with a dissociation constant K_d in the order of 10^{-14} to 10^{-15} mol/L. Examples of avidin-type molecules include avidin, streptavidin, neutravidin, captavidin, and any other species that engage in an avidin-biotin interaction, such as a nonimmunogenic or low immunogenic forms of streptavidin. *See*, *e.g.*, Published U.S. Appl. No. 2012/0039879. Typically, but not necessarily, avidin exists as a tetrameric protein, wherein each of the four monomer units that form the tetramer is capable of binding at least one biotin moiety to form what can be termed a “biotin-avidin bond.” As used herein, the term “biotin-avidin bond” and its variants refers to a specific linkage formed between a biotin moiety and an avidin moiety. Typically, a biotin moiety can bind with high affinity to an avidin

What is claimed is:

1. A compound of the Formula (V):



(V)

or a pharmaceutically acceptable salt, polymorph, solvate or clathrate thereof, wherein:

X^2 is a chelating agent, an imaging agent, a diagnostic agent or a therapeutic agent;

L^1 is a linker group;

L^5 is a linker group or a bond, wherein L^1 and L^5 can be the same or different, optionally wherein L^1 and/or L^5 has a chain length of from 1 to 40 atoms;

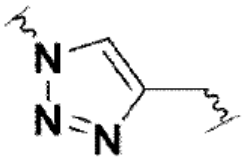
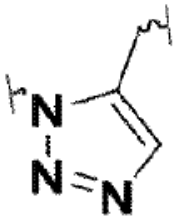
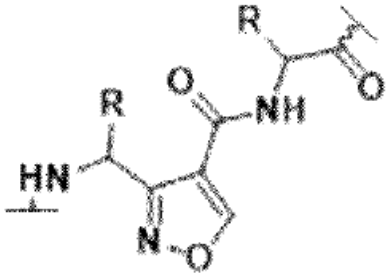
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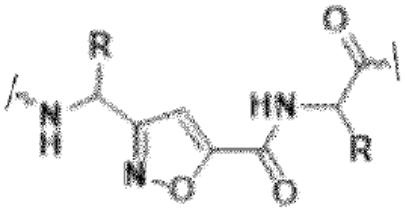
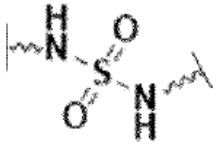
G^1 is a forward primer binding site;

Q is a randomized single-stranded DNA; and

G^2 is a reverse primer binding site,

wherein the click-chemistry-derived core is (i) an azole, (ii) an oxazole, (iii) a heterocycle derivable from electrocyclization chemistry, or (iv) selected from one of the following formula:

(a) , (b) , (c) ,

(d) , (e) , or (f) .

2. The compound of claim 1, wherein X^2 is a chelating agent, optionally wherein the chelating agent is EDTA, DTPA, DOTA, TETA, NOTA, Cyclam, PCBA, DADT or MAMA.

3. The compound of claim 1 or 2, further comprising at least one of a radioactive isotope and a non-radioactive isotope chelated to the chelating agent, optionally wherein the radioactive isotope is at least one of an alpha particle emitter, a beta particle emitter, and an Auger-electron emitter.

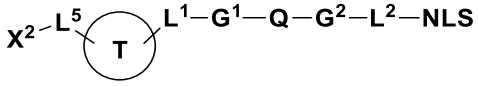
4. The compound of claim 3, wherein: (i) the non-radioactive isotope is ^{113}In; (ii) the alpha particle emitter is at least one of ^{211}At, ^{213}Bi, ^{223}Ra, ^{227}Th and ^{225}Ac; (iii) the beta particle emitter is at least one of ^{33}P, ^{177}Lu, ^{67}Cu, ^{131}I, ^{186}Re, ^{165}Dy, ^{89}Sr, ^{32}P, ^{166}Ho, ^{188}Re, and ^{90}Y; or (iv) the Auger-electron emitter is at least one of ^{125}I, ^{123}I, ^{77}Br, ^{111}In, and ^{195m}Pt.

5. The compound of claim 1, wherein the randomized single-stranded DNA has 10 to 100 nucleotides; or -G^1-Q-G^2- is a single-stranded DNA sequence -TGCGTGTGTAGTGTGTCTG-Q-CTCTTAGGGATTTGGGCGG- (SEQ ID NO: 21), optionally comprises at least one bonding arrangement that renders at least one of G^1, Q, and G^2 nuclease resistant.

6. The compound of claim 1, wherein at least one of L^1 and L^5 is (i) a click chemistry-derived linker, wherein at least one of L^1 and L^5 is derived from copper-catalyzed azide-alkyne cycloaddition (CuAAC), strain-promoted azide-alkyne cycloaddition (SPAAC), inverse electron demand Diels-Alder reaction (IEDDA), and Staudinger ligation (SL); or (ii) a releasable group, optionally wherein the linker group is photochemically-, chemically- or enzymatically-cleavable group.

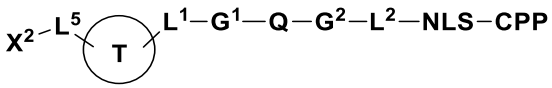
7. The compound of claim 1, wherein at least one of G^1, Q, and G^2 comprises at least one bonding arrangement that renders at least one of G^1, Q, and G^2 nuclease resistant, optionally wherein the at least one bonding arrangement is a 5'-phosphorothioate, 5-modified uracil, 4'-thio, 2'-fluoro, 5'-α-P-borano, 2'-amino, 2'-deoxy-L-ribose, 2'-methoxy, capping with 3' end with inverted thymidine, bridged nucleic acids (BNAs), locked nucleic acids (LNAs), and xeno nucleic acids (XNAs).

8. The compound of claim 1, further comprising a nuclear localization signal (NLS), such that the compound of the Formula (V) is a compound of the Formula (VI):



(VI)

9. The compound of claim 1, further comprising a nuclear localization signal (NLS) and further comprising a cell penetrating peptide (CPP) such that the compound of the Formula (V) is a compound of the Formula (VII):

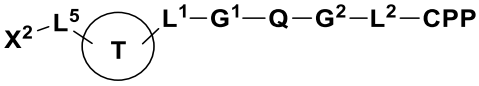


(VII)

10. The compound of claim 1, further comprising a linker, L^3, linking NLS to CPP, optionally wherein at least one of L^2 and L^3 is a succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate-based linker.

11. The compound of claim 8 or 9, wherein the NLS comprises the amino acid sequence PKKKRKV (SEQ ID NO: 1).

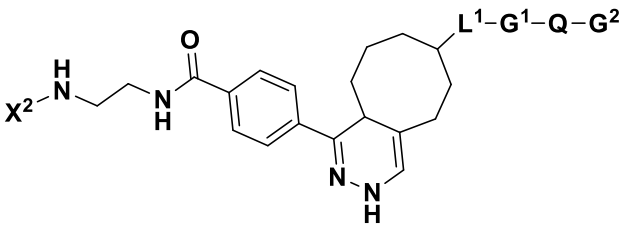
12. The compound of claim 1, further comprising a cell penetrating peptide (CPP) such that the compound of the Formula (V) is a compound of the Formula (VIII):



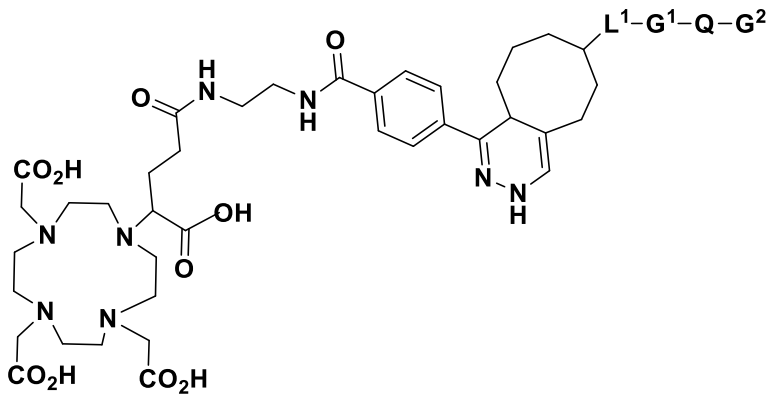
(VIII)

13. The compound of any one of claims 8, 9 or 12, wherein the CPP comprises the amino acid sequence RRRRRRRR (SEQ ID NO: 5).

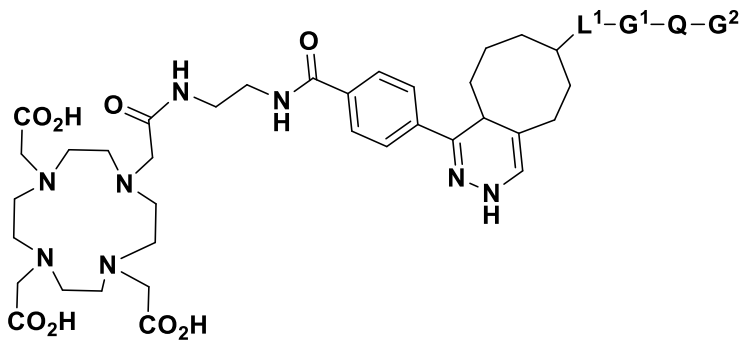
14. The compound of claim 1, wherein the compound is a compound of the formula:



or a pharmaceutically acceptable salt, polymorph, solvate or clathrate thereof, optionally wherein the compound is a compound of the formula:

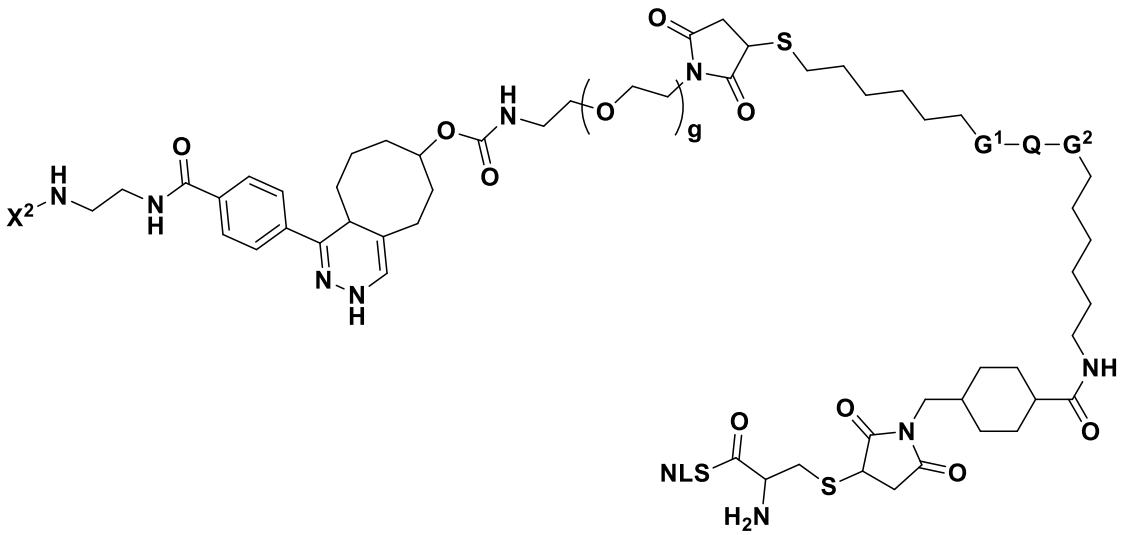


, or

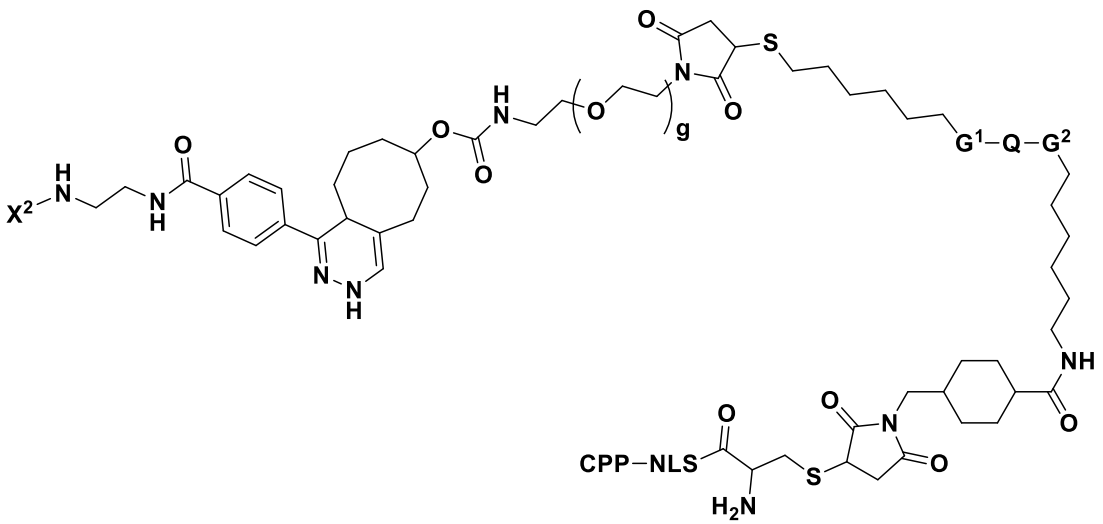


or a pharmaceutically acceptable salt, polymorph, solvate or clathrate thereof.

15. The compound of claim 1, wherein the compound is a compound of the formula:



or



wherein g is an integer such that the number average molecular weight (Mn) of the

$-OCH_2CH_2-$ moiety is from about 500 g/mol to about 10,000 g/mol.

16. A pharmaceutical composition comprising one or more compounds of claim 1 and a pharmaceutically acceptable carrier or excipient.

17. Use of a compound according to any one of claims 1 to 15, or the composition according to claim 16, in the manufacture of a medicament for treating cancer in a subject in need of such treatment, optionally wherein the cancer is selected from all possible cancers, including prostate cancer, breast cancer, pancreatic cancer, thyroid cancer, bone cancer, glioblastoma and neuroendocrine tumors; or optionally wherein the compound or composition is to be administered in combination with at least one anticancer agent.

18. A compound according to any one of claims 1 to 15, or the composition according to claim 16, for use in therapy.