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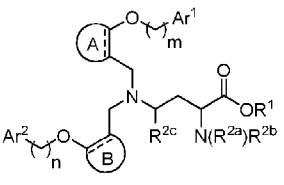
(54) **Title:** DIBENZYL AMINES AS AMINO ACID TRANSPORT INHIBITORS

(57) Abstract: These compounds are amino acid transporter inhibitors. Amino acid transporter inhibitors are useful to treat a variety of diseases disorders, or conditions including cancer.



(I)

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DIBENZYL AMINES AS AMINO ACID TRANSPORT INHIBITORS

Field of the Invention

[0001] The present disclosure provides compounds as amino acid transport inhibitors, e.g., glutamine transport inhibitors, e.g., alanine, serine, cysteine transporter 2 (ASCT2) inhibitors. Amino acid transport inhibitors are useful to treat a variety of diseases, disorders, or conditions including cancer.

Background of the Invention

[0002] Glutamine and other amino acids are involved in multiple aspects of cancer metabolism (Hensley *et al., J. Clin. Invest.* 723:3678-3684 (2013)). For example, glutamine is the most abundant amino acid in the blood and muscle and is utilized for energy generation. Glutamine is also a precursor for the biomass required for rapid cancer cell proliferation (Windmueller and Spaeth, *J. Biol. Chem. 249*:5070-5079 (1974)). In addition to providing a carbon source, glutamine metabolism also acts as a source of nitrogen for the synthesis of nucleic acids and other amino acids. Glutamine also participates in the regulation of cellular redox homeostasis through a variety of mechanisms (Altman *et al., Nat. Rev. Cancer 16:773* (2016)). Cancer cells are thus dependent on glutamine and cannot survive in the absence of exogenous glutamine. Choi and Park, *Biomol Ther 26(1). 19-2^* (2018).

[0003] Several membrane transport proteins in humans ensure glutamine homeostasis by coordinating glutamine's absorption, reabsorption, and delivery to tissues. Amino acid transporters include ASCT2, BOAT1, SNAT1, SNAT2, SNAT3, SNAT5, SNAT7, LAT1, and LAT2. *See, e.g.,* Pochini *et al, Frontiers in Chemistry 2 (Article 61):\-22* (2014); Bhutia and Ganapathy, *Biochimica et Biophysica Acta* 7563:2531-2539 (2016).

[0004] ASCT2 is a cell surface solute-carrying transporter that mediates uptake of neutral amino acids including glutamine (Kanai and Hediger, Pflugers Arch 447:469-479 (2004); Kekuda *et al, J Biol Chem* 277: 18657-18661 (1996)). Blocking ASCT2 to prevent glutamine uptake has been shown to successfully prevent tumor cell proliferation in melanoma (Wang Q *et al, Int J Cancer* 735:1060-1071 (2014)), non-small cell lung cancer (Hassanein *et al, Clin Cancer Res* 79:560-570 (2013); Hassanein *et al, Int J Cancer* 737:1587-1597 (2015)), prostate cancer (Wang *et al,* J Pathol 236: 278-289 (2015)), acute myeloid leukemia (Willems *et al,* Blood 122: 3521-3532 (2013)), and triple-negative breast cancer (van Geldermalsen *et al.,* Oncogene 35, 3201-3208 (2016)).

[0005] ASCT2 inhibitors are disclosed in WO 2018/107173, Schulte *et al., Bioorg Med Chem Lett 25(1):* 113-116 (2015), Schulte *et al, Bioorg Med Chem Lett 26(3)*:1044-1047 (2016), and Schulte *et al., Nat Med 24(2):* \94-202 (2018). In light of the importance of glutamine in cancer cell biology, there exists a need in the art for new ASCT2 and other glutamine transporter inhibitors. *See, e.g.,* Scalise *et al., Front Cell Dev Biol 6:96* (2018).

Brief Summary of the Invention

[0006] In one aspect, the present disclosure provides compounds represented by any one of Formulae **I, II-A, II-B, III-A, III-B, III-C, III-D, IV, V-A, V-B, VI-A, VI-B, VI-C,** or **VI-D,** below, and the pharmaceutically acceptable salts and solvates thereof, collectively referred to herein as "Compounds of the Disclosure."

[0007] In another aspect, the present disclosure provides a pharmaceutical composition comprising a Compound of the Disclosure and one or more pharmaceutically acceptable carriers.

[0008] In another aspect, the present disclosure provides a method of inhibiting one or more amino acid, e.g., glutamine, transporters, including ASCT2, BOAT1, SNAT1, SNAT2, SNAT3, SNAT5, SNAT7, LAT1, and/or LAT2, in a subject, comprising administering to the subject an effective amount of at least one Compound of the Disclosure.

[0009] In another aspect, the present disclosure provides methods for treating a disease, disorder, or condition in a subject, comprising administering a therapeutically effective amount of a Compound of the Disclosure to the subject.

[0010] In another aspect, the present disclosure provides methods for treating a disease, disorder, or condition in a subject, comprising administering a therapeutically effective amount of a Compound of the Disclosure in combination with one or more optional therapeutic agents to the subject.

[0011] In another aspect, the present disclosure provides methods for treating a disease, disorder, or condition responsive to inhibition of one or more amino acid, e.g., glutamine, transporters, including ASCT2, BOAT1, SNAT1, SNAT2, SNAT3, SNAT5, SNAT7, LAT1, and/or LAT2, comprising administering a therapeutically effective amount of a Compound of the Disclosure to a subject.

[0012] In another aspect, the present disclosure provides the use of a Compound of the Disclosure to inhibit one or more amino acid, e.g., glutamine, transporters, including ASCT2, BOAT1, SNAT1, SNAT2, SNAT3, SNAT5, SNAT7, LAT1, and/or LAT2.

[0013] In another aspect, the present disclosure provides a pharmaceutical composition for treating a disease, disorder, or condition in a subject, wherein the pharmaceutical composition

comprises a therapeutically effective amount of a Compound of the Disclosure in a mixture with one or more pharmaceutically acceptable carriers.

[0014] In another aspect, the present disclosure provides Compounds of the Disclosure for use in treating cancer in a subject in need thereof

[0015] In another aspect, the present disclosure provides a Compound of the Disclosure for use in the manufacture of a medicament for treating cancer in a mammal.

[0016] In another aspect, the present disclosure provides a therapeutic or prophylactic agent for cancer, which comprises a Compound of the Disclosure.

[0017] In another aspect, the present disclosure provides a kit comprising a Compound of the Disclosure.

[0018] In another aspect, the present disclosure provides a method of treating a subject having cancer, the method comprising administering a therapeutically effective amount of a Compound of the Disclosure to the subject if a mutation in any one or more of BRAF, KRAS, p53, and/or PI3KCA is present in a biological sample of the subject.

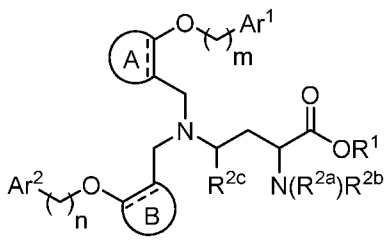
[0019] In another aspect, the present disclosure provides a method of treating a subject having cancer, the method comprising administering a therapeutically effective amount of a Compound of the Disclosure to the subject if an overexpression of MYC is present in a biological sample of the subject.

[0020] Additional embodiments and advantages of the disclosure will be set forth, in part, in the description that follows, and will flow from the description, or can be learned by practice of the disclosure. The embodiments and advantages of the disclosure will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing summary and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention as claimed.

Detailed Description of the Invention

I. Compounds of the Disclosure

[0021] In one embodiment, Compounds of the Disclosure are compounds of Formula I:



I,

wherein:

[0022] R^1 is selected from the group consisting of hydrogen and C_1-C_6 alkyl;

[0023] R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, and -C(=O)R^7; and

[0024] R^{2c} is hydrogen; or

[0025] R^{2a} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and -C(=O)R^7; and

[0026] R^{2b} and R^{2c} taken together form a 5- or 6-membered heterocyclo group;

[0027]  is selected from the group consisting of optionally substituted C_6-C_{10} aryl and optionally substituted 5- to 10-membered heteroaryl;

[0028]  is selected from the group consisting of optionally substituted C_6-C_{10} aryl and optionally substituted 5- to 10-membered heteroaryl;

[0029] Ar^1 is selected from the group consisting of optionally substituted C_6-C_{10} aryl and optionally substituted 5- to 10-membered heteroaryl;

[0030] Ar^2 is selected from the group consisting of optionally substituted C_6-C_{10} aryl and optionally substituted 5- to 10-membered heteroaryl;

[0031] m is 0, 1, 2, or 3;

[0032] n is 1, 2, or 3;

[0033] with the proviso that m does not equal n;

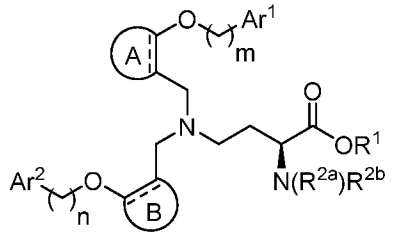
[0034] R^7 is selected from the group consisting of C_1-C_6 alkyl and -OR^8;

[0035] R^8 is selected from the group consisting of C_1-C_6 alkyl and aralkyl; and

[0036] ⎓ represents a single or double bond,

[0037] or a pharmaceutically acceptable salt or solvate thereof.

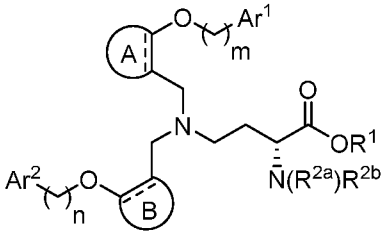
[0038] In another embodiment, Compounds of the Disclosure are compounds of Formula II-A:



II-A,

wherein R^1, R^{2a}, R^{2b}, Ar^1, Ar^2,  ,  , ⎓, m, and n are as defined in connection with Formula **I,** or a pharmaceutically acceptable salt or solvate thereof.

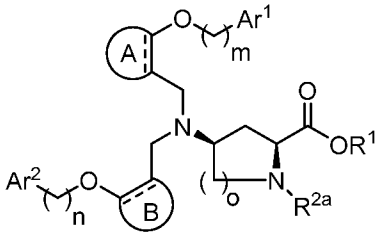
[0039] In another embodiment, Compounds of the Disclosure are compounds of Formula **II-B:**



II-B,

wherein R^1, R^{2a}, R^{2b}, Ar^1, Ar^2,  ,  , ---, m, and n are as defined in connection with Formula I, or a pharmaceutically acceptable salt or solvate thereof.

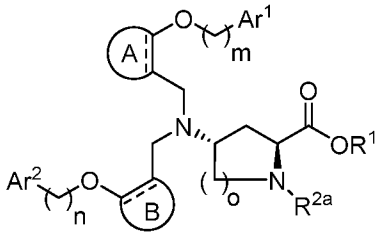
[0040] In another embodiment, Compounds of the Disclosure are compounds of Formula III-A:



III-A,

wherein o is 1 or 2; and R^1, R^{2a}, Ar^1, Ar^2,  ,  , ---, m, and n are as defined in connection with Formula I, or a pharmaceutically acceptable salt or solvate thereof.

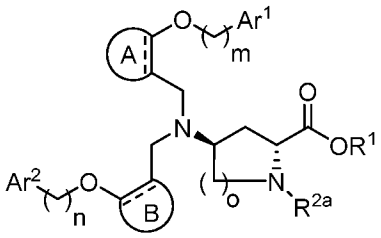
[0041] In another embodiment, Compounds of the Disclosure are compounds of Formula III-B:



III-B,

wherein o is 1 or 2; and R^1, R^{2a}, Ar^1, Ar^2,  ,  , ---, m, and n are as defined in connection with Formula I, or a pharmaceutically acceptable salt or solvate thereof.

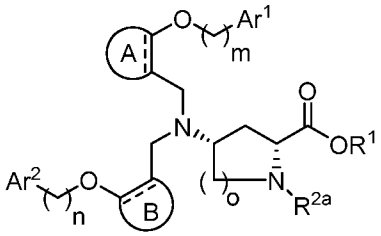
[0042] In another embodiment, Compounds of the Disclosure are compounds of Formula III-C:



III-C,

wherein o is 1 or 2; and R^1, R^{2a}, Ar^1, Ar^2, A, B, ---, m, and n are as defined in connection with Formula **I,** or a pharmaceutically acceptable salt or solvate thereof.

[0043] In another embodiment, Compounds of the Disclosure are compounds of Formula **III-D:**



III-D,

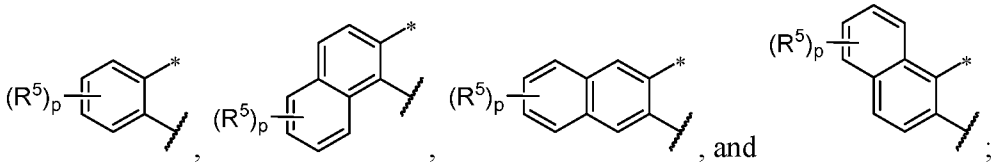
wherein o is 1 or 2; and R^1, R^{2a}, Ar^1, Ar^2, A, B, ---, m, and n are as defined in connection with Formula **I,** or a pharmaceutically acceptable salt or solvate thereof.

[0044] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **III-A, III-B, III-C,** or **III-D,** wherein o is 1, or a pharmaceutically acceptable salt or solvate thereof.

[0045] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **III-A, III-B, III-C,** or **III-D,** wherein o is 2, or a pharmaceutically acceptable salt or solvate thereof.

[0046] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C,** or **III-D,** wherein:

[0047] A is selected from the group consisting of:



;

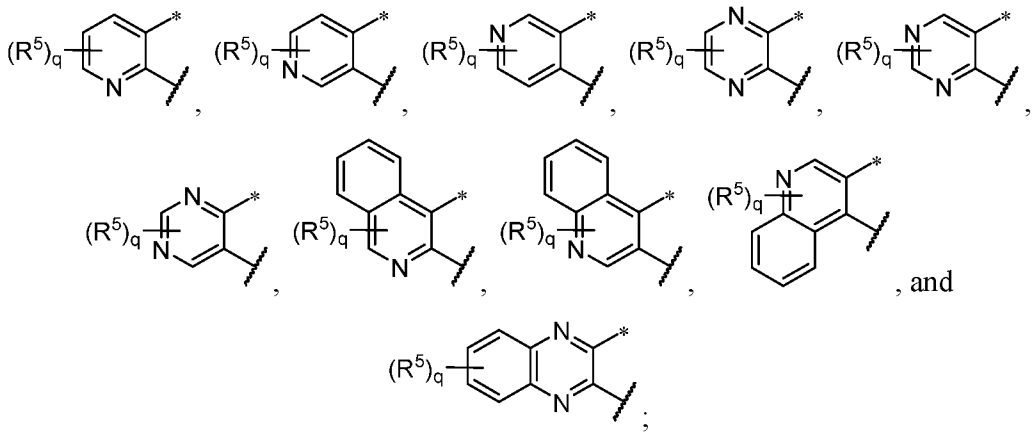
[0048] the bond designated with an "*" is attached to $-O(CH_2)_m-Ar^1$;

[0049] each R^5 is independently selected from the group consisting of halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy; and

[0050] p is 0, 1, 2, 3, or 4.

[0051] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C,** or **III-D,** wherein:

[0052] A is selected from the group consisting of:



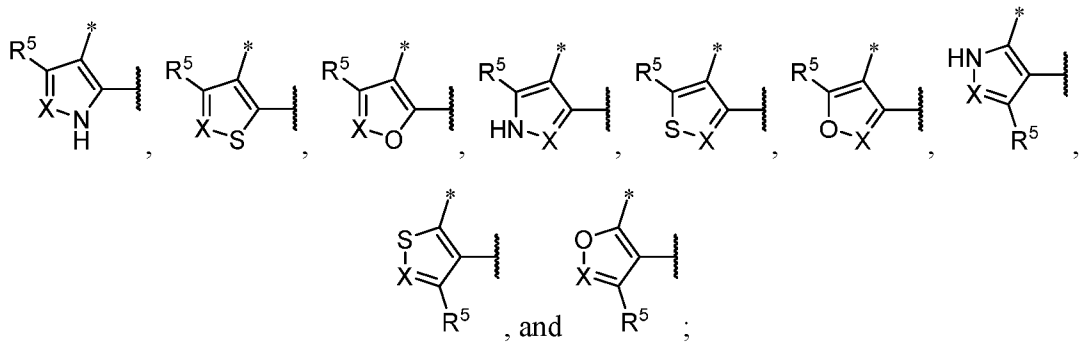
[0053] the bond designated with an "*" is attached to -0$(CH_2)_m$-Ar^1;

[0054] each R^5 is independently selected from the group consisting of halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy; and

[0055] q is 0, 1, 2, or 3.

[0056] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C,** or **III-D,** wherein:

[0057]  is selected from the group consisting of



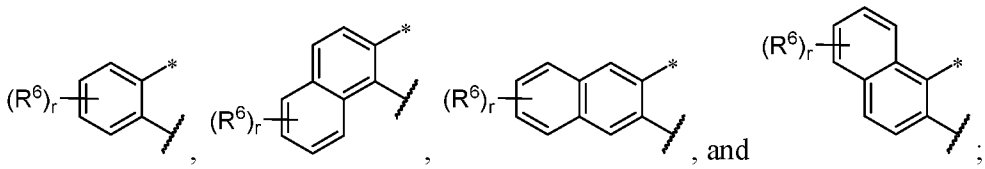
[0058] the bond designated with an "*" is attached to **-O(CH_2)m-Ar^1 ;**

[0059] **X** is selected from the group consisting of **-C(H)=, -C(R^5)=,** and **-N=;** and

[0060] each **R^5** is independently selected from the group consisting of halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy.

[0061] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C,** or **III-D,** wherein:

[0062]  are independently selected from the group consisting of:



wherein:

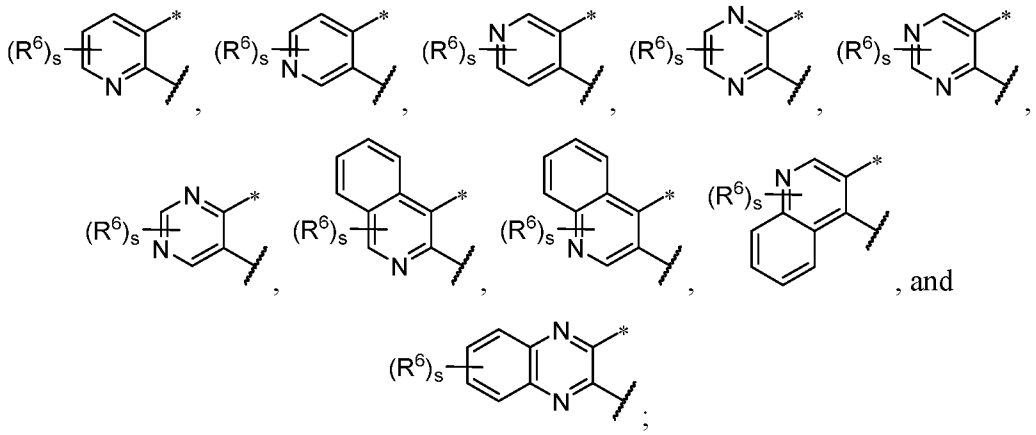
the bond designated with an "*" is attached to -0(CH_2)n-Ar^2, respectively;

each R^6 is independently selected from the group consisting of halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy; and

r is 0, 1, 2, 3, or 4.

[0063] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C,** or **III-D,** wherein:

[0064] B is selected from the group consisting of:



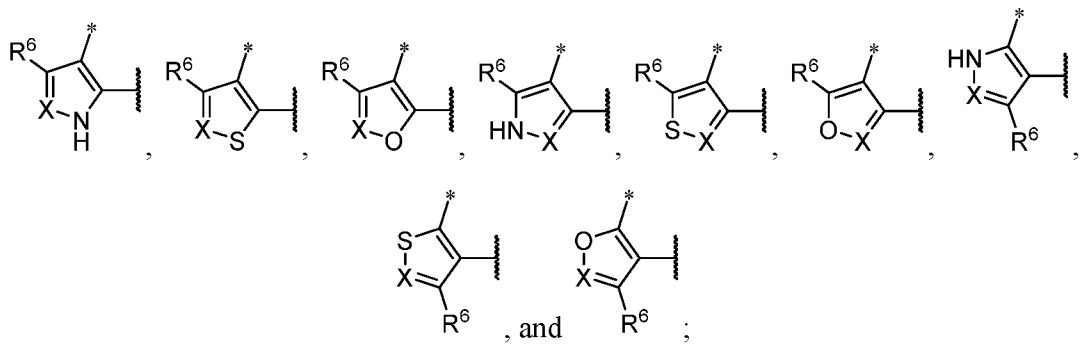
the bond designated with an "*" is attached to -O(CH_2)n-Ar^2;

each R^6 is independently selected from the group consisting of halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy; and

s is 0, 1, 2, or 3.

[0065] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C,** or **III-D,** wherein:

[0066] B is selected from the group consisting of

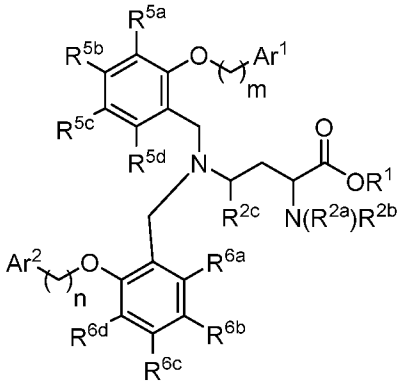


[0067] the bond designated with an "*" is attached to -O(CH_2)m-Ar^1;

[0068] X is selected from the group consisting of -C(H)=, -C(R^5)=, and -N=; and

[0069] each R^6 is independently selected from the group consisting of halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, and C_1-C_4 haloalkoxy.

[0070] **In another embodiment, Compounds of the Disclosure are compounds of Formula IV:**



IV,

wherein:

[0071] **R^1, R^{2a}, R^{2b}, R^{2c}, Ar^1, Ar^2, m, and n are as defined in connection with Formula I; and**

[0072] R^{5a}, R^{5b}, R^{5c}, and R^{5d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy; or

[0073] R^{5a} and R^{5b} taken together form a fused optionally substituted phenyl or fused optionally substituted 5- or 6-membered heteroaryl group; and

[0074] R^{5c} and R^{5d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy; or

[0075] R^{5b} and R^{5c} taken together form a fused optionally substituted phenyl or fused optionally substituted 5- or 6-membered heteroaryl group; and

[0076] R^{5a} and R^{5d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy; or

[0077] R^{5c} and R^{5d} taken together form a fused optionally substituted phenyl or fused optionally substituted 5- or 6-membered heteroaryl group; and

[0078] **R^{5a} and R^{5b} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy;**

[0079] R^{6a}, R^{6b}, R^{6c}, and R^{6d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy; or

[0080] R^{6a} and R^{6b} taken together form a fused optionally substituted phenyl or fused optionally substituted 5- or 6-membered heteroaryl group; and

[0081] R^{6c} and R^{6d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy; or

[0082] R^{6b} and R^{6c} taken together form a fused optionally substituted phenyl or fused optionally substituted 5- or 6-membered heteroaryl group; and

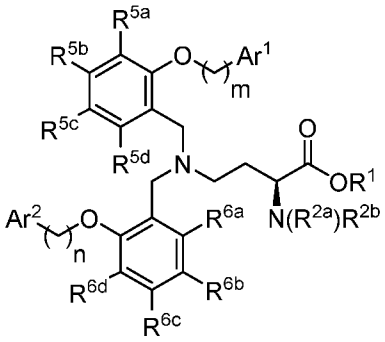
[0083] R^{6a} and R^{6d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy; or

[0084] R^{6c} and R^{6d} taken together form a fused optionally substituted phenyl or fused optionally substituted 5- or 6-membered heteroaryl group; and

[0085] R^{6a} and R^{6b} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy,

[0086] or a pharmaceutically acceptable salt or solvate thereof.

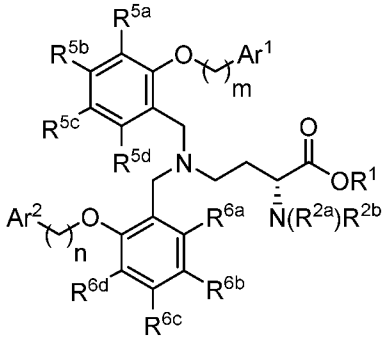
[0087] In another embodiment, Compounds of the Disclosure are compounds of Formula **V-A:**



V-A,

wherein R^1, R^{2a}, R^{2b}, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{6a}, R^{6b}, R^{6c}, R^{6d}, Ar^1, Ar^2, m, and n are as defined in connection with Formula **IV,** or a pharmaceutically acceptable salt or solvate thereof.

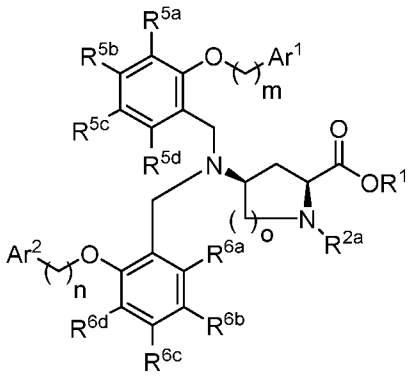
[0088] In another embodiment, Compounds of the Disclosure are compounds of Formula **V-B:**



V-B,

wherein R^1, R^{2a}, R^{2b}, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{6a}, R^{6b}, R^{6c}, R^{6d}, Ar^1, Ar^2, m, and n are as defined in connection with Formula **IV,** or a pharmaceutically acceptable salt or solvate thereof.

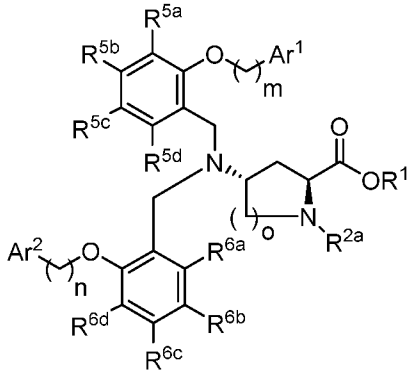
[0089] In another embodiment, Compounds of the Disclosure are compounds of Formula **VI-A:**



VI-A,

wherein o is 1 or 2; and R^1, R^{2a}, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{6a}, R^{6b}, R^{6c}, R^{6d}, Ar^1, Ar^2, m, and n are as defined in connection with Formula **IV,** or a pharmaceutically acceptable salt or solvate thereof.

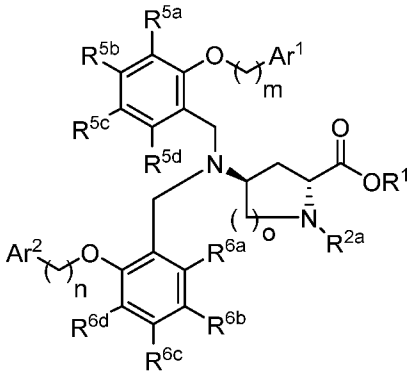
[0090] In another embodiment, Compounds of the Disclosure are compounds of Formula **VI-B:**



VI-B,

wherein o is 1 or 2; and R^1, R^{2a}, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{6a}, R^{6b}, R^{6c}, R^{6d}, Ar^1, Ar^2, m, and n are as defined in connection with Formula **IV,** or a pharmaceutically acceptable salt or solvate thereof.

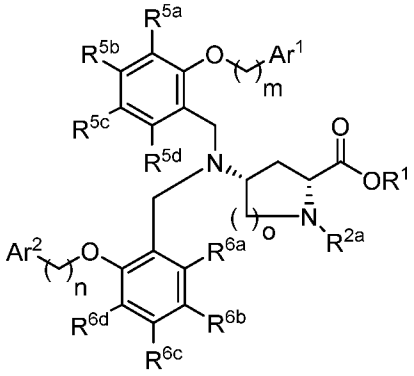
[0091] In another embodiment, Compounds of the Disclosure are compounds of Formula **VI-C:**



VI-C,

wherein o is 1 or 2; and R^1, R^{2a}, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{6a}, R^{6b}, R^{6c}, R^{6d}, Ar^1, Ar^2, m, and n are as defined in connection with Formula **IV,** or a pharmaceutically acceptable salt or solvate thereof.

[0092] In another embodiment, Compounds of the Disclosure are compounds of Formula **VI-D:**



VI-D,

wherein o is 1 or 2; and R^1, R^{2a}, R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{6a}, R^{6b}, R^{6c}, R^{6d}, Ar^1, Ar^2, m, and n are as defined in connection with Formula **IV,** or a pharmaceutically acceptable salt or solvate thereof.

[0093] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **VI-A, VI-B, VI-C,** or **VI-D,** wherein o is 1, or a pharmaceutically acceptable salt or solvate thereof.

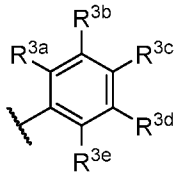
[0094] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **VI-A, VI-B, VI-C,** or **VI-D,** wherein o is 2, or a pharmaceutically acceptable salt or solvate thereof.

[0095] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **IV, V-A, V-B, VI-A, VI-B, VI-C,** or **VI-D,** wherein R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{6a}, R^{6b}, R^{6c}, and R^{6d} are independently selected from the group consisting of hydrogen, halo, C_1-C_4 alkyl, Ci-C4 haloalkyl, and C_1-C_4 alkoxy, or a pharmaceutically acceptable salt or solvate thereof

[0096] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **IV, V-A, V-B, VI-A, VI-B, VI-C,** or **VI-D,** wherein R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{6a}, R^{6b}, R^{6c}, and R^{6d} are hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

[0097] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C, III-D, IV, V-A, V-B, VI-A, VI-B, VI-C,** or **VI-D,** wherein Ar^1 is an optionally substituted 5- to 10-membered heteroaryl, or a pharmaceutically acceptable salt or solvate thereof.

[0098] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C, III-D, IV, V-A, V-B, VI-A, VI-B, VI-C,** or **VI-D,** wherein Ar^1 is an optionally substituted phenyl, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, Ar^1 is:

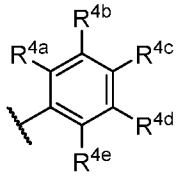


; and

[0099] R^{3a}, R^{3b}, R^{3c}, and R^{3d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy.

[0100] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C, III-D, IV, V-A, V-B, VI-A, VI-B, VI-C,** or **VI-D,** wherein Ar^2 is an optionally substituted 5- to 10-membered heteroaryl, or a pharmaceutically acceptable salt or solvate thereof.

[0101] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C, III-D, IV, V-A, V-B, VI-A, VI-B, VI-C,** or **VI-D,** wherein Ar^2 is an optionally substituted phenyl, or a pharmaceutically acceptable salt or solvate thereof. In another embodiment, Ar^2 is:



; and

[0102] R^{4a}, R^{4b}, R^{4c}, and R^{4d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy.

[0103] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C, III-D, IV, V-A, V-B, VI-A, VI-B, VI-C,** or **VI-D,** wherein m is 0 and n is 1, or a pharmaceutically acceptable salt or solvate thereof.

[0104] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C, III-D, IV, V-A, V-B, VI-A, VI-B, VI-C,** or **VI-D,** wherein m is 0 and n is 2, or a pharmaceutically acceptable salt or solvate thereof.

[0105] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C, III-D, IV, V-A, V-B, VI-A, VI-B, VI-C,** or **VI-D,** wherein m is 0 and n is 3, or a pharmaceutically acceptable salt or solvate thereof.

[0106] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C, III-D, IV, V-A, V-B, VI-A, VI-B, VI-C,** or **VI-D,** wherein m is 1 and n is 2, or a pharmaceutically acceptable salt or solvate thereof.

[0107] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C, III-D, IV, V-A, V-B, VI-A, VI-B, VI-C,** or **VI-D,** wherein m is 1 and n is 3, or a pharmaceutically acceptable salt or solvate thereof.

[0108] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C, III-D, IV, V-A, V-B, VI-A, VI-B, VI-C,** or **VI-D,** wherein m is 2 and n is 3, or a pharmaceutically acceptable salt or solvate thereof.

[0109] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, IV, V-A,** or **V-B,** wherein R^{2b} is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

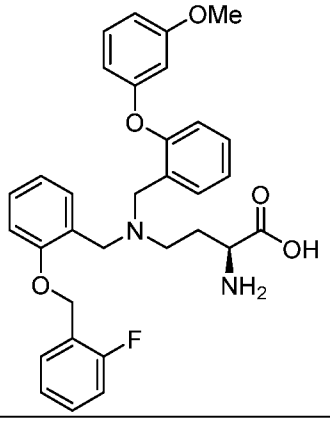
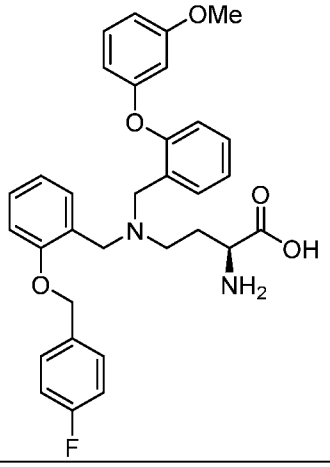
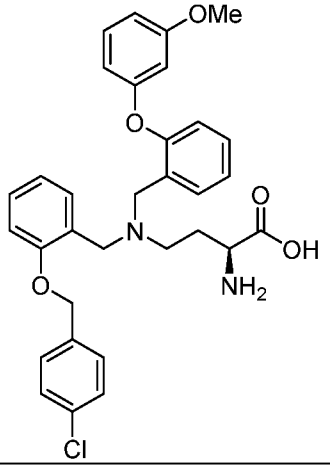
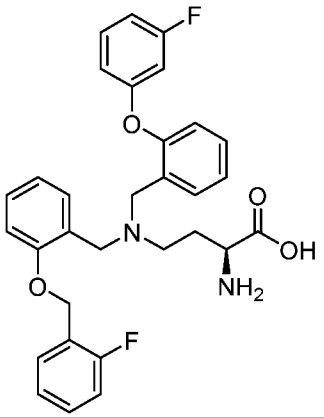
[0110] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C, III-D, IV, V-A, V-B, VI-A, VI-B, VI-C,** or **VI-D,** wherein R^{2a} is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

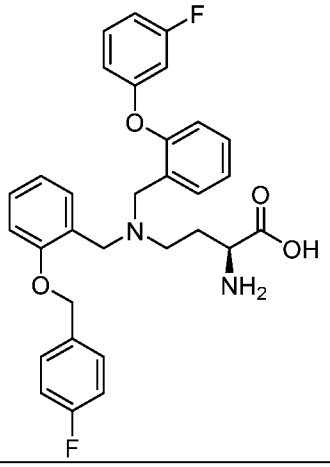
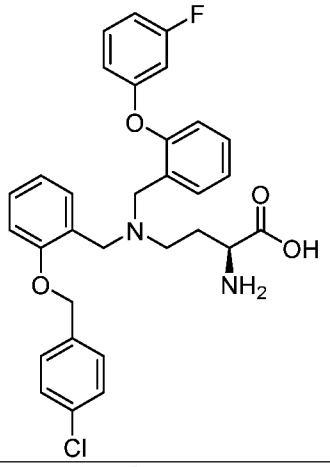
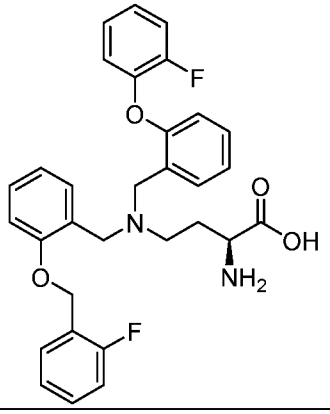
[0111] In another embodiment, Compounds of the Disclosure are compounds of any one of Formulae **I, II-A, II-B, III-A, III-B, III-C, III-D, IV, V-A, V-B, VI-A, VI-B, VI-C,** or **VI-D,** wherein R^1 is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

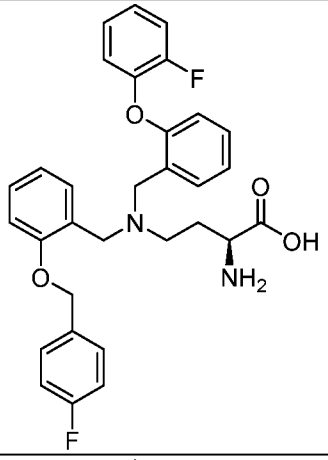
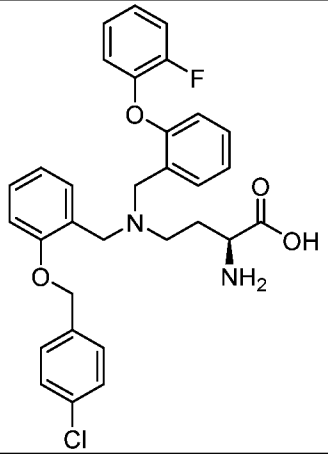
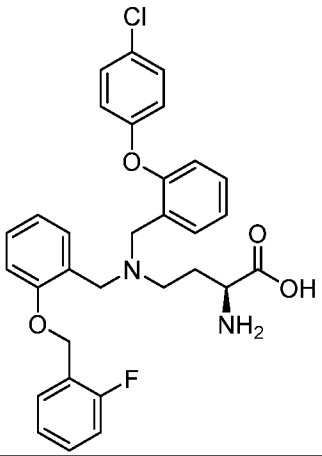
[0112] In another embodiment, Compounds of the Disclosure are compounds selected from any one or more of the compounds of Table 1, or a pharmaceutically acceptable salt or solvate thereof.

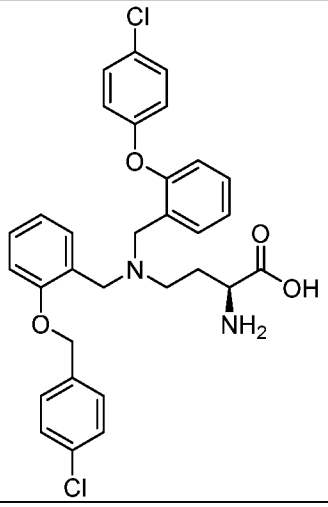
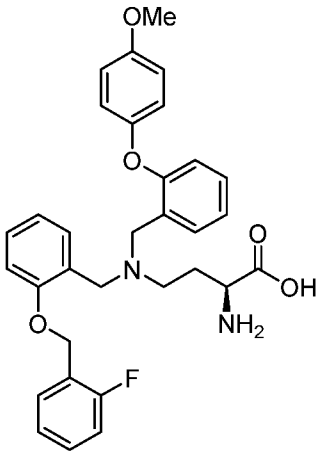
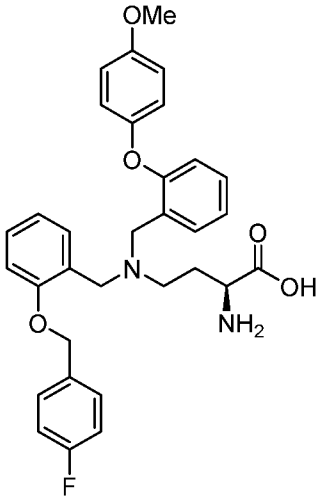
Table 1

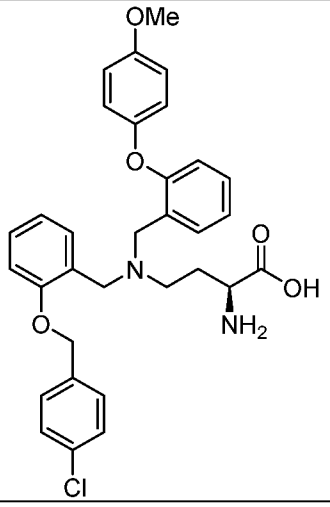
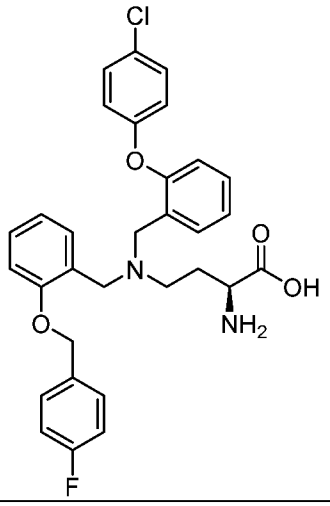
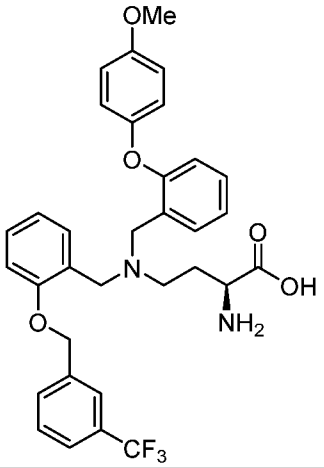
Cpd. No.	Structure	Name

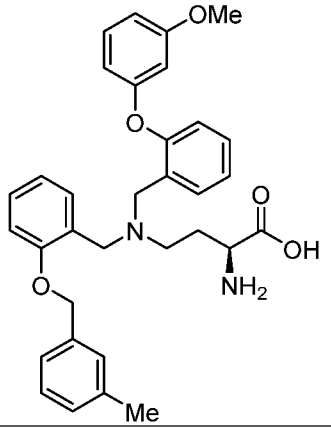
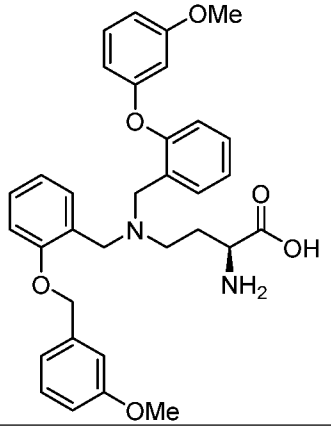
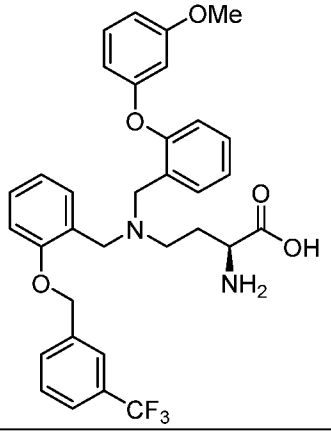
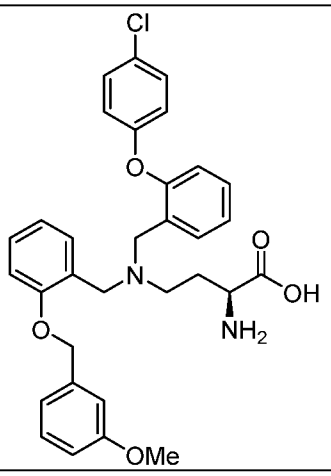
1		(S)-2-amino-4-((2-((2-fluorobenzyl)oxy)benzyl)(2-(3-methoxyphenoxy)benzyl)amino)butanoic acid
2		(S)-2-amino-4-((2-((4-fluorobenzyl)oxy)benzyl)(2-(3-methoxyphenoxy)benzyl)amino)butanoic acid
3		(S)-2-amino-4-((2-((4-chlorobenzyl)oxy)benzyl)(2-(3-methoxyphenoxy)benzyl)amino)butanoic acid
4		(S)-2-amino-4-((2-((2-fluorobenzyl)oxy)benzyl)(2-(3-fluorophenoxy)benzyl)amino)butanoic acid

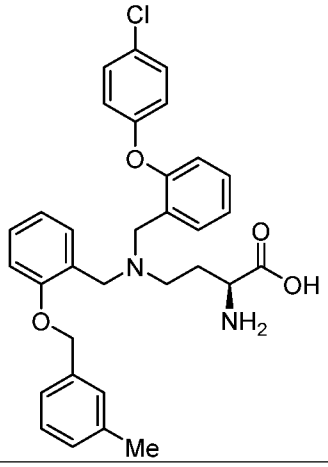
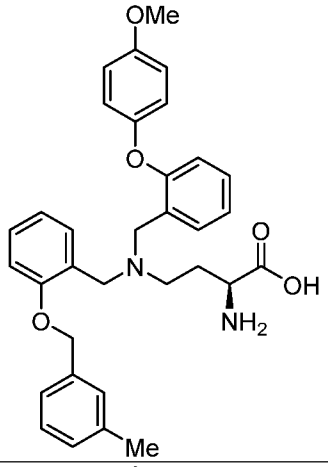
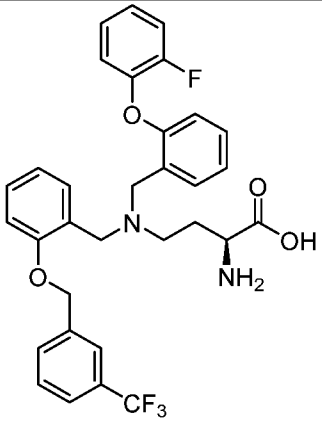
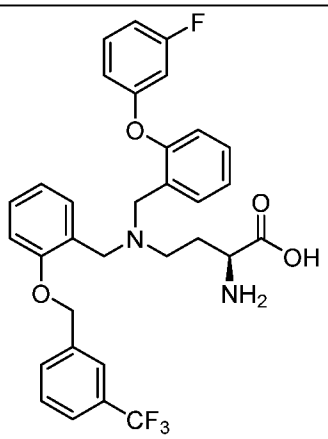
5		(S)-2-amino-4-((2-((4-fluorobenzyl)oxy)benzyl)(2-(3-fluorophenoxy)benzyl)amino)butanoic acid
6		(S)-2-amino-4-((2-((4-chlorobenzyl)oxy)benzyl)(2-(3-fluorophenoxy)benzyl)amino)butanoic acid
7		(S)-2-amino-4-((2-((2-fluorobenzyl)oxy)benzyl)(2-(2-fluorophenoxy)benzyl)amino)butanoic acid

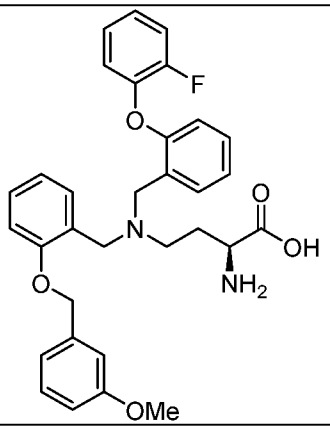
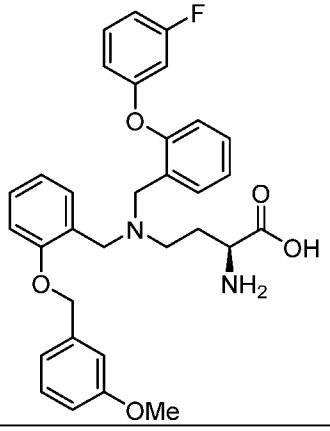
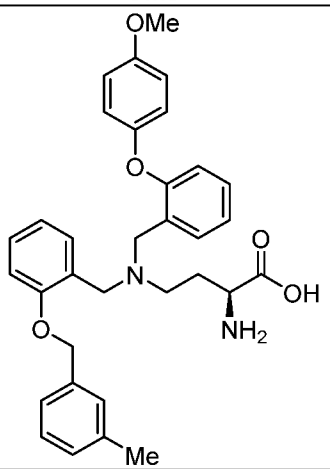
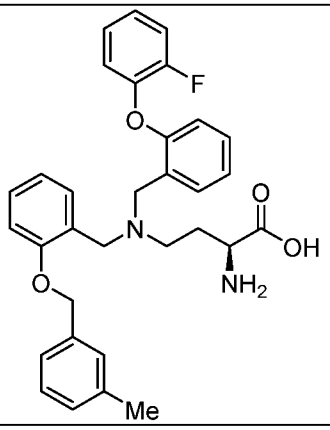
8		(S)-2-amino-4-((2-((4-fluorobenzyl)oxy)benzyl)(2-(2-fluorophenoxy)benzyl)amino)butanoic acid
9		(S)-2-amino-4-((2-((4-chlorobenzyl)oxy)benzyl)(2-(2-fluorophenoxy)benzyl)amino)butanoic acid
10		(S)-2-amino-4-((2-(4-chlorophenoxy)benzyl)(2-((2-fluorobenzyl)oxy)benzyl)amino)butanoic acid

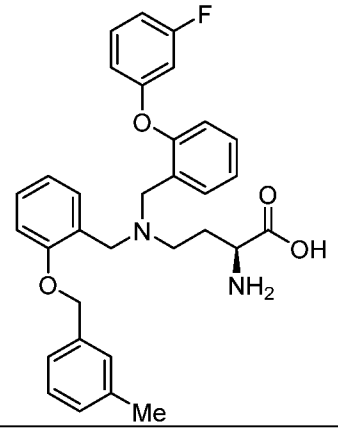
11		(S)-2-amino-4-((2-((4-chlorobenzyl)oxy)benzyl)(2-(4-chlorophenoxy)benzyl)amino)butanoic acid
12		(S)-2-amino-4-((2-((2-fluorobenzyl)oxy)benzyl)(2-(4-methoxyphenoxy)benzyl)amino)butanoic acid
13		(S)-2-amino-4-((2-((4-fluorobenzyl)oxy)benzyl)(2-(4-methoxyphenoxy)benzyl)amino)butanoic acid

14		(S)-2-amino-4-((2-((4-chlorobenzyl)oxy)benzyl)(2-(4-methoxyphenoxy)benzyl)amino)butanoic acid
15		(S)-2-amino-4-((2-(4-chlorophenoxy)benzyl)(2-((4-fluorobenzyl)oxy)benzyl)amino)butanoic acid
16		(S)-2-amino-4-((2-(4-methoxyphenoxy)benzyl)(2-((3-(trifluoromethyl)benzyl)oxy)benzyl)amino)butanoic acid

17		(S)-2-amino-4-((2-(3-methoxyphenoxy)benzyl)(2-((3-methylbenzyl)oxy)benzyl)amino)butanoic acid
18		(S)-2-amino-4-((2-((3-methoxybenzyl)oxy)benzyl)(2-(3-methoxyphenoxy)benzyl)amino)butanoic acid
19		(S)-2-amino-4-((2-(3-methoxyphenoxy)benzyl)(2-((3-(trifluoromethyl)benzyl)oxy)benzyl)amino)butanoic acid
20		(S)-2-amino-4-((2-(4-chlorophenoxy)benzyl)(2-((3-methoxybenzyl)oxy)benzyl)amino)butanoic acid

21		(S)-2-amino-4-((2-(4-chlorophenoxy)benzyl)(2-((3-methylbenzyl)oxy)benzyl)amino)butanoic acid
22		(S)-2-amino-4-((2-(4-methoxyphenoxy)benzyl)(2-((3-methylbenzyl)oxy)benzyl)amino)butanoic acid
23		(S)-2-amino-4-((2-(2-fluorophenoxy)benzyl)(2-((3-(trifluoromethyl)benzyl)oxy)benzyl)amino)butanoic acid
24		(S)-2-amino-4-((2-(3-fluorophenoxy)benzyl)(2-((3-(trifluoromethyl)benzyl)oxy)benzyl)amino)butanoic acid

25		(S)-2-amino-4-((2-(2-fluorophenoxy)benzyl)(2-((3-methoxybenzyl)oxy)benzyl)amino)butanoic acid
26		(S)-2-amino-4-((2-(3-fluorophenoxy)benzyl)(2-((3-methoxybenzyl)oxy)benzyl)amino)butanoic acid
27		(S)-2-amino-4-((2-(4-methoxyphenoxy)benzyl)(2-((3-methylbenzyl)oxy)benzyl)amino)butanoic acid
28		(S)-2-amino-4-((2-(2-fluorophenoxy)benzyl)(2-((3-methylbenzyl)oxy)benzyl)amino)butanoic acid

29		(S)-2-amino-4-((2-(3-fluorophenoxy)benzyl)(2-((3-methylbenzyl)oxy)benzyl)amino)butanoic acid

[0113] Salts, hydrates, and solvates of the Compounds of the Disclosure can also be used in the methods disclosed herein. The present disclosure further includes all possible stereoisomers and geometric isomers of Compounds of the Disclosure to include both racemic compounds and optically active isomers. When a Compound of the Disclosure is desired as a single enantiomer, it can be obtained either by resolution of the final product or by stereospecific synthesis from either isomerically pure starting material or use of a chiral auxiliary reagent, for example, see Z. Ma et al, *Tetrahedron: Asymmetry, 8(6),* pages 883-888 (1997). Resolution of the final product, an intermediate, or a starting material can be achieved by any suitable method known in the art. Additionally, in situations where tautomers of the Compounds of the Disclosure are possible, the present disclosure is intended to include all tautomeric forms of the compounds.

[0114] The present disclosure encompasses the preparation and use of salts of Compounds of the Disclosure, including pharmaceutically acceptable salts. As used herein, the pharmaceutical "pharmaceutically acceptable salt" refers to salts or zwitterionic forms of Compounds of the Disclosure. Salts of Compounds of the Disclosure can be prepared during the final isolation and purification of the compounds or separately by reacting the compound with an acid having a suitable cation. The pharmaceutically acceptable salts of Compounds of the Disclosure can be acid addition salts formed with pharmaceutically acceptable acids. Examples of acids which can be employed to form pharmaceutically acceptable salts include inorganic acids such as nitric, boric, hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Nonlimiting examples of salts of compounds of the disclosure include, but are not limited to, the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, 2-hydroxyethansulfonate, phosphate, hydrogen phosphate, acetate, adipate, alginate, aspartate, benzoate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerolphsphate, hemisulfate, heptanoate, hexanoate, formate, succinate, fumarate, maleate, ascorbate, isethionate, salicylate, methanesulfonate, mesitylenesulfonate, naphthyl enesulfonate, nicotinate,

2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, paratoluenesulfonate, undecanoate, lactate, citrate, tartrate, gluconate, methanesulfonate, ethanedisulfonate, benzene sulfonate, and p-toluenesulfonate salts. In addition, available amino groups present in the compounds of the disclosure can be quatemized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. In light of the foregoing, any reference Compounds of the Disclosure appearing herein is intended to include compounds of Compounds of the Disclosure as well as pharmaceutically acceptable salts, hydrates, or solvates thereof.

[0115] The present disclosure encompasses the use of solvates of a Compound of the Disclosure. Solvates typically do not significantly alter the physiological activity or toxicity of a compound, and as such may function as pharmacological equivalents. The term "solvate" as used herein is a combination, physical association and/or solvation of a Compound of the Disclosure with a solvent molecule such as, *e.g.,* a disolvate, monosolvate or hemisolvate, where the ratio of solvent molecule a Compound of the Disclosure is about 2:1, about 1:1 or about 1:2, respectively. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate can be isolated, such as when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. Thus, "solvate" encompasses both solution-phase and isolatable solvates. A Compound of the Disclosure can be present as solvated forms with a pharmaceutically acceptable solvent, such as water, methanol, ethanol, and the like, and it is intended that the disclosure includes both solvated and unsolvated forms of a Compound of the Disclosure. One type of solvate is a hydrate. A "hydrate" relates to a particular subgroup of solvates where the solvent molecule is water. Solvates typically can function as pharmacological equivalents. Preparation of solvates is known in the art. See, for example, M. Caira *et al, J. Pharmaceut. Sci., 93(3):* 601-611 (2004), which describes the preparation of solvates of fluconazole with ethyl acetate and with water. Similar preparation of solvates, hemisolvates, hydrates, and the like are described by E.C. van Tonder *et al. ,AAPS Pharm. Sci. Tech, 5(l)*:Article 12 (2004), and A.L. Bingham *et al, Chem. Commun.* 603-604 (2001). A typical, non-limiting, process of preparing a solvate involves dissolving a Compound of the Disclosure in a desired solvent (organic, water, or a mixture thereof) at temperatures above 20°C to about 25°C, then cooling the solution at a rate sufficient to form crystals, and isolating the crystals by known methods, *e.g.,* filtration. Analytical techniques such as infrared spectroscopy can be used to confirm the presence of the solvent in a crystal of the solvate.

II. Therapeutic Methods of the Disclosure and Kits

[0116] Compounds of the Disclosure inhibit ASCT2-, BOAT1-, SNAT1-, SNAT2-, SNAT3-, SNAT5-, SNAT7-, LAT1-, and/or LAT2-mediated amino acid, e.g., glutamine, transport and thus are useful in the treatment of a variety of diseases, disorders, and conditions. In particular, Compounds of the Disclosure are useful in methods of treating diseases, disorders, and conditions wherein inhibition of ASCT2-, BOAT1-, SNAT1-, SNAT2-, SNAT3-, SNAT5-, SNAT7-, LAT1-, and/or LAT2-mediated glutamine transport provides a benefit. Diseases, disorders, and conditions treatable by the methods of the present disclosure include, but are not limited to, cancer and other proliferative disorders. Compounds of the Disclosure typically bind to ASCT2, BOAT1, SNAT1, SNAT2, SNAT3, SNAT5, SNAT7, LAT1, and/or LAT2 with an inhibition constant *(Ki)* of less than 500 μM, e.g., less than 300 μM, less than 200 pM, less than 100 pM, less than 50 pM, less than 25 pM, less than 5 pM, or less than about 1 pM.

[0117] In one embodiment, the disclosure provides therapeutic methods, uses, and compositions relating to the treatment of cancer. These methods, uses, and compositions comprise administering a therapeutically effective amount of a Compound of the Disclosure to a subject in need thereof.

[0118] In another embodiment, a Compound of the Disclosure is administered to a subject having cancer as a single chemotherapeutic agent.

[0119] In another embodiment, a Compound of the Disclosure is administered to a subject having cancer in combination with one or more optional therapeutic agents. A Compound of the Disclosure and optional therapeutic agent(s) can be administered in combination under one or more of the following conditions: at different periodicities, at different durations, at different concentrations, by different administration routes, *etc.* In some embodiments, a Compound of the Disclosure is administered to the patient according to an intermittent dosing schedule.

[0120] In some embodiments, a Compound of the Disclosure is administered prior to the optional therapeutic agent(s), *e.g.,* 0.5, 1, 2, 3, 4, 5, 10, 12, or 18 hours, 1, 2, 3, 4, 5, or 6 days, or 1, 2, 3, or 4 weeks prior to the administration of the immune checkpoint inhibitor.

[0121] In some embodiments, a Compound of the Disclosure is administered after the optional therapeutic agent(s), *e.g.,* 0.5, 1, 2, 3, 4, 5, 10, 12, or 18 hours, 1, 2, 3, 4, 5, or 6 days, or 1, 2, 3, or 4 weeks after the administration of the immune checkpoint inhibitor.

[0122] In some embodiments, a Compound of the Disclosure and the optional therapeutic agent(s) are administered concurrently but on different schedules, *e.g.,* a Compound of the Disclosure is administered daily while the optional therapeutic agent(s) is administered once a week, once every two weeks, once every three weeks, or once every four weeks. In other

embodiments, a Compound of the Disclosure is administered once a day while the optional therapeutic agent(s) is administered once a week, once every two weeks, once every three weeks, or once every four weeks.

[0123] The therapeutic methods provided herein comprise administering a Compound of the Disclosure to a cancer patient in an amount which is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typically, a Compound of the Disclosure is administered in an amount from about 0.05 mg/kg to about 500 mg/kg, about 0.05 mg/kg to about 100 mg/kg, about 0.05 mg/kg to about 50 mg/kg, or about 0.05 mg/kg to about 10 mg/kg. The dosage of a composition can be at any dosage including, but not limited to, about 0.05 mg/week to about 100 mg/week. Particular doses include 0.05, 1, 2, 5, 10, 20, 500, and 100 mg/kg once daily, or once weekly. In one embodiment, a Compound of the Disclosure is administered one, two, three, four, or five times a week, i.e., the Compound of the Disclosure is administered according to an intermittent dosing schedule. These dosages are exemplary, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of this disclosure. In practice, the physician determines the actual dosing regimen that is most suitable for an individual patient, which can vary with the age, weight, and response of the particular patient.

[0124] The unit oral dose of a Compound of the Disclosure may comprise from about 0.01 to about 1000 mg, e.g., about 0.01 to about 100 mg of Compound of the Disclosure. In one embodiment, the unit oral dose of Compound of the Disclosure is 0.05 mg, 1 mg, 3 mg, 5 mg, 7 mg, 9 mg, 10 mg 12 mg, 14 mg, 15 mg, 17 mg, 20 mg, 22 mg, 25 mg, 27 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, or 100 mg. The unit dose may be administered one or more times daily, e.g., as one or more tablets or capsules. The unit does may also be administered by IV or subcutaneously to the subject. In practice, the physician determines the actual dosing regimen that is most suitable for an individual patient, which can vary with the age, weight, and response of the particular patient.

[0125] In addition to administering a Compound of the Disclosure as a raw chemical, it may be administered as part of a pharmaceutical preparation or composition. In some embodiments, the pharmaceutical preparation or composition can include one or more pharmaceutically acceptable carriers, excipients, and/or auxiliaries. In some embodiments, the one or more carriers, excipients, and auxiliaries facilitate processing of a Compound of the Disclosure into a preparation or composition which can be used pharmaceutically. The preparations, particularly those preparations which can be administered orally, subcutaneously, or topically, and which can be used for one type of administration, such as tablets, dragees, slow release lozenges

and capsules, mouth rinses and mouth washes, gels, liquid suspensions, hair rinses, hair gels, and shampoos, and also preparations which can be administered rectally, such as suppositories, as well as suitable solutions for administration by intravenous infusion, subcutaneous injection, topically or orally, contain from about 0.01 to 99 percent, in one embodiment from about 0.25 to 75 percent of active compound(s), together with the one or more carriers, excipients, and/or auxiliaries.

[0126] The compounds and pharmaceutical compositions provided herein may be administered to any subject which may experience the beneficial effects of a Compound of the Disclosure. Foremost among such subjects are mammals, *e.g.*, humans, although the methods and compositions provided herein are not intended to be so limited. Other subjects include veterinary animals (cows, sheep, pigs, horses, dogs, cats and the like). In one embodiment, the subject is a human cancer patient.

[0127] The pharmaceutical preparations provided herein are manufactured by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

[0128] Suitable excipients are, in particular, fillers such as saccharides, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate. Auxiliaries can be suitable flow-regulating agents and lubricants. Suitable auxiliaries include, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

[0129] Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules which may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are in one embodiment dissolved or suspended in suitable liquids, such as fatty oils, or liquid paraffin. In addition, stabilizers may be added.

[0130] Possible pharmaceutical preparations which can be used rectally include, for example, suppositories, which consist of a combination of one or more of the active compounds with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the active compounds with a base. Possible base materials include, for example, liquid triglycerides, polyethylene glycols, or paraffin hydrocarbons.

[0131] Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts and alkaline solutions. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

[0132] Therapeutically effective amounts of a Compound of the Disclosure and optional therapeutic agent(s) can be formulated in accordance with standard pharmaceutical practices, are administered to a human subject in need thereof. Whether such a treatment is indicated depends on the individual case and is subject to medical assessment (diagnosis) that takes into consideration signs, symptoms, and/or malfunctions that are present, the risks of developing particular signs, symptoms and/or malfunctions, and other factors.

[0133] A Compound of the Disclosure and optional therapeutic agent(s) can be administered by any suitable route, for example by oral, buccal, inhalation, sublingual, rectal, vaginal, intracistemal or intrathecal through lumbar puncture, transurethral, nasal, percutaneous, i.e., transdermal, or parenteral (including intravenous, intramuscular, subcutaneous, intracoronary, intradermal, intramammary, intraperitoneal, intraarticular, intrathecal, retrobulbar, intrapulmonary injection and/or surgical implantation at a particular site) administration. Parenteral administration can be accomplished using a needle and syringe or using a high pressure technique.

[0134] Pharmaceutical compositions include those wherein a Compound of the Disclosure and optional therapeutic agent(s) are administered in an effective amount to achieve its intended purpose. The exact formulation, route of administration, and dosage is determined by an individual physician in view of the diagnosed condition or disease. Dosage amount and interval can be adjusted individually to provide levels of Compound of the Disclosure and the optional therapeutic agent(s) that is sufficient to maintain therapeutic effects.

[0135] Toxicity and therapeutic efficacy of a Compound of the Disclosure and optional therapeutic agent(s) can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the maximum tolerated dose (MTD) of a compound, which defines as the highest dose that causes no toxicity in a patient. The dose ratio between the maximum tolerated dose and therapeutic effects (e.g. inhibiting of tumor growth) is the therapeutic index. The dosage can vary within this range depending upon the dosage form employed, and the route of administration utilized. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0136] A therapeutically effective amount of a Compound of the Disclosure and optional therapeutic agent(s) for use in therapy varies with the nature of the condition being treated, the length of time that activity is desired, and the age and the condition of the subject, and ultimately is determined by the attendant physician. For example, dosage amounts and intervals can be adjusted individually to provide plasma levels of a Compound of the Disclosure and/or optional therapeutic agent(s) that are sufficient to maintain the desired therapeutic effects. The desired dose conveniently can be administered in a single dose, or as multiple doses administered at appropriate intervals, for example as one, two, three, four or more subdoses per day. Multiple doses often are desired, or required. For example, a Compound of the Disclosure can be administered at a frequency of: one dose per day; four doses delivered as one dose per day at four-day intervals (q4d x 4); four doses delivered as one dose per day at three-day intervals (q3d x 4); one dose delivered per day at five-day intervals (qd x 5); one dose per week for three weeks (qwk3); five daily doses, with two days rest, and another five daily doses (5/2/5); or, any dose regimen determined to be appropriate for the circumstance.

[0137] The optional therapeutic agent(s) is administered in therapeutically effective amounts. For example, when the optional therapeutic agent(s) is an immune checkpoint inhibitor, and the immune checkpoint inhibitor is a monoclonal antibody, 1-20 mg/kg is administered as an intravenous infusion every 2-4 weeks. For example, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200

mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg and 2000 mg of the antibody may be administered.

[0138] For example, when the immune checkpoint inhibitor is the anti-PD-1 antibody nivolumab, 3 mg/kg may be administered by intravenous infusion over 60 minutes every two weeks. When the immune checkpoint inhibitor is the anti-PD-1 antibody pembrolizumab, 2 mg/kg may be administered by intravenous infusion over 30 minutes every two or three weeks. When the immune checkpoint inhibitor is the anti-PD-Ll antibody avelumab, 10 mg/kg may be administered by intravenous infusion as frequently as every 2 weeks. Disis *et al*, *J. Clin Oncol. 33* (2015) (suppl; abstr 5509). When the immune checkpoint inhibitor is the anti-PD-Ll antibody MPDL3280A, 20 mg/kg may be administered by intravenous infusion every 3 weeks. Herbst *et al*, *Nature* 575:563-80 (2014). When the immune checkpoint inhibitor is the anti-CTLA-4 antibody ipilumumab, 3 mg/kg may be administered by intravenous infusion over 90 minutes every 3 weeks. When the immune checkpoint inhibitor is the anti-CTLA-4 antibody tremelimumab, 15 mg/kg may be administered by intravenous infusion every 12 weeks. Naido *et al., British Journal of Cancer* 777:2214-19 (2014); *Drugs R D*, 70:123-32 (2010). When the immune checkpoint inhibitor is the anti-LAG3 antibody GSK2831781, 1.5 to 5 mg/kg may be administered by intravenous infusion over 120 minutes every 2-4 weeks. When the immune checkpoint inhibitor is an anti-TIM3 antibody, 1-5 mg/kg may be administered by intravenous infusion over 30-90 minutes every 2-4 weeks. When an inhibitor of indoleamine 2,3-dioxygenase (IDO) pathway is inhibitor indoximod in combination with temozolomide, 18.5 mg/kg/dose BID with an escalation to 27.7 mg/kg/dose BID of indoximod with 200 mg/m^2 every 5 days of temozolomide.

[0139] In one embodiment, the immune checkpoint inhibitor is an antibody and 1-20 mg/kg is administered by intravenous infusion every 2-4 weeks. In another embodiment, 50-2000 mg of the antibody is administered by intravenous infusion every 2-4 weeks. In another embodiment, a Compound of the Disclosure is administered prior to administration of the antibody. In another embodiment, a Compound of the Disclosure is administered 3-7 days prior to the day of administration of the antibody. In another embodiment, a Compound of the Disclosure is also administered the day the antibody is administered and on consecutive days thereafter until disease progression or until Compound of the Disclosure administration is no longer beneficial.

[0140] In one embodiment, the cancer patient receives 2 mg/kg pembrolizumab administered by intravenous infusion every three weeks and, e.g., about 0.1 to 100 mg of a Compound of the Disclosure administered for 1-7 days prior to pembrolizumab administration, optionally, on the day of pembrolizumab administration, and, optionally, thereafter until disease progression or until there is no therapeutic benefit.

[0141] In another embodiment, the cancer patient receives 3 mg/kg nivolumab administered by intravenous infusion every 2 weeks and, e.g., about 0.1 to 100 mg of a Compound of the Disclosure administered for 1-7 days prior to nivolumab administration, optionally, on the day of nivolumab administration, and, optionally, thereafter until disease progression or until there is no therapeutic benefit.

[0142] In another embodiment, the cancer patient receives 3 mg/kg nivolumab administered by intravenous infusion every 2 weeks and, e.g., about 0.1 to 100 mg of a Compound of the Disclosure administered for 1-7 days prior to nivolumab administration, optionally, on the day of nivolumab administration, and, optionally, thereafter until disease progression or until there is no therapeutic benefit.

[0143] In another embodiment, the treatment of the cancer patient with a Compound of the Disclosure and an immune checkpoint inhibitor induces anti-proliferative response faster than when the immune checkpoint inhibitor is administered alone.

[0144] In one embodiment, the disclosure provides a method of treating cancer in a subject, wherein the cancer is a solid tumor. In another embodiment, the cancer is a hematological cancer.

[0145] In another embodiment, the cancer is any one or more of the cancers of Table 3.

Table 3

adrenal cancer	acinic cell carcinoma	acoustic neuroma	acral lentigious melanoma
acrospiroma	acute eosinophilic leukemia	acute erythroid leukemia	acute lymphoblastic leukemia
acute megakaryoblastic leukemia	acute monocytic leukemia	acute promyelocytic leukemia	adenocarcinoma
adenoid cystic carcinoma	adenoma	adenomatoid odontogenic tumor	adenosquamous carcinoma
adipose tissue neoplasm	adrenocortical carcinoma	adult T-cell leukemia/lymphoma	aggressive NK-cell leukemia
AIDS-related lymphoma	alveolar rhabdomyosarcoma	alveolar soft part sarcoma	ameloblastic fibroma
anaplastic large cell lymphoma	anaplastic thyroid cancer	angioimmunoblastic T-cell lymphoma	angiomyolipoma
angiosarcoma	astrocytoma	atypical teratoid rhabdoid tumor	B-cell chronic lymphocytic leukemia
B-cell prolymphocytic leukemia	B-cell lymphoma	basal cell carcinoma	biliary tract cancer
bladder cancer	blastoma	bone cancer	Brenner tumor
Brown tumor	Burkitt's lymphoma	breast cancer	brain cancer
carcinoma	carcinoma in situ	carcinosarcoma	cartilage tumor
cementoma	myeloid sarcoma	chondroma	chordoma

choriocarcinoma	choroid plexus papilloma	clear-cell sarcoma of the kidney	craniopharyngioma
cutaneous T-cell lymphoma	cervical cancer	colorectal cancer	Degos disease
desmoplastic small round cell tumor	diffuse large B-cell lymphoma	dysembryoplastic neuroepithelial tumor	dysgerminoma
embryonal carcinoma	endocrine gland neoplasm	endodermal sinus tumor	enteropathy-associated T-cell lymphoma
esophageal cancer	fetus in fetu	fibroma	fibrosarcoma
follicular lymphoma	follicular thyroid cancer	ganglioneuroma	gastrointestinal cancer
germ cell tumor	gestational choriocarcinoma	giant cell fibroblastoma	giant cell tumor of the bone
glial tumor	glioblastoma multiforme	glioma	gliomatosis cerebri
glucagonoma	gonadoblastoma	granulosa cell tumor	gynandroblastoma
gallbladder cancer	gastric cancer	hairy cell leukemia	hemangioblastoma
head and neck cancer	hemangiopericytoma	hematological cancer	hepatoblastoma
hepatosplenic T-cell lymphoma	Hodgkin's lymphoma	non-Hodgkin's lymphoma	invasive lobular carcinoma
intestinal cancer	kidney cancer	laryngeal cancer	lentigo maligna
lethal midline carcinoma	leukemia	leydig cell tumor	liposarcoma
lung cancer	lymphangioma	lymphangiosarcoma	lymphoepithelioma
lymphoma	acute lymphocytic leukemia	acute myelogeous leukemia	chronic lymphocytic leukemia
liver cancer	small cell lung cancer	non-small cell lung cancer	MALT lymphoma
malignant fibrous histiocytoma	malignant peripheral nerve sheath tumor	malignant triton tumor	mantle cell lymphoma
marginal zone B-cell lymphoma	mast cell leukemia	mediastinal germ cell tumor	medullary carcinoma of the breast
medullary thyroid cancer	medulloblastoma	melanoma	meningioma
merkel cell cancer	mesothelioma	metastatic urothelial carcinoma	mixed Mullerian tumor
mucinous tumor	multiple myeloma	muscle tissue neoplasm	mycosis fungoides
myxoid liposarcoma	myxoma	myxosarcoma	nasopharyngeal carcinoma
neurinoma	neuroblastoma	neurofibroma	neuroma
nodular melanoma	ocular cancer	oligoastrocytoma	oligodendroglioma
oncocytoma	optic nerve sheath meningioma	optic nerve tumor	oral cancer
osteosarcoma	ovarian cancer	Pancoast tumor	papillary thyroid cancer

paraganglioma	pinealoblastoma	pineocytoma	pituicytoma
pituitary adenoma	pituitary tumor	plasmacytoma	polyembryoma
precursor T-lymphoblastic lymphoma	primary central nervous system lymphoma	primary effusion lymphoma	preimary peritoneal cancer
prostate cancer	pancreatic cancer	pharyngeal cancer	pseudomyxoma periotonei
renal cell carcinoma	renal medullary carcinoma	retinoblastoma	rhabdomyoma
rhabdomyosarcoma	Richter's transformation	rectal cancer	sarcoma
Schwannomatosis	seminoma	Sertoli cell tumor	sex cord-gonadal stromal tumor
signet ring cell carcinoma	skin cancer	small blue round cell tumors	small cell carcinoma
soft tissue sarcoma	somatostatinoma	soot wart	spinal tumor
splenic marginal zone lymphoma	squamous cell carcinoma	synovial sarcoma	Sezary's disease
small intestine cancer	squamous carcinoma	stomach cancer	T-cell lymphoma
testicular cancer	thecoma	thyroid cancer	transitional cell carcinoma
throat cancer	urachal cancer	urogenital cancer	urothelial carcinoma
uveal melanoma	uterine cancer	verrucous carcinoma	visual pathway glioma
vulvar cancer	vaginal cancer	Waldenstrom's macroglobulinemia	Warthin's tumor
Wilms' tumor			

[0146] Exemplary hematological cancers include, but are not limited to, the cancers listed in Table 4. In another embodiment, the hematological cancer is acute lymphocytic leukemia, chronic lymphocytic leukemia (including B-cell chronic lymphocytic leukemia), or acute myeloid leukemia.

Table 4

acute lymphocytic leukemia (ALL)	acute eosinophilic leukemia
acute myeloid leukemia (AML)	acute erythroid leukemia
chronic lymphocytic leukemia (CLL)	acute lymphoblastic leukemia
small lymphocytic lymphoma (SLL)	acute megakaryoblastic leukemia
multiple myeloma (MM)	acute monocytic leukemia
Hodgkins lymphoma (HL)	acute promyelocytic leukemia
non-Hodgkin's lymphoma (NHL)	acute myelogeous leukemia
mantle cell lymphoma (MCL)	B-cell prolymphocytic leukemia
marginal zone B-cell lymphoma	B-cell lymphoma
splenic marginal zone lymphoma	MALT lymphoma
follicular lymphoma (FL)	precursor T-lymphoblastic lymphoma
Waldenstrom's macroglobulinemia (WM)	T-cell lymphoma
diffuse large B-cell lymphoma (DLBCL)	mast cell leukemia

marginal zone lymphoma (MZL)	adult T cell leukemia/lymphoma
hairy cell leukemia (HCL)	aggressive NK-cell leukemia
Burkitt's lymphoma (BL)	angioimmunoblastic T-cell lymphoma
Richter's transformation	

[0147] In another embodiment, the cancer is selected from the group consisting of squamous cell carcinoma of the head and neck, adenocarcinoma squamous cell carcinoma of the esophagus, adenocarcinoma of the stomach, adenocarcinoma of the colon, hepatocellular carcinoma, cholangiocarcinoma of the biliary system, adenocarcinoma of gall bladder, adenocarcinoma of the pancreas, ductal carcinoma in situ of the breast, adenocarcinoma of the breast, adenocarcinoma of the lungs, squamous cell carcinoma of the lungs, transitional cell carcinoma of the bladder, squamous cell carcinoma of the bladder, squamous cell carcinoma of the cervix, adenocarcinoma of the cervix, endometrial carcinoma, penile squamous cell carcinoma, and squamous cell carcinoma of the skin.

[0148] In another embodiment, a precancerous tumor is selected from the group consisting of leukoplakia of the head and neck, Barrett's esophagus, metaplasia of the stomach, adenoma of the colon, chronic hepatitis, bile duct hyperplasia, pancreatic intraepithelial neoplasia, atypical adenomatous hyperplasia of the lungs, dysplasia of the bladder, cervical initraepithelial neoplasia, penile intraepithelial neoplasia, and actinic keratosis of the skin.

[0149] In another embodiment, the cancer is selected from the group consisting of hepatocellular carcinoma, glioblastoma, lung cancer, breast cancer, head and neck cancer, prostate cancer, melanoma, and colorectal cancer.

[0150] In another embodiment, the cancer is selected from the group consisting of colorectal cancer, breast cancer, lymphoma, melanoma, kidney cancer, and lung cancer.

[0151] In another embodiment, the cancer has become resistant to conventional cancer treatments. The term "conventional cancer treatments" as used herein refers to any cancer drugs, biologies, or radiotherapy, or combination of cancer drugs and/or biologies and/or radiotherapy that have been tested and/or approved for therapeutic use in humans by the U.S. Food and Drug Administration, European Medicines Agency, or similar regulatory agency.

[0152] In another embodiment, the subject has been treated previously with an anticancer agent, e.g., an immune checkpoint inhibitor, without a Compound of the Disclosure. For example, the previous immune checkpoint therapy may be an anti-PD-1 or anti-PD-Ll therapy.

[0153] In another embodiment, the present disclosure provides therapeutic methods of treating a subject having cancer, comprising administering to the subject a therapeutically effective

amount of a Compound of the Disclosure, wherein the Compound of the Disclosure is administered to the subject according to an intermittent dosing schedule.

[0154] In another embodiment, the present disclosure provides therapeutic methods of treating a subject having cancer, comprising administering to the subject therapeutically effective amounts of a Compound of the Disclosure, and an optional therapeutic agent, e.g., an immune checkpoint inhibitor, wherein the Compound of the Disclosure is administered to the subject according to an intermittent dosing schedule.

[0155] In another embodiment, the present disclosure provides therapeutic methods of treating a subject having cancer, comprising administering to the subject therapeutically effective amounts of a Compound of the Disclosure, an immune checkpoint inhibitor, and a third optional therapeutic agent, e.g., radiation.

[0156] In another embodiment, the present disclosure provides kits comprising a Compound of the Disclosure (or a composition comprising a Compound of the Disclosure) packaged in a manner that facilitates their use to practice methods of the present disclosure. In one embodiment, the kit includes a Compound of the Disclosure (or a composition comprising a Compound of the Disclosure) packaged in a container, such as a sealed bottle or vessel, with a label affixed to the container or included in the kit that describes use of the compound or composition to practice the method of the disclosure. In one embodiment, the compound or composition is packaged in a unit dosage form. The kit further can include a device suitable for administering the composition according to the intended route of administration.

[0157] The present disclosure provides the following particular embodiments with regard to therapeutic methods.

[0158] Embodiment I. A method of treating cancer a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the a Compound of the Disclosure.

[0159] Embodiment II. The method of Embodiment I, wherein the cancer is a solid tumor.

[0160] Embodiment III. The method of Embodiment I, wherein the cancer is a hematological cancer.

[0161] Embodiment IV. The method of Embodiment I, wherein the cancer is any one or more of the cancers of Table 3.

[0162] Embodiment V. The method of Embodiment I, wherein the cancer is any one or more of the cancers of Table 4.

[0163] Embodiment VI. The method of any one of Embodiments I-V further comprising administering to the subject a therapeutically effective amount of one or more optional therapeutic agents useful in the treatment of cancer.

[0164] Embodiment VII. The pharmaceutical composition comprising a Compound of the Disclosure and one or more pharmaceutically acceptable excipients for use in treating cancer.

[0165] Embodiment VIII. The pharmaceutical composition of Embodiment VII, wherein the cancer is a solid tumor.

[0166] Embodiment IX. The pharmaceutical composition of Embodiment VII, wherein the cancer is a hematological cancer.

[0167] Embodiment X The pharmaceutical composition of Embodiment VII, wherein the cancer is any one or more of the cancers of Table 3.

[0168] Embodiment XI. The pharmaceutical composition of Embodiment VII, wherein the cancer is any one or more of the cancers of Table 4.

[0169] Embodiment XII. A Compound of the Disclosure for use in treating of cancer.

[0170] Embodiment XIII. The compound for use of Embodiment XII, wherein the cancer is a solid tumor.

[0171] Embodiment XIV. The compound for use of Embodiment XII, wherein the cancer is a hematological cancer.

[0172] Embodiment XV The compound for use of Embodiment XII, wherein the cancer is any one or more of the cancers of Table 3.

[0173] Embodiment XVI. The compound for use of Embodiment XII, wherein the cancer is any one or more of the cancers of Table 4.

[0174] Embodiment XVII. The compound for use of any one of Embodiments XII-XVI, wherein the compound is to be administered to the subject in combination with a therapeutically effective amount of one or more optional therapeutic agents useful in the treatment of cancer.

[0175] Embodiment XVIII. Use of a Compound of the Disclosure for the manufacture of a medicament for treatment of cancer.

[0176] Embodiment XIX. The use of Embodiment XVIII, wherein the cancer is a solid tumor.

[0177] Embodiment XX. The use of Embodiment XVIII, wherein the cancer is a hematological cancer.

[0178] Embodiment XXI The use of Embodiment XVIII, wherein the cancer is any one or more of the cancers of Table 3.

[0179] Embodiment XXII. The use of Embodiment XVIII, wherein the cancer is any one or more of the cancers of Table 4.

[0180] Embodiment XXIII. The use of any one of Embodiments XVIII-XXII, wherein the compound is to be administered to the in combination with a therapeutically effective amount of one or more optional therapeutic agents useful in the treatment of cancer.

[0181] Embodiment XXIV. A therapeutic or prophylactic agent for cancer, which comprises a Compound of the Disclosure.

[0182] Embodiment XXV. A kit comprising a Compound of the Disclosure and instructions for administering the compound to a subject having cancer.

[0183] Embodiment XXVI. The kit of Embodiment XXV, wherein the cancer is a solid tumor.

[0184] Embodiment XXVII. The kit of Embodiment XXV, wherein the cancer is a hematological cancer.

[0185] Embodiment XXVIII. The kit of Embodiment XXV, wherein the cancer is any one or more of the cancers of Table 3.

[0186] Embodiment XXIX. The kit of Embodiment XXV, wherein the cancer is any one or more of the cancers of Table 4.

[0187] Embodiment XXX. The kit of any one of Embodiments XXV-XXIX further comprising one or more optional therapeutic agents useful in the treatment of cancer.

III. Optional Therapeutic agents

[0188] In some therapeutic methods and uses of the disclosure, a Compound of the Disclosure is administered to a subject having a disease, disorder, or condition, e.g., cancer, as a single agent. In other therapeutic methods and uses of the disclosure, a Compound of the Disclosure is administered to a subject having a disease, disorder, or condition, e.g., cancer, in combination with one or more optional therapeutic agents. In one embodiment, a Compound of the Disclosure is administered in combination with one optional therapeutic agent. In another embodiment, a Compound of the Disclosure is administered in combination with two optional therapeutic agents. In another embodiment, a Compound of the Disclosure is administered in combination with three optional therapeutic agents. Optional therapeutic agents useful in treating cancer patients include those known in the art as well as those developed in the future.

[0189] Optional therapeutic agents are administered in an amount to provide their desired therapeutic effect. The effective dosage range for each optional therapeutic agent is known in the art, and the optional therapeutic agent is administered to an individual in need thereof within such established ranges.

[0190] A Compound of the Disclosure and the optional therapeutic agent(s) can be administered together as a single-unit dose or separately as multi-unit doses, and in any order, e.g., wherein a Compound of the Disclosure is administered before the optional therapeutic agent(s), or vice versa. One or more doses of a Compound of the Disclosure and the optional therapeutic agent(s) can be administered to the subject.

[0191] In one embodiment, the optional therapeutic agent is an immune checkpoint inhibitor. Immune checkpoint inhibitors are therapies that blockade immune system inhibitor checkpoints. Immune checkpoints can be stimulatory or inhibitory. Blockade of inhibitory immune checkpoint activates immune system function and can be used for cancer immunotherapy. Pardoll, *Nature Reviews. Cancer* 72:252-64 (2012). Tumor cells turn off activated T cells when they attach to specific T-cell receptors. Immune checkpoint inhibitors prevent tumor cells from attaching to T cells, which results in T cells remaining activated. In effect, the coordinated action by cellular and soluble components combats pathogens and injuries by cancers. The modulation of immune system pathways may involve changing the expression or the functional activity of at least one component of the pathway to then modulate the response by the immune system. U.S. 2015/0250853. Examples of immune checkpoint inhibitors include PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors, LAG3 inhibitors, TIM3 inhibitors, cd47 inhibitors, and B7-H1 inhibitors. Thus, in one embodiment, the immune checkpoint inhibitor is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, a LAG3 inhibitor, a TIM3 inhibitor, and a cd47 inhibitor.

[0192] In another embodiment, the immune checkpoint inhibitor is a programmed cell death (PD-1) inhibitor. PD-1 is a T-cell coinhibitory receptor that plays a pivotal role in the ability of tumor cells to evade the host's immune system. Blockage of interactions between PD-1 and PD-Ll, a ligand of PD-1, enhances immune function and mediates antitumor activity. Examples of PD-1 inhibitors include antibodies that specifically bind to PD-1. Particular anti-PD-1 antibodies include, but are not limited to nivolumab, pembrolizumab, STI-A1014, and pidilzumab. For a general discussion of the availability, methods of production, mechanism of action, and clinical studies of anti-PD-1 antibodies, see U.S. 2013/0309250, U.S. 6,808,710, U.S. 7,595,048, U.S. 8,008,449, U.S. 8,728,474, U.S. 8,779,105, U.S. 8,952,136, U.S. 8,900,587, U.S. 9,073,994, U.S. 9,084,776, and Naido *et al., British Journal of Cancer* 777:2214-19 (2014).

[0193] In another embodiment, the immune checkpoint inhibitor is a PD-L1 (also known as B7-H1 or CD274) inhibitor. Examples of PD-L1 inhibitors include antibodies that specifically bind to PD-L1. Particular anti-PD-Ll antibodies include, but are not limited to, avelumab, atezolizumab, durvalumab, and BMS-936559. For a general discussion of the availability,

methods of production, mechanism of action, and clinical studies, see U.S. 8,217,149, U.S. 2014/0341917, U.S. 2013/0071403, WO 2015036499, and Naido *et al, British Journal of Cancer* 777:2214-19 (2014).

[0194] In another embodiment, the immune checkpoint inhibitor is a CTLA-4 inhibitor. CTLA-4, also known as cytotoxic T-lymphocyte antigen 4, is a protein receptor that downregulates the immune system. CTLA-4 is characterized as a "brake" that binds costimulatory molecules on antigen-presenting cells, which prevents interaction with CD28 on T cells and also generates an overtly inhibitory signal that constrains T cell activation. Examples of CTLA-4 inhibitors include antibodies that specifically bind to CTLA-4. Particular anti-CTLA-4 antibodies include, but are not limited to, ipilimumab and tremelimumab. For a general discussion of the availability, methods of production, mechanism of action, and clinical studies, see U.S. 6,984,720, U.S. 6,207,156, and Naido *et al., British Journal of Cancer* 777:2214-19 (2014).

[0195] In another embodiment, the immune checkpoint inhibitor is a LAG3 inhibitor. LAG3, Lymphocyte Activation Gene 3, is a negative co-simulatory receptor that modulates T cell homeostatis, proliferation, and activation. In addition, LAG3 has been reported to participate in regulatory T cells (Tregs) suppressive function. A large proportion of LAG3 molecules are retained in the cell close to the microtubule-organizing center, and only induced following antigen specific T cell activation. U.S. 2014/0286935. Examples of LAG3 inhibitors include antibodies that specifically bind to LAG3. Particular anti-LAG3 antibodies include, but are not limited to, GSK2831781. For a general discussion of the availability, methods of production, mechanism of action, and studies, see, U.S. 2011/0150892, U.S. 2014/0093511, U.S. 20150259420, and Huang *et al, Immunity* 21:503-13 (2004).

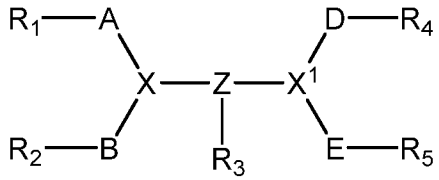
[0196] In another embodiment, the immune checkpoint inhibitor is a TIM3 inhibitor. TIM3, T-cell immunoglobulin and mucin domain 3, is an immune checkpoint receptor that functions to limit the duration and magnitude of T_H1 and T_C1 T-cell responses. The TIM3 pathway is considered a target for anticancer immunotherapy due to its expression on dysfunctional $CD8^+$ T cells and Tregs, which are two reported immune cell populations that constitute immunosuppression in tumor tissue. Anderson, *Cancer Immunology Research* 2:393-98 (2014). Examples of TIM3 inhibitors include antibodies that specifically bind to TIM3. For a general discussion of the availability, methods of production, mechanism of action, and studies of TIM3 inhibitors, see U.S. 20150225457, U.S. 20130022623, U.S. 8,522,156, Ngiow *et al, Cancer Res 71:* 6567-71 (2011), Ngiow, *et al, Cancer Res* 77:3540-51 (2011), and *Anderson, Cancer Immunology Res* 2:393-98 (2014).

[0197] In another embodiment, the immune checkpoint inhibitor is a cd47 inhibitor. *See* Unanue, E.R., *PNAS* 110: 10886-87 (2013).

[0198] The term "antibody" is meant to include intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least two intact antibodies, and antibody fragments, so long as they exhibit the desired biological activity. In another embodiment, "antibody" is meant to include soluble receptors that do not possess the Fc portion of the antibody. In one embodiment, the antibodies are humanized monoclonal antibodies and fragments thereof made by means of recombinant genetic engineering.

[0199] Another class of immune checkpoint inhibitors include polypeptides that bind to and block PD-1 receptors on T-cells without triggering inhibitor signal transduction. Such peptides include B7-DC polypeptides, B7-H1 polypeptides, B7-1 polypeptides and B7-2 polypeptides, and soluble fragments thereof, as disclosed in U.S. Pat. 8,114,845.

[0200] Another class of immune checkpoint inhibitors include compounds with peptide moieties that inhibit PD-1 signaling. Examples of such compounds are disclosed in U.S. Pat. 8,907,053 and have the structure:



or a pharmaceutically acceptable salt thereof, wherein the compound comprises at least 5 amino acids useful as therapeutic agents capable of inhibiting the PD-1 signaling pathway.

[0201] Another class of immune checkpoint inhibitors include inhibitors of certain metabolic enzymes, such as indoleamine 2,3 dioxygenase (IDO), which is expressed by infiltrating myeloid cells and tumor cells. The IDO enzyme inhibits immune responses by depleting amino acids that are necessary for anabolic functions in T cells or through the synthesis of particular natural ligands for cytosolic receptors that are able to alter lymphocyte functions. Pardoll, *Nature Reviews. Cancer* 72:252-64 (2012); Lob, *Cancer Immunol Immunother 58:* 153-57 (2009). Particular IDO blocking agents include, but are not limited to levo-1-methyl typtophan (L-1MT) and 1-methyl-tryptophan (1MT). Qian *et al*, *Cancer Res* 69:5498-504 (2009); and Lob *et al*, *Cancer Immunol Immunother 58:* 153-7 (2009).

[0202] In one embodiment, the immune checkpoint inhibitor is nivolumab, pembrolizumab, pidilizumab, STI-A1110, avelumab, atezolizumab, durvalumab, STI-A1014, ipilimumab, tremelimumab, GSK2831781, BMS-936559 or MED14736.

[0203] In another embodiment, the optional therapeutic agent is an epigenetic drug. As used herein, the term "epigenetic drug" refers to a therapeutic agent that targets an epigenetic regulator. Examples of epigenetic regulators include the histone lysine methyltransferases, histone arginine methyl transferases, histone demethylases, histone deacetylases, histone acetylases, and DNA methyltransferases. Histone deacetylase inhibitors include, but are not limited to, vorinostat.

[0204] In another embodiment, the optional therapeutic agent is a chemotherapeutic agent or other anti-proliferative agent that can be administered in combination with a Compound of the Disclosure to treat cancer. Examples of conventional therapies and anticancer agents that can be used in combination with a Compound of the Disclosure include surgery, radiotherapy (e.g., gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes), endocrine therapy, a biologic response modifier (e.g., an interferon, an interleukin, tumor necrosis factor (TNF), hyperthermia and cryotherapy, an agent to attenuate any adverse effect (e.g., an antiemetic), and any other approved biologic therapy or chemotherapy, e.g., a treatment regimen that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. Chemotherapy may be given by mouth, injection, or infusion, or on the skin, depending on the type and stage of the cancer being treated.

[0205] Nonlimiting exemplary antiproliferative compounds include an aromatase inhibitor; an anti-estrogen; an anti-androgen; a gonadorelin agonist; a topoisomerase I inhibitor; a topoisomerase II inhibitor; a microtubule active agent; an alkylating agent, e.g., temozolomide; a retinoid, a carontenoid, or a tocopherol; a cyclooxygenase inhibitor; an MMP inhibitor; an mTOR inhibitor; an antimetabolite; a platin compound; a methionine aminopeptidase inhibitor; a bisphosphonate; an antiproliferative antibody; aheparanase inhibitor; an inhibitor of Ras oncogenic isoforms; a telomerase inhibitor; a proteasome inhibitor; a compound used in the treatment of hematologic malignancies; a Flt-3 inhibitor; an Hsp90 inhibitor; a kinesin spindle protein inhibitor; a MEK inhibitor; an antitumor antibiotic; a nitrosourea; a compound targeting/decreasing protein or lipid kinase activity, a compound targeting/decreasing protein or lipid phosphatase activity, or any further anti-angiogenic compound.

[0206] Nonlimiting exemplary aromatase inhibitors include steroids, such as atamestane, exemestane, and formestane, and non-steroids, such as aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole, and letrozole.

[0207] Nonlimiting anti-estrogens include tamoxifen, fulvestrant, raloxifene, and raloxifene hydrochloride. Anti-androgens include, but are not limited to, bicalutamide. Gonadorelin agonists include, but are not limited to, abarelix, goserelin, and goserelin acetate.

[0208] Nonlimiting exemplary topoisomerase I inhibitors include topotecan, gimatecan, irinotecan, camptothecin and its analogues, 9-nitrocamptothecin, and the macromolecular camptothecin conjugate PNU-166148. Topoisomerase II inhibitors include, but are not limited to, anthracyclines, such as doxorubicin, daunorubicin, epirubicin, idarubicin, and nemorubicin; anthraquinones, such as mitoxantrone and losoxantrone; and podophillotoxines, such as etoposide and teniposide.

[0209] Microtubule active agents include microtubule stabilizing, microtubule destabilizing compounds, and microtububn polymerization inhibitors including, but not limited to, taxanes, such as pacbtaxel and docetaxel; discodermolides; cochicine and epothilones and derivatives thereof.

[0210] Nonlimiting exemplary alkylating agents include cyclophosphamide, ifosfamide, melphalan, and nitrosoureas, such as carmustine and lomustine.

[0211] Nonlimiting exemplary matrix metalloproteinase inhibitors ("MMP inhibitors") include collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, batimastat, marimastat, prinomastat, metastat, BMS-279251, BAY 12-9566, TAA211, MMI270B, and AAJ996.

[0212] Nonlimiting exemplary mTOR inhibitors include compounds that inhibit the mammalian target of rapamycin (mTOR) and possess antiproliferative activity such as sirolimus, everolimus, CCI-779, and ABT578.

[0213] Nonlimiting exemplary antimetabolites include 5-fluorouracil (5-FU), capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists, such as pemetrexed.

[0214] Nonlimiting exemplary platin compounds include carboplatin, cis-platin, cisplatinum, and oxabplatin.

[0215] Nonlimiting exemplary methionine aminopeptidase inhibitors include bengamide or a derivative thereof and PPI-2458.

[0216] Nonlimiting exemplary bisphosphonates include etridonic acid, clodronic acid, tiludronic acid, pamidronic acid, alendronic acid, ibandronic acid, risedronic acid, and zoledronic acid.

[0217] Nonlimiting exemplary heparanase inhibitors include compounds that target, decrease, or inhibit heparin sulfate degradation, such as PI-88 and OGT21 15.

[0218] Nonlimiting exemplary compounds which target, decrease, or inhibit the oncogenic activity of Ras include famesyl transferase inhibitors, such as L-744832, DK8G557, tipifamib, and lonafamib.

[0219] Nonlimiting exemplary telomerase inhibitors include compounds that target, decrease, or inhibit the activity of telomerase, such as compounds that inhibit the telomerase receptor, such as telomestatin.

[0220] Nonlimiting exemplary proteasome inhibitors include compounds that target, decrease, or inhibit the activity of the proteasome including, but not limited to, bortezomib. In some embodiments, the proteasome inhibitor is carfilzomib.

[0221] Nonlimiting exemplary FMS-like tyrosine kinase inhibitors, which are compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R) include interferon, I-β-D-arabinofuransylcytosine (ara-c), and bisulfan; and ALK inhibitors, which are compounds which target, decrease, or inhibit anaplastic lymphoma kinase.

[0222] Nonlimiting exemplary Flt-3 inhibitors include PKC412, midostaurin, a staurosporine derivative, SU11248, and MLN518.

[0223] Nonlimiting exemplary HSP90 inhibitors include compounds targeting, decreasing, or inhibiting the intrinsic ATPase activity of HSP90; or degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins, or antibodies that inhibit the ATPase activity of HSP90, such as 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

[0224] Nonlimiting exemplary protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, include a) a compound targeting, decreasing, or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as a compound that targets, decreases, or inhibits the activity of PDGFR, such as an N-phenyl-2-pyrimidine-amine derivatives, such as imatinib, SUIOI, SU6668, and GFB-111; b) a compound targeting, decreasing, or inhibiting the activity of the fibroblast growth factor-receptors (FGFR); c) a compound targeting, decreasing, or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as a compound that targets, decreases, or inhibits the activity of IGF-IR; d) a compound targeting, decreasing, or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors; e) a compound targeting, decreasing, or inhibiting the activity of the Axl receptor tyrosine kinase family; f) a compound targeting, decreasing, or inhibiting the activity of the Ret receptor tyrosine kinase; g) a compound targeting, decreasing, or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, such as imatinib; h) a compound targeting, decreasing, or inhibiting the activity of the c-Kit receptor tyrosine kinases, such as imatinib; i) a compound targeting, decreasing, or inhibiting the activity of members of the c-Abl family, their

gene-fusion products (e.g. Bcr-Abl kinase) and mutants, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib or nilotinib; PD180970; AG957; NSC 680410; PD173955; or dasatinib; j) a compound targeting, decreasing, or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK1, PKB/Akt, and Ras/MAPK family members, and/or members of the cyclin-dependent kinase family (CDK), such as a staurosporine derivative disclosed in U.S. Patent No. 5,093,330, such as midostaurin; examples of further compounds include UCN-01, safmgol, BAY 43-9006, bryostatin 1, perifosine; ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; a isochinoline compound; a famesyl transferase inhibitor; PD184352 or QAN697, or AT7519; k) a compound targeting, decreasing or inhibiting the activity of a protein-tyrosine kinase, such as imatinib mesylate or a tyrphostin, such as Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino} -benzoic acid adamantyl ester; NSC 680410, adaphostin); 1) a compound targeting, decreasing, or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as CP 358774, ZD 1839, ZM 105180; trastuzumab, cetuximab, gefitinib, erlotinib, osimertinib, OSI-774, Cl-1033, EKB-569, GW-2016, antibodies ELI, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 and E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives; and m) a compound targeting, decreasing, or inhibiting the activity of the c-Met receptor.

[0225] Nonlimiting exemplary compounds that target, decrease, or inhibit the activity of a protein or lipid phosphatase include inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[0226] Further anti-angiogenic compounds include compounds having another mechanism for their activity unrelated to protein or lipid kinase inhibition, e.g., thalidomide and TNP-470.

[0227] Additional, nonlimiting, exemplary chemotherapeutic compounds, one or more of which may be used in combination with a Compound of the Disclosure include: avastin, daunorubicin, adriamycin, Ara-C, VP-16, teniposide, mitoxantrone, idarubicin, carboplatinum, PKC412, 6-mercaptopurine (6-MP), fludarabine phosphate, octreotide, SOM230, FTY720, 6-thioguanine, cladribine, 6-mercaptopurine, pentostatin, hydroxyurea, 2-hydroxy-lH-isoindole-l,3-dione derivatives, l-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, l-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine succinate, angiostatin, endostatin, anthranilic acid amides, ZD4190, ZD6474, SU5416, SU6668, bevacizumab, rhuMAb, rhuFab, macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgGI antibody, RPI 4610,

bevacizumab, porfimer sodium, anecortave, triamcinolone, hydrocortisone, 11-a-epihydrocotisol, cortex olone, 17a-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone, dexamethasone, fluocinolone, a plant alkaloid, a hormonal compound and/or antagonist, a biological response modifier, such as a lymphokine or interferon, an antisense oligonucleotide or oligonucleotide derivative, shRNA, and siRNA.

[0228] A number of suitable optional therapeutic, e.g., anticancer, agents are contemplated for use in the therapeutic methods provided herein. Indeed, the methods provided herein can include, but are not limited to, administration of numerous optional therapeutic agents such as: agents that induce apoptosis; polynucleotides *(e.g.,* anti-sense, ribozymes, siRNA); polypeptides *(e.g.,* enzymes and antibodies); biological mimetics *(e.g.,* gossypol or BH3 mimetics); agents that bind *(e.g.,* oligomerize or complex) with a Bcl-2 family protein such as Bax; alkaloids; alkylating agents; antitumor antibiotics; antimetabolites; hormones; platinum compounds; monoclonal or polyclonal antibodies *(e.g.,* antibodies conjugated with anticancer drugs, toxins, defensins), toxins; radionuclides; biological response modifiers *(e.g.,* interferons *(e.g.,* IFN-a) and interleukins *(e.g.,* IL-2)); adoptive immunotherapy agents; hematopoietic growth factors; agents that induce tumor cell differentiation *(e.g.,* all-trans-retinoic acid); gene therapy reagents *(e.g.,* antisense therapy reagents and nucleotides); tumor vaccines; angiogenesis inhibitors; proteosome inhibitors: NF-KB modulators; anti-CDK compounds; HDAC inhibitors; and the like. Numerous other examples of optional therapeutic agents such as chemotherapeutic compounds and anticancer therapies suitable for co-administration with the disclosed compounds are known to those skilled in the art.

[0229] In certain embodiments, anticancer agents comprise agents that induce or stimulate apoptosis. Agents that induce or stimulate apoptosis include, for example, agents that interact with or modify DNA, such as by intercalating, cross-linking, alkylating, or otherwise damaging or chemically modifying DNA. Agents that induce apoptosis include, but are not limited to, radiation *(e.g.,* X-rays, gamma rays, UV); tumor necrosis factor (TNF)-related factors *(e.g.,* TNF family receptor proteins, TNF family ligands, TRAIL, antibodies to TRAIL-R1 or TRAIL-R2); kinase inhibitors *(e.g.,* epidermal growth factor receptor (EGFR) kinase inhibitor. Additional anticancer agents include: vascular growth factor receptor (VGFR) kinase inhibitor, fibroblast growth factor receptor (FGFR) kinase inhibitor, platelet-derived growth factor receptor (PDGFR) kinase inhibitor, and Bcr-Abl kinase inhibitors (such as GLEEVEC)); antisense molecules; antibodies *(e.g.,* HERCEPTIN, RITUXAN, ZEVALIN, and AVASTIN); anti-estrogens *(e.g.,* raloxifene and tamoxifen); anti-androgens *(e.g.,* flutamide, bicalutamide, finasteride, aminoglutethamide, ketoconazole, and corticosteroids); cyclooxygenase 2 (COX-2) inhibitors *(e.g.,* celecoxib, meloxicam, NS-398, and non-steroidal anti-inflammatory drugs (NSAIDs)); anti-inflammatory

drugs *(e.g.,* butazolidin, DECADRON, DELTASONE, dexamethasone, dexamethasone intensol, DEXONE, HEXADROL, hydroxychloroquine, METICORTEN, ORADEXON, ORASONE, oxyphenbutazone, PEDIAPRED, phenylbutazone, PLAQUENIL, prednisolone, prednisone, PRELONE, and TANDEARIL); and cancer chemotherapeutic drugs *(e.g.,* irinotecan (CAMPTOSAR), CPT-11, fludarabine (FLUDARA), dacarbazine (DTIC), dexamethasone, mitoxantrone, MYLOTARG, VP-16, cisplatin, carboplatin, oxaliplatin, 5-FU, doxorubicin, gemcitabine, bortezomib, gefitinib, bevacizumab, TAXOTERE or TAXOL); cellular signaling molecules; ceramides and cytokines; staurosporine, and the like.

[0230] In still other embodiments, the therapeutic methods provided herein include administering to a subject having cancer (a cancer patient) therapeutically effective amounts of a Compound of the Disclosure, an immune checkpoint inhibitor, and at least one additional optional therapeutic agent, e.g., an anti-hyperproliferative or antineoplastic agent selected from alkylating agents, antimetabolites, and natural products *(e.g.,* herbs and other plant and/or animal derived compounds).

[0231] Alkylating agents suitable for use in the present methods include, but are not limited to: 1) nitrogen mustards *(e.g.,* mechlorethamine, cyclophosphamide, ifosfamide, melphalan (L-sarcolysin); and chlorambucil); 2) ethylenimines and methylmelamines *(e.g.,* hexamethylmelamine and thiotepa); 3) alkyl sulfonates *(e.g.,* busulfan); 4) nitrosoureas *(e.g.,* carmustine (BCNU); lomustine (CCNU); semustine (methyl-CCNU); and streptozocin (streptozotocin)); and 5) triazenes *(e.g.,* dacarbazine (DTIC; dimethyltriazenoimid-azolecarboxamide).

[0232] In some embodiments, antimetabolites suitable for use in the present methods include, but are not limited to: 1) folic acid analogs *(e.g.,* methotrexate (amethopterin)); 2) pyrimidine analogs *(e.g.,* fluorouracil (5-fluorouracil; 5-FU), floxuridine (fluorode-oxyuridine; FudR), and cytarabine (cytosine arabinoside)); and 3) purine analogs *(e.g.,* mercaptopurine (6-mercaptopurine; 6-MP), thioguanine (6-thioguanine; TG), and pentostatin (2'-deoxycoformycin)).

[0233] In still further embodiments, chemotherapeutic agents suitable for use in the methods of the present disclosure include, but are not limited to: 1) vinca alkaloids *(e.g.,* vinblastine (VLB), vincristine); 2) epipodophyllotoxins *(e.g.,* etoposide and teniposide); 3) antibiotics *(e.g.,* dactinomycin (actinomycin D), daunorubicin (daunomycin; rubidomycin), doxorubicin, bleomycin, plicamycin (mithramycin), and mitomycin (mitomycin C)); 4) enzymes *(e.g.,* L-asparaginase); 5) biological response modifiers *(e.g.,* interferon-alfa); 6) platinum coordinating complexes *(e.g.,* cisplatin (cis-DDP) and carboplatin); 7) anthracenediones *(e.g.,* mitoxantrone); 8) substituted ureas *(e.g.,* hydroxyurea); 9) methylhydrazine derivatives *(e.g.,* procarbazine (N-

methylhydrazine; MIH)); 10) adrenocortical suppressants *(e.g.,* mitotane (o,p'-DDD) and aminoglutethimide); 11) adrenocorticosteroids *(e.g.,* prednisone); 12) progestins *(e.g.,* hydroxyprogesterone caproate, medroxyprogesterone acetate, and megestrol acetate); 13) estrogens *(e.g.,* diethylstilbestrol and ethinyl estradiol); 14) antiestrogens *(e.g.,* tamoxifen); 15) androgens (e.g., testosterone propionate and fluoxymesterone); 16) antiandrogens (e.g, flutamide): and 17) gonadotropin-releasing hormone analogs (e.g, leuprolide).

[0234] Any oncolytic agent that is routinely used in a cancer therapy context finds use in the therapeutic methods of the present disclosure. For example, the U.S. Food and Drug Administration (FDA) maintains a formulary of oncolytic agents approved for use in the United States. International counterpart agencies to the FDA maintain similar formularies. Those skilled in the art will appreciate that the "product labels" required on all U.S. approved chemotherapeutics describe approved indications, dosing information, toxicity data, and the like, for the exemplary agents.

[0235] Anticancer agents further include compounds which have been identified to have anticancer activity. Examples include, but are not limited to, 3-AP, 12-O-tetradecanoylphorbol-13-acetate, 17AAG, 852A, ABI-007, ABR-217620, ABT-751, ADI-PEG 20, AE-941, AG-013736, AGRO100, alanosine, AMG 706, antibody G250, antineoplastons, AP23573, apaziquone, APC8015, atiprimod, ATN-161, atrasenten, azacitidine, BB-10901, BCX-1777, bevacizumab, BG00001, bicalutamide, BMS 247550, bortezomib, bryostatin-1, buserelin, calcitriol, CCI-779, CDB-2914, cefixime, cetuximab, CG0070, cilengitide, clofarabine, combretastatin A4 phosphate, CP-675,206, CP-724,714, CpG 7909, curcumin, decitabine, DENSPM, doxercalciferol, E7070, E7389, ecteinascidin 743, efaproxiral, eflomithine, EKB-569, enzastaurin, erlotinib, exisulind, fenretinide, flavopiridol, fludarabine, flutamide, fotemustine, FR901228, G17DT, galiximab, gefitinib, genistein, glufosfamide, GTI-2040, histrelin, HKI-272, homoharringtonine, HSPPC-96, hul4.18-interleukin-2 fusion protein, HuMax-CD4, iloprost, imiquimod, infliximab, interleukin-12, IPI-504, irofulven, ixabepilone, lapatinib, lenalidomide, lestaurtinib, leuprolide, LMB-9 immunotoxin, lonafamib, luniliximab, mafosfamide, MB07133, MDX-010, MLN2704, monoclonal antibody 3F8, monoclonal antibody J591, motexafm, MS-275, MVA-MUC1-IL2, nilutamide, nitrocamptothecin, nolatrexed dihydrochloride, nolvadex, NS-9, 06-benzylguanine, oblimersen sodium, ONYX-015, oregovomab, OSI-774, panitumumab, paraplatin, PD-0325901, pemetrexed, PHY906, pioglitazone, pirfenidone, pixantrone, PS-341, PSC 833, PXD101, pyrazoloacridine, R 115777, RAD001, ranpimase, rebeccamycin analogue, rhuAngiostatin protein, rhuMab 2C4, rosiglitazone, rubitecan, S-l, S-8184, satraplatin, SB-, 15992, SGN-0010, SGN-40, sorafenib, SR31747A, ST1571, SU011248, suberoylanilide hydroxamic acid, suramin, talabostat,

talampanel, tariquidar, temsirolimus, TGFa-PE38 immunotoxin, thalidomide, thymalfasin, tipifamib, tirapazamine, TLK286, trabectedin, trimetrexate glucuronate, TroVax, UCN-1, valproic acid, vinflunine, VNP40101M, volociximab, vorinostat, VX-680, ZD1839, ZD6474, zileuton, and zosuquidar trihydrochloride.

[0236] In one embodiment, the optional therapeutic agent comprises one of the anti-cancer drugs or anti-cancer drug combinations listed in Table 5.

Table 5

Abemaciclib	Abiraterone Acetate	Abraxane (Paclitaxel Albumin-stabilized Nanoparticle Formulation)	ABVD
ABVE	ABVE-PC	AC	Acalabrutinib
AC-T	Actemra (Tocilizumab)	Adcetris (Brentuximab Vedotin)	ADE
Ado-Trastuzumab Emtansine	Adriamycin (Doxorubicin Hydrochloride)	Afatinib Dimaleate	Afinitor (Everolimus)
Akynzeo (Netupitant and Palonosetron Hydrochloride)	Aldara (Imiquimod)	Aldesleukin	Alecensa (Alectinib)
Alectinib	Alemtuzumab	Alimta (Pemetrexed Disodium)	Aliqopa (Copanlisib Hydrochloride)
Alkeran for Injection (Melphalan Hydrochloride)	Alkeran Tablets (Melphalan)	Aloxi (Palonosetron Hydrochloride)	Alunbrig (Brigatinib)
Ameluz (Aminolevulinic Acid)	Amifostine	Aminolevulinic Acid	Anastrozole
Apalutamide	Aprepitant	Aranesp (Darbepoetin Alfa)	Aredia (Pamidronate Disodium)
Arimidex (Anastrozole)	Aromasin (Exemestane)	Arranon (Nelarabine)	Arsenic Trioxide
Arzerra (Ofatumumab)	Asparaginase Erwinia chrysanthemi	Atezolizumab	Avastin (Bevacizumab)
Avelumab	Axicabtagene Ciloleucel	Axitinib	Azacitidine
Azedra (Iobenguane I 131)	Bavencio (Avelumab)	BEACOPP	Beleodaq (Belinostat)
Belinostat	Bendamustine Hydrochloride	Bendeka (Bendamustine Hydrochloride)	BEP
Besponsa (Inotuzumab Ozogamicin)	Bevacizumab	Bexarotene	Bicalutamide

BiCNU (Carmustine)	Binimetinib	Bleomycin	Blinatumomab
Blincyto (Blinatumomab)	Bortezomib	Bosulif (Bosutinib)	Bosutinib
Braftovi (Encorafenib)	Brentuximab Vedotin	Brigatinib	BuMel
Busulfan	Busulfex (Busulfan)	Cabazitaxel	Cabometyx (Cabozantinib-S-Malate)
Cabozantinib-S-Malate	CAF	Calquence (Acalabrutinib)	Campath (Alemtuzumab)
Camptosar (Irinotecan Hydrochloride)	Capecitabine	CAPOX	Carac (Fluorouracil--Topical)
Carboplatin	CARBOPLATIN-TAXOL	Carfilzomib	Carmustine
Carmustine Implant	Casodex (Bicalutamide)	CEM	Cemiplimab-rwlc
Ceritinib	Cerubidine (Daunorubicin Hydrochloride)	Cervarix (Recombinant HPV Bivalent Vaccine)	Cetuximab
CEV	Chlorambucil	CHLORAMBUCIL-PREDNISONE	CHOP
Cisplatin	Cladribine	Clofarabine	Clolar (Clofarabine)
CMF	Cobimetinib	Cometriq (Cabozantinib-S-Malate)	Copanlisib Hydrochloride
COPDAC	Copiktra (Duvelisib)	COPP	COPP-ABV
Cosmegen (Dactinomycin)	Cotellic (Cobimetinib)	Crizotinib	CVP
Cyclophosphamide	Cyramza (Ramucirumab)	Cytarabine	Cytarabine Liposome
Cytosar-U (Cytarabine)	Dabrafenib	Dacarbazine	Dacogen (Decitabine)
Dacomitinib	Dactinomycin	Daratumumab	Darbepoetin Alfa
Darzalex (Daratumumab)	Dasatinib	Daunorubicin Hydrochloride	Daunorubicin Hydrochloride and Cytarabine Liposome
Decitabine	Defibrotide Sodium	Defitelio (Defibrotide Sodium)	Degarelix
Denileukin Diftitox	Denosumab	DepoCyt (Cytarabine Liposome)	Dexamethasone
Dexrazoxane Hydrochloride	Dinutuximab	Docetaxel	Doxil (Doxorubicin Hydrochloride Liposome)

Doxorubicin Hydrochloride	Doxorubicin Hydrochloride Liposome	Dox-SL (Doxorubicin Hydrochloride Liposome)	Durvalumab
Duvelisib	Efudex (Fluorouracil--Topical)	Eligard (Leuprolide Acetate)	Elitek (Rasburicase)
Ellence (Epirubicin Hydrochloride)	Elotuzumab	Eloxatin (Oxaliplatin)	Eltrombopag Olamine
Emend (Aprepitant)	Empliciti (Elotuzumab)	Enasidenib Mesylate	Encorafenib
Enzalutamide	Epirubicin Hydrochloride	EPOCH	Epoetin Alfa
Epogen (Epoetin Alfa)	Erbitux (Cetuximab)	Eribulin Mesylate	Erivedge (Vismodegib)
Erleada (Apalutamide)	Erlotinib Hydrochloride	Erwinaze (Asparaginase Erwinia chrysanthemi)	Ethyol (Amifostine)
Etopophos (Etoposide Phosphate)	Etoposide	Etoposide Phosphate	Evacet (Doxorubicin Hydrochloride Liposome)
Everolimus	Evista (Raloxifene Hydrochloride)	Evomela (Melphalan Hydrochloride)	Exemestane
5-FU (Fluorouracil Injection)	5-FU (Fluorouracil--Topical)	Fareston (Toremifene)	Farydak (Panobinostat)
Faslodex (Fulvestrant)	FEC	Femara (Letrozole)	Filgrastim
Firmagon (Degarelix)	Fludarabine Phosphate	Fluoroplex (Fluorouracil--Topical)	Fluorouracil Injection
Fluorouracil--Topical	Flutamide	FOLFIRI	FOLFIRI-BEVACIZUMAB
FOLFIRI-CETUXIMAB	FOLFIRINOX	FOLFOX	Folotyn (Pralatrexate)
Fostamatinib Disodium	FU-LV	Fulvestrant	Fusilev (Leucovorin Calcium)
Gardasil (Recombinant HPV Quadrivalent Vaccine)	Gardasil 9 (Recombinant HPV Nonavalent Vaccine)	Gazyva (Obinutuzumab)	Gefitinib
Gemcitabine Hydrochloride	GEMCITABINE-CISPLATIN	GEMCITABINE-OXALIPLATIN	Gemtuzumab Ozogamicin
Gemzar (Gemcitabine Hydrochloride)	Gilotrif (Afatinib Dimaleate)	Gleevec (Imatinib Mesylate)	Gliadel Wafer (Carmustine Implant)
Glucarpidase	Goserelin Acetate	Granisetron	Granisetron Hydrochloride
Granix (Filgrastim)	Halaven (Eribulin Mesylate)	Hemangeol (Propranolol Hydrochloride)	Herceptin (Trastuzumab)

HPV Bivalent Vaccine, Recombinant	HPV Nonavalent Vaccine, Recombinant	HPV Quadrivalent Vaccine, Recombinant	Hycamtin (Topotecan Hydrochloride)
Hydrea (Hydroxyurea)	Hydroxyurea	Hyper-CVAD	Ibrance (Palbociclib)
Ibritumomab Tiuxetan	Ibrutinib	ICE	Iclusig (Ponatinib Hydrochloride)
Idarubicin Hydrochloride	Idelalisib	Idhifa (Enasidenib Mesylate)	Ifex (Ifosfamide)
Ifosfamide	IL-2 (Aldesleukin)	Imatinib Mesylate	Imbruvica (Ibrutinib)
Imfinzi (Durvalumab)	Imiquimod	Imlygic (Talimogene Laherparepvec)	Inlyta (Axitinib)
Inotuzumab Ozogamicin	Interferon Alfa-2b, Recombinant	Interleukin-2 (Aldesleukin)	Intron A (Recombinant Interferon Alfa-2b)
Iobenguane I 131	Ipilimumab	Iressa (Gefitinib)	Irinotecan Hydrochloride
Irinotecan Hydrochloride Liposome	Istodax (Romidepsin)	Ivosidenib	Ixabepilone
Ixazomib Citrate	Ixempra (Ixabepilone)	Jakafi (Ruxolitinib Phosphate)	JEB
Jevtana (Cabazitaxel)	Kadcyla (Ado-Trastuzumab Emtansine)	Kepivance (Palifermin)	Keytruda (Pembrolizumab)
Kisqali (Ribociclib)	Kymriah (Tisagenlecleucel)	Kyprolis (Carfilzomib)	Lanreotide Acetate
Lapatinib Ditosylate	Larotrectinib Sulfate	Lartruvo (Olaratumab)	Lenalidomide
Lenvatinib Mesylate	Lenvima (Lenvatinib Mesylate)	Letrozole	Leucovorin Calcium
Leukeran (Chlorambucil)	Leuprolide Acetate	Levulan Kerastik (Aminolevulinic Acid)	Libtayo (Cemiplimab-rwlc)
LipoDox (Doxorubicin Hydrochloride Liposome)	Lomustine	Lonsurf (Trifluridine and Tipiracil Hydrochloride)	Lorbrena (Lorlatinib)
Lorlatinib	Lumoxiti (Moxetumomab Pasudotox-tdfk)	Lupron (Leuprolide Acetate)	Lupron Depot (Leuprolide Acetate)
Lutathera (Lutetium Lu 177-Dotatate)	Lutetium (Lu 177-Dotatate)	Lynparza (Olaparib)	Marqibo (Vincristine Sulfate Liposome)

Matulane (Procarbazine Hydrochloride)	Mechlorethamine Hydrochloride	Megestrol Acetate	Mekinist (Trametinib)
Mektovi (Binimetinib)	Melphalan	Melphalan Hydrochloride	Mercaptopurine
Mesna	Mesnex (Mesna)	Methotrexate	Methylnaltrexone Bromide
Midostaurin	Mitomycin C	Mitoxantrone Hydrochloride	Mogamulizumab-kpkc
Moxetumomab Pasudotox-tdfk	Mozobil (Plerixafor)	Mustargen (Mechlorethamine Hydrochloride)	MVAC
Myleran (Busulfan)	Mylotarg (Gemtuzumab Ozogamicin)	Nanoparticle Paclitaxel (Paclitaxel Albumin-stabilized Nanoparticle Formulation)	Navelbine (Vinorelbine Tartrate)
Necitumumab	Nelarabine	Neratinib Maleate	Nerlynx (Neratinib Maleate)
Netupitant and Palonosetron Hydrochloride	Neulasta (Pegfilgrastim)	Neupogen (Filgrastim)	Nexavar (Sorafenib Tosylate)
Nilandron (Nilutamide)	Nilotinib	Nilutamide	Ninlaro (Ixazomib Citrate)
Niraparib Tosylate Monohydrate	Nivolumab	Nplate (Romiplostim)	Obinutuzumab
Odomzo (Sonidegib)	OEPA	Ofatumumab	OFF
Olaparib	Olaratumab	Omacetaxine Mepesuccinate	Oncaspar (Pegaspargase)
Ondansetron Hydrochloride	Onivyde (Irinotecan Hydrochloride Liposome)	Ontak (Denileukin Diftitox)	Opdivo (Nivolumab)
OPPA	Osimertinib	Oxaliplatin	Paclitaxel
Paclitaxel Albumin-stabilized Nanoparticle Formulation	PAD	Palbociclib	Palifermin
Palonosetron Hydrochloride	Palonosetron Hydrochloride and Netupitant	Pamidronate Disodium	Panitumumab
Panobinostat	Pazopanib Hydrochloride	PCV	PEB
Pegaspargase	Pegfilgrastim	Peginterferon Alfa-2b	PEG-Intron (Peginterferon Alfa-2b)
Pembrolizumab	Pemetrexed Disodium	Perjeta (Pertuzumab)	Pertuzumab

Plerixafor	Pomalidomide	Pomalyst (Pomalidomide)	Ponatinib Hydrochloride
Portrazza (Necitumumab)	Poteligeo (Mogamulizumab-kpkc)	Pralatrexate	Prednisone
Procarbazine Hydrochloride	Procrit (Epoetin Alfa)	Proleukin (Aldesleukin)	Prolia (Denosumab)
Promacta (Eltrombopag Olamine)	Propranolol Hydrochloride	Provenge (Sipuleucel-T)	Purinethol (Mercaptopurine)
Purixan (Mercaptopurine)	Radium 223 Dichloride	Raloxifene Hydrochloride	Ramucirumab
Rasburicase	R-CHOP	R-CVP	Recombinant Human Papillomavirus (HPV) Bivalent Vaccine
Recombinant Human Papillomavirus (HPV) Nonavalent Vaccine	Recombinant Human Papillomavirus (HPV) Quadrivalent Vaccine	Recombinant Interferon Alfa-2b	Regorafenib
Relistor (Methylnaltrexone Bromide)	R-EPOCH	Retacrit (Epoetin Alfa)	Revlimid (Lenalidomide)
Rheumatrex (Methotrexate)	Ribociclib	R-ICE	Rituxan (Rituximab)
Rituxan Hycela (Rituximab and Hyaluronidase Human)	Rituximab	Rituximab and Hyaluronidase Human	Rolapitant Hydrochloride
Romidepsin	Romiplostim	Rubidomycin (Daunorubicin Hydrochloride)	Rubraca (Rucaparib Camsylate)
Rucaparib Camsylate	Ruxolitinib Phosphate	Rydapt (Midostaurin)	Sancuso (Granisetron)
Sclerosol Intrapleural Aerosol (Talc)	Siltuximab	Sipuleucel-T	Somatuline Depot (Lanreotide Acetate)
Sonidegib	Sorafenib Tosylate	Sprycel (Dasatinib)	STANFORD V
Sterile Talc Powder (Talc)	Steritalc (Talc)	Stivarga (Regorafenib)	Sunitinib Malate
Sustol (Granisetron)	Sutent (Sunitinib Malate)	Sylatron (Peginterferon Alfa-2b)	Sylvant (Siltuximab)
Synribo (Omacetaxine Mepesuccinate)	Tabloid (Thioguanine)	TAC	Tafinlar (Dabrafenib)

Tagrisso (Osimertinib)	Talc	Talimogene Laherparepvec	Tamoxifen Citrate
Tarabine PFS (Cytarabine)	Tarceva (Erlotinib Hydrochloride)	Targretin (Bexarotene)	Tasigna (Nilotinib)
Tavalisse (Fostamatinib Disodium)	Taxol (Paclitaxel)	Taxotere (Docetaxel)	Tecentriq (Atezolizumab)
Temodar (Temozolomide)	Temozolomide	Temsirolimus	Thalidomide
Thalomid (Thalidomide)	Thioguanine	Thiotepa	Tibsovo (Ivosidenib)
Tisagenlecleucel	Tocilizumab	Tolak (Fluorouracil--Topical)	Topotecan Hydrochloride
Toremifene	Torisel (Temsirolimus)	Totect (Dexrazoxane Hydrochloride)	TPF
Trabectedin	Trametinib	Trastuzumab	Treanda (Bendamustine Hydrochloride)
Trexall (Methotrexate)	Trifluridine and Tipiracil Hydrochloride	Trisenox (Arsenic Trioxide)	Tykerb (Lapatinib Ditosylate)
Unituxin (Dinutuximab)	Uridine Triacetate	VAC	Valrubicin
Valstar (Valrubicin)	Vandetanib	VAMP	Varubi (Rolapitant Hydrochloride)
Vectibix (Panitumumab)	VeIP	Velcade (Bortezomib)	Vemurafenib
Venclexta (Venetoclax)	Venetoclax	Verzenio (Abemaciclib)	Vidaza (Azacitidine)
Vinblastine Sulfate	Vincristine Sulfate	Vincristine Sulfate Liposome	Vinorelbine Tartrate
VIP	Vismodegib	Vistogard (Uridine Triacetate)	Vitrakvi (Larotrectinib Sulfate)
Vizimpro (Dacomitinib)	Voraxaze (Glucarpidase)	Vorinostat	Votrient (Pazopanib Hydrochloride)
Vyxeos (Daunorubicin Hydrochloride and Cytarabine Liposome)	Xalkori (Crizotinib)	Xeloda (Capecitabine)	XELIRI
XELOX	Xgeva (Denosumab)	Xofigo (Radium 223 Dichloride)	Xtandi (Enzalutamide)
Yervoy (Ipilimumab)	Yescarta (Axicabtagene Ciloleucel)	Yondelis (Trabectedin)	Zaltrap (Ziv-Aflibercept)

Zarxio (Filgrastim)	Zejula (Niraparib Tosylate Monohydrate)	Zelboraf (Vemurafenib)	Zevalin (Ibritumomab Tiuxetan)
Zinecard (Dexrazoxane Hydrochloride)	Ziv-Aflibercept	Zofran (Ondansetron Hydrochloride)	Zoladex (Goserelin Acetate)
Zoledronic Acid	Zolinza (Vorinostat)	Zometa (Zoledronic Acid)	Zydelig (Idelalisib)
Zykadia (Ceritinib)	Zytiga (Abiraterone Acetate)		

[0237] For a more detailed description of anticancer agents and other optional therapeutic agents, those skilled in the art are referred to any number of instructive manuals including, but not limited to, the Physician's Desk Reference and to Goodman and Gilman's "Pharmaceutical Basis of Therapeutics" tenth edition, Eds. Hardman *et al.*, 2002.

[0238] In some embodiments, methods provided herein comprise administering a Compound of the Disclosure in combination with radiation therapy. The methods provided herein are not limited by the types, amounts, or delivery and administration systems used to deliver the therapeutic dose of radiation to a patient. For example, the patient may receive photon radiotherapy, particle beam radiation therapy, other types of radiotherapies, and combinations thereof. In some embodiments, the radiation is delivered to the patient using a linear accelerator. In still other embodiments, the radiation is delivered using a gamma knife.

[0239] The source of radiation can be external or internal to the patient. External radiation therapy is most common and involves directing a beam of high-energy radiation to a tumor site through the skin using, for instance, a linear accelerator. While the beam of radiation is localized to the tumor site, it is nearly impossible to avoid exposure of normal, healthy tissue. However, external radiation is usually well tolerated by patients. Internal radiation therapy involves implanting a radiation-emitting source, such as beads, wires, pellets, capsules, particles, and the like, inside the body at or near the tumor site including the use of delivery systems that specifically target cancer cells (*e.g.*, using particles attached to cancer cell binding ligands). Such implants can be removed following treatment, or left in the body inactive. Types of internal radiation therapy include, but are not limited to, brachytherapy, interstitial irradiation, intracavity irradiation, radioimmunotherapy, and the like.

[0240] The patient may optionally receive radiosensitizers *(e.g.,* metronidazole, misonidazole, intra-arterial Budr, intravenous iododeoxyuridine (IudR), nitroimidazole, 5-substituted-4-nitroimidazoles, 2H-isoindolediones, [[(2-bromoethyl)-amino] methyl] -nitro-lH-imidazole-1 -ethanol, nitroaniline derivatives, DNA-affmic hypoxia selective cytotoxins,

halogenated DNA ligand, 1,2,4 benzotriazine oxides, 2-nitroimidazole derivatives, fluorine-containing nitroazole derivatives, benzamide, nicotinamide, acridine-intercalator, 5-thiotretrazole derivative, 3-nitro-1,2,4-triazole, 4,5-dinitroimidazole derivative, hydroxylated texaphrins, cisplatin, mitomycin, tiripazamine, nitrosourea, mercaptopurine, methotrexate, fluorouracil, bleomycin, vincristine, carboplatin, epirubicin, doxorubicin, cyclophosphamide, vindesine, etoposide, paclitaxel, heat (hyperthermia), and the like), radioprotectors (e.g, cysteamine, aminoalkyl dihydrogen phosphorothioates, amifostine (WR 2721), IL-1, IL-6, and the like). Radiosensitizers enhance the killing of tumor cells. Radioprotectors protect healthy tissue from the harmful effects of radiation.

[0241] Any type of radiation can be administered to a patient, so long as the dose of radiation is tolerated by the patient without unacceptable negative side-effects. Suitable types of radiotherapy include, for example, ionizing (electromagnetic) radiotherapy (e.g., X-rays or gamma rays) or particle beam radiation therapy (e.g, high linear energy radiation). Ionizing radiation is defined as radiation comprising particles or photons that have sufficient energy to produce ionization, *i.e.,* gain or loss of electrons (as described in, for example, U.S. 5,770,581 incorporated herein by reference in its entirety). The effects of radiation can be at least partially controlled by the clinician. In one embodiment, the dose of radiation is fractionated for maximal target cell exposure and reduced toxicity.

[0242] In one embodiment, the total dose of radiation administered to a patient is about .01 Gray (Gy) to about 100 Gy. In another embodiment, about 10 Gy to about 65 Gy (e.g, about 15 Gy, 20 Gy, 25 Gy, 30 Gy, 35 Gy, 40 Gy, 45 Gy, 50 Gy, 55 Gy, or 60 Gy) are administered over the course of treatment. While in some embodiments a complete dose of radiation can be administered over the course of one day, the total dose is ideally fractionated and administered over several days. Desirably, radiotherapy is administered over the course of at least about 3 days, *e.g.,* at least 5, 7, 10, 14, 17, 21, 25, 28, 32, 35, 38, 42, 46, 52, or 56 days (about 1-8 weeks). Accordingly, a daily dose of radiation will comprise approximately 1-5 Gy *(e.g,* about 1 Gy, 1.5 Gy, 1.8 Gy, 2 Gy, 2.5 Gy, 2.8 Gy, 3 Gy, 3.2 Gy, 3.5 Gy, 3.8 Gy, 4 Gy, 4.2 Gy, or 4.5 Gy), or 1-2 Gy (e.g, 1.5-2 Gy). The daily dose of radiation should be sufficient to induce destruction of the targeted cells. If stretched over a period, in one embodiment, radiation is not administered every day, thereby allowing the animal to rest and the effects of the therapy to be realized. For example, radiation desirably is administered on 5 consecutive days, and not administered on 2 days, for each week of treatment, thereby allowing 2 days of rest per week. However, radiation can be administered 1 day/week, 2 days/week, 3 days/week, 4 days/week, 5 days/week, 6 days/week, or all 7 days/week, depending on the animal's responsiveness and any potential side effects. Radiation

therapy can be initiated at any time in the therapeutic period. In one embodiment, radiation is initiated in week 1 or week 2, and is administered for the remaining duration of the therapeutic period. For example, radiation is administered in weeks 1-6 or in weeks 2-6 of a therapeutic period comprising 6 weeks for treating, for instance, a solid tumor. Alternatively, radiation is administered in weeks 1-5 or weeks 2-5 of a therapeutic period comprising 5 weeks. These exemplary radiotherapy administration schedules are not intended, however, to limit the methods provided herein.

IV. Biomarkers

[0243] In another embodiment, present disclosure provides methods of treating a subject having cancer comprising administering a therapeutically effective amount of a Compound of the Disclosure to the subject if a biomarker is present in a biological sample of the subject. In another embodiment, the method comprises determining whether a biomarker is present or absent in the biological sample. *See, e.g.*. Goossens *el al, Transl Cancer Res. 4*:256-269 (2015); Kamel and Al-Amodi, *Genomics Proteomics Bioinformatics* 75:220-235 (2017); and Konikova and Kusenda, *Neoplasma* 50:31-40 (2003).

[0244] The term "biomarker" as used herein refers to any biological compound, such as a gene, a protein, a fragment of a protein, a peptide, a polypeptide, a nucleic acid, etc., or chromosome abnormality, such as a chromosome translocation, that can be detected and/or quantified in a cancer patient *in vivo* or in a biological sample obtained from a cancer patient. A biomarker can be the entire intact molecule, or it can be a portion or fragment thereof. In one embodiment, the expression level of the biomarker is measured. The expression level of the biomarker can be measured, for example, by detecting the protein or RNA, e.g., mRNA, level of the biomarker. In some embodiments, portions or fragments of biomarkers can be detected or measured, for example, by an antibody or other specific binding agent. In some embodiments, a measurable aspect of the biomarker is associated with a given state of the patient, such as a particular stage of cancer. For biomarkers that are detected at the protein or RNA level, such measurable aspects may include, for example, the presence, absence, or concentration, i.e., expression level, of the biomarker in a cancer patient, or biological sample obtained from the cancer patient. For biomarkers that are detected at the nucleic acid level, such measurable aspects may include, for example, allelic versions of the biomarker or type, rate, and/or degree of mutation of the biomarker, also referred to herein as mutation status.

[0245] For biomarkers that are detected based on expression level of protein or RNA, expression level measured between different phenotypic statuses can be considered different, for example, if the mean or median expression level of the biomarker in the different groups is

calculated to be statistically significant. Common tests for statistical significance include, among others, t-test, ANOVA, Kruskal-Wallis, Wilcoxon, Mann-Whitney, Significance Analysis of Microarrays, odds ratio, etc. Biomarkers, alone or in combination, provide measures of relative likelihood that a subject belongs to one phenotypic status or another. Therefore, they are useful, inter alia, as markers for disease and as indicators that particular therapeutic treatment regimens will likely result in beneficial patient outcomes. In one embodiment, the measurable aspect of the biomarker is its expression status. In one embodiment, the measurable aspect of the biomarker is its mutation status.

[0246] In one embodiment, the biomarker is the mutation status of any one or more of BRAF, KRAS, p53, and/or PI3KCA, which is differentially present in a subject of one phenotypic status, e.g., a subject having a hematological cancer, as compared with another phenotypic status, e.g., a normal undiseased subject or a patient having cancer without a mutation in BRAF, KRAS, etc. Methods to detect mutations in these biomarkers are known in the art.

[0247] In another embodiment, the biomarker is the expression status of MYC which is differentially present in a subject of one phenotypic status, e.g., a subject having a hematological cancer, as compared with another phenotypic status, e.g., a normal undiseased subject or a patient having cancer without an overexpression of MYC. Methods the expression status of MYC are known in the art.

[0248] In another embodiment, the biomarker is the mutation status of BRAF, KRAS, or both, which is differentially present in a subject of one phenotypic status, e.g., a subject having a hematological cancer, as compared with another phenotypic status, e.g., a normal undiseased subject or a patient having cancer without a mutation in BRAF, KRAS, or both. Methods to detect mutations in BRAF and KRAS are known in the art. *See, e.g.,* Loes *el al, Tumour Biol.* 36(2): 1003-1013 (2015).

[0249] Biomarker standards can be predetermined, determined concurrently, or determined after a biological sample is obtained from the subject. Biomarker standards for use with the methods described herein can, for example, include data from samples from subjects without cancer; data from samples from subjects with cancer, e.g., breast cancer, that is not metastatic; and data from samples from subjects with cancer, e.g., breast cancer, that metastatic. Comparisons can be made to establish predetermined threshold biomarker standards for different classes of subjects, e.g., diseased vs. non-diseased subjects. The standards can be run in the same assay or can be known standards from a previous assay.

[0250] A biomarker is differentially present between different phenotypic status groups if the mean or median expression or mutation levels of the biomarker is calculated to be different,

i.e., higher or lower, between the groups. Thus, biomarkers provide an indication that a subject, e.g., a cancer patient, belongs to one phenotypic status or another.

[0251] In addition to individual biological compounds, e.g., BRAF or KRAS, the term "biomarker" as used herein is meant to include groups, sets, or arrays of multiple biological compounds. For example, the combination of BRAF and KRAS mutation status may comprise a biomarker. The term "biomarker" may comprise one, two, three, four, five, six, seven, eight, nine, ten, fifteen, twenty, twenty five, thirty, or more, biological compounds.

[0252] The determination of the expression level or mutation status of a biomarker in a patient can be performed using any of the many methods known in the art. Any method known in the art for quantitating specific proteins and/or detecting BRAF and/or KRAS mutation status, or the expression or mutation levels of any other biomarker in a patient or a biological sample may be used in the methods of the disclosure. Examples include, but are not limited to, PCR (polymerase chain reaction), or RT-PCR, flow cytometry, Northern blot, Western blot, ELISA (enzyme linked immunosorbent assay), RIA (radioimmunoassay), gene chip analysis of RNA expression, immunohistochemistry or immunofluorescence. *See, e.g.*, Slagle et al. Cancer 83: 1401 (1998). Certain embodiments of the disclosure include methods wherein biomarker RNA expression (transcription) is determined. Other embodiments of the disclosure include methods wherein protein expression in the biological sample is determined. *See, e.g.,* Harlow *et al,* Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, (1988); Ausubel *et al,* Current Protocols in Molecular Biology, John Wiley & Sons, New York 3rd Edition, (1995); Kamel and Al-Amodi, *Genomics Proteomics Bioinformatics* 75:220-235 (2017). For northern blot or RT-PCR analysis, RNA is isolated from the tumor tissue sample using RNAse free techniques. Such techniques are commonly known in the art.

[0253] In one embodiment of the disclosure, a biological sample is obtained from the patient and the biological sample is assayed for determination of a biomarker expression or mutation status.

[0254] In another embodiment of the disclosure, Northern blot analysis of biomarker transcription in a tumor cell sample is performed. Northern analysis is a standard method for detection and/or quantitation of mRNA levels in a sample. Initially, RNA is isolated from a sample to be assayed using Northern blot analysis. In the analysis, the RNA samples are first separated by size via electrophoresis in an agarose gel under denaturing conditions. The RNA is then transferred to a membrane, crosslinked and hybridized with a labeled probe. Typically, Northern hybridization involves polymerizing radiolabeled or nonisotopically labeled DNA, in vitro, or generation of oligonucleotides as hybridization probes. Typically, the membrane holding the RNA

sample is prehybridized or blocked prior to probe hybridization to prevent the probe from coating the membrane and, thus, to reduce non-specific background signal. After hybridization, typically, unhybridized probe is removed by washing in several changes of buffer. Stringency of the wash and hybridization conditions can be designed, selected and implemented by any practitioner of ordinary skill in the art. Detection is accomplished using detectably labeled probes and a suitable detection method. Radiolabeled and non-radiolabled probes and their use are well known in the art. The presence and or relative levels of expression of the biomarker being assayed can be quantified using, for example, densitometry.

[0255] In another embodiment, biomarker expression and/or mutation status is determined using RT-PCR. RT-PCR allows detection of the progress of a PCR amplification of a target gene in real time. Design of the primers and probes required to detect expression and/or mutation status of a biomarker of the disclosure is within the skill of a practitioner of ordinary skill in the art. RT-PCR can be used to determine the level of RNA encoding a biomarker of the disclosure in a tumor tissue sample. In an embodiment of the disclosure, RNA from the biological sample is isolated, under RNAse free conditions, than converted to DNA by treatment with reverse transcriptase. Methods for reverse transcriptase conversion of RNA to DNA are well known in the art. A description of PCR is provided in the following references: Mullis et al, *Cold Spring Harbor Symp. Quant. Biol.* 57:263 (1986); EP 50,424; EP 84,796; EP 258,017; EP 237,362; EP 201,184; U.S. Patent Nos. 4,683,202; 4,582,788; 4,683,194.

[0256] RT-PCR probes depend on the 5'-3' nuclease activity of the DNA polymerase used for PCR to hydrolyze an oligonucleotide that is hybridized to the target amplicon (biomarker gene). RT-PCR probes are oligonucleotides that have a fluorescent reporter dye attached to the 5' end and a quencher moiety coupled to the 3' end (or vice versa). These probes are designed to hybridize to an internal region of a PCR product. In the unhybridized state, the proximity of the fluor and the quench molecules prevents the detection of fluorescent signal from the probe. During PCR amplification, when the polymerase replicates a template on which an RT-PCR probe is bound, the 5'-3' nuclease activity of the polymerase cleaves the probe. This decouples the fluorescent and quenching dyes and FRET no longer occurs. Thus, fluorescence increases in each cycle, in a manner proportional to the amount of probe cleavage. Fluorescence signal emitted from the reaction can be measured or followed over time using equipment which is commercially available using routine and conventional techniques.

[0257] In another embodiment of the disclosure, expression of proteins encoded by biomarkers are detected by western blot analysis. A western blot (also known as an immunoblot) is a method for protein detection in a given sample of tissue homogenate or extract. It uses gel

electrophoresis to separate denatured proteins by mass. The proteins are then transferred out of the gel and onto a membrane *(e.g.,* nitrocellulose or polyvinylidene fluoride (PVDF)), where they are detected using a primary antibody that specifically bind to the protein. The bound antibody can then detected by a secondary antibody that is conjugated with a detectable label *(e.g.,* biotin, horseradish peroxidase or alkaline phosphatase). Detection of the secondary label signal indicates the presence of the protein.

[0258] In another embodiment of the disclosure, the expression of a protein encoded by a biomarker is detected by enzyme-linked immunosorbent assay (ELISA). In one embodiment of the disclosure, "sandwich ELISA" comprises coating a plate with a capture antibody; adding sample wherein any antigen present binds to the capture antibody; adding a detecting antibody which also binds the antigen; adding an enzyme-linked secondary antibody which binds to detecting antibody; and adding substrate which is converted by an enzyme on the secondary antibody to a detectable form. Detection of the signal from the secondary antibody indicates presence of the biomarker antigen protein.

[0259] The RAF kinases (A-RAF, BRAF, and C-RAF) are key components of the mitogen-activated protein kinase (MAPK) pathway that controls cell proliferation and survival signaling. (Downward, *Nature Reviews Cancer 3(1):* 11-22 (2003); Wellbrock *et al, Nature Reviews Molecular Cell Biology* 5*(11)*:875-85 (2004). The MAP kinase (MAPK) pathway is a central signal transduction pathway that is dysregulated in a large number of developmental disorders. The MAPK pathway, which is composed of RAS, RAF, MAPK or extracellular signal-regulated kinase (MEK), and extracellular signal-regulated kinase (ERK), integrates signals from receptors on the cell surface including cancer-related receptor tyrosine kinases such as the epidermal growth factor receptor, mesenchymal-epithelial transition factor (MET), and vascular endothelial growth factor receptor (Avruch, *Biochim Biophys Acta 1773(8):* 1150-60 (2007). Genetic alterations in the MAPK pathway are among the most common in human cancers. Up to 60% of melanomas harbor BRAF mutations (Davies *et al., Nature 417:949-54* (2002)) and KRAS mutations have been estimated in roughly 60%, 30%, and 15% of pancreatic, colon, and lung tumors, respectively (Vakiani e/a/., *J Pathol 223(2)*:219-29 (2011). BRAF mutations are also found in 40% of papillary or anaplastic thyroid cancers (Kimura *et al., Cancer Res 63(7):* 1454-7 (2003) and in a small percentage of several other types of tumor (Vakiani *et al., J Pathol 223(2):2\9-29* (2011). A majority of reported BRAF mutations are a substitution of glutamic acid for valine at the amino acid position of 600 (the V600E mutation). The BRAF V600E mutation constitutively activates BRAF and downstream signal transduction in the MAPK pathway (Davies *et al., Nature 417:949-*54 (2002).

[0260] In one embodiment, the disclosure provides a method of treating a subject having cancer, the method comprising administering a therapeutically effective amount of a Compound of the Disclosure to the subject if a mutation in BRAF, KRAS, p53, and/or PI3KCA is present in a biological sample of the subject. In another embodiment, the method comprises determining whether a mutation in BRAF, KRAS, p53, and/or PI3KCA is present or absent in the biological sample.

[0261] In another embodiment, the disclosure provides a method of identifying whether a subject having cancer as a candidate for treatment with a Compound of the Disclosure, the method comprising:

[0262] (a) identifying the subject as being a candidate for treatment if a mutation in BRAF, KRAS, p53, and/or PI3KCA is present; or

[0263] (b) identifying the subject as not being a candidate for treatment if a mutation in BRAF, KRAS, p53, and/or PI3KCA is absent. In another embodiment, the method comprises determining whether a mutation in BRAF, KRAS, p53, and/or PI3KCA is present or absent in the biological sample.

[0264] In another embodiment, the disclosure provides a method of predicting treatment outcome in a subject having cancer, the method comprising:

[0265] (a) if there is a mutation in BRAF, KRAS, p53, and/or PI3KCA in the biological sample, then administering a Compound of the Disclosure to the subject will likely cause a favorable therapeutic response; and

[0266] (b) if there is an absence of a mutation in BRAF, KRAS, p53, and/or PI3KCA in the biological sample, then administering a Compound of the Disclosure to the subject will likely cause an unfavorable therapeutic response. In another embodiment, the method comprises determining whether a mutation in BRAF, KRAS, p53, and/or PI3KCA is present or absent in the biological sample.

[0267] In another embodiment, the disclosure provides a method, comprising administering a therapeutically effective amount of a Compound of the Disclosure to a subject in need thereof, wherein:

[0268] (a) the subject has cancer; and

[0269] (b) the cancer is characterized as having a mutation in BRAF, KRAS, p53, and/or PI3KCA.

[0270] In another embodiment, the disclosure provides any of the above biomarker-related methods, wherein the mutation is a mutation in BRAF. In another embodiment, the mutation in BRAF is a V600E mutation.

[0271] In another embodiment, the disclosure provides a method of treating a subject having cancer, the method comprising administering a therapeutically effective amount of a Compound of the Disclosure to the subject if an overexpression of MYC is present in a biological sample of the subject. In another embodiment, the method comprises determining whether an overexpression of MYC is present or absent in the biological sample.

[0272] In another embodiment, the disclosure provides a method of identifying whether a subject having cancer as a candidate for treatment with a Compound of the Disclosure, the method comprising:

[0273] (a) identifying the subject as being a candidate for treatment if an overexpression of MYC is present; or

[0274] (b) identifying the subject as not being a candidate for treatment if an overexpression of MYC is absent. In another embodiment, the method comprises determining whether an overexpression of MYC is present or absent in the biological sample.

[0275] In another embodiment, the disclosure provides a method of predicting treatment outcome in a subject having cancer, the method comprising:

[0276] (a) if there is an overexpression of MYC in the biological sample, then administering a Compound of the Disclosure to the subject will likely cause a favorable therapeutic response; and

[0277] (b) if there is an absence of an overexpression of MYC in the biological sample, then administering a Compound of the Disclosure to the subject will likely cause an unfavorable therapeutic response. In another embodiment, the method comprises determining whether an overexpression of MYC is present or absent in the biological sample.

[0278] In another embodiment, the disclosure provides a method, comprising administering a therapeutically effective amount of a Compound of the Disclosure to a subject in need thereof, wherein:

[0279] (a) the subject has cancer; and

[0280] (b) the cancer is characterized as having an overexpression of MYC.

V. Definitions

[0281] The terms "a", "an", "the", and similar referents in the context of describing the disclosure (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated. Recitation of ranges of values herein merely are intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The use of any and all examples, or

exemplary language, e.g., "such as," provided herein, is intended to better illustrate the disclosure and is not a limitation on the scope of the disclosure unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the disclosure.

[0282] The term "about," as used herein, includes the recited number ± 10%. Thus, "about 10" means 9 to 11.

[0283] As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. However, in one embodiment, administration of a Compound of the Disclosure to a subject, with or without one or more optional therapeutic agents, leads to remission of the cancer.

[0284] The term "therapeutically effective amount," as used herein, refers to that amount of the therapeutic agent sufficient to result in amelioration of one or more symptoms of a disorder, or prevent advancement of a disorder, or cause regression of the disorder. For example, with respect to the treatment of cancer, in one embodiment, a therapeutically effective amount will refer to the amount of a therapeutic agent that causes a therapeutic response, e.g., normalization of blood counts, decrease in the rate of tumor growth, decrease in tumor mass, decrease in the number of metastases, increase in time to tumor progression, and/or increase subject survival time by at least about 2%. In another embodiment, the therapeutic response is at least about 5%. In another embodiment, the therapeutic response is at least about 10%. In another embodiment, the therapeutic response is at least about 15%. In another embodiment, the therapeutic response is at least about 20%. In another embodiment, the therapeutic response is at least about 25%. In another embodiment, the therapeutic response is at least about 30%. In another embodiment, the therapeutic response is at least about 35%. In another embodiment, the therapeutic response is at least about 40%. In another embodiment, the therapeutic response is at least about 45%. In another embodiment, the therapeutic response is at least about 50%. In another embodiment, the therapeutic response is at least about 55%. In another embodiment, the therapeutic response is at least about 60%. In another embodiment, the therapeutic response is at least about 65%. In another embodiment, the therapeutic response is at least about 70%. In another embodiment, the therapeutic response is at least about 75%. In another embodiment, the therapeutic response is at least about 80%. In another embodiment, the therapeutic response is at least about 85%. In another embodiment, the therapeutic response is at least about 90%. In another embodiment, the

therapeutic response is at least about 95%. In another embodiment, the therapeutic response is at least about 100%, or more.

[0285] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable vehicle" encompasses any of the standard pharmaceutical carriers, solvents, surfactants, or vehicles. Suitable pharmaceutically acceptable vehicles include aqueous vehicles and nonaqueous vehicles. Standard pharmaceutical carriers and their formulations are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 19th ed. 1995.

[0286] The term "container" means any receptacle and closure therefore suitable for storing, shipping, dispensing, and/or handling a pharmaceutical product.

[0287] The term "insert" means information accompanying a pharmaceutical product that provides a description of how to administer the product, along with the safety and efficacy data required to allow the physician, pharmacist, and patient to make an informed decision regarding use of the product. The package insert generally is regarded as the "label" for a pharmaceutical product.

[0288] In some embodiments, when administered in combination, two or more agents can have a synergistic effect. The terms "synergy," "synergistic," "synergistically" and derivations thereof, such as in a "synergistic effect" or a "synergistic combination" or a "synergistic composition" as used herein refer to circumstances under which the biological activity of a combination of an agent and at least one additional therapeutic agent is greater than the sum of the biological activities of the respective agents when administered individually. For example, the term "synergistically effective" as used herein refers to the interaction between a Compound of the Disclosure and the optional therapeutic agent, e.g., an immune checkpoint inhibitor, that causes the total effect of the drugs to be greater than the sum of the individual effects of each drug. *See, e.g,* Berenbaum, *Pharmacological Reviews* 47:93-141 (1989).

[0289] Synergy can be expressed in terms of a "Synergy Index (SI)," is determined by the method described by F. C. Kull et al, *Applied Microbiology* 9:538 (1961), from the ratio determined by:

$$Q_aQA + Q_bQB = \text{Synergy Index (SI)}$$

wherein:

[0290] Q_A is the concentration of a component A, acting alone, which produced an end point in relation to component A;

[0291] Q_a is the concentration of component A, in a mixture, which produced an end point;

[0292] Q_B is the concentration of a component B, acting alone, which produced an end point in relation to component B; and

[0293] Q_b is the concentration of component B, in a mixture, which produced an end point.

[0294] Generally, when the sum of Q_a/Q_A and Q_b/QB is greater than one, antagonism is indicated. When the sum is equal to one, additivity is indicated. When the sum is less than one, synergism is demonstrated. The lower the SI, the greater the synergy shown by that particular mixture. Thus, a "synergistic combination" has an activity higher that what can be expected based on the observed activities of the individual components when used alone. Further, a "synergistically effective amount" of a component refers to the amount of the component necessary to elicit a synergistic effect in, for example, another therapeutic agent present in the composition.

[0295] The term "halo" as used herein by itself or as part of another group refers to -Cl, -F, -Br, or -I.

[0296] The term "cyano" as used herein by itself or as part of another group refers to -CN.

[0297] The term "hydroxy" as herein used by itself or as part of another group refers to -OH.

[0298] The term "alkyl" as used herein by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one to twelve carbon atoms, i.e., a C_1-C_{12} alkyl, or the number of carbon atoms designated, e.g., a Ci alkyl such as methyl, a C_2-alkyl such as ethyl, etc. In one embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl, i.e., methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, or iso-butyl. In another embodiment, the alkyl is a C_1-C3 alkyl, i.e., methyl, ethyl, propyl, or isopropyl. Non-limiting exemplary C_1-C_{12} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, **tert**-butyl. *iso*-butyl, 3-pentyl, hexyl, heptyl, octyl, nonyl, and decyl.

[0299] The term "alkenyl" as used herein by itself or as part of another group refers to an alkyl group containing one or two carbon-to-carbon double bonds. In one embodiment, the alkenyl group is a C_2-C_6 alkenyl group. In another embodiment, the alkenyl group is a C_2-C_4 alkenyl group. In another embodiment, the alkenyl group has one carbon-to-carbon double bond. Non-limiting exemplary alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, sec-butenyl. pentenyl, and hexenyl.

[0300] The term "alkynyl" as used herein by itself or as part of another group refers to an alkyl group containing one carbon-to-carbon triple bond. In one embodiment, the alkynyl is a C_2-C_6 alkynyl. In another embodiment, the alkynyl is a C_2-C_4 alkynyl. Non-limiting exemplary alkynyl groups include ethynyl, propynyl, butynyl, 2-butynyl, pentynyl, and hexynyl groups.

[0301] The terms "aralkyl" or "(aryl)alkyl" as used herein by themselves or as part of another group refers to an alkyl substituted with one, two, or three optionally substituted aryl groups. In one embodiment, the alkyl is substituted with one optionally substituted aryl group. In

one embodiment, the aryl is an optionally substituted phenyl or optionally substituted naphthyl. In another embodiment, the aryl is an optionally substituted phenyl. In one embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl. In another embodiment, the alkyl is a C_1 or C_2 alkyl. Non-limiting exemplary (aryl)alkyl groups include benzyl, phenethyl, -$CHPh_2$, and -$CH(4\text{-F-Ph})_2$.

[0302] The term "haloalkyl" as used herein by itself or as part of another group refers to an alkyl group substituted by one or more fluorine, chlorine, bromine, and/or iodine atoms. In one embodiment, the alkyl is substituted by one, two, or three fluorine and/or chlorine atoms. In another embodiment, the alkyl is substituted by one, two, or three fluorine atoms. In another embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl. In another embodiment, the alkyl group is a C_1 or C_2 alkyl. Non-limiting exemplary haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, and trichloromethyl groups.

[0303] The term "alkoxy" as used herein by itself or as part of another group refers to an alkyl group attached to a terminal oxygen atom. In one embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl group. Non-limiting exemplary alkoxy groups include methoxy, ethoxy, and tert-butoxy.

[0304] The term "amino" as used by itself or as part of another group refers to a radical of the formula -$NR^{a1}R^{a2}$, wherein R^{a1} and R^{a2} are independently hydrogen, cycloalkyl, optionally substituted heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, or (aryl)alkyl; or R^{a1} and R^{a2} are taken together with the nitrogen atom to which they are attached form a 4- to 7-membered optionally substituted heterocyclo. Non-limiting exemplary amino groups include -NH_2, -$NH(CH_3)$, and -$N(CH_3)_2$.

[0305] The term "hydroxyalkyl" as used herein by itself or as part of another group refers to an alkyl group substituted with one or two hydroxy groups. In one embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl. In another embodiment, the alkyl is a C_1 or C_2 alkyl. In another embodiment, the hydroxyalkyl is a monohydroxyalkyl group, i.e., substituted with one hydroxy group. In another embodiment, the hydroxyalkyl group is a dihydroxyalkyl group, i.e., substituted with two hydroxy groups. Non-limiting exemplary hydroxyl alkyl groups include hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxybutyl groups, such as 1-hydroxyethyl, 2-hydroxyethyl, 1,2-dihydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 3-hydroxybutyl, 4-hydroxybutyl, 2-hydroxy-1-methylpropyl, and 1,3-dihydroxyprop-2-yl.

[0306] The term "carboxamido" as used herein by itself or as part of another group refers to a radical of formula -C(=o)NR ^{bl}R^{b2}, wherein R^{bl} and R^{b2} are independently hydrogen, cycloalkyl, optionally substituted heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, or (aryl)alkyl; or R^{bl} and R^{b2} are taken together with the nitrogen atom to which they are attached form a 4- to 7-membered optionally substituted heterocyclo. A non-limiting exemplary amino groups is -C(=O)NH_2.

[0307] The term "sulfonamido" as used herein by itself or as part of another group refers to a radical of formula -S(=O)$_2$NR^{c1}R^{c2}, wherein R^{c1} and R^{c2} are independently hydrogen, cycloalkyl, optionally substituted heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, or (aryl)alkyl; or Rc^{al} and R^{c2} are taken together with the nitrogen atom to which they are attached form a 4- to 7-membered optionally substituted heterocyclo. A non-limiting exemplary amino groups is -S(=O)2NH_2.

[0308] The term "alkylcarbonyl" as used herein by itself or as part of another group refers to a carbonyl group, i.e., -C(=O)-, substituted by an alkyl group. In one embodiment, the alkyl is a C_1-C_4 alkyl. A non-limiting exemplary alkylcarbonyl group is -$COCH_3$.

[0309] The term "alkylsulfonyl" as used herein by itself or as part of another group refers to a sulfonyl group, i.e., -SO_2-, substituted by an alkyl group. In one embodiment, the alkyl is a C_1-C_4 alkyl. A non-limiting exemplary alkylsulfonyl group is -SO_2CH_3.

[0310] The term "alkoxyalkyl" as used herein by itself or as part of another group refers to an alkyl group substituted with one alkoxy group. In one embodiment, the alkoxy is a C_1-C_6 alkoxy. In another embodiment, the alkoxy is a C_1-C_4 alkoxy. In another embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl. Non-limiting exemplary alkoxyalkyl groups include methoxymethyl, methoxyethyl, methoxypropyl, methoxybutyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, ethoxybutyl, propoxymethyl, iso-propoxymethyl, propoxyethyl, propoxypropyl, butoxymethyl, tert-butoxymethyl, isobutoxymethyl, sec-butoxymethyl, and pentyloxymethyl.

[0311] The term "(amino)alkyl" as used herein by itself or as part of another group refers to an alkyl substituted with one amino group. In one embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl. Non-limiting exemplary (amino)alkyl groups include -CH_2NH_2, $CH_2CH_2N(H)CH_3$ and -$CH_2CH_2N(CH_3)_2$.

[0312] The term "(cyano)alkyl" as used herein by itself or as part of another group refers to an alkyl substituted with one cyano group. In one embodiment, the alkyl is a C_1-C_6 alkyl. In another embodiment, the alkyl is a C_1-C_4 alkyl. Non-limiting exemplary (cyano)alkyl groups include -CH_2CH_2CN and -$CH_2CH_2CH_2CN$.

[0313] The term "(carboxamido)alkyl" as used herein by itself or as part of another group refers to an alkyl substituted with a carboxamido group. In one embodiment, the alkyl is a C_1-C_4 alkyl. In another embodiment, the alkyl is a Ci or C2 alkyl. Non-limiting exemplary (carboxamido)alkyl groups include $-CH_2C(=O)NH_2$ and $-CH_2C(=O)N(CH_3)_2$.

[0314] The term "haloalkoxy" as used herein by itself or as part of another group refers to an haloalkyl group attached to a terminal oxygen atom. In one embodiment, the haloalkyl is a C_1-C4 haloalkyl group. A non-limiting exemplary haloalkoxy group is -OCF3.

[0315] The term "aryl" as used herein by itself or as part of another group refers to an aromatic ring system having six to fourteen carbon atoms, i.e., C_6-C_{14} aryl. Non-limiting exemplary aryl groups include phenyl (abbreviated as "Ph") and naphthyl, In one embodiment, the aryl group is phenyl.

[0316] The term "optionally substituted aryl" as used herein by itself or as part of another group refers to aryl that is either unsubstituted or substituted with one, two, three, four, or five substituents, wherein the substituents are each independently halo, nitro, cyano, hydroxy, amino, e.g., -NH2, alkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, carboxamido, sulfonamido, alkylcarbonyl, alkylsulfonyl, alkoxyalkyl, (amino)alkyl, (cyano)alkyl, or (carboxamido)alkyl.

[0317] In one embodiment, the optionally substituted aryl is an optionally substituted phenyl. In another embodiment, the optionally substituted phenyl has four substituents. In another embodiment, the optionally substituted phenyl has three substituents. In another embodiment, the optionally substituted phenyl has two substituents. In another embodiment, the optionally substituted phenyl has one substituent. Non-limiting exemplary optionally substituted aryl groups include 2-methylphenyl, 2-methoxyphenyl, 2-fluorophenyl, 2-chlorophenyl, 2-bromophenyl, 3-methylphenyl, 3-methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 4-methylphenyl, 4-ethylphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 2,6-di-fluorophenyl, 2,6-di-chlorophenyl, 2-methyl, 3-methoxyphenyl, 2-ethyl, 3-methoxyphenyl, 3,4-di-methoxyphenyl, 3,5-di-fluorophenyl 3,5-di-methylphenyl, 3,5-dimethoxy, 4-methylphenyl, 2-fluoro-3-chlorophenyl, and 3-chloro-4-fluorophenyl. The term optionally substituted aryl includes aryl groups having fused optionally substituted cycloalkyl groups and fused optionally substituted heterocyclo groups. Non-limiting examples include: 2,3-dihydro-lH-inden-l-yl, 1,2,3,4-tetrahydronaphthalen-l-yl, l,3,4,5-tetrahydro-2H-benzo[c]azepin-2-yl, 1,2,3,4-tetrahydroisoquinolin-l-yl, and 2-oxo-2,3,4,5-tetrahydro-1H-benzo[d]azepin-1-yl.

[0318] The term "heteroaryl" as used herein by itself or as part of another group refers to monocyclic and bicyclic aromatic ring systems having 5 to 14 ring members, i.e., a 5- to 14-membered heteroaryl, comprising one, two, three, or four heteroatoms. Each heteroatom is

independently oxygen, sulfur, or nitrogen. In one embodiment, the heteroaryl has three heteroatoms. In another embodiment, the heteroaryl has two heteroatoms. In another embodiment, the heteroaryl has one heteroatom. In another embodiment, the heteroaryl is a 5- to 10-membered heteroaryl. In another embodiment, the heteroaryl has 5 ring atoms, e.g., thienyl (a 5-membered heteroaryl having four carbon atoms and one sulfur atom). In another embodiment, the heteroaryl has 6 ring atoms, e.g., pyridyl (a 6-membered heteroaryl having five carbon atoms and one nitrogen atom). Non-limiting exemplary heteroaryl groups include thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, benzofuryl, pyranyl, isobenzofuranyl, benzooxazonyl, chromenyl, xanthenyl, 2//-pyrrolyl. pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isoindolyl, 3//-indolyl. indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, cinnolinyl, quinazolinyl, pteridinyl, 4a//-carbazolyl. carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, thiazolyl, isothiazolyl, phenothiazolyl, isoxazolyl, furazanyl, and phenoxazinyl. In one embodiment, the heteroaryl is chosen from thienyl (e.g., thien-2-yl and thien-3-yl), furyl (e.g., 2-furyl and 3-furyl), pyrrolyl (e.g., lH-pyrrol-2-yl and lH-pyrrol-3-yl), imidazolyl (e.g., 2H-imidazol-2-yl and 2H-imidazol-4-yl), pyrazolyl (e.g., lH-pyrazol-3-yl, lH-pyrazol-4-yl, and lH-pyrazol-5-yl), pyridyl (e.g., pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl), pyrimidinyl (e.g., pyrimidin-2-yl, pyrimidin-4-yl, and pyrimidin-5-yl), thiazolyl (e.g., thiazol-2-yl, thiazol-4-yl, and thiazol-5-yl), isothiazolyl (e.g., isothiazol-3-yl, isothiazol-4-yl, and isothiazol-5-yl), oxazolyl (e.g., oxazol-2-yl, oxazol-4-yl, and oxazol-5-yl) and isoxazolyl (e.g., isoxazol-3-yl, isoxazol-4-yl, and isoxazol-5-yl). The term heteroaryl also includes N-oxides. A non-limiting exemplary N-oxide is pyridyl N-oxide.

[0319] The term "optionally substituted heteroaryl" as used herein by itself or as part of another group refers to a heteroaryl that is either unsubstituted or substituted with one, two, three, or four substituents, wherein the substituents are each independently halo, nitro, cyano, hydroxy, amino, e.g., $-NH_2$, alkyl, haloalkyl, hydroxy alkyl, alkoxy, haloalkoxy, carboxamido, sulfonamido, alkylcarbonyl, alkylsulfonyl, alkoxyalkyl, (amino)alkyl, (cyano)alkyl, or (carboxamido)alkyl. In one embodiment, the optionally substituted heteroaryl has two substituents. In another embodiment, the optionally substituted heteroaryl has one substituent. Any available carbon or nitrogen atom can be substituted.

[0320] The term "cycloalkyl" as used herein by itself or as part of another group refers to saturated and partially unsaturated, e.g., containing one or two double bonds, monocyclic, bicyclic, or tricyclic aliphatic hydrocarbons containing three to twelve carbon atoms, i.e., a C_{3-12} cycloalkyl, or the number of carbons designated, e.g., a C3 cycloalkyl such a cyclopropyl, a C_4 cycloalkyl such as cyclobutyl, etc. In one embodiment, the cycloalkyl is bicyclic, i.e., it has two rings. In another

embodiment, the cycloalkyl is monocyclic, i.e., it has one ring. In another embodiment, the cycloalkyl is a C_{3-8} cycloalkyl. In another embodiment, the cycloalkyl is a C_{3-6} cycloalkyl, i.e., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. Non-limiting exemplary C_{3-12} cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, norbomyl, decalin, adamantyl, cyclohexenyl, and spiro[3.3]heptane.

[0321] The term "optionally substituted cycloalkyl" as used herein by itself or as part of another group refers to a cycloalkyl group is either unsubstituted or substituted with one, two, or three substituents, wherein the substituents are each independently halo, nitro, cyano, hydroxy, amino, e.g., $-NH_2$, alkyl, haloalkyl, hydroxy alkyl, alkoxy, haloalkoxy, carboxamido, sulfonamido, alkylcarbonyl, alkylsulfonyl, alkoxyalkyl, (amino)alkyl, (cyano)alkyl, or (carboxamido)alkyl. In one embodiment, the optionally substituted cycloalkyl has two substituents. In another embodiment, the optionally substituted cycloalkyl has one substituent.

[0322] The term "heterocyclo" as used herein by itself or as part of another group refers to saturated and partially unsaturated, e.g., containing one or two double bonds, monocyclic, bicyclic, or tricyclic groups containing three to fourteen ring members, i.e., a 3- to 14-membered heterocyclo, comprising one, two, three, or four heteroatoms. Each heteroatom is independently oxygen, sulfur, or nitrogen. Each sulfur atom is independently oxidized to give a sulfoxide, i.e., S(=O), or sulfone, i.e., $S(=O)_2$.

[0323] The term heterocyclo includes groups wherein one or more -CEE- groups is replaced with one or more -C(=O)- groups, including cyclic ureido groups such as imidazolidinyl-2-one, cyclic amide groups such as pyrrolidin-2-one or piperidin-2-one, and cyclic carbamate groups such as oxazolidinyl-2-one.

[0324] The term heterocyclo also includes groups having fused optionally substituted aryl or optionally substituted heteroaryl groups such as indoline, indolin-2-one, 2,3-dihydro-lH-pyrrolo[2,3-c]pyridine, 2,3,4,5-tetrahydro-lH-benzo[d]azepine, or l,3,4,5-tetrahydro-2H-benzo[d]azepin-2-one.

[0325] In one embodiment, the heterocyclo group is a 4- to 8-membered cyclic group containing one ring and one or two oxygen atoms, e.g., tetrahydrofuran or tetrahydropyran, or one or two nitrogen atoms, e.g., pyrrolidine, piperidine, or piperazine, or one oxygen and one nitrogen atom, e.g., morpholine, and, optionally, one -CEE- group is replaced with one -C(=O)- group, e.g., pyrrolidin-2-one or piperazin-2-one. In another embodiment, the heterocyclo group is a 5- to 8-membered cyclic group containing one ring and one or two nitrogen atoms and, optionally, one $-CH_2-$ group is replaced with one -C(=O)- group. In another embodiment, the heterocyclo group is a 5- or 6-membered cyclic group containing one ring and one or two nitrogen atoms and,

optionally, one -CH_2- group is replaced with one -C(=O)- group. In another embodiment, the heterocyclo group is a 8- tol2-membered cyclic group containing two rings and one or two nitrogen atoms. The heterocyclo can be linked to the rest of the molecule through any available carbon or nitrogen atom.

[0326] The term "optionally substituted heterocyclo" as used herein by itself or part of another group refers to a heterocyclo group that is either unsubstituted or substituted with one, two, three, or four substituents, wherein the substituents are each independently halo, nitro, cyano, hydroxy, amino, e.g., -NH_2, alkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, carboxamido, sulfonamido, alkylcarbonyl, alkylsulfonyl, alkoxyalkyl, (amino)alkyl, (cyano)alkyl, or (carboxamido)alkyl. In one embodiment, the optionally substituted heterocyclo has two substituents. In another embodiment, the optionally substituted heterocyclo has one substituent Substitution may occur on any available carbon or nitrogen atom of the heterocyclo group.

[0327] The present disclosure encompasses any of the Compounds of the Disclosure being isotopically -labelled (i.e., radiolabeled) by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H (or deuterium (D)), ^{3}H, ^{n}C, ^{13}C, ^{14}C, ^{15}N, $^{18}0$, $^{17}0$, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and $^{36}C'_{1}$, respectively, e.g., ^{3}H, ^{11}C, and ^{14}C. In one embodiment, provided is a composition wherein substantially all of the atoms at a position within the Compound of the Disclosure are replaced by an atom having a different atomic mass or mass number. In another embodiment, provided is a composition wherein a portion of the atoms at a position within the Compound of the disclosure are replaced, i.e., the Compound of the Disclosure is enriched at a position with an atom having a different atomic mass or mass number." Isotopically -labelled Compounds of the Disclosure can be prepared by methods known in the art.

[0328] Compounds of the Disclosure may contain one or more chiral centers and thus may give rise to enantiomers, diastereomers, and other stereoisomers. The present disclosure encompasses the use of all possible stereoisomeric forms of a Compound of the Disclosure, as well as their racemic and resolved forms and mixtures thereof. The individual enantiomers can be separated according to methods known in the art in view of the present disclosure. When the compounds described herein contain olefmic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that they include both E and Z geometric isomers. All tautomers are also encompassed by the present disclosure.

[0329] As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes

enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

[0330] The term "chiral center" or "asymmetric carbon atom" refers to a carbon atom to which four different groups are attached.

[0331] The terms "enantiomer" and "enantiomeric" refer to a molecule that cannot be superimposed on its mirror image and hence is optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image compound rotates the plane of polarized light in the opposite direction.

[0332] The term "racemic" refers to a mixture of equal parts of enantiomers and which mixture is optically inactive. In one embodiment, Compounds of the Disclosure are racemic.

[0333] The term "absolute configuration" refers to the spatial arrangement of the atoms of a chiral molecular entity (or group) and its stereochemical description, e.g., R or S.

[0334] The stereochemical terms and conventions used in the specification are meant to be consistent with those described in *Pure &Appl. Chem 68:* 2193 (1996), unless otherwise indicated.

[0335] The term "enantiomeric excess" or "ee" refers to a measure for how much of one enantiomer is present compared to the other. For a mixture of *R* and *S* enantiomers, the percent enantiomeric excess is defined as $|R - S| * 100$, where *R* and *S* are the respective mole or weight fractions of enantiomers in a mixture such that $R + S = 1$. With knowledge of the optical rotation of a chiral substance, the percent enantiomeric excess is defined as $([a]_{obs}/[a]_{max}) * 100$, where $[a]_{obs}$ is the optical rotation of the mixture of enantiomers and $[a]_{max}$ is the optical rotation of the pure enantiomer. Determination of enantiomeric excess is possible using a variety of analytical techniques, including NMR spectroscopy, chiral column chromatography or optical polarimetry.

[0336] In one embodiment, Compounds of the Disclosure having one or more chiral centers are enantiomerically enriched, e.g., the ee is about 5% or more. In another embodiment, the ee is about 10%. In another embodiment, the ee is about 20%. In another embodiment, the ee is about 30%. In another embodiment, the ee is about 40%. In another embodiment, the ee is about 50%. In another embodiment, the ee is about 60%. In another embodiment, the ee is about 70%. In another embodiment, the ee is about 80%. In another embodiment, the ee is about 85%. In another embodiment, the ee is about 90%. In another embodiment, the ee is about 91%. In another embodiment, the ee is about 92%. In another embodiment, the ee is about 93%. In another embodiment, the ee is about 94%. In another embodiment, the ee is about 95%. In another embodiment, the ee is about 96%. In another embodiment, the ee is about 97%. In another embodiment, the ee is about 98%. In another embodiment, the ee is about 99%.

[0337] The term "disease" or "condition" or "disorder" denotes disturbances and/or anomalies that as a rule are regarded as being pathological conditions or functions, and that can manifest themselves in the form of particular signs, symptoms, and/or malfunctions. Compounds of the Disclosure inhibit amino acid, e.g., glutamine, transporters, e.g., ASCT2, and can be used in treating diseases and conditions such as cancer and proliferative diseases, wherein inhibition of an amino acid, e.g., glutamine, transporter, e.g., ASCT2, provides a benefit.

[0338] The term "amino acid transporter" and the like as used herein refer membrane transport proteins that transport amino acids including, but not limited to glutamine, across the cell membrane. Amino acid transporters are well known in the art.

[0339] The terms "glutamine transporter" or " glutamine transport protein" and the like as used herein refer membrane transport proteins that transport glutamine across the cell membrane. ASCT2 and other glutamine transporters are well known in the art. For example, the sodium-dependent neutral amino acid transporter or "BOAT1 " is a membrane transport protein encoded by the *SLC6A19* gene. The sodium-coupled neutral amino acid transporter l or "SNAT1" is a membrane transport protein encoded by the *SLC38A1* gene. The sodium-coupled neutral amino acid transporter 2 or "SNAT" is a membrane transport protein encoded by the *SLC38A2* gene. The sodium-coupled neutral amino acid transporter 3 or "SNAT3" is a membrane transport protein encoded by the *SLC38A3* gene. The sodium-coupled neutral amino acid transporter 5 or "SNAT5" is a membrane transport protein encoded by the *SLC38A5* gene. The sodium-coupled neutral amino acid transporter 7 or "SNAT7" is a membrane transport protein encoded by ths *SLC38A7* gene. The large neutral amino acids transporter small subunit 1 or "LAT1" is a membrane transport protein encoded by the *SLC7A5* gene. The large neutral amino acids transporter small subunit 2 or "LAT2" is a membrane transport protein encoded by the *SLC7A8* gene.

[0340] In some embodiments, the Compounds of the Disclosure can be used to treat a "glutamine transporter-mediated disorder," i.e., a disease, disorder, or condition wherein inhibition of ASCT2-, BOAT1-, SNAT1-, SNAT2-, SNAT3-, SNAT5-, SNAT7-, LAT1-, and/or LAT2-mediated glutamine transport provides a benefit. Such glutamine transporter-mediated disorders are represented by any pathological condition in which a glutamine transporter is known to play a role. In some embodiments, a glutamine transporter-mediated disorder is a proliferative disease such as cancer.

[0341] In some embodiments, the Compounds of the Disclosure can be used to treat an "ASCT2-mediated disorder," i.e., a disease, disorder, or condition wherein inhibition of ASCT2-mediated amino acid, e.g., glutamine, transport provides a benefit. Such ASCT2-mediated

disorders are represented by any pathological condition in which ASCT2 is known to play a role. In some embodiments, the ASCT2-mediated disorder is a proliferative disease such as cancer.

[0342] In some embodiments, the Compounds of the Disclosure can be used to treat a "BOAT1-mediated disorder," i.e., a disease, disorder, or condition wherein inhibition of BOAT1-mediated amino acid, e.g., glutamine, transport provides a benefit. Such BOAT1-mediated disorders are represented by any pathological condition in which BOAT1 is known to play a role. In some embodiments, a BOAT1-mediated disorder is a proliferative disease such as cancer.

[0343] In some embodiments, the Compounds of the Disclosure can be used to treat a "SNAT1-mediated disorder," i.e., a disease, disorder, or condition wherein inhibition of SNAT1-mediated amino acid, e.g., glutamine, transport provides a benefit. Such SNAT1-mediated disorders are represented by any pathological condition in which SNAT1 is known to play a role. In some embodiments, a SNAT1-mediated disorder is a proliferative disease such as cancer.

[0344] In some embodiments, the Compounds of the Disclosure can be used to treat a "SNAT2-mediated disorder," i.e., a disease, disorder, or condition wherein inhibition of SNAT2-mediated amino acid, e.g., glutamine, transport provides a benefit. Such SNAT2-mediated disorders are represented by any pathological condition in which SNAT2 is known to play a role. In some embodiments, a SNAT2-mediated disorder is a proliferative disease such as cancer.

[0345] In some embodiments, the Compounds of the Disclosure can be used to treat a "SNAT3-mediated disorder," i.e., a disease, disorder, or condition wherein inhibition of SNAT3-mediated amino acid, e.g., glutamine, transport provides a benefit. Such SNAT3-mediated disorders are represented by any pathological condition in which SNAT3 is known to play a role. In some embodiments, a SNAT3-mediated disorder is a proliferative disease such as cancer.

[0346] In some embodiments, the Compounds of the Disclosure can be used to treat a "SNAT5-mediated disorder," i.e., a disease, disorder, or condition wherein inhibition of SNAT5-mediated amino acid, e.g., glutamine, transport provides a benefit. Such SNAT5-mediated disorders are represented by any pathological condition in which SNAT5 is known to play a role. In some embodiments, a SNAT5-mediated disorder is a proliferative disease such as cancer.

[0347] In some embodiments, the Compounds of the Disclosure can be used to treat a "SNAT7-mediated disorder," i.e., a disease, disorder, or condition wherein inhibition of SNAT7-mediated amino acid, e.g., glutamine, transport provides a benefit. Such SNAT7-mediated disorders are represented by any pathological condition in which SNAT7 is known to play a role. In some embodiments, a SNAT7-mediated disorder is a proliferative disease such as cancer.

[0348] In some embodiments, the Compounds of the Disclosure can be used to treat a "LAT1-mediated disorder," i.e., a disease, disorder, or condition wherein inhibition of LAT1-

mediated amino acid, e.g., glutamine, transport provides a benefit. Such LATl-mediated disorders are represented by any pathological condition in which LAT1 is known to play a role. In some embodiments, a LATl-mediated disorder is a proliferative disease such as cancer.

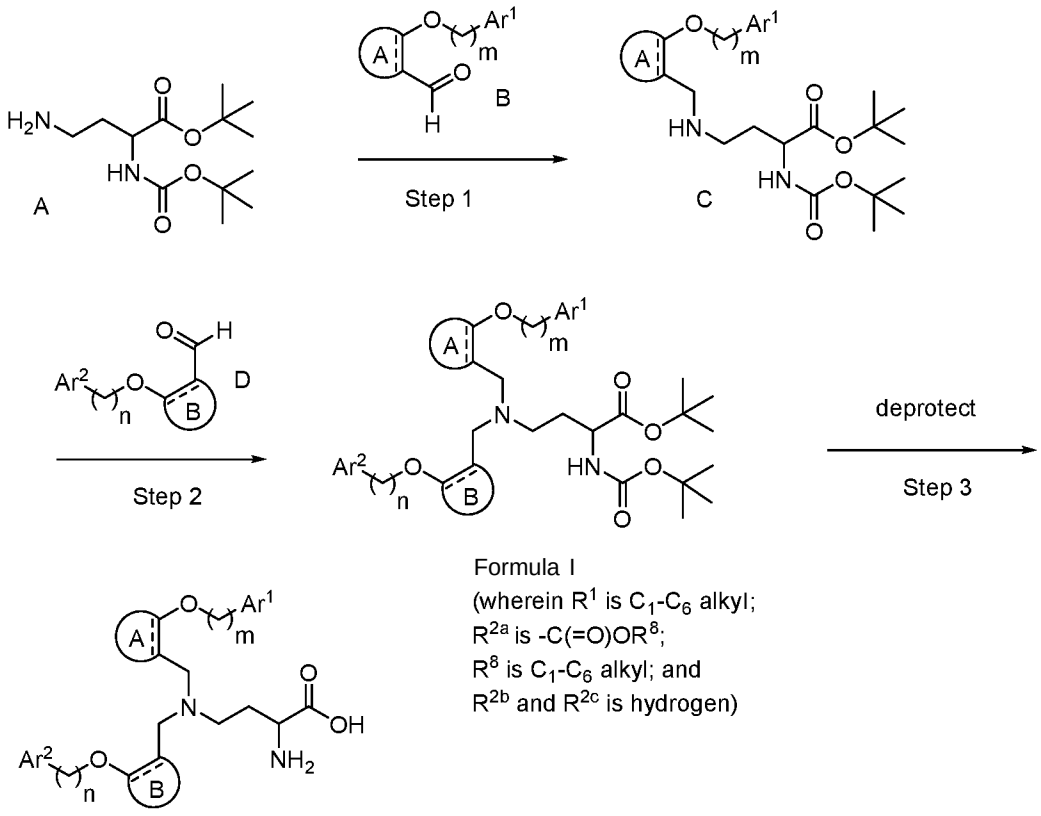
[0349] In some embodiments, the Compounds of the Disclosure can be used to treat a "LAT2-mediated disorder," i.e., a disease, disorder, or condition wherein inhibition of LAT2-mediated amino acid, e.g., glutamine, transport provides a benefit. Such LAT2-mediated disorders are represented by any pathological condition in which LAT2 is known to play a role. In some embodiments, a LAT2-mediated disorder is a proliferative disease such as cancer.

[0350] The term "biological sample" as used herein refers any tissue or fluid from a subj ect that is suitable for detecting the expression status and/or mutation status in a biomarker. Examples of useful biological samples include, but are not limited to, biopsied tissues and/or cells, e.g., solid tumor, lymph gland, inflamed tissue, tissue and/or cells involved in a condition or disease, blood, plasma, serous fluid, cerebrospinal fluid, saliva, urine, lymph, cerebral spinal fluid, and the like. Other suitable biological samples will be familiar to those of ordinary skill in the relevant arts. A biological sample can be analyzed for biomarkers using any technique known in the art. Such techniques include, but are not limited to, polymerase chain reaction (PCR) methodology, reverse transcription-polymerase chain reaction (RT-PCR) methodology, or cytoplasmic light chain immunofluorescence combined with fluorescence in situ hybridization (clg-FISH). A biological sample can be obtained using techniques that are well within the scope of ordinary knowledge of a clinical practioner. In one embodiment of the disclosure, the biological sample comprises tumor cells or blood cells.

VI. General Synthetic Methods

[0351] Compounds of the Disclosure can be prepared as shown in General Scheme 1.

General Scheme 1



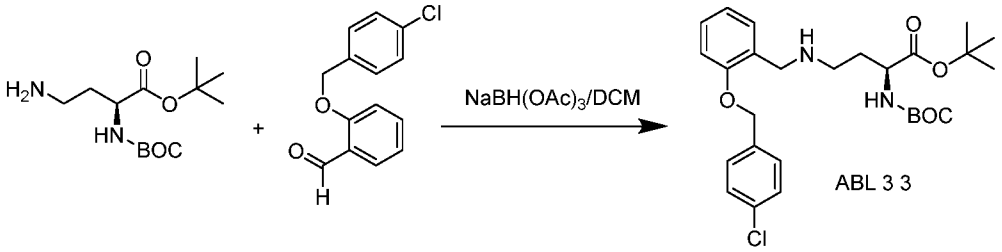
[0352] Briefly, compound A is made undergo reductive amination with compound B is the presence of a reducing agent, e.g., sodium cyanoborohydride (NaBFbCN) or sodium triacetoxyborohydride (NaBH(OCOCH$_3$)$_3$, to give compound C. Compound C is made to go a second reductive amination with compound D to give a compound of Formula I, wherein R^1 is Ci-C_6 alkyl, R^{2a} is -C(=O)0tBu (Boc), R^{2b} is hydrogen, and R^{2c} is hydrogen. Deprotection of this compound give a compound of Formula I, wherein R^1, R^{2a}, R^{2b}, and R^{2c} are hydrogen.

Examples

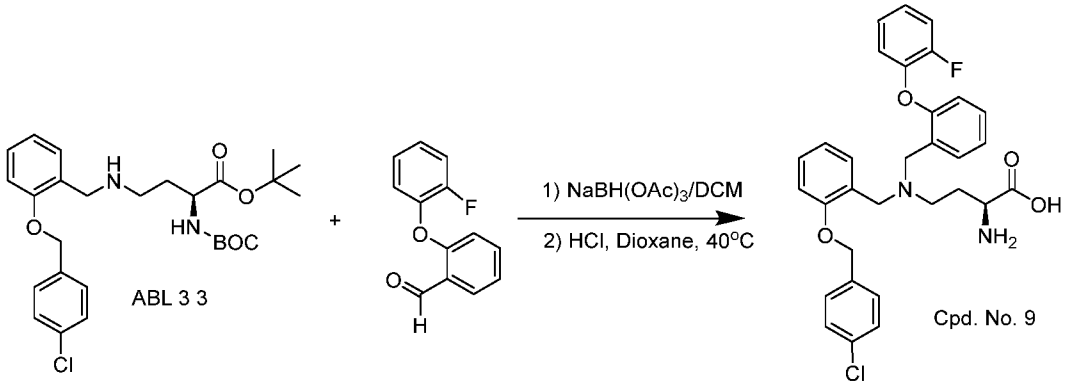
EXAMPLE 1

Synthesis of (S)-2-Amino-4-((2-((4-chlorobenzyl)oxy)benzyl)(2-(2-fluorophenoxy)benzyl)amino)butanoic acid (Cpd. No. 9)

Scheme 1A



Scheme 1B



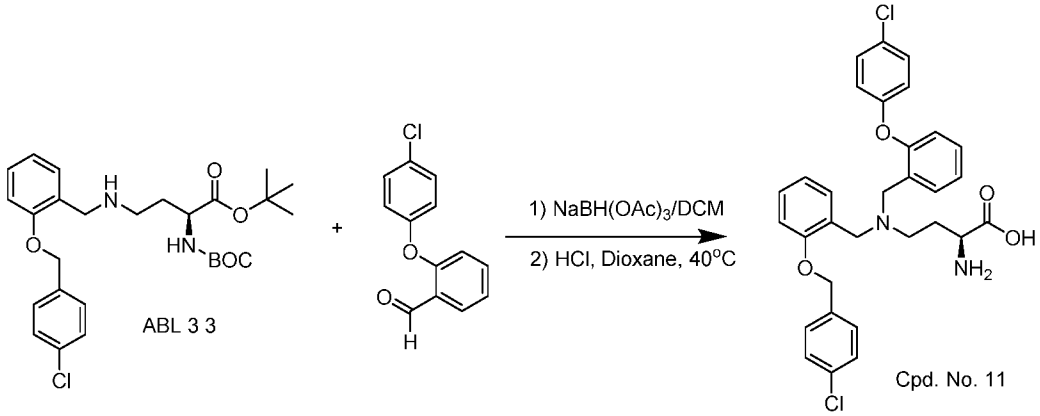
[0353] ABL 3 3 was prepared in >95% yield by reductive animation as shown in Scheme 1A. The crude product was purified by column chromatography on silica gel eluting with DCM:MeOH (calculated mass = 505; found = 506).

[0354] Cpd. No. 9 was prepared from ABL 3 3 in >95% yield by reductive amination as shown in Scheme IB. The crude product was purified by reverse-phase chromatography (calculated mass = 548; found = 549).

EXAMPLE 2

Synthesis of (S)-2-Amino-4-((2-((4-chlorobenzyl)oxy)benzyl)(2-(4-chlorophenoxy)benzyl)amino)butanoic acid (Cpd. No. 11)

Scheme 2

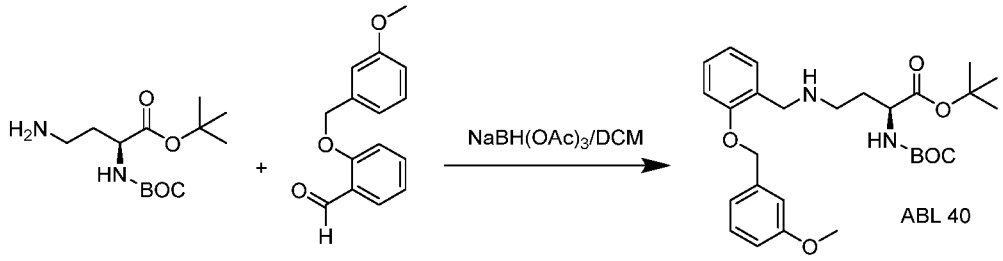


[0355] Cpd. No. 11 was prepared from ABL 3 3 (see Scheme 1A) in >99% yield by reductive animation as shown in Scheme 2. The crude product was purified by reverse-phase chromatography (calculated mass 564; found 565).

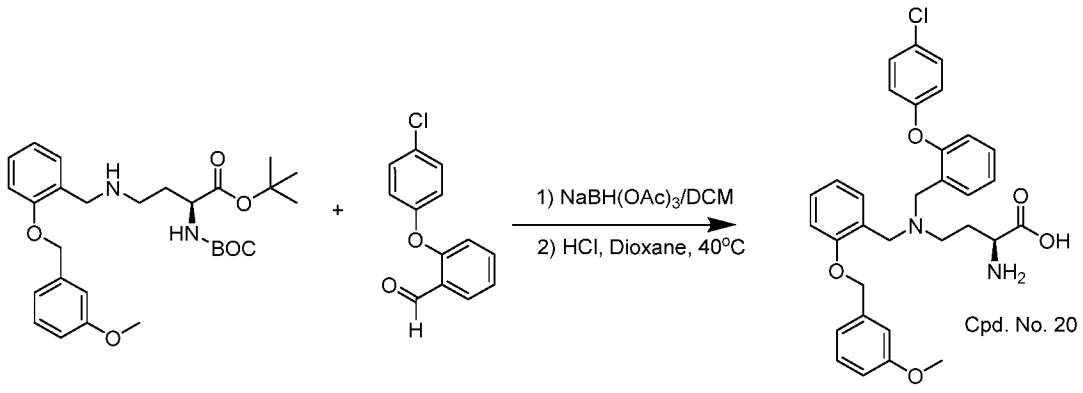
EXAMPLE 3

Synthesis of (S)-2-amino-4-((2-(4-chlorophenoxy)benzyl)(2-((3-methoxybenzyl)oxy)benzyl)amino)butanoic acid (Cpd. No. 20)

Scheme 3A



Scheme 3B



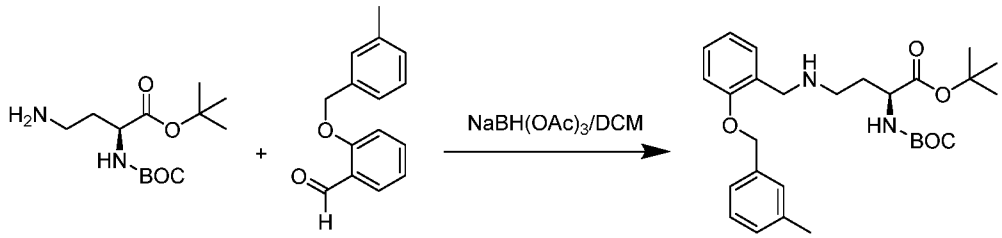
[0356] ABL 40 was prepared in >99% yield by reductive amination as shown in Scheme 3A. The crude product was purified by column chromatography on silica gel eluting with DCM;MeOH (calculated mass 500; found 501).

[0357] Cpd. No. 20 was prepared in >99% yield by reductive amination as shown in Scheme 3B. The crude product was purified by reverse-phase chromatography (calculated mass = 561; found = 562).

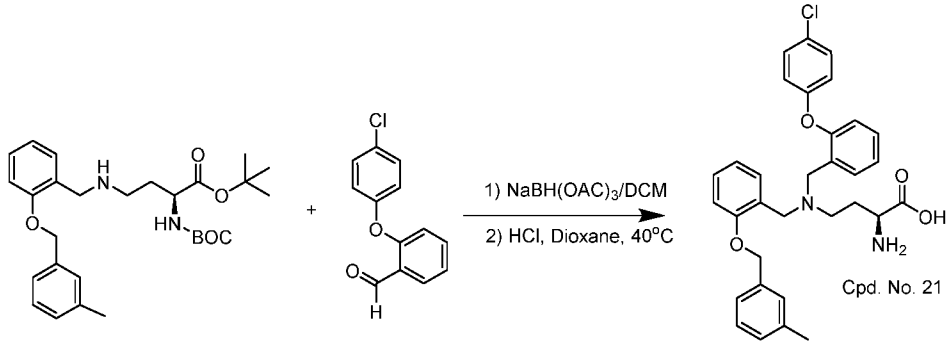
EXAMPLE 4

Synthesis of (S)-2-Amino-4-((2-(4-chlorophenoxy)benzyl)(2-((3-methylbenzyl)oxy)benzyl)amino)butanoic acid (Cpd. No. 21)

Scheme 4A



Scheme 4B



[0358] Cpd No. 21 was prepared in 76% yield using the two-step reductive amination process described im EXAMPLE 1 (calculated mass 545; found 546).

EXAMPLE 5

Glutamine uptake inhibition assay

[0359] Twenty-four hours prior to assay, HEK293 cells were seeded at a density of 12K cells per well into a 96 well plate (coated with poly-D-Lysine). At the time of the assay (24 hrs later), these conditioned resulted in a confluence of approximately 50%. Accumulation of 3H-labeled glutamine (3H-GLN) in live cells was assessed by incubation for 15 minutes with vehicle or test reagent at the concentrations indicated. The final concentration of 3H-GLN was 500 nM. Each compound was evaluated in triplicate. For the assay, cells were rinsed with assay buffer (pH

6) three times (lOOuL). Compounds were transferred in a single-add protocol and incubated for 15 minutes with 3H-GLN. After the uptake period, the supernatant was removed and cell monolayers were washed 3x with 100 pi assay buffer. Subsequently, cells were lysed with 50 µï 1M NaOH and 150 µï scintillation liquid was added to each well. The plate was incubated at room temperature for 20 minutes, transferred to 4 °C storage overnight, and read the next day using a top-count plate reader (Perkin Elmer). The results for representative Compounds of the Disclosure are provided in Table 2.

[0360] Viability (Cell Titer) was evaluated using a commercially available chemiluminescent reagents (CellTiter-Glo, Promega Corp. G7572) in 96-well plate format according to the manufacturers protocol. Cells were exposed to either vehicle or test agent at the indicated concentrations and incubated for a period of 48 h. Subsequently, CellTiter-Glo reagent was added and the plates were read using a plate reader (BioTek Synergy 4) with standard settings.

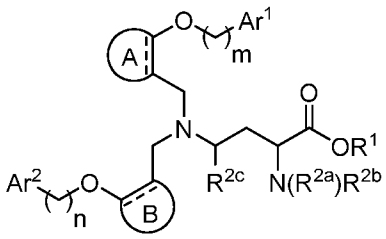
Table 2

Cpd. No.	^{3}H Glut IC_{50} (µM)	Cell Titer IC_{50} (µM)
7	94.15	18.7
8	116.8	
10	42.99	
11	< 100	12.7
13	28.99	
14	163.7	
15	31.43	
20	3.19	13.9
21	25.13	28.9

[0361] Having now fully described the methods, compounds, and compositions herein, it will be understood by those of skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the methods, compounds, and compositions provided herein or any embodiment thereof. All patents, patent applications and publications cited herein are fully incorporated by reference herein in their entirety.

WHAT IS CLAIMED IS:

1. A compound of Formula **I**:



I,

wherein:

R^1 is selected from the group consisting of hydrogen and C_1-C_6 alkyl;

R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, and -C(=O)R^7; and

R^{2c} is hydrogen; or

R^{2a} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and -C(=O)R^7; and

R^{2b} and R^{2c} taken together form a 5- or 6-membered heterocyclo group;

 is selected from the group consisting of optionally substituted C_6-C_{10} aryl and optionally substituted 5- to 10-membered heteroaryl;

 is selected from the group consisting of optionally substituted C_6-C_{10} aryl and optionally substituted 5- to 10-membered heteroaryl;

Ar^1 is selected from the group consisting of optionally substituted C_6-C_{10} aryl and optionally substituted 5- to 10-membered heteroaryl;

Ar^2 is selected from the group consisting of optionally substituted C_6-C_{10} aryl and optionally substituted 5- to 10-membered heteroaryl;

m is 0, 1, 2, or 3;

n is 1, 2, or 3;

with the proviso that m does not equal n;

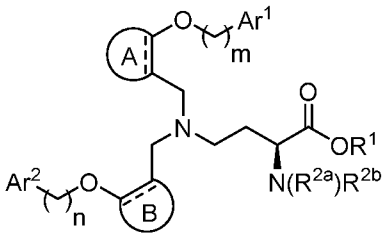
R^7 is selected from the group consisting of C_1-C_6 alkyl and -OR^8;

R^8 is selected from the group consisting of C_1-C_6 alkyl and aralkyl; and

=== represents a single or double bond,

or a pharmaceutically acceptable salt or solvate thereof.

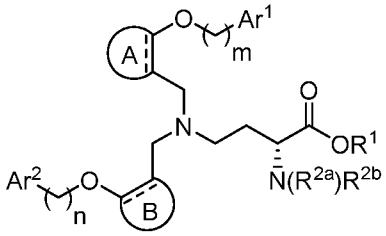
2. The compound of claim 1 of Formula II-A:



II-A,

or a pharmaceutically acceptable salt or solvate thereof.

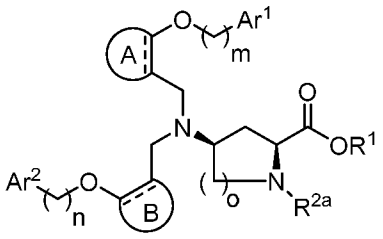
3. The compound of claim 1 of Formula II-B:



II-B,

or a pharmaceutically acceptable salt or solvate thereof.

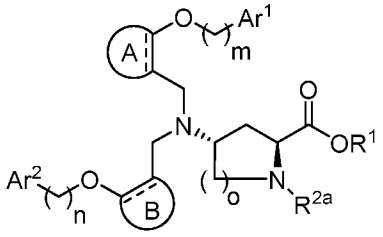
4. The compound of claim 1 of Formula III-A:



III-A,

wherein o is 1 or 2, or a pharmaceutically acceptable salt or solvate thereof.

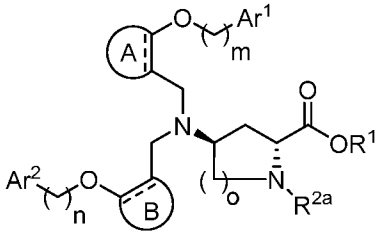
5. The compound of claim 1 of Formula III-B:



III-B ,

wherein o is 1 or 2, or a pharmaceutically acceptable salt or solvate thereof.

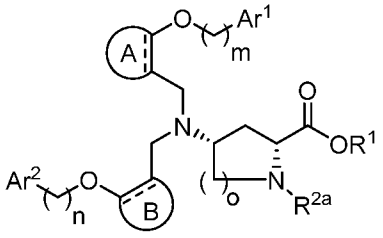
6. The compound of claim 1 of Formula III-C:



III-C ,

wherein o is 1 or 2, or a pharmaceutically acceptable salt or solvate thereof.

7. The compound of claim 1 of Formula III-D:



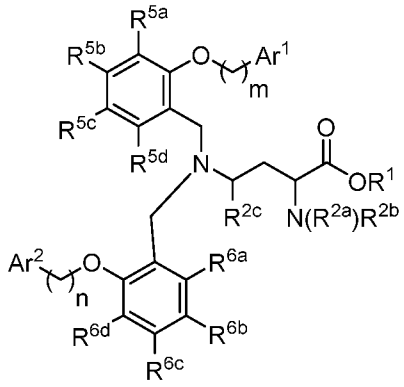
III-D,

wherein o is 1 or 2, or a pharmaceutically acceptable salt or solvate thereof.

8. The compound of any one of claims 4-7, wherein o is 1, or a pharmaceutically acceptable salt or solvate thereof.

9. The compound of any one of claims 4-7, wherein o is 2, or a pharmaceutically acceptable salt or solvate thereof.

10. The compound of claim 1 of Formula IV:



IV,

wherein:

R^{5a}, R^{5b}, R^{5c}, and R^{5d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy; or

R^{5a} and R^{5b} taken together form a fused optionally substituted phenyl or fused optionally substituted 5- or 6-membered heteroaryl group; and

R^{5c} and R^{5d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy; or

R^{5b} and R^{5c} taken together form a fused optionally substituted phenyl or fused optionally substituted 5- or 6-membered heteroaryl group; and

R^{5a} and R^{5d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy; or

R^{5c} and R^{5d} taken together form a fused optionally substituted phenyl or fused optionally substituted 5- or 6-membered heteroaryl group; and

R^{5a} and R^{5b} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy;

R^{6a}, R^{6b}, R^{6c}, and R^{6d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy; or

R^{6a} and R^{6b} taken together form a fused optionally substituted phenyl or fused optionally substituted 5- or 6-membered heteroaryl group; and

R^{6c} and R^{6d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy; or

R^{6b} and R^{6c} taken together form a fused optionally substituted phenyl or fused optionally substituted 5- or 6-membered heteroaryl group; and

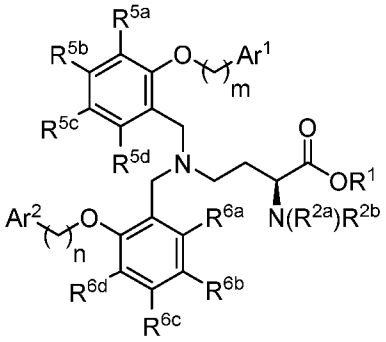
R^{6a} and R^{6d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy; or

R^{6c} and R^{5d} taken together form a fused optionally substituted phenyl or fused optionally substituted 5- or 6-membered heteroaryl group; and

R^{6a} and R^{6b} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy,

or a pharmaceutically acceptable salt or solvate thereof.

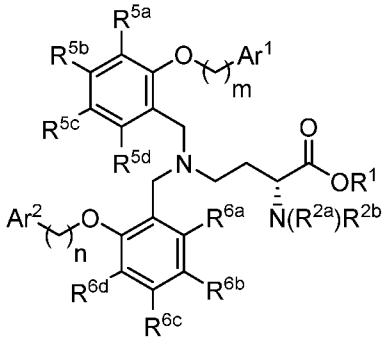
11. The compound of claim 10 of Formula V-A:



V-A,

or a pharmaceutically acceptable salt or solvate thereof.

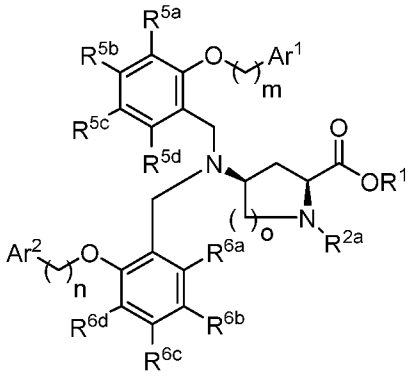
12. The compound of claim 10 of Formula V-B:



V-B,

or a pharmaceutically acceptable salt or solvate thereof.

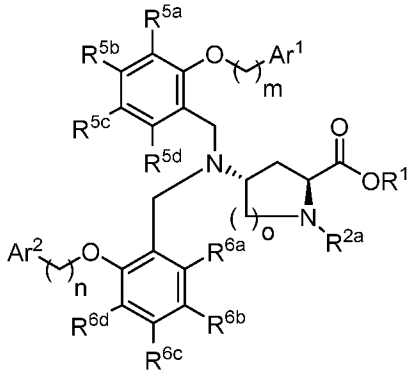
13. The compound of claim 10 of Formula VI-A:



VI-A,

wherein o is 1 or 2, or a pharmaceutically acceptable salt or solvate thereof.

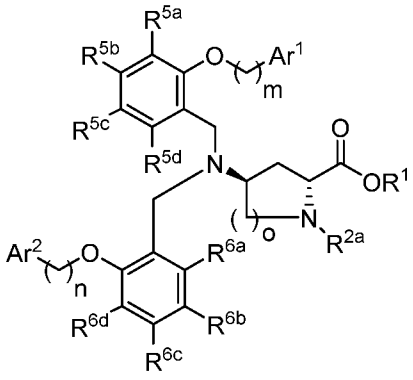
14. The compound of claim 10 of Formula VI-B:



VI-B,

wherein o is 1 or 2, or a pharmaceutically acceptable salt or solvate thereof.

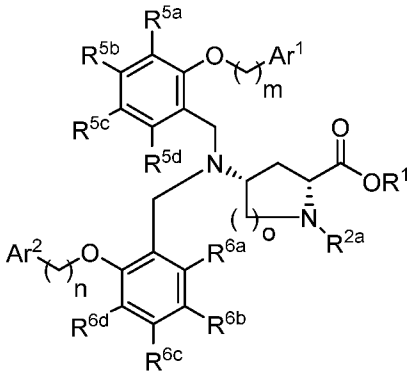
15. The compound of claim 10 of Formula VI-C:



VI-C,

wherein o is 1 or 2, or a pharmaceutically acceptable salt or solvate thereof.

16. The compound of claim 10 of Formula VI-D:



VI-D,

wherein o is 1 or 2, or a pharmaceutically acceptable salt or solvate thereof.

17. The compound of any one of claims 13-16, wherein o is 1, or a pharmaceutically acceptable salt or solvate thereof.

18. The compound of any one of claims 13-16, wherein o is 2, or a pharmaceutically acceptable salt or solvate thereof.

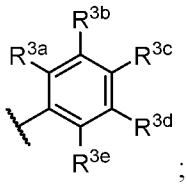
19. The compound of any one of claims 10-18, wherein R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{6a}, R^{6b}, R^{6c}, and R^{6d} are hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

20. The compound of any one of claims 1-19, wherein Ar^1 is an optionally substituted 5- to 10-membered heteroaryl, or a pharmaceutically acceptable salt or solvate thereof.

21. The compound of any one of claims 1-19, wherein Ar^1 is an optionally substituted phenyl, or a pharmaceutically acceptable salt or solvate thereof.

22. The compound of claim 21, wherein:

Ar^1 is:



; and

R^{3a}, R^{3b}, R^{3c}, and R^{3d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy,

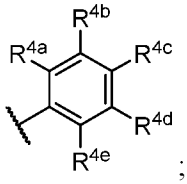
or a pharmaceutically acceptable salt or solvate thereof.

23. The compound of any one of claims 1-22, wherein Ar^2 is an optionally substituted 5- to 10-membered heteroaryl, or a pharmaceutically acceptable salt or solvate thereof.

24. The compound of any one of claims 1-22, wherein Ar^2 is an optionally substituted phenyl, or a pharmaceutically acceptable salt or solvate thereof.

25. The compound of claim 24, wherein:

Ar^2 is:



; and

R^{4a}, R^{4b}, R^{4c}, and R^{4d} are independently selected from the group consisting of hydrogen, halo, cyano, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkoxy,

or a pharmaceutically acceptable salt or solvate thereof.

26. The compound of any one of claims 1-25, wherein m is 0, or a pharmaceutically acceptable salt or solvate thereof.

27. The compound of any one of claims 1-26, wherein n is 1, or a pharmaceutically acceptable salt or solvate thereof

28. The compound of any one of claims 1-3, 10-12, or 19-27, wherein R^{2b} is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

29. The compound of any one of claims 1-28, wherein R^{2a} is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

30. The compound of any one of claims 1-29, wherein R^{1} is hydrogen, or a pharmaceutically acceptable salt or solvate thereof.

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

(S)-2-amino-4-((2-((2-fluorobenzyl)oxy)benzyl)(2-(3-methoxyphenoxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-((4-fluorobenzyl)oxy)benzyl)(2-(3-methoxyphenoxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-((4-chlorobenzyl)oxy)benzyl)(2-(3-methoxyphenoxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-((2-fluorobenzyl)oxy)benzyl)(2-(3-fluorophenoxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-((4-fluorobenzyl)oxy)benzyl)(2-(3-fluorophenoxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-((4-chlorobenzyl)oxy)benzyl)(2-(3-fluorophenoxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-((2-fluorobenzyl)oxy)benzyl)(2-(2-fluorophenoxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-((4-fluorobenzyl)oxy)benzyl)(2-(2-fluorophenoxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-((4-chlorobenzyl)oxy)benzyl)(2-(2-fluorophenoxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-(4-chlorophenoxy)benzyl)(2-((2-fluorobenzyl)oxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-((4-chlorobenzyl)oxy)benzyl)(2-(4-chlorophenoxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-((2-fluorobenzyl)oxy)benzyl)(2-(4-methoxyphenoxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-((4-fluorobenzyl)oxy)benzyl)(2-(4-methoxyphenoxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-((4-chlorobenzyl)oxy)benzyl)(2-(4-methoxyphenoxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-(4-chlorophenoxy)benzyl)(2-((4-fluorobenzyl)oxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-(4-methoxyphenoxy)benzyl)(2-((3-(trifluoromethyl)benzyl)oxy) benzyl)amino)butanoic acid;

(S)-2-amino-4-((2-(3-methoxyphenoxy)benzyl)(2-((3-methylbenzyl)oxy)benzyl) amino)butanoic acid;

(S)-2-amino-4-((2-((3-methoxybenzyl)oxy)benzyl)(2-(3-methoxyphenoxy)benzyl) amino)butanoic acid;

(S)-2-amino-4-((2-(3-methoxyphenoxy)benzyl)(2-((3-(trifluoromethyl)benzyl)oxy) benzyl)amino)butanoic acid;

(S)-2-amino-4-((2-(4-chlorophenoxy)benzyl)(2-((3-methoxybenzyl)oxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-(4-chlorophenoxy)benzyl)(2-((3-methylbenzyl)oxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-(4-methoxyphenoxy)benzyl)(2-((3-methylbenzyl)oxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-(2-fluorophenoxy)benzyl)(2-((3-(trifluoromethyl)benzyl)oxy)benzyl) amino)butanoic acid;

(S)-2-amino-4-((2-(3-fluorophenoxy)benzyl)(2-((3-(trifluoromethyl)benzyl)oxy)benzyl) amino)butanoic acid;

(S)-2-amino-4-((2-(2-fluorophenoxy)benzyl)(2-((3-methoxybenzyl)oxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-(3-fluorophenoxy)benzyl)(2-((3-methoxybenzyl)oxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-(4-methoxyphenoxy)benzyl)(2-((3-methylbenzyl)oxy)benzyl)amino) butanoic acid;

(S)-2-amino-4-((2-(2-fluorophenoxy)benzyl)(2-((3-methylbenzyl)oxy)benzyl)amino) butanoic acid; and

(S)-2-amino-4-((2-(3-fluorophenoxy)benzyl)(2-((3-methylbenzyl)oxy)benzyl)amino) butanoic acid,

or a pharmaceutically acceptable salt or solvate thereof.

32. A pharmaceutical composition comprising the compound of any one of claims 1-31, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

33. A method of treating cancer a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-31, or a pharmaceutically acceptable salt or solvate thereof.

34. The method of claim 33, wherein the cancer is a solid tumor.

35. The method of claim 33, wherein the cancer is a hematological cancer.

36. The method of claim 33, wherein the cancer is any one or more of the cancers of Table 3.

37. The method of claim 33, wherein the cancer is any one or more of the cancers of Table 4.

38. The method of any one of claims 33-37 further comprising administering to the subject a therapeutically effective amount of one or more optional therapeutic agents useful in the treatment of cancer.

39. The pharmaceutical composition of claim 32 for use in treating cancer.

40. The pharmaceutical composition of claim 39, wherein the cancer is a solid tumor.

41. The pharmaceutical composition of claim 39, wherein the cancer is a hematological cancer.

42 The pharmaceutical composition of claim 39, wherein the cancer is any one or more of the cancers of Table 3.

43. The pharmaceutical composition of claim 39, wherein the cancer is any one or more of the cancers of Table 4.

44. A compound of any one of claims 1-31, or a pharmaceutically acceptable salt or solvate thereof, for use in treating of cancer.

45. The compound for use of claim 44, wherein the cancer is a solid tumor.

46. The compound for use of claim 44, wherein the cancer is a hematological cancer.

47 The compound for use of claim 44, wherein the cancer is any one or more of the cancers of Table 3.

48. The compound for use of claim 44, wherein the cancer is any one or more of the cancers of Table 4.

49. The compound for use of any one of claims 44-48, wherein the compound is to be administered to the subject in combination with a therapeutically effective amount of one or more optional therapeutic agents useful in the treatment of cancer.

50. Use of a compound of any one of claims 1-31, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for treatment of cancer.

51. The use of claim 50, wherein the cancer is a solid tumor.

52. The use of claim 50, wherein the cancer is a hematological cancer.

53 The use of claim 50, wherein the cancer is any one or more of the cancers of Table 3.

54. The use of claim 50, wherein the cancer is any one or more of the cancers of Table 4.

55. The use of any one of claims 50-54, wherein the compound is to be administered to the in combination with a therapeutically effective amount of one or more optional therapeutic agents useful in the treatment of cancer.

56. A therapeutic or prophylactic agent for cancer, which comprises the compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof.

57. A kit comprising the compound of any one of claims 1-31, or a pharmaceutically acceptable salt or solvate thereof, and instructions for administering the compound, or a pharmaceutically acceptable salt or solvate thereof, to a subject having cancer.

58. The kit of claim 57, wherein the cancer is a solid tumor.

59. The kit of claim 57, wherein the cancer is a hematological cancer.

60. The kit of claim 57, wherein the cancer is any one or more of the cancers of Table 3.

61. The kit of claim 57, wherein the cancer is any one or more of the cancers of Table 4.

62. The kit of any one of claims 57-62 further comprising one or more optional therapeutic agents useful in the treatment of cancer.

63. A method of treating a subject having cancer, the method comprising administering a therapeutically effective amount of a compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, to the subject if a mutation in BRAF, KRAS, p53, or PI3KCA, or a combination thereof, is present in a biological sample of the subject.

64. A method of identifying whether a subject having cancer as a candidate for treatment with a compound of any one of claims 1-31, or a pharmaceutically acceptable salt or solvate thereof, the method comprising:

(a) identifying the subject as being a candidate for treatment if a mutation in BRAF, KRAS, p53, or PI3KCA, or a combination thereof is present in a biological sample of the subject; or

(b) identifying the subject as not being a candidate for treatment if a mutation in BRAF, KRAS, p53, or PI3KCA, or a combination thereof is absent in a biological sample of the subject.

65. A method of predicting treatment outcome in a subject having cancer, the method comprising:

(a) if a mutation in BRAF, KRAS, p53, or PI3KCA, or a combination thereof is present in a biological sample of the subject, then administering a compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, to the subject will likely cause a favorable therapeutic response; and

(b) if a mutation in BRAF, KRAS, p53, or PI3KCA, or a combination thereof is absent in the biological sample, then administering a compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, to the subject will likely cause an unfavorable therapeutic response.

66. A method, comprising administering a therapeutically effective amount of a compound of any one of claims 1-31, or a pharmaceutically acceptable salt or solvate thereof, to a subject in need thereof, wherein:

(a) the subject has cancer; and

(b) the cancer is characterized as having a mutation in BRAF, KRAS, p53, or PI3KCA, or a combination thereof.

67. The method of any one of claims 63-66, wherein the mutation is a mutation in BRAF.

68. The method of claim 67, wherein the mutation in BRAF is a V600E mutation.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/037527

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C229/26 A61P35/00 A61K31/132
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018/107173 A1 (UNIV VANDERBILT [US]) 14 June 2018 (2018-06-14) cited in the application claims 1-21 page 24 -----	1-68
X	SCHULTE MICHAEL L ET AL: "2-Amino-4-bis(aryloxybenzyl)aminobutanoic acids: A novel scaffold for inhibition of ASCT2-mediated glutamine transport", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 26, no. 3, 11 December 2015 (2015-12-11), pages 1044-1047, XP02939 1894, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2015.12.031 page 1046; table 2 ----- -/--	1-3, **10-12**, **21,22**, 24,25, 27-62

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2020	04/08/2020

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/037527

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category'	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MICHAEL L SCHULTE ET AL: "Pharmacological blockade of ASCT2-dependent glutamine transport leads to antitumor efficacy in preclinical models", NATURE MEDICINE, vol. 24, no. 2, 15 January 2018 (2018-01-15), pages 194-202, XP055717151, New York ISSN: 1078-8956, DOI: 10.1038/nm.4464 page 195; figure 1a ----	1-3, 10-12, 21,22, 24,25, 27-62

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2020/037527

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2018107173 A1	14-06-2018	US 2020095190 A1	26-03-2020
		WO 2018107173 A1	14-06-2018