COMPOSITION AND METHOD FOR DUAL TARGETING IN TREATMENT OF NEUROENDOCRINE TUMORS

TECHNICAL FIELD

[0001] The present disclosure relates generally to compositions for targeting and treating neuroendocrine tumors. The composition in particular may include thyroid hormone □v□3 integrin receptor antagonists (referred to as "thyrointegrin antagonists") and compounds that are targets of the norepinephrine transporter (NET) or the catecholamine transporter (such as benzyl guanidine ("BG") or its derivatives).

BACKGROUND

[0002] The norepinephrine/catecholamine transporter ("norepinephrine transporter") is essential for norepinephrine uptake at the synaptic terminals and adrenal chromaffin cells. In neuroendocrine tumors, the norepinephrine transporter is highly active and can be targeted for imaging and/or therapy with localized radiotherapy. One of the most widely used theranostic agents targeting the norepinephrine transporter is meta-iodobenzylguanidine (MIBG), a guanidine analog of norepinephrine. 123I/131I-MIBG theranostics have been applied in the clinical evaluation and management of neuroendocrine tumors, especially in neuroblastoma, paraganglioma, and pheochromocytoma. 123I-MIBG imaging has been used in the evaluation of neuroblastoma, and 131I-MIBG for the treatment of relapsed high-risk neuroblastoma, however, the outcome remains sub-optimal. Positron Emission Tomography (PET) tracers targeting the norepinephrine transporter and its targets represent a better option for the imaging and assessment after treatment of neuroblastoma, paraganglioma / pheochromocytoma, and carcinoids.

[0003] Integrins are a super-family of cell surface adhesion receptors, which control the attachment of cells with the solid extracellular environment, both to the extracellular matrix (ECM), and to other cells. Adhesion is of fundamental importance to a cell; it provides anchorage, cues for migration, and signals for growth and differentiation. Integrins are directly involved in numerous normal and pathological conditions, and as such are primary targets for therapeutic intervention. Integrins are integral transmembrane proteins, heterodimers, whose binding specificity depends on which of the 14 α-chains are combined with which of the 8 β-chains. The integrins are classified in four overlapping subfamilies, containing the β1, β2, β3 or αv chains. A cell may express several different integrins from each subfamily. In the last several decades, it has been shown that integrins are major receptors involved in cell adhesion, and so may be a suitable target for therapeutic intervention. Integrin αvβ3 regulates cell growth and survival, since ligation of this receptor can, under some circumstances, induce apoptosis in tumor cells. Disruption of cell adhesion with anti-αvβ3 antibodies, RGD peptides, peptide mimetic or non-peptide derivatives, and other integrin antagonists has been shown to slow tumor growth.

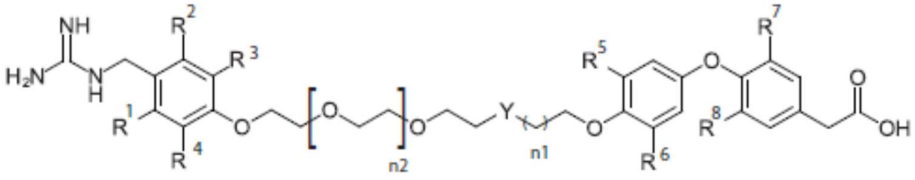
[0004] Thyrointegrin antagonists have been shown to effect tumor angiogenesis by interaction with integrin αvβ3. The effect of thyrointegrin antagonists is described in U.S. Pat. Pub. No. 2017/0348425 titled Non-Cleavable Polymer Conjugated with Alpa V Beta 3 Integrin Thyroid Antagonists, the contents of which are incorporated by reference.

[0005] A composition comprising both a thyrointegrin antagonist compound and a norepinephrine transporter target compound would be well received in the art.

SUMMARY

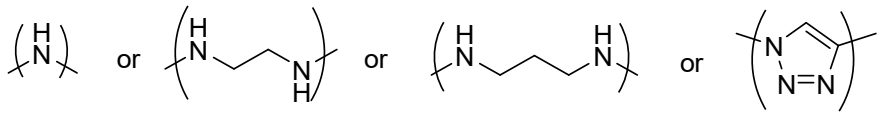
[0006] According to one aspect, a composition comprises N-benzyl guanidine and a thyrointegrin αvβ3 receptor antagonist, wherein the N-benzyl guanidine and the thyrointegrin αvβ3 receptor antagonist are connected by a linker.

[0007] According to another aspect, a composition comprises a general formula:



or a salt thereof, wherein R1, R2, R3, and R4 are each independently selected from the group consisting of hydrogen, iodine, fluorine, bromine, a methoxy group, a nitro group, an amine group, and a nitrile group, wherein R5, R6, R7, and R8 are each independently selected from the group consisting of hydrogen, iodine, and an alkane group, and $n1 \geq 0$; $n2 \geq 1$, and

Y =



[0008] According to another aspect, a composition for dual targeting of tumor cells comprises a norepinephrine transporter target and a thyrointegrin αvβ3 receptor antagonist, wherein the norepinephrine transporter target and the αvβ3 thyrointegrin receptor antagonist are connected by a linker, further wherein the composition is configured to dual target tumor cells via a) the norepinephrine transporter and b) reaction with the integrin αvβ3 receptor.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0010] Some of the embodiments will be described in detail with reference made to the following figures, in which like designations denote like members, wherein:

[0011] Figure 1 depicts a general formula of an exemplary composition for use in dual targeting of neuroendocrine tumors;

[0012] Figure 2a depicts another general formula of an exemplary composition having a linker with a monoamine;

[0013] Figure 2b depicts another general formula of an exemplary composition having a linker with a diamine;

[0014] Figure 2c depicts another general formula of an exemplary composition having a linker with a triazole;

[0015] Figure 3 depicts one exemplary composition for use in dual targeting of neuroendocrine tumors, referred to as Composition 300, BG-PEG-TAT, or BG-P-TAT;

[0016] Figure 4a depicts an overview of a synthetic pathway for Composition 300 from Figure 3;

[0017] Figure 4b depicts a detailed schematic of the synthetic pathway of Figure 4a;

[0018] Figure 4c depicts an overview of possible synthetic pathways for the production of two other exemplary compositions, referred to as Composition 201 (BG-PEG-MAT) and Composition 202 (BG-PEG-DAT), in which the production uses either a tosylate group or an aldehyde;

[0019] Figure 4d depicts an overview of alternative synthetic pathways for the production of the compositions shown in Figure 4c in which the production uses either a tosylate group or an aldehyde;

[0020] Figure 4e depicts a detailed schematic of the synthetic pathways of Figures 4c and 4d that use an aldehyde;

[0021] Figure 4f depicts a detailed schematic of the synthetic pathways of Figures 4c and 4d using a tosylate group;

[0022] Figure 5 depicts a graph showing no significant changes in body weight of mice during multi-day treatment with either a control or Composition 300 when administered at different doses ranging from 1-10 mg/kg subcutaneously daily for 15 days;

[0023] Figure 6 depicts a graph showing dose-dependent decreases in tumor volume over time (15 days) in the mice during the multi-day treatment at 1-10 mg/kg, subcutaneously with Composition 300, compared with increase in tumor volume for a control group;

[0024] Figure 7a shows images of mice in the control group with visible large subcutaneous tumors, along with abnormal animal head movements suggesting accompanying central behavioral changes;

[0025] Figure 7b shows images of mice that have been treated with Composition 300 and demonstrate significant reduction or absence of visible subcutaneous tumors (significant shrinkage to elimination of tumors) in a dose-dependent manner along with disappearance of the observed abnormal animal head movements;

[0026] Figure 8 is a graph of tumor weight as a function of dosage of Composition 300 showing significant tumor shrinkage to complete disappearance of the tumor;

[0027] Figure 9a are photographs of tumors showing relative tumor size and de-vascularization as a function of dosage of Composition 300;

[0028] Figure 9b are photographs of tumors showing absolute tumor size as a function of dosage of Composition 300 demonstrating distinct tumor shrinkage to disappearance at the 10 mg/kg dosage level;

[0029] Figure 10 is a graph of neuroblastoma cancer cell viability as a function of dosage of Composition 300 showing loss of cancer cell viability to complete loss at the 10 mg/kg dosage level;

[0030] Figure 11 is a graph of neuroblastoma cancer cell necrosis as a function of dosage of Composition 300 showing increase in cancer cell necrosis from 80-100% at the 3 and 10 mg/kg doses;

[0031] Figure 12a is a graph of tumor weight shrinkage as a function of treatment with different benzyl guanidine derivatives including MIBG, BG, and polymer conjugated BG administered subcutaneously daily for 15 days at 3 mg/kg showing comparable shrinkage ranging from 40-50% as compared to control (PBS vehicle);

[0032] Figure 12b is a graph of tumor weight shrinkage as a function of treatment with benzyl guanidine, TAT derivative, or BG and TAT derivative co-administered versus BG-P-TAT (Composition 300) all administered at 3 mg/kg, subcutaneously daily for 15 days (data demonstrated 40-50% tumor shrinkage with BG, TAT, or BG co-administered with TAT versus 80% shrinkage with BG-P-TAT (Composition 300) as well as maximal loss of cancer cell viability with BG-P-TAT);

[0033] Figure 13a are photographs of fluorescence images of various mice at 1 and 2 hours post-administration of Cy5 labeled polymer conjugated TAT (Group 1), polymer conjugated BG (Group 2), and Polymer conjugated BG-TAT (Composition 300) (Group 3); and

[0034] Figure 13b are photographs of fluorescence images of the mice of Figure 13a at 4, 6, and 24 hours post-administration (data clearly showed distinct and highest intensity accumulation (delineation and imaging) in neuroblastoma tumor and its spread with Cy5-labeled polymer conjugated BG-P-TAT (Composition 300)).

DETAILED DESCRIPTION

[0035] A detailed description of the hereinafter-described embodiments of the disclosed composition and method is presented herein by way of exemplification and not limitation with reference to the Figures. Although certain embodiments are shown and described in detail, it should be understood that various changes and modifications might be made without departing from the scope of the appended claims. The scope of the present disclosure will in no way be limited to the number of constituting components, the materials thereof, the shapes thereof, colors thereof, the relative arrangement thereof, etc., and are disclosed simply as an example of embodiments of the present disclosure. A more complete understanding of the present embodiments and advantages thereof may be acquired by referring to the following description taken in conjunction with the accompanying drawings, in which like reference numbers indicate like features.

[0036] As a preface to the detailed description, it should be noted that, as used in this specification and the appended claims, the singular forms “a”, “an” and “the” include plural referents, unless the context clearly dictates otherwise.

OVERVIEW

[0037] Embodiments of the present disclosure describe new chemical compositions, and methods of synthesis thereof. The compositions disclosed and described herein may be directed toward anti-angiogenic agents, particularly thyrointegrin antagonists, which may be capable of interacting with one or more cell surface receptors of the integrin αvβ3 receptor family. The compositions disclosed and described herein may also be directed toward targets of the norepinephrine transporter (also known as the catecholamine transporter). Targets of the norepinephrine transporter may act as neuroendocrine tumor cell targeting agents.

[0038] The compositions disclosed and described herein may be directed toward a composition containing both a thyrointegrin antagonist and a norepinephrine transporter target. Further, the composition may use a polymer or other linker to link the thyrointegrin antagonist and the norepinephrine transporter target.

[0039] The norepinephrine transporter is a regulator of catecholamine uptake in normal physiology and is highly expressed and over-active in neuroendocrine tumors like neuroblastoma. Although the norepinephrine analog, meta-iodobenzylguanidine (MIBG), is an established substrate for the norepinephrine transporter, analogs such as (123)I / (131)I- MIBG or analogs having Fluoride (F18) instead of Iodide (radioactive) may also be used for diagnostic imaging of neuroblastoma and other neuroendocrine tumors.

[0040] Investigations have demonstrated that various neuroblastoma cell lines highly express the αvβ3 integrin receptors (90-95%). However, high affinity αvβ3 integrin receptor antagonists showed limited (40-50%) efficacy in term of tumor growth rate and cancer viability inhibition. Similarly, benzyl guanidine and its derivatives demonstrated limited anti-cancer efficacy of neuroblastoma despite its maximal (90-100%) uptake into neuroblastoma and other neuroendocrine tumors. Furthermore, treatment combinations of norepinephrine transporter targets such as benzyl guanidine or its derivatives together with thyrointegrin antagonists such as triazole tetraiodothyroacetic acid derivatives did not exceed 50% suppression of neuroblastoma growth and viability.

[0041] In contrast and unexpectedly, conjugation of norepinephrine transporter targets such as benzyl guanidine derivatives and thyrointegrin antagonists such as triazole tetraiodothryoacetic acid derivatives via different polymer linker such as Polyethylene Glycol (PEG) into a single novel chemical entity resulted in maximal uptake into neuroblastoma and other neuroendocrine tumors along with maximal (80-100%) suppression of tumor growth and viability at different doses. A thyrointegrin antagonist conjugated via a linker with a norepinephrine / catecholamine transporter target compound may provide a composition that has a dual targeting effect for neuroendocrine tumor targeting. For example, the composition may comprise an alpha-V-beta-3 (αvβ3) integrin-thyroid hormone receptor

antagonist linked to benzyl guanidine (or a benzyl guanidine derivative) according to one embodiment of the invention.

[0042] The compositions described herein may be comprised of compounds, for example a thyrointegrin antagonist or derivative thereof covalently linked to a target of the norepinephrine transporter to form a single chemical entity. The thyrointegrin antagonist and the norepinephrine target may be joined via a linker.

[0043] Reference may be made to specific thyrointegrin compounds and norepinephrine compounds, for example, tetrac, triac, and benzyl guanidine. These phrases include derivatives of such compounds in accordance with the full teachings of this disclosure, even where such derivatives are not specifically listed.

[0044] Referring to the drawings, Figure 1 depicts an embodiment of a general formula 100 comprising a thyrointegrin antagonist 110 joined to a norepinephrine transporter target 120 via a linker 130. The composition may be referred to as a thyrointegrin antagonist derivative conjugated to a benzyl guanidine derivative via the linker 130, or a thyrointegrin antagonist derivative conjugated to a benzyl guanidine derivative modified with the linker 130. Figure 1 depicts a carboxylic acid form of the general formula 100. As would be apparent to one skilled in the art, a salt (e.g. a sodium salt) of the general formula 100 may also be used.

[0045] The linker 130 comprises a spacer 132 and a polymer 131. The linker 130 resists biodegradation such that the linker remains uncleaved under physiological conditions. In one embodiment, the spacer 132 comprises a CH_2 unit and an adjacent repeating linkage of methylene (CH_2) units which may be defined by n1 repeats wherein n1 is an integer that is ≥ 0. In other embodiments, n1 may be ≥ 1, ≥ 2 or ≥ 3. The linker 130 further comprises a moiety "Y." Embodiments of the moiety "Y", may in some instances be may be an amine. For example, the moiety Y of the general formula may be a divalent alkane having one amine group or a divalent alkane having two amine groups as shown by the examples of general formula 200a and 200b of Figures 2a and 2b. In another embodiment, the moiety Y may be a triazole as shown by the example of general formula 200c shown in Figure 2c. The polymer 131 may comprise a polyether such as polyethylene glycol (PEG). Other polymers may be used, including chitosan, alginic acid, hyaluronic acid, and other polymers. In embodiments using PEG as the polymer 131, the polymer may have a molecular weight between 200 and 4,000g per mole.

[0046] The term thyroid antagonist describes a compound that has the ability to inhibit or antagonize one or more thyroid hormone receptors known by a person skilled in the art, for example the integrin family of thyroid hormone receptors, such as the thyroid hormone cell surface receptor αvβ3. The thyrointegrin antagonist 110 may be an anti-angiogenic thyroid hormone or a thyroid hormone receptor antagonist. For example, the thyrointegrin antagonist 110 may be an alpha-V-beta-3 (αvβ3) integrin-thyroid hormone receptor antagonist.

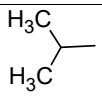
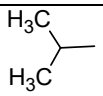
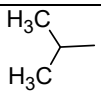
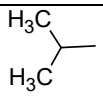
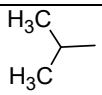
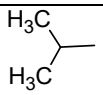
[0047] Specific embodiments of the thyrointegrin antagonist 110 may include tetraiodothyroacetic acid (tetrac), triiodothyroacetic acid (triac), derivatives thereof and variations thereof. Examples of one or more variations of the thyrointegrin antagonist comprising tetrac and triac may

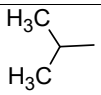
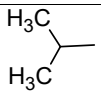
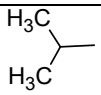
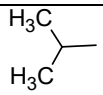
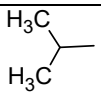
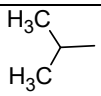
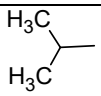
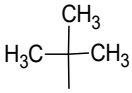
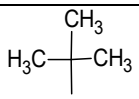
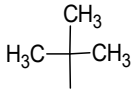
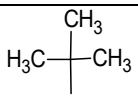
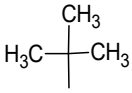
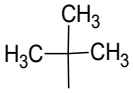
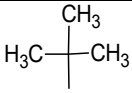
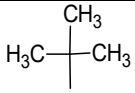
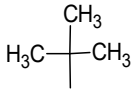
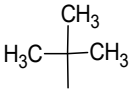
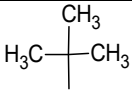
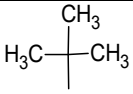
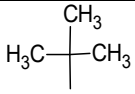
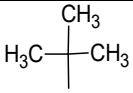
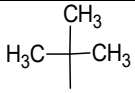
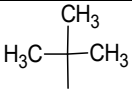
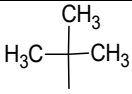
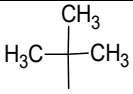
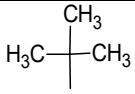
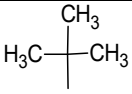
include, in some embodiments Diaminotetrac (DAT) or Diaminotriac (DATri) (hereinafter may be referred to interchangeably as “DAT”), Monoaminotetrac (MAT) or Monoaminotriac (MATri) (hereinafter referred to interchangeable as “MAT”), Triazoletetrac (TAT) or Triazoletriac (TATri) (hereinafter referred to interchangeable as “TAT”), derivatives thereof or other thyroid antagonist known by those skilled in the art. Thyrointegrin antagonists may be of the type described in U.S. Pat. Pub. No. 2017/0348425 titled Non-Cleavable Polymer Conjugated with Alpa V Beta 3 Integrin Thyroid Antagonists, the contents of which are incorporated by reference.

[0048] Exemplary thyrointegrin antagonists based on the general structure 100 from Figure 1 are shown below in Table 1.

[0049] Table 1

Exemplary Thyrointegrin Antagonists

1	R^5	R^6	R^7	R^8
2	H	H	H	H
3	I	H	H	H
4	H	I	H	H
5	H	H	I	H
6	H	H	H	I
7	I	I	H	H
8	I	H	I	H
9	H	H	I	I
10	I	I	I	H
11	H	I	I	I
12	I	I	I	I
13	H	H	H	H
14		H	H	H
15	H		H	H
16	H	H		H
17	H	H	H	
18			H	H

19		H		H
20	H	H		
21				H
22	H			
23				
24		H	H	H
25	H		H	H
26	H	H		H
27	H	H	H	
28			H	H
29		H		H
30	H	H		
31				H
32	H			
33				

[0050] In some embodiments of the thyrointegrin antagonist 110, the variables depicted as R5, R6, R7, and R8 may each independently be substituted for molecules such as hydrogen, iodine, and alkanes. In some embodiments, the alkanes have four or fewer carbons. For example, as shown in Table

1, in some embodiments of the thyrointegrin antagonist 110, the variables depicted as R5, R6, R7, and R8 may each independently be substituted for molecules of hydrogen, iodine, or alkane groups such as isopropyl or isobutyl. In the embodiments of Table 1, the alkanes have four or fewer carbons.

[0051] The norepinephrine transporter target 120 may be a neuroendocrine tumor cell targeting agent. As an example, the norepinephrine transporter target 120 may be benzyl guanidine or a benzyl guanidine derivative. As a further example, the norepinephrine transporter target 120 may be N-benzyl guanidine or a derivative thereof.

[0052] Exemplary norepinephrine transporter targets 120 based on the general formula 100 from Figure 1 are shown below in Table 2.

[0053] Table 2

Exemplary Norepinephrine Transporter Targets				
	R_1	R_2	R_3	R_4
1	F	H	H	H
2	H	F	H	H
3	H	H	F	H
4	H	H	H	F
5	Br	H	H	H
6	H	Br	H	H
7	H	H	Br	H
8	H	H	H	Br
9	I	H	H	H
10	H	I	H	H
11	H	H	I	H
12	H	H	H	I
13	OH	H	H	H
14	H	OH	H	H
15	H	H	OH	H
16	H	H	H	OH
17	OMe	H	H	H
18	H	OMe	H	H
19	H	H	OMe	H
20	H	H	H	OMe
21	NO2	H	H	H
22	H	NO2	H	H
23	H	H	NO2	H

24	H	H	H	NO2
25	NH2	H	H	H
26	H	NH2	H	H
27	H	H	NH2	H
28	H	H	H	NH2
29	CN	H	H	H
30	H	CN	H	H
31	H	H	CN	H
32	H	H	H	CN

[0054] In some embodiments of the norepinephrine transporter target 120, the variables depicted as R1, R2, R3, and R4 may be each independently be substituted for molecules such as hydrogen, iodine, fluorine, bromine, a methoxy group, a nitro group, an amine group, and a nitrile group. For example, in some embodiments of the norepinephrine transporter target 120, the variables depicted as R1, R2, R3, and R4 may be each independently be substituted for molecules of hydrogen, iodine, fluorine, bromine, a methoxy group, a nitro group, an amine group, and a nitrile group as described above in Table 2. Additional embodiments and substitutions may also be used. In one embodiment at least one of R1, R2, R3 and R4 is a radiolabel. Examples of suitable radiolabels include I(123), I(131) and F(18). The compound may be administered to humans or animals.

[0055] Any of the exemplary thyrointegrin antagonists 110 (along with any of the other thyrointegrin antagonist embodiments taught herein) may be joined via the linker 130 to any of the exemplary norepinephrine transporter targets 120 (along with any of the other norepinephrine transporter target embodiments taught herein) to form a composition.

[0056] As is clear from Table 1 and Table 2, there are a large number of compounds that may be used as the thyrointegrin antagonist 110 and a large number of compounds that may be used as the norepinephrine transporter target 120 in the composition. Further, the various thyrointegrin antagonists 110 may be combined with various norepinephrine transporter targets 120, resulting in a large number of potential chemical structures for the composition described herein.

[0057] Embodiments of each of the compositions described herein may have multiple types of utility for treating a plurality of different diseases modulated by angiogenesis or the inhibition thereof. Each of the compositions described in the present disclosure, in view of presence of the thyrointegrin antagonist 110 present in the described compositions, may have an affinity for targeting the integrin receptor $\alpha v\beta 3$ located on numerous types of cells found throughout the human body and various animal bodies.

[0058] Moreover, embodiments of each of the compositions described in the current application may have utility for treating a plurality of different diseases characterized by activity of the norepinephrine transporter. Each of the compositions described in the present disclosure, in view of

presence of the norepinephrine transporter target 120 present in the described compositions, may each have an affinity for targeting numerous types of cells found throughout the human body and various animal bodies that utilize the norepinephrine transporter. Each of the compositions described in the present disclosure may have increased affinity for targeting cells demonstrating increased or above average activity of the norepinephrine transporter, such as neuroendocrine tumor cells. As a more specific example, the composition may have increased affinity for targeting neuroblastoma, pheochromocytoma, pancreatic neuroendocrine tumor, and carcinoid tumor cells.

[0059] Still further, due to the composition's use of both a thyrointegrin antagonist 110 and a norepinephrine transporter target 120, the composition may have increased utility and efficacy against certain diseases and/or conditions. For example, neuroendocrine tumors are susceptible to treatment with thyrointegrin antagonists while also demonstrating increased activity of the norepinephrine transporter. The compositions described herein make use of both compounds for a dual targeting effect in treatment of neuroendocrine tumor cells. Further, the increased effect surpasses any increase expected or achieved by simultaneous separate treatment with a thyrointegrin antagonist and a norepinephrine transporter target. Further details regarding the beneficial utility is discussed below with respect to experimental studies.

[0060] As shown by the chemical structure of the general formula 100 of Figure 1, embodiments of the chemical structure may include one or more variables defining the additional features of the thyrointegrin antagonist 110 of the general formula 100. For example, in some embodiments of the thyrointegrin antagonist 110, the variables depicted as R5, R6, R7, and R8 may be each independently be hydrogen, iodine, and alkanes as described above in Table 1.

[0061] There is thus a wide range of thyrointegrin antagonist compounds that may be used as the thyrointegrin antagonist 110 of the general formula 100. For example, as shown in Figure 2a, the thyrointegrin antagonist 110a may comprise a substitution of iodine for R5–R8, resulting in the formation of a tetraiodothyroacetic acid (tetrac) derivative having a three-carbon linker and a monoamine as the Y moiety. General formula 200a may be referred to as monoamine-tetrac (MAT) conjugated via PEG to benzyl guanidine or a benzyl guanidine derivative. Likewise, in Figure 2b, the tetrac molecule further comprises a diamino Y moiety connected to the carbon linker. This general formula 200b may be referred to as diamino tetrac (DAT) conjugated via PEG to benzyl guanidine or a benzyl guanidine derivative. In the alternative embodiment of Figure 2c, the general formula 200c may comprise a triazole moiety connected to the single carbon of the carbon linker. This general formula 200c may be referred to as triazole tetrac (TAT) conjugated via PEG to benzyl guanidine or a benzyl guanidine derivative.

[0062] Other thyrointegrin antagonist compounds may also be used in forming the compositions described herein. For example, the general structure of the thyrointegrin antagonists 110a, 110b, and 110c may be used wherein only R5–R7 include iodine, thereby giving similar triac derivatives. Further, as shown in Table 1 above, similar structures may be used in which the thyrointegrin antagonist comprises a substitution of other elements or functional groups for any and/or all of R5–R8.

[0063] The norepinephrine transporter target 120 may comprise benzyl guanidine or a benzyl guanidine derivative. Embodiments of the chemical structure of the norepinephrine transporter target 120

may include one or more variables defining the additional features of the norepinephrine transporter target 120 of the general formula 100 shown in Figure 1. For example, in some embodiments of the norepinephrine transporter target 120, the variables depicted as R1, R2, R3, and R4 may be each independently be substituted for molecules of hydrogen, iodine, fluorine, bromine, a methoxy group, a nitro group, an amine group, and a nitrile group as described above in Table 2.

[0064] Figure 3 depicts an exemplary Composition 300 of the general formula 100. Composition 300 comprises triazole tetrac conjugated to benzyl guanidine modified PEG. Composition 300 may also be referred to as BG-PEG-TAT or BG-P-TAT.

[0065] Synthesis of the compositions described herein is demonstrated below, primarily with reference to the exemplary composition shown in Figure 3, namely Composition 300. Synthesis of similar compositions, namely Composition 201 and Composition 202 (see Figure 4c–4f) are also provided as examples and without limiting the disclosure to such compositions.

[0066] Example 1a: Synthesis of Exemplary Composition 300

[0067] This example provides a sample method for preparing Composition 300 shown in Figure 3. Composition 300 is referred to as BG-PEG-TAT or BG-P-TAT. Composition 300 has the chemical name of 2-(4-(4-(4-((1-(20-(4-(guanidinomethyl)phenoxy)-3,6,9,12,15,18-hexaoxaicosyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-diiodophenoxy)-3,5-diiodophenyl)acetic acid, or [4-(4-{1-[2-(2-{2-[2-(2-{2-[2-(4-Guanidinomethyl-phenoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethyl]-1H-[1, 2,3]triazol-4-ylmethoxy}-3,5-diiodo-phenoxy)-3,5-diiodo-phenyl]-acetic acid. The molecular weight of Composition 300 is 1284.44g/mol.

[0068] All commercially available chemicals were used without further purification. All solvents were dried and anhydrous solvents were obtained using activated molecular sieves (0.3 or 0.4 nm depending on the type of solvent). All reactions (if not specifically containing water as reactant, solvent or co-solvent) were performed under Ar or N_2 atmosphere, in oven-dried glassware. All new compounds gave satisfactory ^{1}H NMR and mass spectrometry results. Melting points were determined on an Electrothermal MEL-TEMP® melting point apparatus and then on a Thomas HOOVER Uni-mel capillary melting point apparatus. Infrared spectra were recorded on a Thermo Electron Nicolet Avatar 330 FT-IR apparatus. UV spectra were obtained from a SHIMADZU UV-1650PC UV-vis spectrophotometer. The solution-state NMR experiments were all performed a Bruker Advance II 800 MHz spectrometer equipped with a cryogenically cooled probe (TCI) with z-axis gradients (Bruker BioSpin, Billerica, MA) at the Center for Biotechnology and Interdisciplinary Studies, Rensselaer Polytechnic Institute (RPI, Troy, NY). All tubes used were 5 mm outside diameter. NMR data were referenced to chloroform ($CDCl_3$; 7.27 ppm ^{1}H, 77.20 ppm ^{13}C) or DMSO-d6 (δ= 2.50 ppm, 38.92 ppm ^{13}C) as internal reference. Chemical shifts δ are given in ppm; multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad); coupling constants, J, are reported in Hz. Thin layer chromatography was performed on silica gel plates with fluorescent indicator. Visualization was accomplished by UV light (254 and/or 365 nm) and/or by staining in ceric ammonium molybdate or sulfuric acid solution. Flash column chromatography was performed following the procedure indicated in

J. Org. Chem. 43, 14, 1978, 2923-2925, with 230-400 mesh silica gel. High resolution mass spectral analysis was performed on either an Applied Biosystems API4000 LC/MS/MS or Applied Biosystems QSTAR XL mass spectrometers.

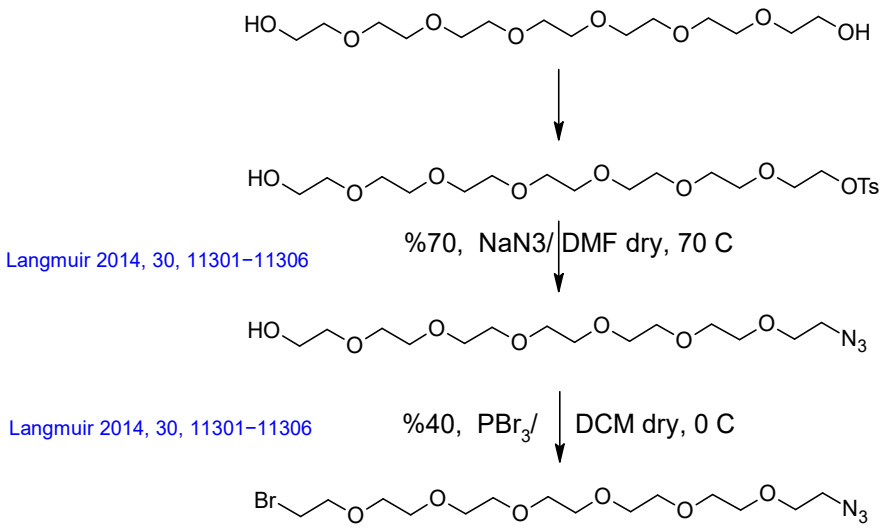
[0069] This example uses propargylated tetrac (PGT). Preparation of PGT or a derivative thereof from tetrac is described in U.S. Pat. Pub. No. 2017/0348425 titled Non-Cleavable Polymer Conjugated with Alpa V Beta 3 Integrin Thyroid Antagonists, the contents of which are incorporated by reference.

[0070] Figure 4a depicts an overview of a synthetic pathway for Composition 300.

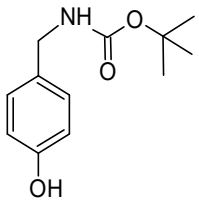
[0071] Figure 4b depicts a detailed schematic of the synthetic pathway from Figure 4a. Figure 4a shows the scheme of synthesis of Composition 300 as an example of conjugation of tetrac analogs to benzyl guanine modified PEG via click chemistry. Other synthetic pathways may be used.

[0072] The individual steps of the scheme of synthesis of Composition 300 shown in Figure 4b will be described in more detail below in which the intermediary products are referred to by the number shown in the click chemistry scheme.

[0073] *Synthesis of heterobifuntional PEG.* Although heterobifunctional linker is commercial available, for the purposes of this example the following synthetic route for preparation is used:



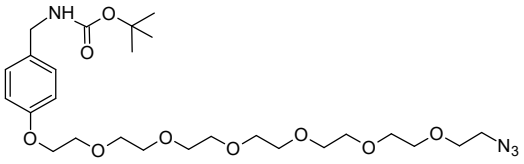
[0074] *Synthesis of Product 2 tert-butyl [(4-hydroxyphenyl)methyl]carbamate 2.*



[0075] *Tert*-butyl [(4-hydroxyphenyl)methyl]carbamate was synthesized according to the protecting method previously published {1) ACS Medicinal Chemistry Letters, 8(10), 1025-1030; 2017. 2) European Journal of Medicinal Chemistry, 126, 384-407; 2017. 3) Tetrahedron Letters, 47(46), 8039-

8042; 3006} the contents of which are hereby incorporated by reference. Product 1, 4-Hydroxybenzylamine (0.62 g, 5 mmol) slowly added with stirring to a solution of di-tert-butyl dicarbonate (1.2 g, 5.1 mmol) at room temperature. After the reaction mixture was stirred for 8 h, the oily residue was purified by column chromatography [SiO2: EtOAc/hexanes (1:4)] to afford 0.82 g of N-Boc-4-hydroxybenzylamine as a colorless oil with 71% yield.

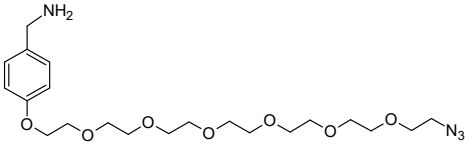
[0076] *Synthesis of Product 3 etherification of tert-Butoxycarbonyl-4-hydroxybenzylamine to Bromo-azido modified PEG(400) 3*



3

[0077] CsCO3 (867 mg, 2.67 mmol, 3 eq) was added with stirring to a solution of tert-Butoxycarbonyl-4-hydroxybenzylamine (300 mg, 0.896 mmol, 1eq) in CAN (25 mL) at room temperature. After the reaction mixture was stirred for 30 min, Bromo-azido modified PEG(400) (445 mg, 1.05 mmol, 1.2 eq) added to mixture and then temperature increased till reflux for 24h. It was filtered to remove excess of CsCO3. The solvents were removed under reduced pressure, and the oily residue was purified by column chromatography [SiO2: EtOAc/hexanes (5:5)] to afford product 3 as a yellow oil. Yield: 433 mg, 87%.

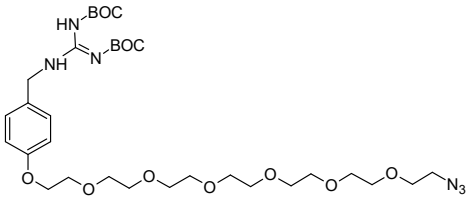
[0078] *Synthesis of Product 4. BOC de-protection*



4

[0079] Product 3 (100 mg, 0.179 mmol, 3 eq) was dissolved in 3 ml anhydrous 1,4-dioxane and 3 ml HCl (4N in dioxane) added to it and stirred at room temperature. After 24 hours, the solvent was removed under reduced pressure, and the oily residue was purified to afford product 4 as a yellow oil in quantitative yield (Yield: 73 g, 90%)

[0080] *Synthesis of Product 5. Guanidination of Product 4*

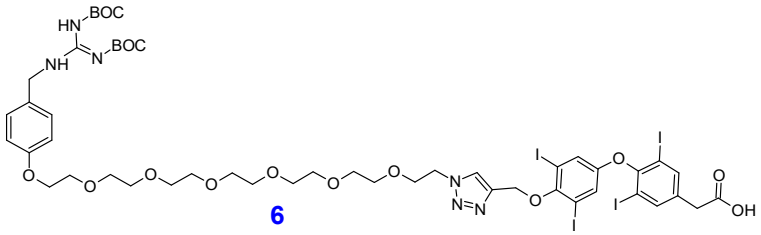


5

[0081] Product 4 (85 mg, 0.17 mmol, 1 eq), N,N′-Di-Boc-1H-pyrazole-1-carboxamidine (54 mg, 17 mg, 1eq) was dissolved in 3-4 ml anhydrous diethylcarbodiimide "DCM" and then triethyl amine "TEA" (48 µl, 0.35 mmol, 2 eq) was added to the solution. The reaction mixture was stirred at room

temperature for 12 h. After completion of the reaction the solvent was removed under reduced pressure and the residue dissolved in EtOAc (30 ml). The organic phase washed with % 5 HCl (25 ml) and brine (25 ml) and then dried (Mg2SO4). The solvent was removed under reduced pressure to yield product 5 which was purified by column chromatography [SiO2: EtOAc/hexanes (2:8)] Yield: 92 mg, 80%.

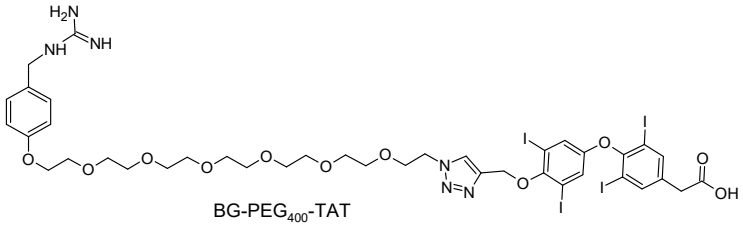
[0082] *Synthesis of Product 6*



6

[0083] Product 5 (100mg, 1 eq) and 1 eq of PGT were dissolved in 20 ml THF and stirred for 5 min then 0.5 eq of NaAscorbate and 0.5 eq of Coppersulfate in 2 ml water added to mixture and stirred for 24 hours in 65 oC. After 24 hours, the solvents were removed under reduced pressure, and Product 6 purified in 65% yield.

[0084] *Synthesis of Composition 300 (2-(4-(4-((1-(20-(4-(guanidinomethyl)phenoxy)-3,6,9,12,15,18-hexaoxaicosyl)-1H-1,2,3-triazol-4-yl)methoxy)-3,5-diiodophenoxy)-3,5-diiodophenyl)acetic acid)*



BG-PEG$_{400}$-TAT

MW = 1284.44 g/mol

7

[0085] Product 6 (50 mg) was dissolved in 3 ml anhydrous 1,4-dioxane and 3 ml HCl (4N in dioxane) added to it and stirred at 40C. After 24 hours, the solvent was removed under reduced pressure, and the oily residue was purified to afford Composition 300 as a yellow powder.

[0086] Other methods of synthesis may be used to reach Composition 300 or to reach other compositions having the general formula 100 shown in the Figure 1.

[0087] Example 1b: Synthesis of Additional Exemplary Compositions

[0088] Figures 4c and 4d depict overviews of synthetic pathway for other exemplary compositions, for example Composition 201 following the general formula 200a and Composition 202 following the general formula 200b, using either a tosylate group or an aldehyde.

[0089] Composition 201 may be referred to as BG-P-MAT, BG-PEG-MAT, or benzyl guanidine conjugated to monoaminotetrac via PEG. Composition 202 may be referred to as BG-P-DAT, BG-PEG-DAT, or benzyl guanidine conjugated to diaminotetrac via PEG. Benzyl guanidine derivatives or other norepinephrine transport targets may be used as described herein. Tetrac derivatives or other

thyrointegrin antagonists may also be used as described herein, including but not limited to triac and triac derivatives.

[0090] Figures 4e and 4f depict detailed schematics of the synthetic pathway from Figures 4c and 4d. Figures 4e and 4f shows the scheme of synthesis of Compositions 201 and 202 as further examples of conjugation of tetrac analogs to benzyl guanine modified PEG via click chemistry. Again, other synthetic pathways may be used.

METHODS OF USE

[0091] The compositions disclosed herein (including but not limited to the exemplary compositions such as Composition 300, Composition 201, and Composition 202) demonstrate novel dual targeting in treatment of cancer cells and tumors, particularly in treatment of neuroendocrine tumors such as neuroblastoma, pheochromocytoma, pancreatic neuroendocrine tumors, and carcinoid tumors. Further, the compositions show increased efficacy against neuroendocrine tumor cells when compared with thyrointegrin antagonist or norepinephrine transporter targets used or administered separately, *i.e.*, not conjugated into a single composition.

[0092] The compositions may also be used for imaging of cancer cell/tumors. For example, the compositions described herein may be used to image neuroblastoma, pheochromocytoma, pancreatic neuroendocrine tumors, and carcinoid tumors. Imaging may be desirable for diagnosis and/or for treatment monitoring. Moreover, the compositions may be used for simultaneous treatment and imaging. For example, the compositions may demonstrate increased retention in the targeted cancer cells/tumors, allowing for enhanced treatment and more effective imaging.

[0093] Example 2: Effect on Subcutaneously Implanted Tumor in Female Nude Mice

[0094] The efficacy of Composition 300 (BG-P-TAT) was tested using neuroblastoma SKNF2 cells implanted into nude female mice.

[0095] Fifteen (15) female nude mice were implanted with twice with 10^6 cells/implant. The SKNF2 cell line was used with subcutaneous xenografts.

[0096] Eight (8) days following implantation, the mice were divided into four groups receiving the following treatment for 15 days:

Group	Treatment Compound	Dosage
Group 1	Control – PBS	
Group 2	Composition 300 (BG-PEG-TAT)	1mg/kg
Group 3	Composition 300 (BG-PEG-TAT)	3mg/kg
Group 4	Composition 300 (BG-PEG-TAT)	10mg/kg

[0097] Following fifteen (15) days of treatment, tumors were collected in order to evaluate histopathology, and the following results were collected:

[0098] Figure 5 shows the effect of the control and Composition 300 (BG-PEG-TAT) treatment on body weight of mice implanted with SKNF2 cell lines. As is shown, the body weight was consistent across all groups. Data demonstrate that daily treatment with Composition 300 (BG-PEG-TAT) at different doses 1, 3 and 10 mg/kg daily for 15 days have no effect on animal body weight versus control animals.

[0099] Figure 6 shows the effect of Composition 300 (BG-PEG-TAT) treatment versus control on tumor volumes of mice implanted with SKNF2 cell lines. As shown, the control group showed an increase in tumor volume from approximately $825mm^3$ to $1050mm^3$ over the 15 days of treatment. All groups receiving treatment with Composition 300 (BG-PEG-TAT) showed decreased tumor size. Further, the groups receiving treatment with Composition 300 (BG-PEG-TAT) showed dose-dependent decreases in tumor size, with the 10 mg/kg Group showing a tumor size reduction from approximately $825mm^3$ to $100mm^3$.

[0100] Figures 7a–7b comprise photographs of mice from each treatment group in which subcutaneous tumors 70 can be visually compared. As shown in Figure 7a, the control group shows large, clearly visible tumors 70. Control animals also showed abnormal circling (head rotation) 79, which was absent in all treatment arms. The abnormal circling is believed to be an effect of the tumor on the central nervous system.

[0101] As shown in Figure 7b, the treatment groups show clear dose dependent reductions in the size of the tumors 70 to complete absence at the 10 mg/kg dose. As shown, in the 10 mg/kg treatment group there is an absence of any visible tumor at the tumor location 70'.

[0102] Figure 8 shows the effect of the control and Composition 300 (BG-PEG-TAT) treatment on tumor weight of mice implanted with SKNF2 cell lines. As can be seen, the treatment groups show a dose-dependent reduction of tumor weight in comparison with the control group. Data showed 60%, 80% and 100% tumor shrinkage at the 1, 3, ad 10 mg/kg doses, respectively.

[0103] Figure 9a and Figure 9b shows the effect of the control and Composition 300 (BG-PEG-TAT) treatment on vasculature and tumor size of mice implanted with SKNF2 cell lines. As can be seen, the control group demonstrated significant increases in size of the tumors 70 as increased vascularization. Vascularized areas 90 of the control group tumors 70 are clearly visible. In contrast, the treatment groups show a dose-dependent reduction in size of the tumors 70, including tumor shrinkage at the 10 mg/kg dose. Tumor vasculature was also clearly diminished as shown. In fact, as shown in Figure 9b, with respect to the 10 mg/kg group, there was only necrotic skin 75 at the location of the implanted tumor 70' (see Figure 7b) to be removed for histopathological examination; the treatment demonstrated tumor shrinkage at this dose.

[0104] Figure 10 shows the effect of the control and Composition 300 (BG-PEG-TAT) treatment on tumor cell viability of mice implanted with SKNF2 cell lines. As can be seen, the treatment groups show a dose-dependent reduction in tumor cell viability. 70-75% cell viability was shown in control with 20-30% necrosis in the center of the tumor. In contrast, Composition 300 (BG-PEG-TAT) treatment at different doses showed loss of cell viability to 50%, 20, and 0.00% at 1, 3, and 10 mg/kg, daily treatment

for 15 days, respectively. The 10mg/kg group demonstrated a total lack of viable tumor cells following fifteen (15) days of treatment.

[0105] Figure 11 shows the effect of the control and Composition 300 (BG-PEG-TAT) treatment on tumor cell necrosis of mice implanted with SKNF2 cell lines. As can be seen, the treatment groups show a dose-dependent increase in tumor cell necrosis. The 10 mg/kg group demonstrated a tumor cell necrosis rate approaching 100%, the 3mg/kg group demonstrated a tumor cell necrosis rate of approximately 80%, and the 1 mg/kg demonstrated a tumor cell necrosis rate of approximately 50%.

[0106] Example 3: Comparative Examples:

[0107] Figures 12a and 12b shown the effect of the control and treatment with BG, BG derivatives, thyrointegrin antagonists such as TAT derivatives, and combinations (co-administration) thereof, versus Composition 300 (BG-P-TAT) on tumor cell necrosis of mice implanted with SKNF2 cell lines.

[0108] In summary, known thyrointegrin antagonists for treatment of tumor cells achieve substantially inferior results when compared with Composition 300 (BG-P-TAT). For example, triazole tetrac derivatives delivered subcutaneously daily for three (3) weeks at 3mg/kg has been shown to reduce tumor growth by approximately 40-50% and reduce tumor viability by approximately 40-50%. Similarly, triazole tetrac derivatives have also been shown to reduce tumor growth by approximately 40-50% and reduce tumor viability by approximately 40-50%. Further, even a combination treatment of two triazole tetrac derivatives in combination delivered subcutaneously daily for three (3) weeks at 3mg/kg only achieves a reduction of 40-50% for tumor growth and tumor viability. Similar results are obtained with treatments using benzyl guanidine and benzyl guanidine derivatives. Further, even co-administration of benzyl guanidine and thyrointegrin antagonists fails to demonstrate increased efficacy over the 40–50% mark.

[0109] In contrast, treatment with Composition 300 (BG-P-TAT) resulted in 80% reduction in tumor where the viability of residual tumor was reduced by 80%.

[0110] Comparative Example 3a: Effect of TAT Derivative on Tumor Weight:

[0111] The αvβ3 integrin receptor antagonists (thyrointegrin antagonists) showed limited (40-50%) efficacy in term of tumor growth rate and cancer viability inhibition in the case of neuroendocrine tumors such as neuroblastoma, pheochromocytoma, pancreatic neuroendocrine tumors, and carcinoid tumors. For example, the graph of Figure 12b includes the effect of a triazole tetrac derivative (referred to as TAT) on tumor weight when compared with a control group (phosphate-buffered saline “PBS”). The specific derivative tested was beta cyclodextrin triazole tetrac. As shown, the 3 mg/kg dosage resulted in approximately 40-50% reduction of tumor weight.

[0112] Comparative Example 3b: Effect of Benzyl Guanidine and Derivatives on Tumor Weight:

[0113] Similarly, benzyl guanidine and its derivatives demonstrate limited (40-50%) efficacy in term of tumor growth rate and cancer viability inhibition in the case of neuroendocrine tumors such as neuroblastoma, pheochromocytoma, pancreatic neuroendocrine tumors, and carcinoid tumors. For

example, the graph in Figure 12a includes the effect of benzyl guanidine (BG) and benzyl guanidine derivatives (such as MIBG and a polymer conjugated benzyl guanidine (specifically PLGA-PEG-BG, referred to as polymer-BG) on tumor weight when compared with a control group (PBS). The treatment compounds demonstrated limited anti-cancer efficacy of neuroblastoma despite its maximal (90-100%) uptake into neuroblastoma and other neuroendocrine tumors.

[0114] Comparative Example 3c: Effect of Co-Administration of Separate Norepinephrine Transporter Target and Thyrointegrin Antagonist:

[0115] Furthermore, treatment combinations comprising co-administration of norepinephrine transporter targets such as benzyl guanidine or derivatives together with thyrointegrin antagonists such as triazole tetraiodothyroacetic acid derivatives did not exceed 40-50% suppression of neuroblastoma growth and viability. For example, benzyl guanidine co-administered with a tetrac derivative (BG+TAT) did not surpass the 40–50% efficacy demonstrated by individual treatment with either compound as shown in Figure 12b (BG+TAT). Again, beta cyclodextrin triazole tetrac was the tetrac derivative used.

[0116] Comparative Example 3d: Effect of Composition 300 (BG-P-TAT) (Benzyl guanidine conjugated to TAT via PEG):

[0117] Again, treatment with Composition 300 (BG-P-TAT) resulted in significant improvement in the effect on tumor weight compared with both the control and other types of treatments as shown in Figure 12b. Composition 300 achieves approximately 80% reduction in tumor. Further, the viability of residual tumor was reduced by 80%. In fact, Composition 300 (TAT conjugated to BG) demonstrated a significant increase in efficacy over even co-administration of TAT and BG separately (BG+TAT).

[0118] The comparative examples from Figures 12a and 12b are summarized in the following Table 3:

[0119] Table 3

Comparative Tumor Growth Suppression and Tumor Survival Suppression Effect

Treatment Compound/Composition	Dosage	Percentage of Tumor Growth Suppression	Percentage of Tumor Survival Suppression
Benzyl guanidine (BG)	3mg/kg	40–50%	40–50%
Metaiodobenzylguanidine (MIBG)	3mg/kg	40–50%	40–50%
Benzyl guanidine with Polymer (PLGA-PEG-GB) (Polymer-BG)	3mg/kg	40–50%	40–50%
Triazole Tetrac Derivative 1 (beta cyclodextrin triazole tetrac) (TAT)	3mg/kg	40–50%	40–50%

Co-Administration of Benzyl guanidine and Triazole Tetrac Derivative 1 (BG+TAT)	3mg/kg	40–50%	40–50%
Composition 300 (BG-P-TAT)	3mg/kg	80–90%	80–90%

[0120] Example 4: Imaging of Subcutaneously Implanted Tumor in Athymic Female Mice.

[0121] Athymic female mice were implanted twice each with 10^6 cells/implant. The SKNF1 cell line was used with subcutaneous xenografts.

[0122] Group 1 consisted of three mice and were treated with PEG-TAT-dye (Cy5). Group 2 consisted of three mice and were treated with PEG-BG-dye (Cy5). Group 3 consisted of three mice and were treated with TAT-PEG-BG-dye (Cy5) wherein the TAT and BG were covalently linked with a PEG linker as compound 300. The treatment groups are shown below:

Group	Treatment Composition
Group 1	PEG modified triazole tetrac derivative with Cy5 dye
Group 2	PEG modified benzyl guanidine derivative with Cy5 dye
Group 3	Composition 300 with Cy5 dye

[0123] Fluorescence imaging (Cy5) was conducted 1 hour, 2 hours, 4 hours, 6 hours, and 24 hours post-administration. Imaging results are shown in Figures 13a and 13b, in which the tumor location is circled in yellow and the Cy5 dye appears as red. As shown in these figures, there was a dramatic increase in the fluorescence signal when the TAT and BG were covalently linked and Composition 300 showed marked improvement in both uptake into the SKNF1 neuroblastoma tumors and retention time within the tumor when compared with either a triazole tetrac derivative alone or a benzyl guanidine derivative alone.

[0124] Neuroblastoma tumor cells were used in the treatment example discussed. Those skilled in the art would appreciate these examples are valid models for treatment of other tumor types, particularly other neuroendocrine tumors. Further, any tumor or disease state demonstrating increased activity of the norepinephrine transporter in which thyrointegrin moderated antiangiogenic activity would be desired may be treated by the disclosed compositions.

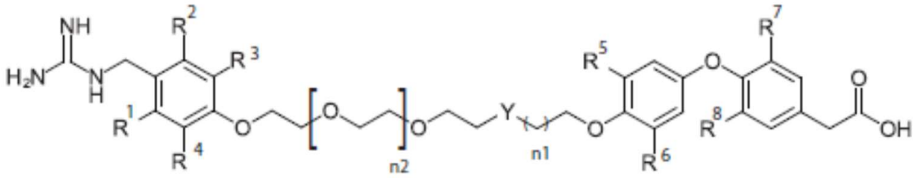
[0125] In light of these examples, the compositions described herein show increased efficacy against tumor cells, particularly neuroendocrine tumors. These compositions may be used to treat neuroendocrine tumors such as neuroblastoma, pheochromocytoma, pancreatic neuroendocrine tumors, and carcinoid tumors, for example by injectable, topical, sublingual, oral, and other routes of administration.

[0126] The descriptions of the various embodiments of the present invention have been presented for purposes of illustration, but are not intended to be exhaustive or limited to the embodiments disclosed. Many modifications and variations will be apparent to those of ordinary skill in the art without departing from the scope and spirit of the described embodiments. The terminology used herein was chosen to best explain the principles of the embodiments, the practical application or technical improvement over technologies found in the marketplace, or to enable others of ordinary skill in the art to understand the embodiments disclosed herein.

CLAIMS

1. A composition comprising:

a general formula:



or a salt thereof;

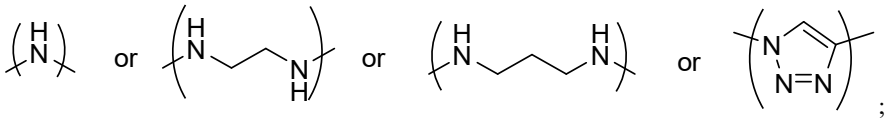
wherein R1, R2, R3, and R4 are each independently selected from the group consisting of hydrogen, iodine, fluorine, bromine, a methoxy group, a nitro group, an amine group, and a nitrile group;

wherein R5, R6, R7, and R8 are each independently selected from the group consisting of hydrogen, iodine, and an alkane group; and

$n_1 \geq 0$;

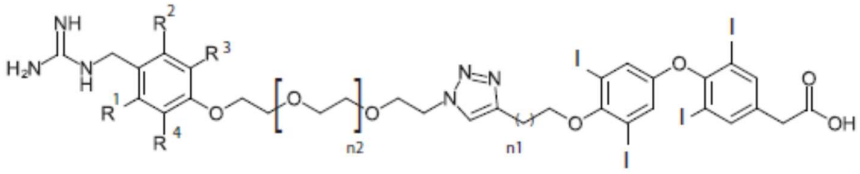
$n_2 \geq 1$; and

Y =

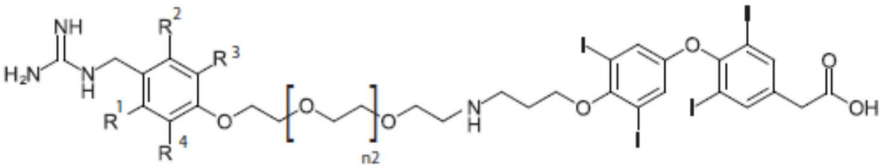


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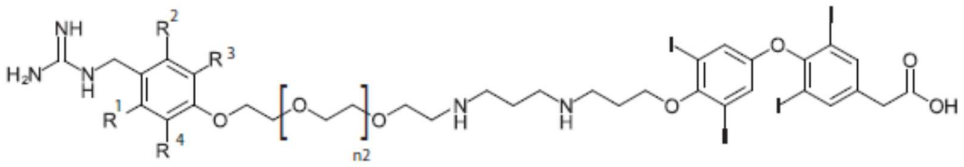
wherein the composition has a chemical formula selected from the group consisting of:



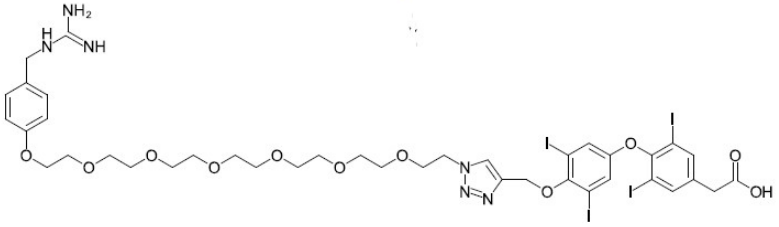
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, and



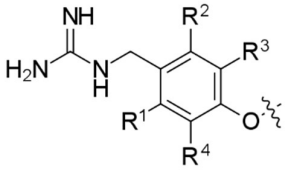
2. The composition of claim 1, wherein the composition has a chemical formula given by



3. The composition of Claim 1, wherein the composition includes N-benzyl guanidine.

4. The composition of claim 1, wherein the composition includes tetraiodothyroacetic acid.

5. The composition of claim 1,



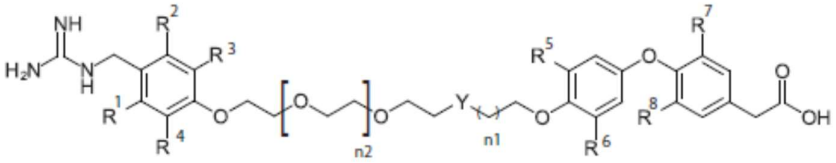
wherein at least one of R1, R2, R3, and R4 is selected from the group consisting of Iodine-123, Iodine-131, and Flourine-18.

6. The composition of claim 5 for use in imaging a neuroendocrine tumor.

7. The composition of claim 5, for use in the treatment of a neuroendocrine tumor by administration in a therapeutic dose.

8. The composition of claim 5, for use in simultaneous imaging and treatment of a neuroendocrine tumor.

9. A composition for use in the dual targeting of tumor cells, comprising:
administering a composition comprising:
a compound of a general formula:



or a salt thereof;

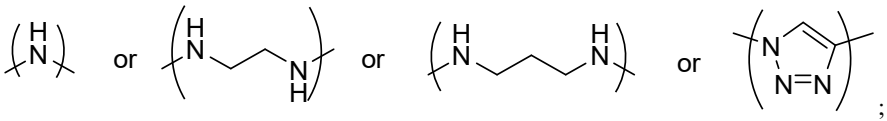
wherein R1, R2, R3, and R4 are each independently selected from the group consisting of hydrogen, iodine, fluorine, bromine, a methoxy group, a nitro group, an amine group, and a nitrile group;

wherein R5, R6, R7, and R8 are each independently selected from the group consisting of hydrogen, iodine, and an alkane group; and

$n_1 \geq 0$;

$n_2 \geq 1$; and

Y =



; and

wherein the compound comprises a thyrointegrin αvβ3 receptor antagonist selected from the group consisting of triiodothyroacetic acid and tetraiodothyroacetic acid.

10. The composition for use of claim 9, wherein the compound includes N-benzyl guanidine.

11. A composition comprising:

N-benzyl guanidine; and

tetraiodothyroacetic;

wherein the N-benzyl guanidine and the tetraiodothyroacetic are conjugated by polyethylene glycol.

12. The composition of claim 11, for use in imaging a neuroendocrine tumor; treatment of a neuroendocrine tumor by administration in a therapeutic dose; and/or simultaneous imaging and treatment of a neuroendocrine tumor αvβ3 integrin receptors.