DENDRIMER CONJUGATES AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application No. 63/327,301, filed April 4, 2022, and U.S. Provisional Patent Application No. 63/209,348, filed June 10, 2021, each of which is hereby incorporated by reference in its entirety.

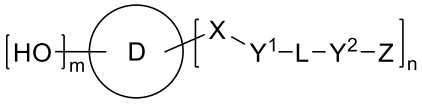
BACKGROUND

[001] Advancements in the field of nanotechnology have resulted in the creation of many new materials and devices with a vast range of applications. Nanotechnology manifests in a wide range of materials and particles, such as fullerenes and dendrimers. However, *in vivo* application of nanoparticles is challenged by the rapid elimination from circulation due to their interactions with biological systems. Alternative strategies in nanoparticle development could allow for the advantageous properties of nanoparticles to be utilized more effectively in the context of clinical applications, diagnostics, and biomedical research.

SUMMARY

[002] In some examples, the disclosure provides therapeutic and/or diagnostic compounds comprising a dendrimer conjugated to an agent through a terminal ether or amide bond. In some examples, the dendrimer comprises terminal hydroxyl groups optionally substituted with the agent. In some examples, the agent is a therapeutic agent or an imaging agent.

[003] In some examples, the disclosure provides a dendrimer conjugate of Formula (**I**):

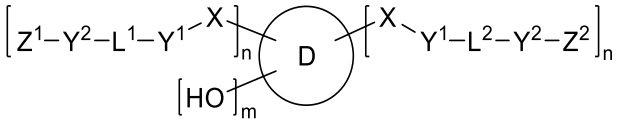


(**I**),

wherein: D is a dendrimer; X is O or NH; Y^1 is optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, or a covalent bond; Y^2 is selected from the group consisting of secondary amides, tertiary amides, sulfonamide, secondary carbamates, tertiary carbamates, carbonates, ureas, carbinols, disulfides, hydrazones, hydrazides, ethers, carbonyls, and combinations thereof; Z is a therapeutic agent or an imaging agent; L is a linker; m is an integer

from 16 to 4096, inclusive; and n is an integer from 1 to 100, inclusive. In some examples, the ratio of m to (m+n) is at least 0.5. In some examples, the ratio of m to (m+n) is between about 0.50 and about 0.99.

[004] In some examples, the disclosure provides a dendrimer conjugate of Formula (**II**):



(**II**),

wherein: D is a dendrimer; each instance of X is independently O or NH; each instance of Y^1 is independently optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, or a covalent bond; each instance of Y^2 is independently selected from the group consisting of secondary amides, tertiary amides, sulfonamide, secondary carbamates, tertiary carbamates, carbonates, ureas, carbinols, disulfides, hydrazones, hydrazides, ethers, carbonyls, and combinations thereof; Z^1 and Z^2 are independently therapeutic agents, targeting agents, or imaging agents, with the proviso that Z^1 and Z^2 are different; L^1 and L^2 are independently linkers; m is an integer from 16 to 4096, inclusive; and each instance of n is independently an integer from 1 to 100, inclusive.

[005] In some examples, the dendrimer of a therapeutic compound or dendrimer conjugate of the disclosure is selected from the group consisting of poly(amidoamine) (PAMAM) polymers, polypropylamine (POPAM) polymers, polyethylenimine polymers, polylysine polymers, polyester polymers, iptycene polymers, aliphatic poly(ether) polymers, aromatic polyether polymers, 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) polymers, and combinations thereof.

[006] In some examples, the linker of a therapeutic compound or dendrimer conjugate comprises a polymer. In some examples, the polymer is a polymeric polyol, a polypeptide, or an unsubstituted alkyl chain. In some examples, the polymer is a polymeric polyol selected from the group consisting of polyethylene glycol (PEG), polypropylene glycol, and polyvinyl alcohol. In some examples, the polymer is a polypeptide comprising at least 2 and up to 25 amino acids. In some examples, the polymer is an unsubstituted C2-30 alkyl chain. In some examples, the linker comprises at least one moiety selected from the group consisting of 1,2,3-triazolyl, 4,5-dihydro-1,2,3-triazolyl, isoxazolyl, 4,5-dihydroisoxazolyl, and 1,4-dihydropyridazyl. In some examples, the linker comprises the polymer and the at least one moiety. In some examples, the linker is non-hydrolyzable under physiological conditions.

[007] In some examples, the therapeutic agent of a therapeutic compound or dendrimer conjugate is selected from the group consisting of angiotensin II receptor blockers, Farnesoid

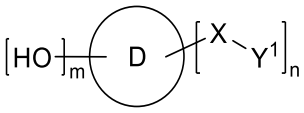
X receptor agonists, death receptor 5 agonists, sodium-glucose cotransporter type-2 inhibitors, lysophosphatidic acid 1 receptor antagonists, endothelin-A receptor antagonist, PPARδ agonists, AT1 receptor antagonists, CCR5/CCR2 antagonists, anti-fibrotic agents, anti-inflammatory agents, antioxidant agents, STING agonists, CSF1R inhibitors, AXL inhibitors, c-Met inhibitors, PARP inhibitors, receptor tyrosine kinase inhibitors, MEK inhibitors, group I p21-activated kinase (PAK1) inhibitors, glutaminase inhibitors, TIE II antagonists, CXCR2 inhibitors, CD73 inhibitors, arginase inhibitors, PI3K inhibitors, TLR4 agonists, TLR7 agonists, SHP2 inhibitors, chemotherapeutic agents, STING antagonists, and JAK1 inhibitors.

[008] In some examples, the therapeutic agent of a therapeutic compound or dendrimer conjugate is a MEK inhibitor. In some examples, the MEK inhibitor is selected from the group consisting of Trametinib, Cobimetinib, Binimetinib, Selumetinib, PD325901, PD035901, PD032901, and TAK-733. In some examples, the therapeutic agent of a therapeutic compound or dendrimer conjugate is a receptor tyrosine kinase inhibitor. In some examples, the receptor tyrosine kinase inhibitor is selected from the group consisting of sunitinib, sorafenib, pazopanib, vandetanib, axitinib, cediranib, vatalanib, dasatinib, bemcentinib (R428), dubermatinib (TP-0903), nintedanib, cabozantinib, and motesanib. In some examples, the therapeutic agent of a therapeutic compound or dendrimer conjugate is a PAK1 inhibitor. In some examples, the PAK1 inhibitor is Frax-1036 (6-[2-chloro-4-(6-methyl-2-pyrazinyl)phenyl]-8-ethyl-2-[[2-(1-methyl-4-piperidinyl)ethyl]amino]-pyrido[2,3-d]pyrimidin-7(8H)-one).

[009] In some examples, the imaging agent of a therapeutic compound or dendrimer conjugate is selected from the group consisting of dyes, fluorescent dyes, near infrared dyes, single-photon emission computed tomography (SPECT) imaging agents, positron emission tomography (PET) imaging agents, magnetic resonance imaging (MRI) contrast agents, and radionuclides.

[0010] In some examples, a therapeutic compound or dendrimer conjugate of the disclosure comprises at least one targeting agent conjugated to the dendrimer. In some examples, the targeting agent is a triantennary-*N*-acetylgalactosamine (GalNAc).

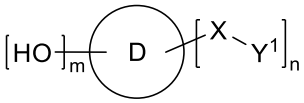
[0011] In some examples, the disclosure provides a composition comprising a carrier and functionalized dendrimers of Formula (**I-A**):



(**I-A**),

wherein: D is a dendrimer selected from the group consisting of poly(amidoamine) (PAMAM) polymers, polypropylamine (POPAM) polymers, polyethylenimine polymers, polylysine polymers, polyester polymers, iptycene polymers, aliphatic poly(ether) polymers, aromatic polyether polymers, 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) polymers, and combinations thereof; X is NH; Y^1 is optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, or a covalent bond; m is an integer from 16 to 4096, inclusive; and n is an integer from 1 to 100, inclusive, wherein the polydispersity value of the functionalized dendrimers in the composition is less than or equal to 1.10.

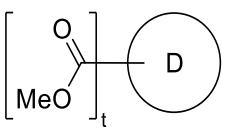
[0012] In some examples, the disclosure provides methods of synthesizing a functionalized dendrimer of Formula (**I-A**):



(**I-A**),

wherein:

D is a dendrimer selected from the group consisting of poly(amidoamine) (PAMAM) polymers, polypropylamine (POPAM) polymers, polyethylenimine polymers, polylysine polymers, polyester polymers, iptycene polymers, aliphatic poly(ether) polymers, aromatic polyether polymers, 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) polymers, and combinations thereof; X is NH; Y^1 is optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, or a covalent bond; m is an integer from 16 to 4096, inclusive; and n is an integer from 1 to 100, inclusive; comprising: reacting a dendrimer of Formula (**II-A**):



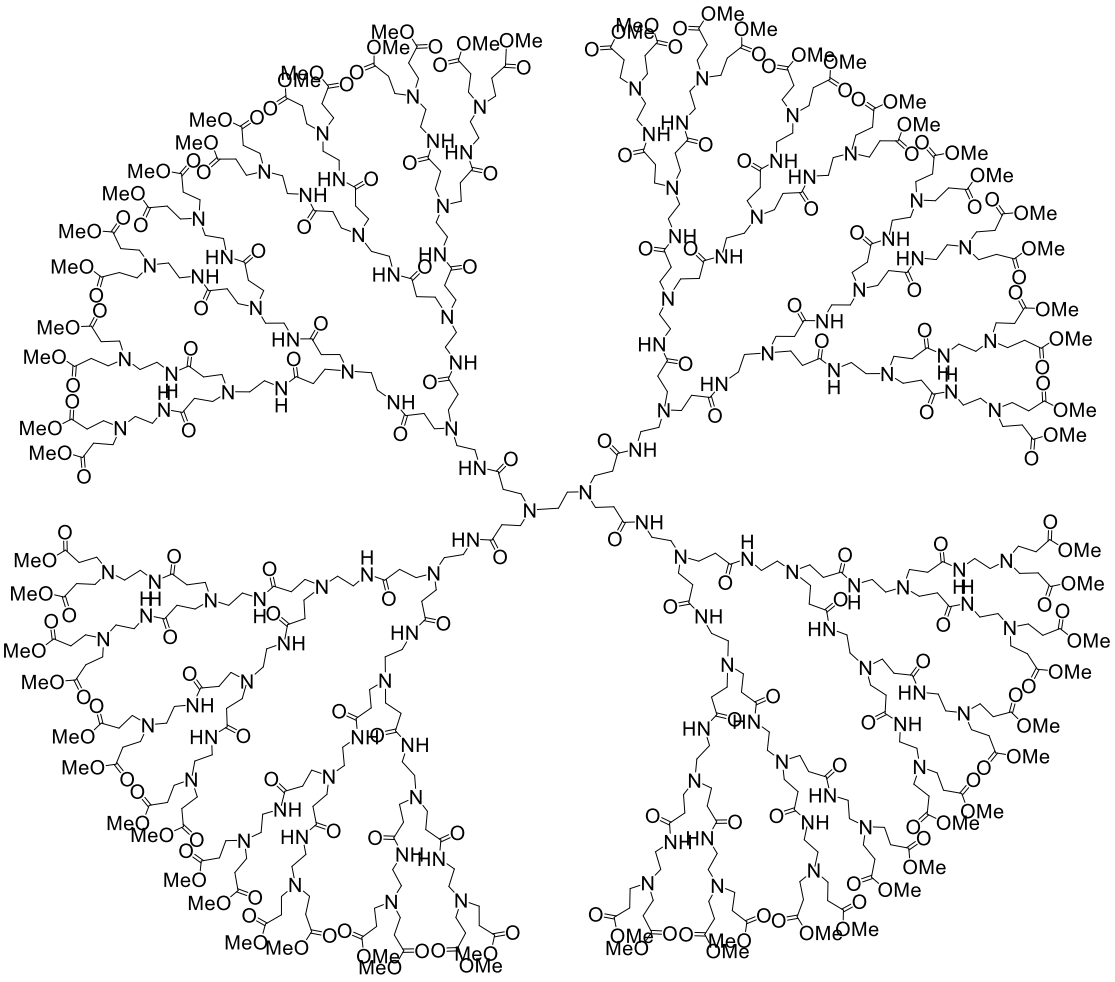
(**II-A**),

under suitable conditions to form the functionalized dendrimer of Formula **(I-A)**;

wherein: D is a dendrimer selected from the group consisting of poly(amidoamine) (PAMAM) polymers, polypropylamine (POPAM) polymers, polyethylenimine polymers, polylysine polymers, polyester polymers, iptycene polymers, aliphatic poly(ether) polymers, aromatic polyether polymers, 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) polymers, and combinations thereof; t is an integer from 16 to 4096, inclusive; with one or more amines, wherein each amine is of the formula H_2NR^1, wherein R^1 is optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, or a covalent bond. In some examples, provided is a functionalized dendrimer described herein, or a salt, solvate, hydrate, stereoisomer, polymorph, tautomer, isotopically enriched form (e.g., isotopically labeled derivative) thereof.

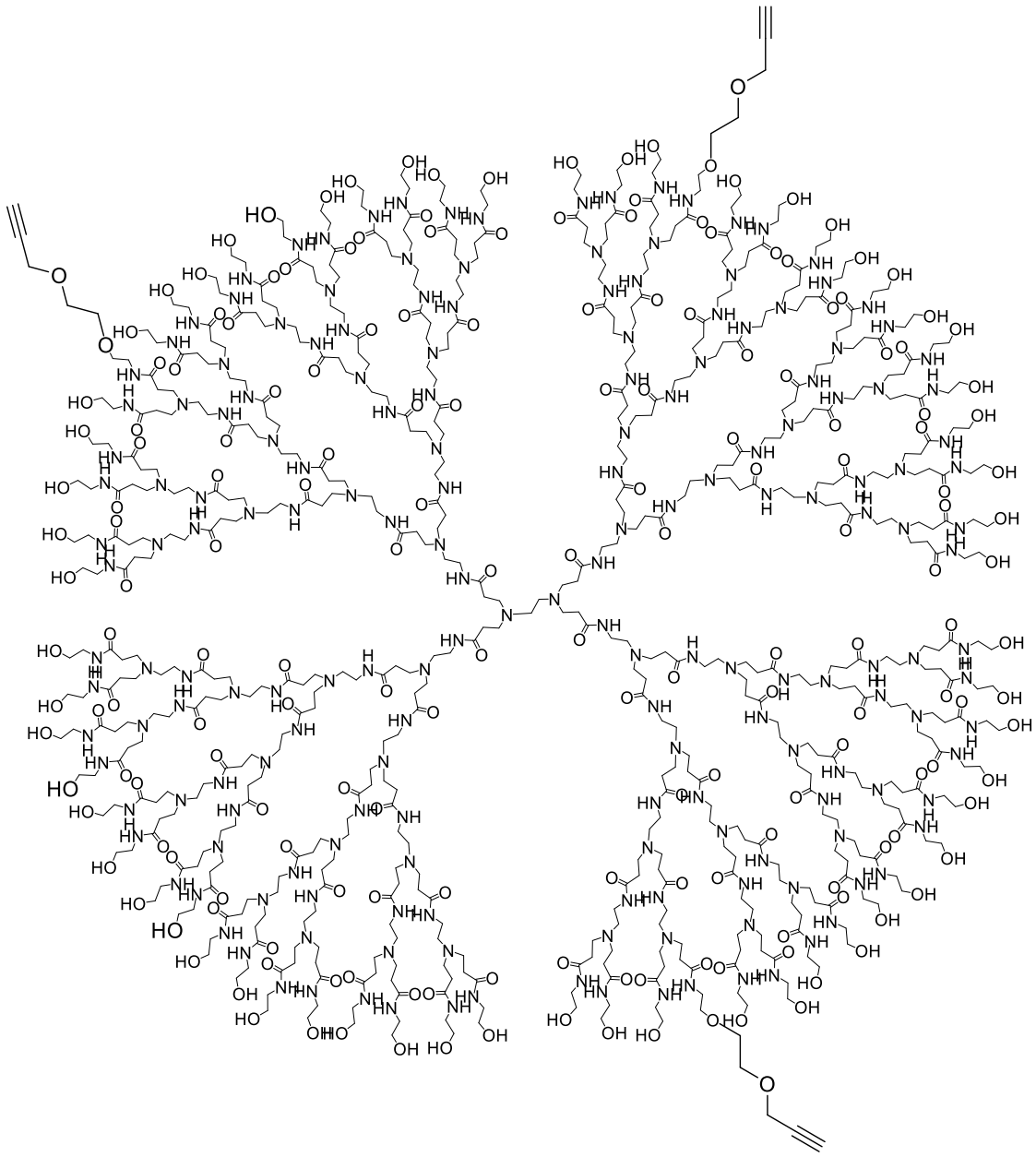
[0013] In some examples, n is approximately 3 or 10 (e.g., 3 or 10). In some examples, m is the value of n subtracted from 64. In some examples, n is 3 and m is 61. In some examples, n is 10 and m is 54. In some examples, m is approximately 61 or 54 (e.g., 61 or 54).

[0014] In some examples, a dendrimer of Formula (**II-A**) is of formula:

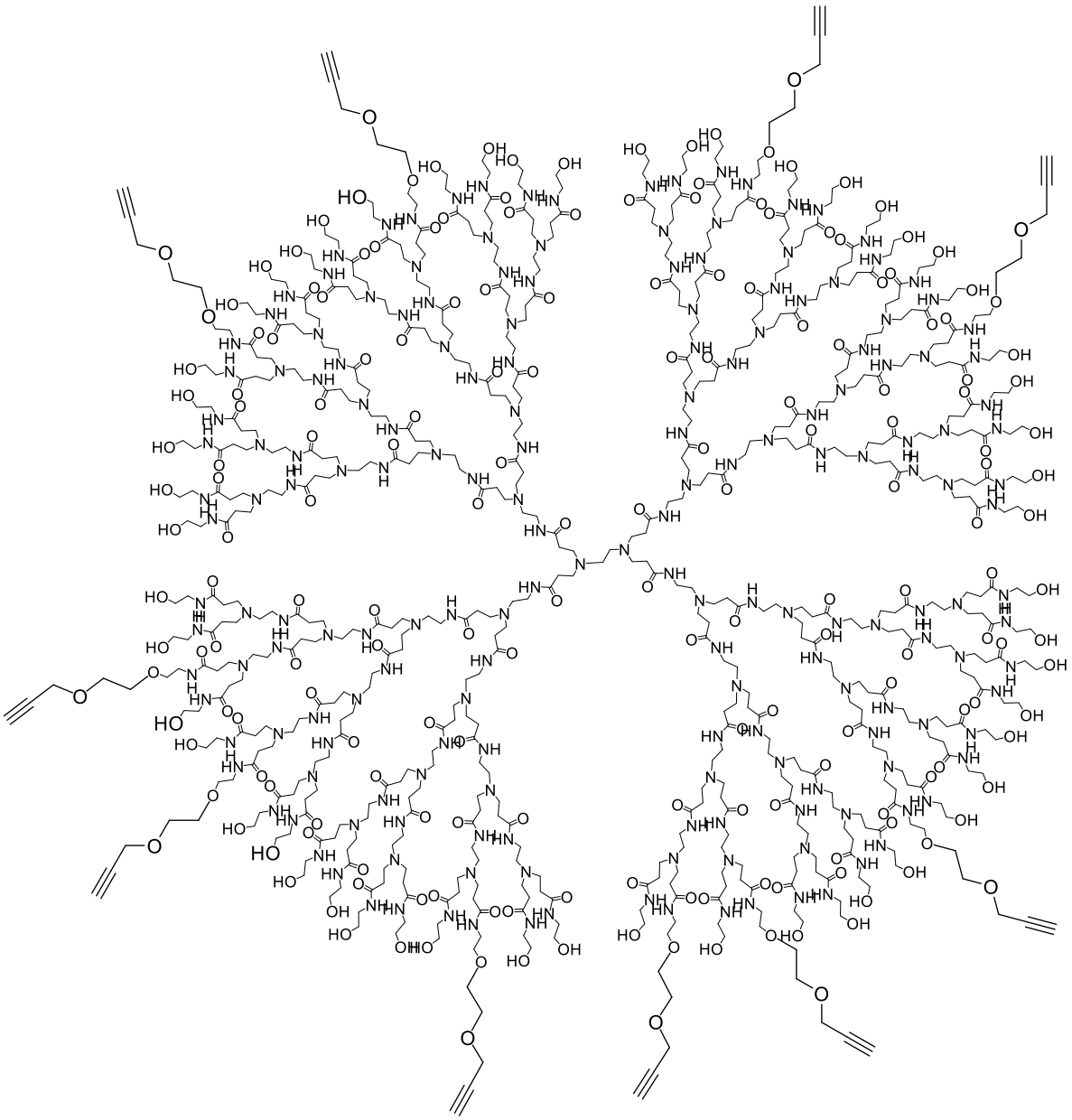


(PAMAM G3.5).

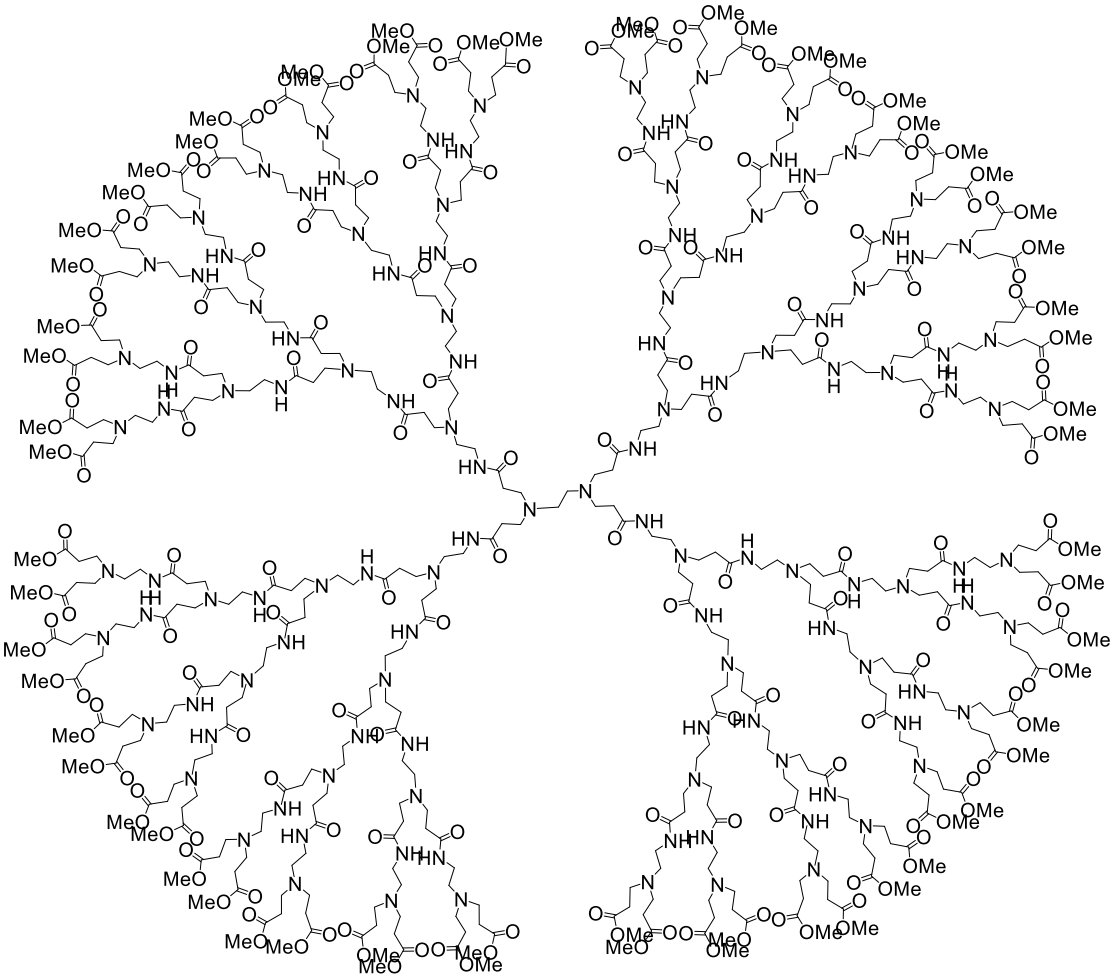
[0015] In some examples, the functionalized dendrimer of Formula (**I-A**) is of formula:



or



[0016] In yet another example, the present disclosure provides functionalized dendrimers of Formula (**I-A**), synthesized by methods described herein. In some examples, provided is a dendrimer of Formula (**II-A**) of formula:



(PAMAM G3.5).

[0017] In some examples, the disclosure provides a composition of a therapeutic compound comprising a dendrimer conjugated to a therapeutic agent through a terminal ether or amide bond. In some examples, the dendrimer comprises a high-density of terminal hydroxyl groups optionally substituted with the therapeutic agent. In some examples, a therapeutic compound comprising a dendrimer conjugated to a therapeutic agent is 10-20% by mass of therapeutic agent. In some examples, the terminal ether or amide bond is conjugated to the therapeutic agent through a linker.

[0018] In some examples, the therapeutic compound is about 10% to about 15% by mass of therapeutic agent. In some examples, the therapeutic compound is about 15% to about 20% by mass of therapeutic agent. In some examples, at least 50% of terminal sites on the dendrimer comprise terminal hydroxyl groups. In some examples, at least 50% and up to 99% (e.g., 50-95%, 50-90%, 50-80%, 50-70%, 50-60%, 60-80%, 70-90%) of terminal sites on the dendrimer comprise terminal hydroxyl groups.

[0019] In some examples, the therapeutic agent has an aqueous solubility that is increased relative to an unconjugated compound comprising the therapeutic agent in absence of the dendrimer. In some examples, the aqueous solubility is increased by at least 10% relative to the unconjugated compound. In some examples, the aqueous solubility is increased by between about 10% and about 100% relative to the unconjugated compound. In some examples, the aqueous solubility is increased by at least about a factor of two relative to the unconjugated compound. In some examples, the aqueous solubility is increased by between about a factor of two and about a factor of ten relative to the unconjugated compound. In some examples, the aqueous solubility is solubility under physiological conditions. In some examples, the aqueous solubility is solubility in water having a pH of between about 7.0 and about 8.0. In some examples, the therapeutic agent is present at a concentration at which the unconjugated compound is insoluble under physiological conditions.

[0020] In some examples, the disclosure provides methods of treating or imaging a disease or disorder of the brain or central nervous system in a subject in need thereof, the methods comprising administering to the subject a composition comprising a dendrimer conjugate described herein in an amount effective to treat or image the disease or disorder of the brain or central nervous system in the subject.

[0021] In some examples, the dendrimer conjugate is selectively taken up by activated microglia and/or activated macrophages in the brain or central nervous system of the subject. In some examples, the activated macrophages are resident macrophage cells of the central nervous system. In some examples, the dendrimer conjugate crosses the blood-brain barrier of the subject. In some examples, the disease or disorder is a tumor of the brain or central nervous system. In some examples, the tumor is a benign or malignant tumor associated with neurofibromatosis. In some examples, the disease or disorder is neurofibromatosis (e.g., neurofibromatosis type 1 (NF1)). Accordingly, in some examples, the subject has or is suspected of having neurofibromatosis (e.g., NF1). In some examples, the dendrimer conjugate is selectively taken up by tumor-associated macrophages of the tumor in the subject. In some examples, the tumor is a brain cancer or a cancer of the central nervous system. In some examples, the tumor is a brain cancer selected from the group consisting of neoplasias and hyperplasias. In some examples, the tumor is a cancer of the central nervous system selected from the group consisting of gliomas, glioblastoma, astrocytoma, oligodendroglioma, meningioma, medulloblastoma, ganglioma, and Schwannoma. In some examples, the dendrimer conjugate is not conjugated to a

targeting moiety. In some examples, the composition is administered to the subject systemically, intravenously, or orally. In some examples, the dendrimer conjugate comprises a therapeutic agent, and the composition has a therapeutic index that is increased relative to a composition comprising the therapeutic agent in absence of the dendrimer. In some examples, the therapeutic agent is a MEK inhibitor (e.g., Trametinib, Cobimetinib, Binimetinib, Selumetinib, PD325901, PD035901, PD032901, or TAK-733). In some examples, the therapeutic agent is a receptor tyrosine kinase inhibitor (e.g., sunitinib, sorafenib, pazopanib, vandetanib, axitinib, cediranib, vatalanib, dasatinib, bemcentinib (R428), dubermatinib (TP-0903), nintedanib, cabozantinib, or motesanib). In some examples, the therapeutic agent is a PAK1 inhibitor (e.g., Frax-1036 (6-[2-chloro-4-(6-methyl-2-pyrazinyl)phenyl]-8-ethyl-2-[[2-(1-methyl-4-piperidinyl)ethyl]amino]-pyrido[2,3-d]pyrimidin-7(8H)-one)).

[0022] In some examples, the disclosure provides methods of treating or imaging a disease or disorder of the eye in a subject in need thereof, the methods comprising administering to the subject a composition comprising a dendrimer conjugate described herein in an amount effective to treat or image the disease or disorder of the eye in the subject.

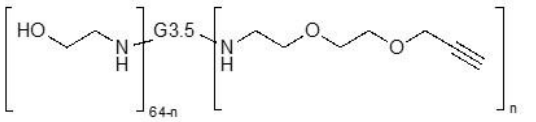
[0023] In some examples, the dendrimer conjugate is selectively taken up by activated microglia and/or activated macrophages in the eye of the subject. In some examples, the dendrimer conjugate crosses the blood-retinal barrier of the subject. In some examples, the dendrimer conjugate is not conjugated to a targeting moiety. In some examples, the composition is administered to the subject systemically, intravenously, or orally. In some examples, the dendrimer conjugate comprises a therapeutic agent, and the composition has a therapeutic index that is increased relative to a composition comprising the therapeutic agent in absence of the dendrimer.

[0024] In some examples, the disclosure provides methods of treating or imaging a proliferative disease in a subject in need thereof, the methods comprising administering to the subject a composition comprising a dendrimer conjugate described herein in an amount effective to treat or image the proliferative disease in the subject.

[0025] In some examples, the proliferative disease is neurofibromatosis. In some examples, the proliferative disease is selected from neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis. In some examples, the proliferative disease is NF1. In some examples, the dendrimer conjugate is not conjugated to a targeting moiety. In some examples, the composition is administered to the subject systemically, intravenously, or orally. In some examples, the dendrimer

conjugate comprises a therapeutic agent, and the composition has a therapeutic index that is increased relative to a composition comprising the therapeutic agent in absence of the dendrimer. In some examples, the therapeutic agent is a MEK inhibitor (e.g., Trametinib, Cobimetinib, Binimetinib, Selumetinib, PD325901, PD035901, PD032901, or TAK-733). In some examples, the therapeutic agent is a receptor tyrosine kinase inhibitor (e.g., sunitinib, sorafenib, pazopanib, vandetanib, axitinib, cediranib, vatalanib, dasatinib, bemcentinib (R428), dubermatinib (TP-0903), nintedanib, cabozantinib, or motesanib). In some examples, the therapeutic agent is a PAK1 inhibitor (e.g., Frax-1036 (6-[2-chloro-4-(6-methyl-2-pyrazinyl)phenyl]-8-ethyl-2-[[2-(1-methyl-4-piperidinyl)ethyl]amino]-pyrido[2,3-d]pyrimidin-7(8H)-one)).

[0025a] In one aspect, the disclosure provides a composition comprising a carrier and functionalized dendrimers of the formula:



,

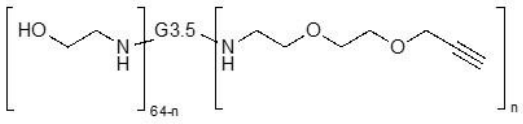
wherein:

G3.5 is a 3.5 generation poly(amidoamine) (PAMAM) dendrimer;

n is an integer from 1 to 64, inclusive,

wherein the polydispersity value of the functionalized dendrimers in the composition is from 1.00 to 1.10.

[0025b] In another aspect, the disclosure provides a method of synthesizing a functionalized dendrimer of formula:

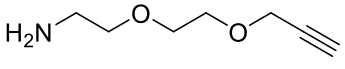


wherein:

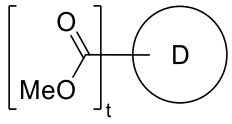
G3.5 is a 3.5 generation poly(amidoamine) (PAMAM) dendrimer;

n is an integer from 1 to 64, inclusive,

the method comprising reacting both ethanolamine and a PEG-alkyne of formula:



, with a dendrimer of Formula (**II-A**):



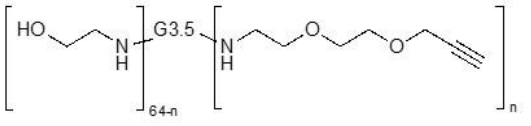
(**II-A**),

under suitable conditions to form the functionalized dendrimer of Formula **(I-A)**; wherein:

D is a 3.5 generation poly(amidoamine) (PAMAM) dendrimer

t is 64.

[0025c] In yet another aspect, the disclosure provides a method comprising reacting the dendrimer of the formula:

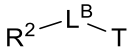


,

G3.5 is a 3.5 generation poly(amidoamine) (PAMAM) dendrimer;

n is an integer from 1 to 64, inclusive;

with a compound of Formula (**B**):



(**B**),

wherein:

R^2 is halogen, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acetyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-N_3$, $-CH(=N)(OH)R^{D1}$, -CN, $-NO_2$, $-OR^{D1}$, $-N(R^{D1a})_2$, $-SO_2OR^{D1}$, or $-SR^{D1}$, wherein R^{D1} is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom;

wherein each occurrence of R^{D1a} is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group; or optionally two instances of R^{D1a} are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

L^B is an alkylene linker, wherein one or more chain atoms of the hydrocarbon chain are independently replaced with amide, ester, hydroxamate, ether, carbonate, carbamate, hydrazone, thioether, thioester, disulfide, orthoester, urethane, or oxime moiety, or a cyclic moiety; and

T is a therapeutic agent.

[0026] The details of certain embodiments of the disclosure are set forth in the Detailed Description, as described below. Other features, objects, and advantages of the disclosure will be apparent from the Examples, Drawings, and Claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] The accompanying drawings, which constitute a part of this specification, illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

[0028] FIG. 1 is a schematic showing the chemical structure of a dendrimer conjugate (compound D-4517.2).

[0029] FIG. 2 is a reaction scheme showing one synthesis strategy of *N, N*-didesethyl sunitinib azide with an amide linkage.

[0030] FIG. 3 is a reaction scheme showing the synthesis of a dendrimer conjugate (D-4517.2) in which *N, N*-didesethyl sunitinib is conjugated to a dendrimer with ether linkages for enhanced *in vivo* stability.

[0031] FIG. 4 is a bar graph showing drug release percentage by weight (0.0%-0.50%) of D-didesethyl sunitinib conjugate, D-4517.2, in human, mouse, and rat plasma conditions over time points for each of 4, 24 and 48 hours, respectively.

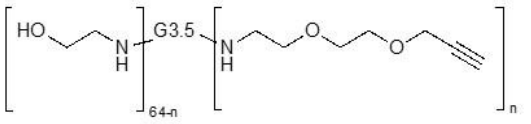
[0032] FIG. 5 is a reaction scheme showing the synthesis of a Dendrimer-N-Acetyl-L-cysteine methyl ester conjugate.

[0033] FIG. 6 is a reaction scheme showing the synthesis of β-GalNAc-triantennary-PEG3-Azide building block for conjugation to dendrimer.

CLAIMS

What is claimed is:

1. A composition comprising a carrier and functionalized dendrimers of the formula:



,

wherein:

G3.5 is a 3.5 generation poly(amidoamine) (PAMAM) dendrimer;

n is an integer from 1 to 64, inclusive,

wherein the polydispersity value of the functionalized dendrimers in the composition is from 1.00 to 1.10.

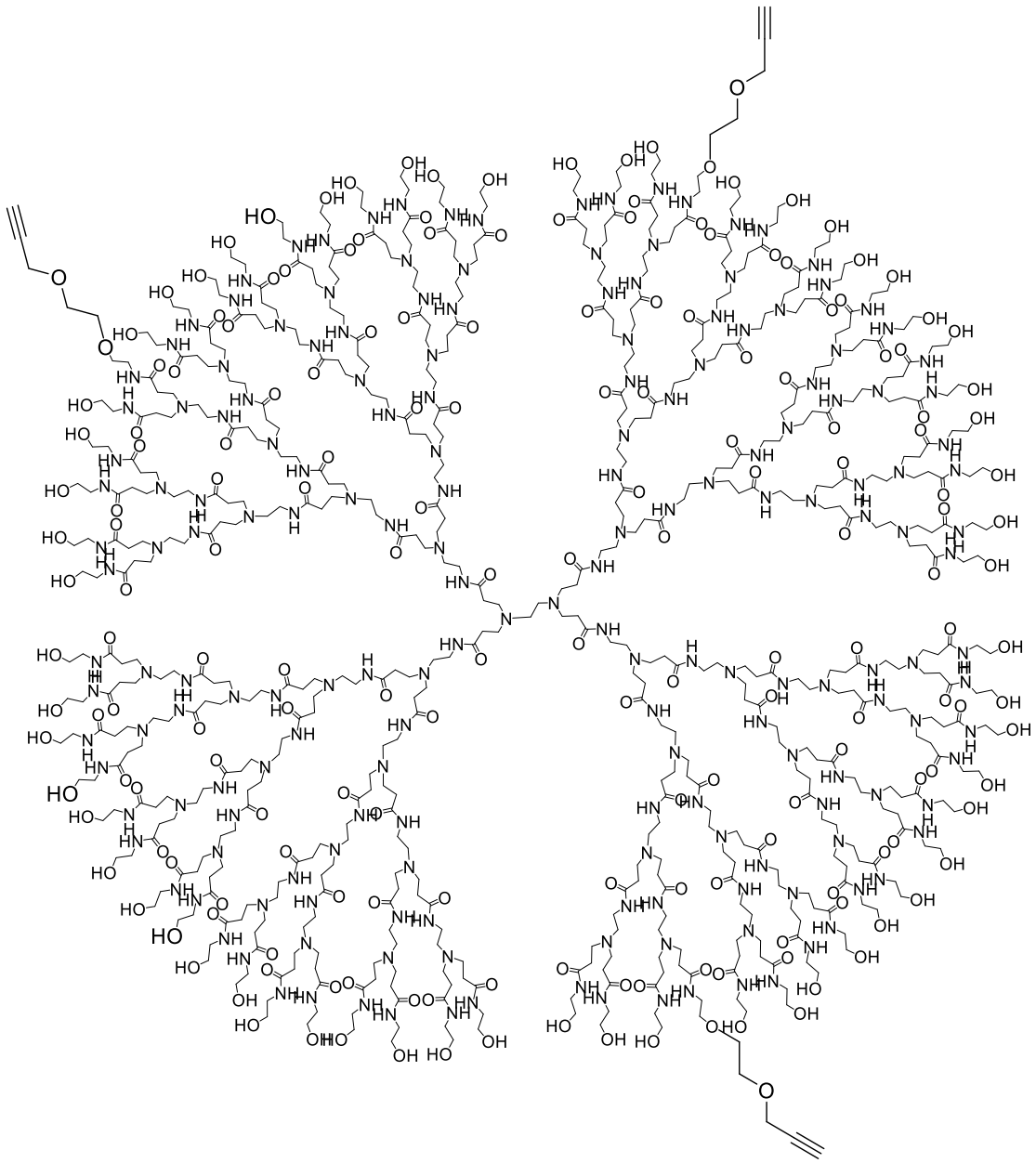
2. The composition of claim 1, wherein the polydispersity value of the functionalized dendrimers in the composition is between 1.00 and 1.05.

3. The composition of claim 1 or 2, wherein the polydispersity value of the functionalized dendrimers in the composition is between 1.00 and 1.04.

4. The composition of any one of claims 1-3, wherein the polydispersity value of the functionalized dendrimers in the composition is between 1.00 and 1.03.

5. The composition of any one of claims 1-4, wherein the composition comprises 20-200 grams, 50-200 grams, or 100-200 grams of the functionalized dendrimer.

6. The composition of any one of claims 1-5, wherein the functionalized dendrimer is of the formula:



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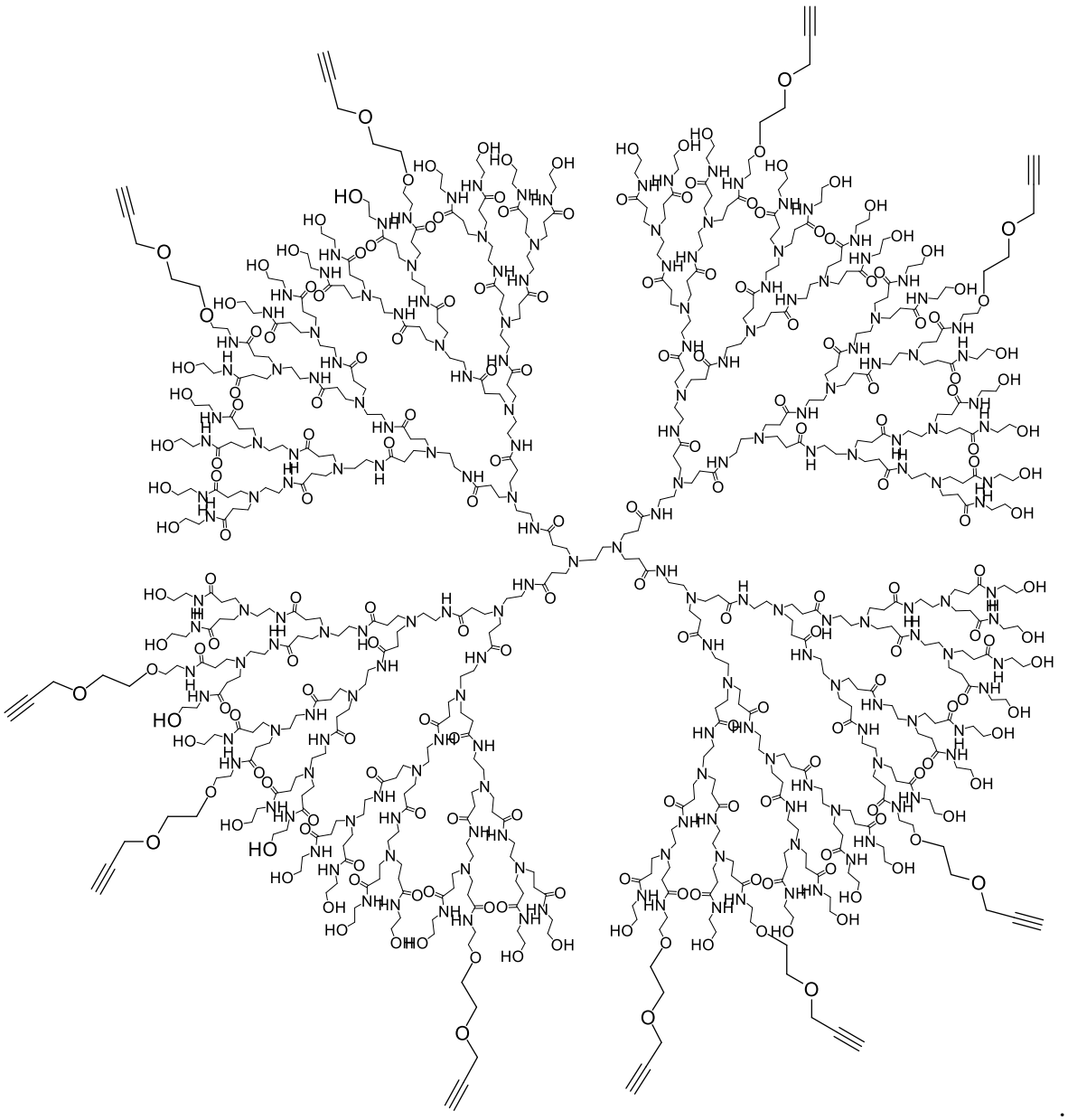
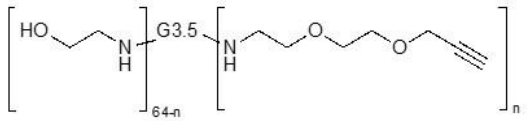
7. The composition of any one of claims 1-5, wherein the functionalized dendrimer is of the formula:



.

8. A method of synthesizing a functionalized dendrimer of formula:

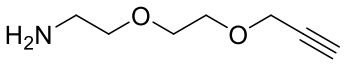


wherein:

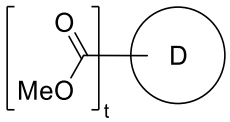
G3.5 is a 3.5 generation poly(amidoamine) (PAMAM) dendrimer;

n is an integer from 1 to 64, inclusive,

the method comprising reacting both ethanolamine and a PEG-alkyne of formula:



, with a dendrimer of Formula (**II-A**):



(**II-A**),

under suitable conditions to form the functionalized dendrimer of Formula **(I-A)**; wherein:

D is a 3.5 generation poly(amidoamine) (PAMAM) dendrimer

t is 64.

9. The method of claim 8, wherein a ratio of the ethanolamine to the PEG-alkyne is used, wherein the ratio is 9.42:1 or 2.2:1.

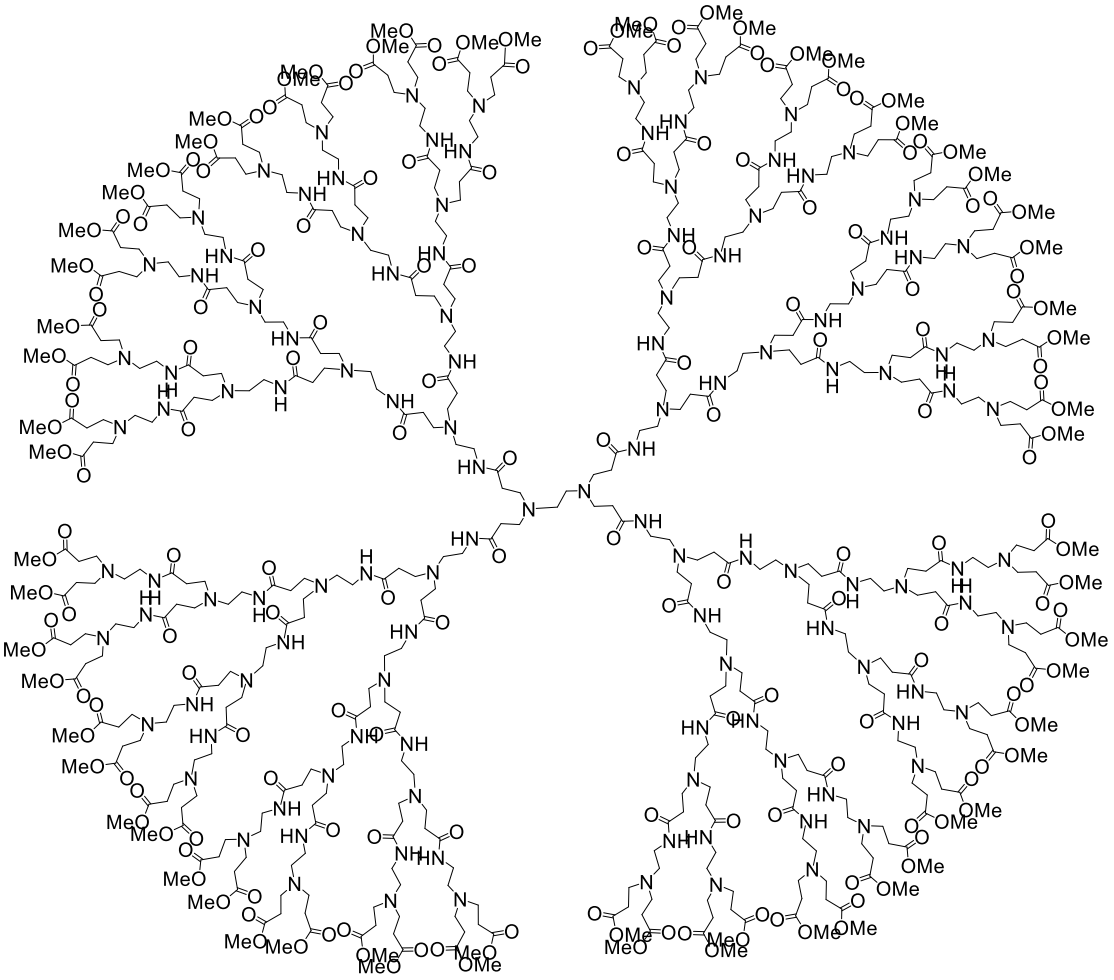
10. The method of claim 8 or 9, wherein a ratio of PEG-alkyne to dendrimer of Formula (**II-A**) is used.

11. The method of claim 10, wherein the ratio of the PEG-alkyne to the dendrimer of Formula (**II-A**) is approximately 150:1, optionally wherein the ratio of the PEG-alkyne to the dendrimer of Formula (**II-A**) is approximately 150:1, the ratio of the ethanolamine to the PEG-Alkyne is 9.42:1, and n is 3.

12. The method of claim 10, wherein the ratio of the PEG-alkyne to the dendrimer of Formula (**II-A**) is approximately 500:1, optionally wherein the ratio of the PEG-alkyne to the dendrimer of Formula (**II-A**) is approximately 500:1, the ratio of the ethanolamine to the PEG-Alkyne is 2.2:1, and n is 10.

13. The method of claim 10, the ratio of the PEG-Alkyne to the dendrimer of Formula (**II-A**) is 495:1.

14. The method of any one of claims 8-13, wherein the dendrimer of Formula (**II-A**) is of formula:



(PAMAM G3.5).

15. The method of any one of claims 8-14, wherein the polydispersity value of the functionalized dendrimer of Formula (**I-A**) is from 1.00 to 1.05; optionally wherein the polydispersity value of the functionalized dendrimer of Formula (**I-A**) is 1.03.

16. The method of any one of claims 8-15, wherein:

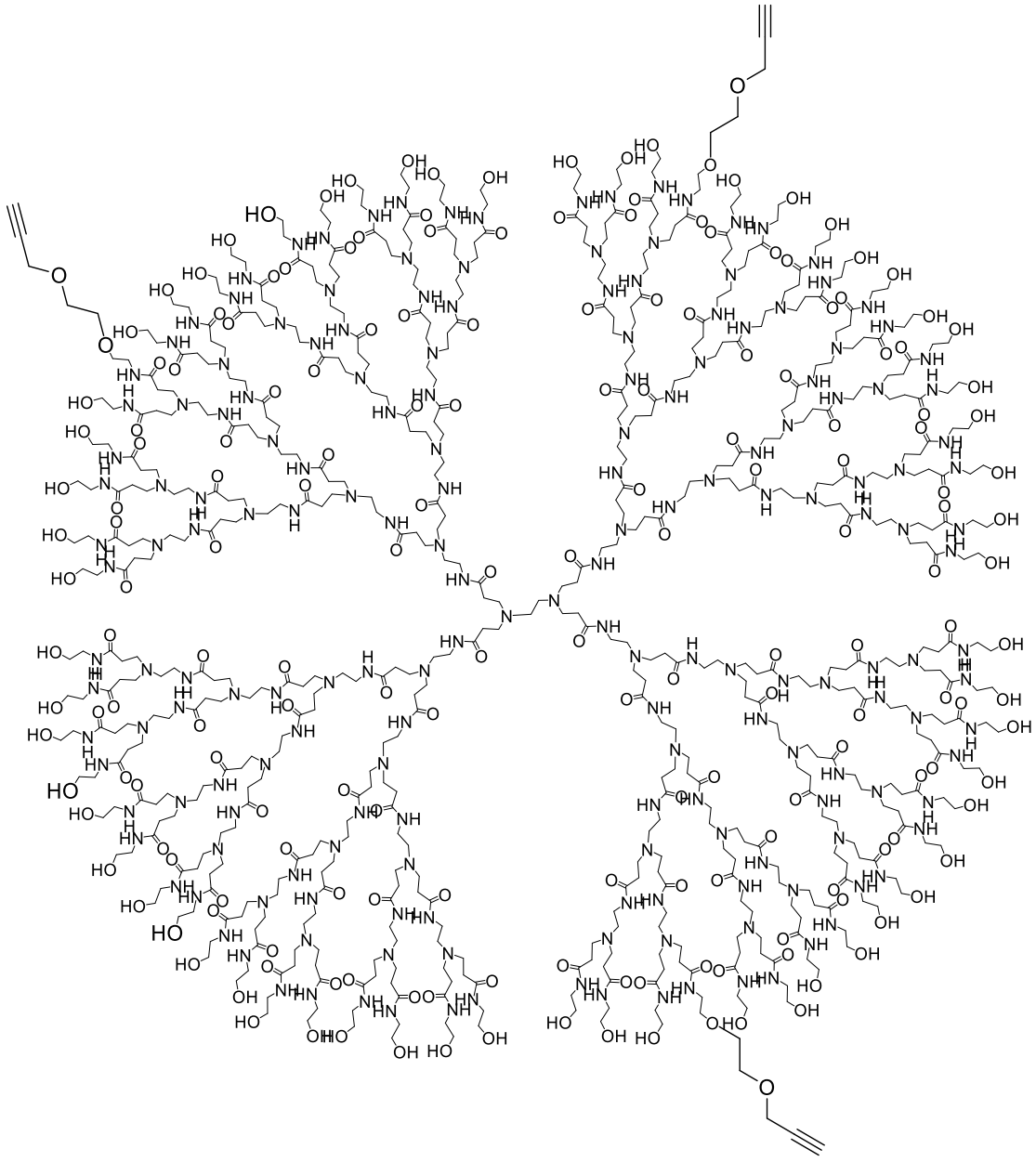
(i) the suitable conditions comprise a protic solvent and reacting at approximately 19 °C to approximately 23 °C; optionally wherein the protic solvent is an alcohol; further optionally wherein the protic solvent is methanol;

(ii) the suitable conditions comprise reacting at approximately 20 °C to approximately 22 °C; and/or

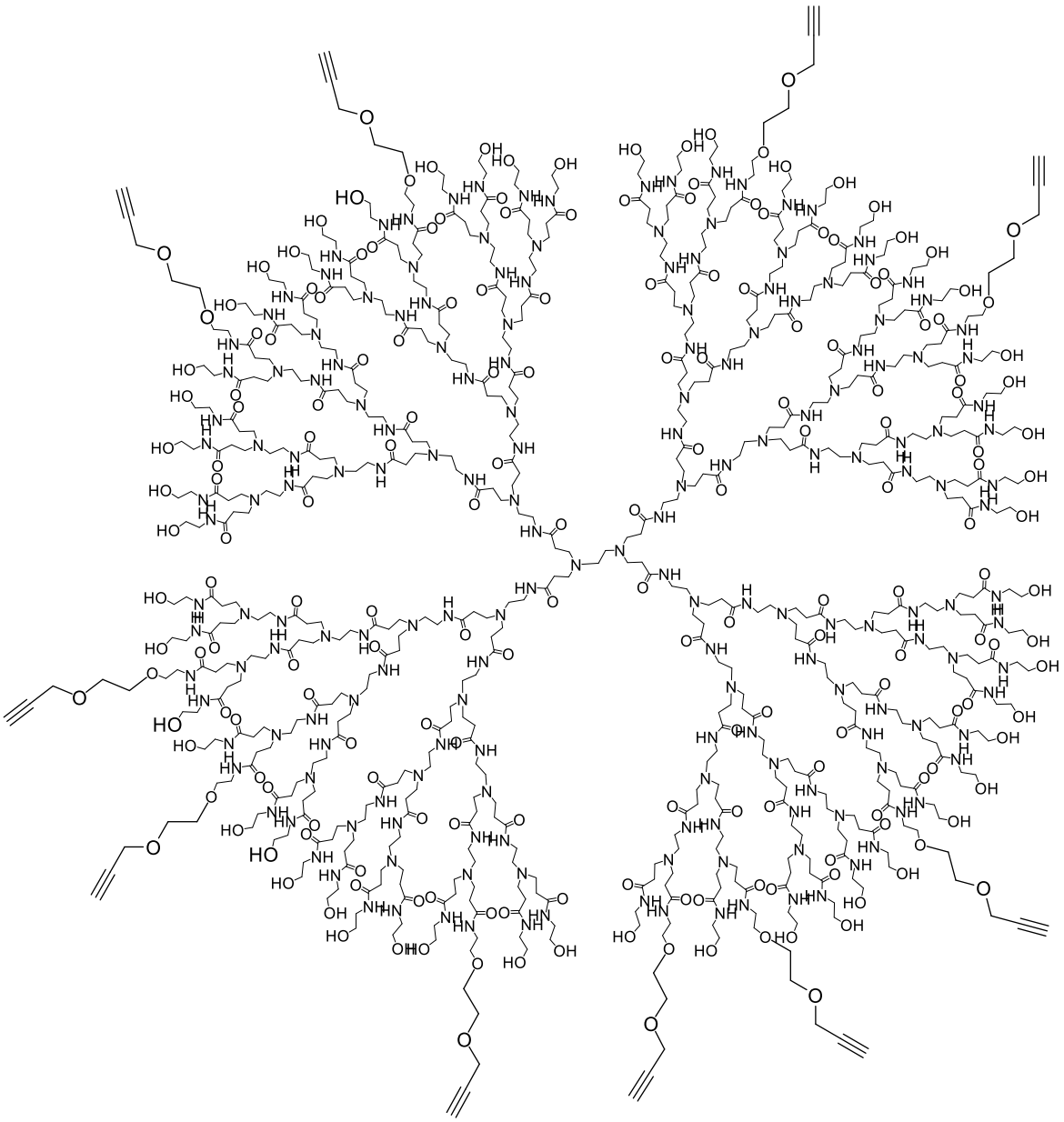
(iii) the suitable conditions comprise methanol and reacting at approximately 20 °C.

17. The method of any one of claims 8-16, wherein the functionalized dendrimer of

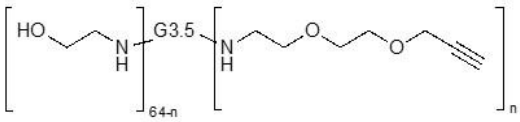
Formula (**I-A**) is of formula:



or



18. A method comprising reacting the dendrimer of the formula:

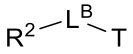


,

G3.5 is a 3.5 generation poly(amidoamine) (PAMAM) dendrimer;

n is an integer from 1 to 64, inclusive;

with a compound of Formula (**B**):



(**B**),

wherein:

R^2 is halogen, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acetyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-N_3$, $-CH(=N)(OH)R^{D1}$, -CN, $-NO_2$, $-OR^{D1}$, $-N(R^{D1a})_2$, $-SO_2OR^{D1}$, or $-SR^{D1}$, wherein R^{D1} is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom;

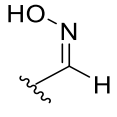
wherein each occurrence of R^{D1a} is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group; or optionally two instances of R^{D1a} are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

L^B is an alkylene linker, wherein one or more chain atoms of the hydrocarbon chain are independently replaced with amide, ester, hydroxamate, ether, carbonate, carbamate, hydrazone, thioether, thioester, disulfide, orthoester, urethane, or oxime moiety, or a cyclic moiety; and

T is a therapeutic agent.

19. The method of claim 18, wherein:

(i) R^2 is $-N_3$;

(ii) R^2 is 

;

(iii) R^2 is -SH .

20. The method of claim 18 or 19, wherein:

(i) at least one instance of T is a proteolysis targeting chimera (PROTAC) drug or a biologic therapeutic agent; optionally wherein the biologic therapeutic agent is a peptide, a nucleic acid, or an antibody, further optionally wherein the nucleic acid is an oligonucleotide, DNA, or RNA, yet further optionally wherein the RNA is siRNA; and/or

(ii) each instance of T is different.