

(51) International Patent Classification:

Not classified

(21) International Application Number:

PCT/US2024/035794

(22) International Filing Date:

27 June 2024 (27.06.2024)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/523,702

28 June 2023 (28.06.2023)

US

(71) Applicant: DANA-FARBER CANCER INSTITUTE, INC. [US/US]: 450 Brookline Avenue, Boston, Massachusetts 02215 (US).

(72) Inventors: KIM, Justin; c/o Dana-Farber Cancer Institute, Inc., 450 Brookline Avenue, Boston, Massachusetts 02215 (US). KIM, Thomas T.; c/o Dana-Farber Cancer Institute, Inc., 450 Brookline Avenue, Boston, Massachusetts 02215 (US).

(74) Agent: CLARKE, Daniel et al.; ArentFox Schiff LLP, 1717 K Street, NW, Washington, District of Columbia 20006-5344 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM,

DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

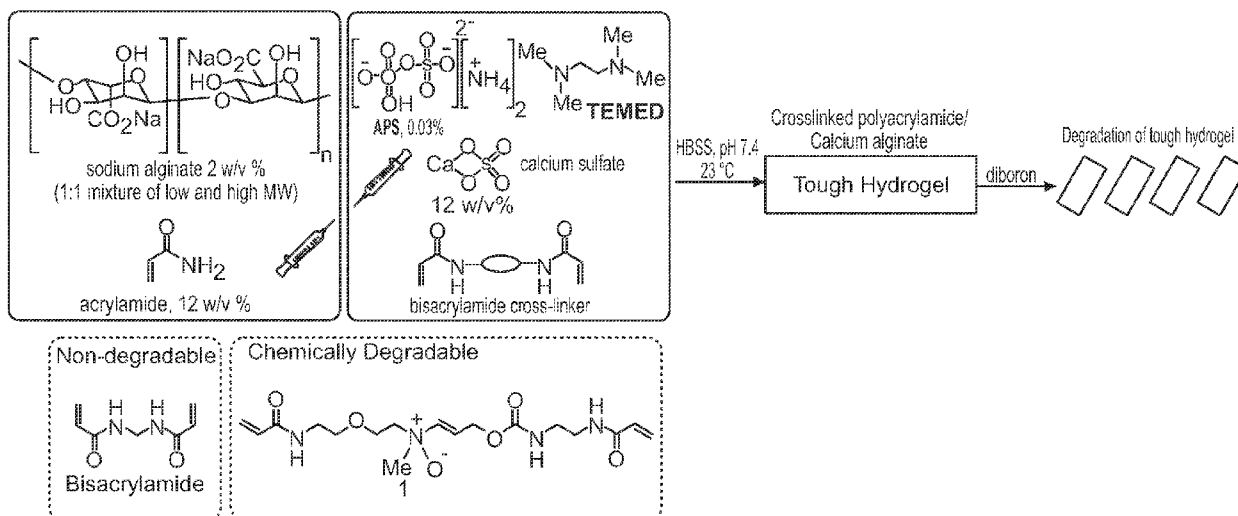
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: CHEMICALLY DEGRADABLE AND FUNCTIONALLY MODIFIABLE POLYMERS AND HYDROGELS

FIG. 2



(57) Abstract: Disclosed are degradable covalent chemical crosslinkers. Also disclosed are methods of making and using the degradable covalent chemical crosslinkers.

CHEMICALLY DEGRADABLE AND FUNCTIONALLY MODIFIABLE POLYMERS AND HYDROGELS

RELATED APPLICATIONS

[0001] This application claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No: 63/523,702, filed June 28, 2023, which is incorporated herein by reference in its entirety.

GOVERNMENT SUPPORT

[0002] This invention was made with government support under grant number DP2 ES030448 awarded by The National Institutes of Health and grant number 2238040 awarded by The National Science Foundation. The government has certain rights in the invention.

BACKGROUND OF THE DISCLOSURE

[0003] Hydrogels are cross-linked polymer networks that comprise a significant volume fraction of water but do not dissolve in water (Wichterle *et al.*, *Nature*, 185:117-118 (1960)). The large water content of these materials makes them highly deformable and enables the rapid diffusion of water-soluble molecules across their surface, making them ideally suited for applications in biology (Correa *et al.*, *Chem. Rev.*, 121:11385-11457 (2021)). Hydrogel-based biomaterials have therefore found major use in wound closure (Kamoun *et al.*, *J. Adv. Res.*, 8:217-233 (2017); Liang *et al.*, *ACS Nano* 15:12687-12722 (2021)), as tissue sealants (Lang *et al.*, *Sci. Trans. Med.*, 6:218ra6 (2014); Ferreira *et al.*, *J. Biol. Macromol.*, 40:144-152 (2007); Mehdizadeh *et al.*, *Macromol. Biosci.*, 13:271-288 (2013)), in drug delivery (Hoffman, *Adv. Drug Delivery Rev.*, 64:18-23 (2012); Blackman *et al.*, *J. Am. Chem. Soc.*, 130:13518-13519 (2008); Mejia Oneto *et al.*, *ACS Cent. Sci.*, 2:476-482 (2016)), and for cell encapsulation in three dimensional cultures (Wang *et al.*, *Adv. Mater. (Weinheim, Ger.)* 27:3717 (2015); Chaudhuri *et al.*, *Nature*, 584:535-546 (2020); Tayalia *et al.*, *Biomaterials*, 32:2634 (2011)) among many other bioengineering applications (Correa *et al.*, *Chem. Rev.*, 121:11385-11457 (2021)).

[0004] Hydrogels have been used as tough tissue adhesives. Tough adhesives are biomaterials that do not fracture under large tensile loads (Li *et al.*, *Science*, 357:378-381 (2017)). Equally strong adhesive forces enable these materials to adhere to tissues without becoming detached in the face of high shearing, tensile, or peeling forces. Materials like these

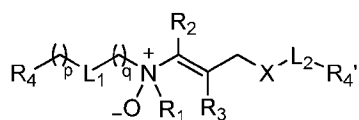
offer appealing alternatives to surgical sutures in closing wounds and sealing tissues because they are faster, are less damaging to tissues, show fewer incidence of infections, and do not require anesthesia (Li *et al.*, *Science*, 357:378-381 (2017); Rahman *et al.*, *Science Advances*, 7:eabk2451 (2021); Liu *et al.*, *Adv. Funct. Mater.*, 32:2107732 (2022)).

[0005] As tissue adhesives have become tougher and more strongly adherent, they introduce new challenges, such as their removal. Leaving them in place at the site of injury risks inflammation and tissue fibrosis, and the hydrogels may outlive their intended impact (Kyriakides, Chapter 5 - Molecular Events at Tissue–Biomaterial Interface, in *Host Response to Biomaterials*, Badylak, S. F., Ed. Academic Press: Oxford, 2015; pp 81; Padmanabhan *et al.*, *WIREs Nanomed. Nanobiotechnol.*, 7:355-370 (2015); Onuki *et al.*, *J. Diabetes Sci. Technol.*, 2:1003-1015 (2008)); however, the act of removing tissue adhesives is a well-known cause of secondary tissue injuries.

SUMMARY OF DISCLOSURE

[0006] The current disclosure solves the problems mentioned above by producing polymers and tough polyacrylamide hydrogels that are susceptible to diboron-mediated degradation.

[0007] A first aspect of the present disclosure is directed to a compound represented by formula I:



(I), or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

p is 0 or 1;

q is 0 or 1;

R₁ is (C₁-C₈) alkyl, (C₃-C₁₀) carbocyclyl, or 4- to 10-membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S, wherein said alkyl, carbocyclyl or heterocyclyl is further optionally substituted, or

R₁ and R₂, together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl, or

R₁ and R₃, together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl;

R₂ is hydrogen, (C₁-C₈) alkyl, chloro, bromo, or iodo;

R₃ is hydrogen, (C₁-C₈) alkyl, chloro, bromo, or iodo;

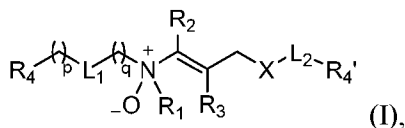
L₁ is absent or a linker;

L₂ is absent or a linker;

X is a leaving group; and

R₄ and R₄' are independently a polymerizable moiety or a chemical moiety, provided that at least one of R₄ and R₄' is a polymerizable moiety.

[0008] Another aspect of the present disclosure is directed to modifiable polymers/hydrogels which are the reaction product of:

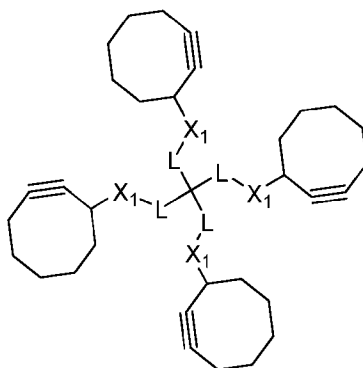


i) a compound of formula I:

ii) a polymerizable moiety, and

iii) an initiator.

[0009] Other aspects of the present disclosure are directed to modifiable polymers/hydrogels which are the reaction product of:



i) a 4-arm-cyclooct-2-yn-1-yl,

; and

ii) a dihydroxylamine, $\begin{matrix} R_5 & & R_5 \\ | & & | \\ N & -L- & N \\ | & & | \\ OH & & OH \end{matrix}$,

wherein:

each X₁ is a leaving group;

each L is a linker; and

each R₅ is (C₁-C₈) alkyl, (C₃-C₁₀) carbocyclyl, or 4- to 10-membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S, wherein said alkyl, carbocyclyl or heterocyclyl is further optionally substituted.

[0010] Further aspects of the present disclosure are directed to methods of degrading hydrogels. The methods entail contacting the hydrogel with a diboron reagent.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] FIG. 1 is a series of images of synthesized and diboron-mediated degraded polyacrylamide hydrogels.

[0012] FIG. 2 is a schematic showing the synthesis and diboron-mediated degradation of polyacrylamide/calcium alginate tough hydrogels.

[0013] FIG. 3A-FIG. 3B are a series of images of synthesized polyacrylamide gels. FIG. 3A is a series of images of synthesized polyacrylamide gels with a varying percentage of cross-linker (0.03 to 0.3 w/v%). FIG. 3B is a series of images of synthesized polyacrylamide gels (0.12 w/v%) showing stretch loading and unloading.

[0014] FIG. 4 is a series of images of synthesized and diboron-mediated degraded tough hydrogels.

[0015] FIG. 5A-FIG. 5C are a series of images of synthesized and diboron-mediated degraded tough hydrogels. FIG. 5A is a series of pre-gelation images. FIG. 5B is a series of post-gelation images. FIG. 5C is a series of images showing diboron-mediated degradation of hydrogels.

[0016] FIG. 6A-FIG. 6C are a series of images of synthesized and diboron-mediated degraded tough hydrogels. FIG. 6A is a series of pre-gelation images. FIG. 6B is a series of post-gelation images. FIG. 6C is a series of images showing diboron-mediated degradation of hydrogels.

DETAILED DESCRIPTION

[0017] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the subject matter herein belongs. As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated in order to facilitate the understanding of the present disclosure.

[0018] As used in the description and the appended claims, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise. Therefore, for example, reference to “a composition” includes mixtures of two or more such compositions, reference to “an inhibitor” includes mixtures of two or more such inhibitors, and the like.

[0019] Unless stated otherwise, the term “about” means within 10% (*e.g.*, within 5%, 2%, or 1%) of the particular value modified by the term “about.”

[0020] The transitional term “comprising,” which is synonymous with “including,” “containing,” or “characterized by,” is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. When used in the context of the number of heteroatoms in a heterocyclic structure, it means that the heterocyclic group that that minimum number of heteroatoms. By contrast, the transitional phrase “consisting of” excludes any element, step, or ingredient not specified in the claim. The transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the disclosure.

[0021] With respect to compounds of the present disclosure, and to the extent the following terms are used herein to further describe them, the following definitions apply.

[0022] As used herein, the term “alkyl” refers to a saturated linear or branched-chain monovalent hydrocarbon radical. In some embodiments, the alkyl radical is a C₁-C₆ group. In some embodiments, and to the extent not disclosed otherwise for any one or more groups of the compounds of formula (I or II) or the hydrogels disclosed herein, the alkyl radical is a C₀-C₆, C₀-C₅, C₀-C₃, C₁-C₆, C₁-C₅, C₁-C₄ or C₁-C₃ group (wherein C₀ alkyl refers to a bond). Examples of alkyl groups include methyl, ethyl, 1-propyl, 2-propyl, i-propyl, 1-butyl, 2-methyl-1-propyl, 2-butyl, 2-methyl-2-propyl, 1-pentyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl, and 3,3-dimethyl-2-butyl. In some embodiments, an alkyl group is a C₁-C₃ alkyl group. In some embodiments, an alkyl group is a C₁-C₂ alkyl group. In some embodiments, an alkyl group is a methyl group.

[0023] As used herein, the term “alkylene” refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to six carbon atoms, for example, methylene, ethylene, propylene, n-butylene, and the like. The alkylene chain may be attached to the rest of the molecule through a single bond and to the radical group through a single bond. In some embodiments, and to the extent not disclosed otherwise for any one or more groups of the compounds of formula (I or II) or the hydrogels disclosed herein, an alkylene group contains one to four carbon atoms (C₁-C₄ alkylene). In other embodiments, an alkylene contains one to three carbon atoms (C₁-C₃ alkylene). In other embodiments, an alkylene group contains one to two carbon atoms (C₁-C₂ alkylene). In other embodiments, an alkylene group contains one carbon atom (C₁ alkylene).

[0024] As used herein, the term "alkenyl" refers to a linear or branched-chain monovalent hydrocarbon radical with at least one carbon-carbon double bond. An alkenyl includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. In some embodiments, the alkenyl radical is a C₂-C₁₅ group. In some embodiments, and to the extent not disclosed otherwise for any one or more groups of the compounds of formula (I or II) or the hydrogels disclosed herein, the alkenyl radical is a C₂-C₁₂, C₂-C₁₀, C₂-C₈, C₂-C₆ or C₂-C₃ group. Examples include ethenyl or vinyl, prop-1-enyl, prop-2-enyl, 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-diene, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl and hexa-1,3-dienyl.

[0025] As used herein, the term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical with at least one carbon-carbon triple bond. In some embodiments, the alkynyl radical is a C₂-C₁₅ group. In some embodiments, and to the extent not disclosed otherwise for any one or more groups of the compounds of formula (I or II) or the hydrogels disclosed herein, the alkynyl radical is C₂-C₁₂, C₂-C₁₀, C₂-C₈, C₂-C₆ or C₂-C₃. Examples include ethynyl prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl and but-3-ynyl.

[0026] The terms "alkoxyl" or "alkoxy" as used herein refer to an alkyl group, as defined above, having an oxygen radical attached thereto, and which is the point of attachment. In some embodiments, the alkoxyl group is methoxy, ethoxy, propyloxy, or tert-butoxy. An "ether" is two hydrocarbonyl groups covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as can be represented by one of -O-alkyl, -O-alkenyl, and -O-alkynyl.

[0027] As used herein, the term "halogen" (or "halo" or "halide") refers to fluorine, chlorine, bromine, or iodine.

[0028] As used herein, the term "cyclic group" refers to any group that used alone or as part of a larger moiety, contains a saturated, partially saturated or aromatic ring system *e.g.*, carbocyclic (cycloalkyl, cycloalkenyl), heterocyclic (heterocycloalkyl, heterocycloalkenyl), aryl and heteroaryl groups. Cyclic groups may have one or more (*e.g.*, fused) ring systems. Therefore, for example, a cyclic group can contain one or more carbocyclic, heterocyclic, aryl or heteroaryl groups.

[0029] As used herein, the term "carbocyclic" (also "carbocyclyl") refers to a group that used alone or as part of a larger moiety, contains a saturated, partially unsaturated, or aromatic ring system having 3 to 12 carbon atoms, that is alone or part of a larger moiety (*e.g.*, an alkcarbocyclic group). The term carbocyclyl includes mono-, bi-, tri-, fused, bridged,

and spiro-ring systems, and combinations thereof. In one embodiment, carbocyclyl includes 3 to 10 carbon atoms (C₃-C₁₀). In one embodiment, carbocyclyl includes 3 to 6 carbon atoms (C₃-C₆). In one embodiment, carbocyclyl includes 5 to 6 carbon atoms (C₅-C₆). In some embodiments, carbocyclyl, as a bicycle, includes C₆-C₁₀. In another embodiment, carbocyclyl, as a spiro system, includes C₅-C₁₁. Representative examples of monocyclic carbocyclyls include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and phenyl; bicyclic carbocyclyls having 7 to 11 ring atoms include [4,3], [4,4], [4,5], [5,5], [5,6] or [6,6] ring systems, such as for example bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, naphthalene, and bicyclo[3.2.2]nonane. Representative examples of spiro carbocyclyls include spiro[2.2]pentane, spiro[2.3]hexane, spiro[2.4]heptane, spiro[2.5]octane and spiro[4.5]decane. The term carbocyclyl includes aryl ring systems as defined herein. The term carbocyclyl also includes cycloalkyl rings (*e.g.*, saturated or partially unsaturated mono-, bi-, or spiro-carbocycles). The term carbocyclic group also includes a carbocyclic ring fused to one or more (*e.g.*, 1, 2 or 3) different cyclic groups (*e.g.*, aryl or heterocyclic rings), where the radical or point of attachment is on the carbocyclic ring.

[0030] Therefore, the term carbocyclic also embraces carbocyclylalkyl groups which as used herein refer to a group of the formula --R^c-carbocyclyl where R^c is an alkylene chain. The term carbocyclic also embraces carbocyclylalkoxy groups which as used herein refer to a group bonded through an oxygen atom of the formula --O--R^c-carbocyclyl where R^c is an alkylene chain.

[0031] As used herein, the term "aryl" used alone or as part of a larger moiety (*e.g.*, "aralkyl", wherein the terminal carbon atom on the alkyl group is the point of attachment, *e.g.*, a benzyl group), "aralkoxy" wherein the oxygen atom is the point of attachment, or "aroxyalkyl" wherein the point of attachment is on the aryl group) refers to a group that includes monocyclic, bicyclic or tricyclic, carbon ring system, that includes fused rings, wherein at least one ring in the system is aromatic. In some embodiments, the aralkoxy group is a benzoxy group. The term "aryl" may be used interchangeably with the term "aryl ring". In one embodiment, aryl includes groups having 6-12 carbon atoms. In another embodiment, aryl includes groups having 6-10 carbon atoms. Examples of aryl groups include phenyl, naphthyl, biphenyl, 1,2,3,4-tetrahydronaphthalenyl, and the like, which may be substituted or independently substituted by one or more substituents described herein. A particular aryl is

phenyl. In some embodiments, an aryl group includes an aryl ring fused to one or more (*e.g.*, 1, 2 or 3) different cyclic groups (*e.g.*, carbocyclic rings or heterocyclic rings), where the radical or point of attachment is on the aryl ring.

[0032] Therefore, the term aryl embraces aralkyl groups (*e.g.*, benzyl) which as disclosed above refer to a group of the formula --R^c-aryl where R^c is an alkylene chain such as methylene or ethylene. In some embodiments, the aralkyl group is an optionally substituted benzyl group. The term aryl also embraces aralkoxy groups which as used herein refer to a group bonded through an oxygen atom of the formula --O—R^c--aryl where R^c is an alkylene chain such as methylene or ethylene.

[0033] As used herein, the term "heterocyclyl" refers to a "carbocyclyl" that used alone or as part of a larger moiety, contains a saturated, partially unsaturated or aromatic ring system, wherein one or more (*e.g.*, 1, 2, 3, 4, or 5) carbon atoms have been replaced with a heteroatom or heteroatom-containing group (*e.g.*, O, N, N(O), S, S(O), or S(O)₂). The term heterocyclyl includes mono-, bi-, tri-, fused, bridged, and spiro-ring systems, and combinations thereof. In some embodiments, a heterocyclyl refers to a 3- to 12-membered heterocyclyl ring system. In some embodiments, a heterocyclyl refers to a saturated ring system, such as a 3- to 12-membered saturated heterocyclyl ring system. In some embodiments, a heterocyclyl refers to a heteroaryl ring system, such as a 5- to 12-membered heteroaryl ring system. The term heterocyclyl also includes C₂-C₈ heterocycloalkyl, which is a saturated or partially unsaturated mono-, bi-, or spiro-ring system containing 2-8 carbons and one or more (*e.g.*, 1, 2, or 3) heteroatoms.

[0034] In some embodiments, a heterocyclyl group includes 3-12 ring atoms and includes monocycles, bicycles, tricycles and spiro ring systems, wherein the ring atoms are carbon, and one to 5 ring atoms is a heteroatom such as nitrogen, sulfur or oxygen. In some embodiments, heterocyclyl includes 3- to 7-membered monocycles having one or more heteroatoms selected from O, N, and S. In some embodiments, heterocyclyl includes 4- to 6-membered monocycles having one or more heteroatoms selected from O, N, and S. In some embodiments, heterocyclyl includes 3-membered monocycles. In some embodiments, heterocyclyl includes 4-membered monocycles. In some embodiments, heterocyclyl includes 5- to 6-membered monocycles. In some embodiments, the heterocyclyl group includes 0 to 3 double bonds. In any of the foregoing embodiments, heterocyclyl includes 1, 2, 3 or 4 heteroatoms. Any nitrogen or sulfur heteroatom may optionally be oxidized (*e.g.*, NO, SO, SO₂), and any nitrogen heteroatom may optionally be substituted (*e.g.*, methyl, isopropyl)

and/or quaternized (*e.g.*, $[\text{NR}_4]^+\text{Cl}^-$, $[\text{NR}_4]^+\text{OH}^-$). Representative examples of heterocyclyls include oxiranyl, aziridinyl, thiranyl, azetidiny, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, pyrrolidinyl, dihydro-1H-pyrrolyl, dihydrofuranyl, tetrahydropyranyl, dihydrothienyl, tetrahydrothienyl, imidazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, dihydropyranyl, tetrahydropyranyl, hexahydrothiopyranyl, hexahydropyrimidinyl, oxazinanyl, thiazinanyl, thioxanyl, homopiperazinyl, homopiperidinyl, azepanyl, oxepanyl, thiepanyl, oxazepinyl, oxazepanyl, diazepanyl, 1,4-diazepanyl, diazepinyl, thiazepinyl, thiazepanyl, tetrahydrothiopyranyl, oxazolidinyl, thiazolidinyl, isothiazolidinyl, 1,1-dioxoisothiazolidinonyl, oxazolidinonyl, imidazolidinonyl, 4,5,6,7-tetrahydro[2H]indazolyl, tetrahydrobenzoimidazolyl, 4,5,6,7-tetrahydrobenzo[d]imidazolyl, 1,6-dihydroimidazol[4,5-d]pyrrolo[2,3-b]pyridinyl, thiazinyl, thiophenyl, oxazinyl, thiadiazinyl, oxadiazinyl, dithiazinyl, dioxazinyl, oxathiazinyl, thiatriazinyl, oxatriazinyl, dithiadiazinyl, imidazolinyl, dihydropyrimidyl, tetrahydropyrimidyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, thiapyranyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrimidinonyl, pyrimidindionyl, pyrimidin-2,4-dionyl, piperazinonyl, piperazindionyl, pyrazolidinylimidazolinyl, 3-azabicyclo[3.1.0]hexanyl, 3,6-diazabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 2-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, 2-azabicyclo[2.2.2]octanyl, 8-azabicyclo[2.2.2]octanyl, 7-oxabicyclo[2.2.1]heptane, azaspiro[3.5]nonanyl, azaspiro[2.5]octanyl, azaspiro[4.5]decanyl, 1-azaspiro[4.5]decan-2-onyl, azaspiro[5.5]undecanyl, tetrahydroindolyl, octahydroindolyl, tetrahydroisindolyl, tetrahydroindazolyl, 1,1-dioxohexahydrothiopyranyl. Examples of 5-membered heterocyclyls containing a sulfur or oxygen atom and one to three nitrogen atoms are thiazolyl (*e.g.*, thiazol-2-yl), thiadiazolyl (*e.g.*, 1,3,4-thiadiazol-5-yl and 1,2,4-thiadiazol-5-yl), oxazolyl (*e.g.*, oxazol-2-yl), and oxadiazolyl (*e.g.*, 1,3,4-oxadiazol-5-yl and 1,2,4-oxadiazol-5-yl). Example of 5-membered heterocyclyls containing 2 to 4 nitrogen atoms include imidazolyl (*e.g.*, imidazol-2-yl), triazolyl (*e.g.*, 1,3,4-triazol-5-yl, 1,2,3-triazol-5-yl, and 1,2,4-triazol-5-yl), and tetrazolyl (*e.g.*, 1H-tetrazol-5-yl). Representative examples of benzo-fused 5-membered heterocyclyls include benzoxazol-2-yl, benzthiazol-2-yl and benzimidazol-2-yl. Example of 6-membered heterocyclyls containing one to three nitrogen atoms and optionally a sulfur or oxygen atom are pyridyl (*e.g.*, pyrid-2-yl, pyrid-3-yl, and pyrid-4-yl), pyrimidyl (*e.g.*, pyrimid-2-yl and pyrimid-4-yl), triazinyl (*e.g.*, 1,3,4-triazin-2-yl

and 1,3,5-triazin-4-yl), pyridazinyl (*e.g.*, pyridazin-3-yl), and pyrazinyl. In some embodiments, a heterocyclic group includes a heterocyclic ring fused to one or more (*e.g.*, 1 or 2) different cyclic groups (*e.g.*, carbocyclic rings or heterocyclic rings), where the radical or point of attachment is on the heterocyclic ring, and in some embodiments wherein the point of attachment is a heteroatom contained in the heterocyclic ring.

[0035] Therefore, the term heterocyclic embraces N-heterocyclyl groups which as used herein refer to a heterocyclyl group containing at least one nitrogen atom and where the point of attachment of the heterocyclyl group to the rest of the molecule is through a nitrogen atom in the heterocyclyl group. Representative examples of N-heterocyclyl groups include 1-morpholinyl, 1-piperidinyl, 1-piperazinyl, 1-pyrrolidinyl, 1-pyrazolidinyl, 1-imidazolinyl and 1-imidazolidinyl. The term heterocyclic also embraces C-heterocyclyl groups which as used herein refer to a heterocyclyl group containing at least one heteroatom and where the point of attachment of the heterocyclyl group to the rest of the molecule is through a carbon atom in the heterocyclyl group. Representative examples of C-heterocyclyl radicals include 2- or 3-morpholinyl, 2- or 3- or 4-piperidinyl, 2-piperazinyl, and 2- or 3-pyrrolidinyl. The term heterocyclic also embraces heterocyclylalkyl groups which as disclosed above refer to a group of the formula --R^c-heterocyclyl where R^c is an alkylene chain. The term heterocyclic also embraces heterocyclylalkoxy groups which as used herein refer to a radical bonded through an oxygen atom of the formula --O--R^c-heterocyclyl where R^c is an alkylene chain.

[0036] As used herein, the term "heteroaryl" used alone or as part of a larger moiety (*e.g.*, "heteroarylalkyl" (also "heteroaralkyl"), or "heteroarylalkoxy" (also "heteroaralkoxy")) refers to a monocyclic, bicyclic or tricyclic ring system having 5 to 12 ring atoms, wherein at least one ring is aromatic and contains at least one heteroatom. In one embodiment, heteroaryl includes 5- to 6- membered monocyclic aromatic groups where one or more ring atoms is O, N, or S. Representative examples of heteroaryl groups include thienyl, furyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, thiatriazolyl, oxatriazolyl, pyridyl, pyrimidyl, imidazopyridyl, pyrazinyl, pyridazinyl, triazinyl, tetrazinyl, tetrazolo[1,5-b]pyridazinyl, purinyl, deazapurinyl, benzoxazolyl, benzofuryl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl, benzoimidazolyl, indolyl, 1,3-thiazol-2-yl, 1,3,4-triazol-5-yl, 1,3-oxazol-2-yl, 1,3,4-oxadiazol-5-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 1H-tetrazol-5-yl, and 1,2,3-triazol-5-yl. The term "heteroaryl" also includes groups in which a heteroaryl is fused to one or more cyclic (*e.g.*, carbocyclyl, or heterocyclyl) rings, where the radical or point of

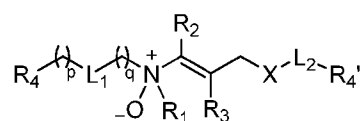
attachment is on the heteroaryl ring. Nonlimiting examples include indolyl, indoliziny, isoindolyl, benzothienyl, benzothiophenyl, methylenedioxyphenyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzodioxazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H-quinoliziny, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolyl, tetrahydroisoquinolyl and pyrido[2,3-b]-1,4-oxazin-3(4H)-one. A heteroaryl group may be mono-, bi- or tri-cyclic. In some embodiments, a heteroaryl group includes a heteroaryl ring fused to one or more (*e.g.*, 1 or 2) different cyclic groups (*e.g.*, carbocyclic rings or heterocyclic rings), where the radical or point of attachment is on the heteroaryl ring, and in some embodiments wherein the point of attachment is a heteroatom contained in the heterocyclic ring.

[0037] Therefore, the term heteroaryl embraces N-heteroaryl groups which as used herein refer to a heteroaryl group as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl group to the rest of the molecule is through a nitrogen atom in the heteroaryl group. The term heteroaryl also embraces C-heteroaryl groups which as used herein refer to a heteroaryl group as defined above and where the point of attachment of the heteroaryl group to the rest of the molecule is through a carbon atom in the heteroaryl group. The term heteroaryl also embraces heteroarylalkyl groups which as disclosed above refer to a group of the formula --R^c-heteroaryl, wherein R^c is an alkylene chain as defined above. The term heteroaryl also embraces heteroaralkoxy (or heteroarylalkoxy) groups which as used herein refer to a group bonded through an oxygen atom of the formula --O--R^c-heteroaryl, where R^c is an alkylene group as defined above.

[0038] Unless stated otherwise, and to the extent not further defined for any particular group(s) in the compounds of formula (I or II) or the hydrogels disclosed herein, any of the groups described herein may be substituted or unsubstituted. To the extent not disclosed otherwise for any particular group(s), representative examples of substituents may include alkyl (*e.g.*, C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂, C₁), substituted alkyl (*e.g.*, substituted C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂, C₁), alkoxy (*e.g.*, C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂, C₁), substituted alkoxy (*e.g.*, substituted C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂, C₁), haloalkyl (*e.g.*, CF₃), alkenyl (*e.g.*, C₂-C₆, C₂-C₅, C₂-C₄, C₂-C₃, C₂), substituted alkenyl (*e.g.*, substituted C₂-C₆, C₂-C₅, C₂-C₄, C₂-C₃, C₂), alkynyl (*e.g.*, C₂-C₆, C₂-C₅, C₂-C₄, C₂-C₃, C₂), substituted alkynyl (*e.g.*, substituted C₂-C₆, C₂-C₅, C₂-C₄, C₂-C₃, C₂), cyclic (*e.g.*, C₃-C₁₂, C₅-C₆), substituted cyclic (*e.g.*, substituted C₃-C₁₂, C₅-C₆), carbocyclic (*e.g.*, C₃-C₁₂, C₅-C₆),

substituted carbocyclic (*e.g.*, substituted C₃-C₁₂, C₅-C₆), heterocyclic (*e.g.*, 3- to 12-membered, 5-to 6-membered), substituted heterocyclic (*e.g.*, substituted 3- to 12-membered, 5-to 6-membered), aryl (*e.g.*, benzyl and phenyl), substituted aryl (*e.g.*, substituted benzyl or substituted phenyl), heteroaryl (*e.g.*, pyridyl or pyrimidyl), substituted heteroaryl (*e.g.*, substituted pyridyl or substituted pyrimidyl), aralkyl (*e.g.*, benzyl), substituted aralkyl (*e.g.*, substituted benzyl), halo, hydroxyl, aryloxy (*e.g.*, C₆-C₁₂, C₆), substituted aryloxy (*e.g.*, substituted C₆-C₁₂, C₆), alkylthio (*e.g.*, C₁-C₆), substituted alkylthio (*e.g.*, substituted C₁-C₆), arylthio (*e.g.*, C₆-C₁₂, C₆), substituted arylthio (*e.g.*, substituted C₆-C₁₂, C₆), cyano, carbonyl, substituted carbonyl, carboxyl, substituted carboxyl, amino, substituted amino, amido, substituted amido, thio, substituted thio, sulfinyl, substituted sulfinyl, sulfonyl, substituted sulfonyl, sulfonamide, substituted sulfonamide, sulfonamide, substituted sulfonamide, urea, substituted urea, carbamate, substituted carbamate, amino acid, and peptide groups. Terminal substituents, unless otherwise stated, may include C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, hydroxyl, cyano or amino.

[0039] In one aspect, compounds of the disclosure are represented by formula I:



(I), or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

p is 0 or 1;

q is 0 or 1;

R₁ is (C₁-C₈) alkyl, (C₃-C₁₀) carbocyclyl, or 4- to 10-membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S, wherein said alkyl, carbocyclyl or heterocyclyl is further optionally substituted, or

R₁ and R₂, together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl, or

R₁ and R₃, together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl;

R₂ is hydrogen, (C₁-C₈) alkyl, chloro, bromo, or iodo;

R₃ is hydrogen, (C₁-C₈) alkyl, chloro, bromo, or iodo;

L₁ is absent or a linker;

L₂ is absent or a linker;

X is a leaving group; and

R₄ and R₄' are independently a polymerizable moiety or a chemical moiety,

provided that at least one of R₄ and R₄' is a polymerizable moiety.

[0040] In some embodiments, L₁ is absent.

[0041] In some embodiments, L₂ is absent.

[0042] In some embodiments, L₁ is a linker.

[0043] In some embodiments, L₂ is a linker.

[0044] The linker provides a covalent attachment between the two atoms to which the linker is bound, and which is nonreactive with the other groups in the compound.

[0045] In some embodiments, the linker is an alkylene chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of -O-, -S-, -N(R')-, -C≡C-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(NOR')-, -C(O)N(R')-, -C(O)N(R')C(O)-, -R'C(O)N(R')R', -C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(Me)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, -N(R')S(O)N(R')-, -OP(O)O(R')O-, -N(R')P(O)N(R'R')N(R')-, C₃-C₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C₁-C₂₄ alkyl, wherein the interrupting and the one or both terminating groups may be the same or different.

[0046] In some embodiments, the alkylene chain is a C₁-C₂₄ alkylene chain. In some embodiments, the alkylene chain is a C₁-C₁₈ alkylene chain. In some embodiments, the alkylene chain is a C₁-C₁₂ alkylene chain. In some embodiments, the alkylene chain is a C₁-C₁₀ alkylene chain. In some embodiments, the alkylene chain is a C₁-C₈ alkylene chain. In some embodiments, the alkylene chain is a C₁-C₆ alkylene chain. In some embodiments, the alkylene chain is a C₁-C₄ alkylene chain. In some embodiments, the alkylene chain is a C₁-C₂ alkylene chain. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) in at least one of -N(R')-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)O-, -OC(O)N(R')-, -S(O)₂-, -N(R')S(O)₂-, -S(O)₂N(R')-, 4- to 6-membered heterocyclyl, or a combination thereof. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with -N(R')-. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with -C(O)-. In some embodiments, the alkylene chain

is interrupted by, and/or terminates (at either or both termini) with $-C(O)O-$. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with $-C(O)N(R')-$. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with $-N(R')S(O)_2-$. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with a 4- to 6-membered heterocyclyl.

[0047] In some embodiments, the linker is a polyethylene glycol chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of $-O-$, $-S-$, $-N(R')-$, $-C\equiv C-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(NOR')-$, $-C(O)N(R')-$, $-C(O)N(R')C(O)-$, $-R'C(O)N(R')R'-$, $-C(O)N(R')C(O)N(R')-$, $-N(R')C(O)-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-OC(O)N(R')-$, $-C(NR')-$, $-N(R')C(NR')-$, $-C(NR')N(R')-$, $-N(R')C(NR')N(R')-$, $-OB(Me)O-$, $-S(O)_2-$, $-OS(O)-$, $-S(O)O-$, $-S(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R')S(O)_2-$, $-S(O)_2N(R')-$, $-N(R')S(O)-$, $-S(O)N(R')-$, $-N(R')S(O)_2N(R')-$, $-N(R')S(O)N(R')-$, $-OP(O)O(R')O-$, $-N(R')P(O)N(R')N(R')-$, C_3-C_{12} carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C_1-C_{24} alkyl, wherein the interrupting and the one or both terminating groups may be the same or different.

[0048] In some embodiments, the polyethylene glycol chain has 1 to 20 $-(CH_2CH_2O)-$ units. In some embodiments, the polyethylene glycol chain has 1 to 15 $-(CH_2CH_2O)-$ units. In some embodiments, the polyethylene glycol chain has 1 to 10 $-(CH_2CH_2O)-$ units. In some embodiments, the polyethylene glycol chain has 1 to 6 $-(CH_2CH_2O)-$ units. In some embodiments, the polyethylene glycol chain has 1 to 2 $-(CH_2CH_2O)-$ units. In some embodiments, the polyethylene glycol is interrupted by, and/or terminates (at either or both termini) in at least one of $-N(R')-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-C(O)N(R')-$, $-N(R')C(O)-$, $-N(R')C(O)O-$, $-OC(O)N(R')-$, $-S(O)_2-$, $-N(R')S(O)_2-$, $-S(O)_2N(R')-$, 4- to 6-membered heterocyclyl, or a combination thereof. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with $-N(R')-$. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with $-C(O)-$. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with $-C(O)O-$. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with $-C(O)N(R')-$. In some embodiments, the polyethylene glycol chain is

interrupted by, and/or terminates (at either or both termini) with $-N(R')S(O)_2-$. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with 4- to 6-membered heterocyclyl.

[0049] In some embodiments, R_1 is (C_1-C_8) alkyl, (C_3-C_{10}) carbocyclyl, or 4- to 10-membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S, wherein said alkyl, carbocyclyl or heterocyclyl is further optionally substituted. In some embodiments, R_1 is (C_1-C_8) alkyl. In some embodiments, R_1 is methyl.

[0050] In some embodiments, R_1 and R_2 , together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl.

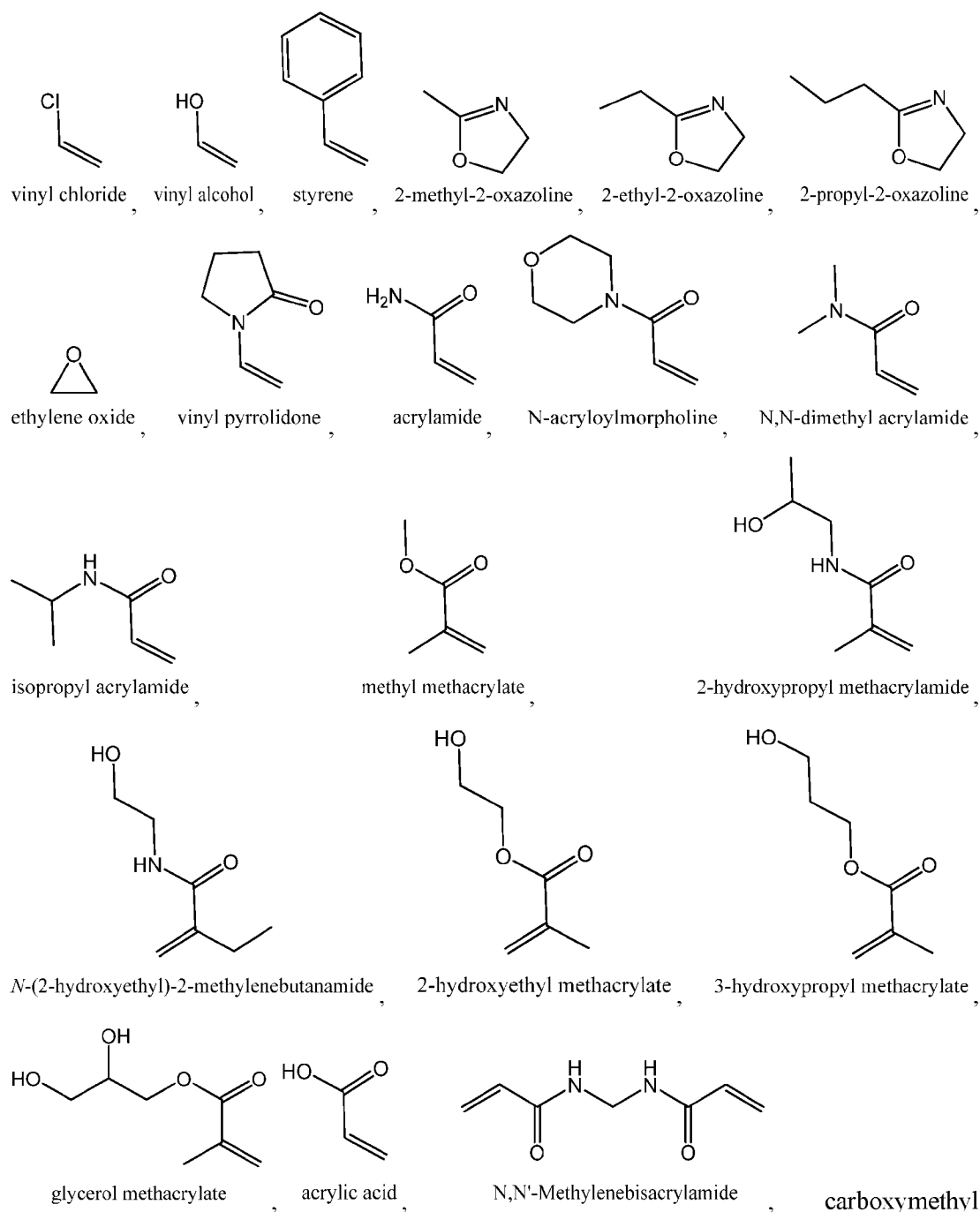
[0051] In some embodiments, R_1 and R_3 , together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl.

[0052] In some embodiments, R_2 is hydrogen. In some embodiments, R_2 is methyl. In some embodiments, R_2 is chloro. In some embodiments, R_2 is bromo. In some embodiments, R_2 is iodo.

[0053] In some embodiments, R_3 is hydrogen. In some embodiments, R_3 is methyl. In some embodiments, R_3 is chloro. In some embodiments, R_3 is bromo. In some embodiments, R_3 is iodo.

[0054] In some embodiments, X is a leaving group, which as known in the art refers to an atom or group of atoms which breaks away from the rest of the molecule, taking with it the electron pair which used to be the bond between the leaving group and the rest of the molecule. Representative examples of leaving groups include esters, carbonates, carbamates, sulfoxides, sulfonates, sulfates, sulfones, thioesters, and thionoesters. In some embodiments, the leaving group is OR_9 , SR_9 , $-OC(O)R_9$, $-OC(O)OR_9$, $-OC(O)NR_9R_9$, $-OC(S)R_9$, $-OC(S)OR_9$, $-OC(S)NR_9R_9$, $-OS(O)_2R_9$, $-OS(O)_2OR_9$, $-OP(O)OR_9OR_9$, $-OP(O)R_9R_9$, $-SC(O)R_9$, $-SC(O)SR_9$, or $-SC(S)SR_9$, wherein each R_9 is independently hydrogen, (C_1-C_6) alkyl, (C_3-C_{10}) carbocyclyl, or 4- to 7-membered heterocyclyl, wherein said alkyl, carbocyclyl, or heterocyclyl is optionally substituted.

[0055] As known in the art, polymerizable moieties refer to a molecule that reacts with another molecule, which may be the same or different, to form a polymer and a co-polymer, respectively. Representative examples of polymerizable moieties that may be suitable for use in preparing the disclosed polymers/hydrogels include:



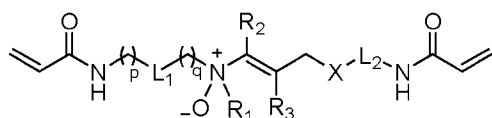
cellulose, hydroxypropyl methyl cellulose, and hydroxyethyl cellulose.

[0056] In some embodiments, R_4 and R_4' are a polymerizable moiety. In some embodiments, R_4 and R_4' are acrylamide.

[0057] In some embodiments, R_4 is a polymerizable moiety and R_4' is a chemical moiety. In some embodiments, R_4 is a chemical moiety and R_4' is a polymerizable moiety. In some

embodiments, the chemical moiety is a carboxylic acid, amine, sulfonic acid, phenol, catechol, a metal chelator, a PEG chain, or a drug molecule.

[0058] In some embodiments, the compound of formula I is of formula Ia:

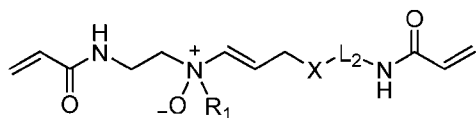


(Ia), or a pharmaceutically acceptable salt or

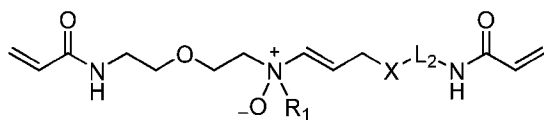
stereoisomer thereof.

[0059] In some embodiments, the optional substituent for a compound of formula I is independently alkyl, alkenyl, alkynyl, halo, haloalkyl, cycloalkyl, heterocycloalkyl, hydroxy, alkoxy, cycloalkoxy, heterocycloalkoxy, haloalkoxy, aryloxy, heteroaryloxy, aralkyloxy, alkylenyloxy, alkynyloxy, amino, alkylamino, cycloalkylamino, heterocycloalkylamino, arylamino, heteroarylamino, aralkylamino, N-alkyl-N-arylamine, N-alkyl-N-heteroarylamine, N-alkyl-N-aralkylamine, hydroxyalkyl, aminoalkyl, alkylthio, haloalkylthio, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocycloalkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aminosulfonyl, alkylaminosulfonyl, cycloalkylaminosulfonyl, heterocycloalkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, N-alkyl-N-arylaminosulfonyl, N-alkyl-N-heteroarylaminosulfonyl, formyl, alkylcarbonyl, haloalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxy carbonyl, alkylcarbonyloxy, amino, alkylsulfonylamino, haloalkylsulfonylamino, cycloalkylsulfonylamino, heterocycloalkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, aralkylsulfonylamino, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, aralkylsulfonylamino, aminocarbonyl, alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, N-alkyl-N-heteroarylaminocarbonyl, cyano, nitro, and azido.

[0060] In some embodiments, the compound of formula Ia is of formula Ia1 or Ia2:



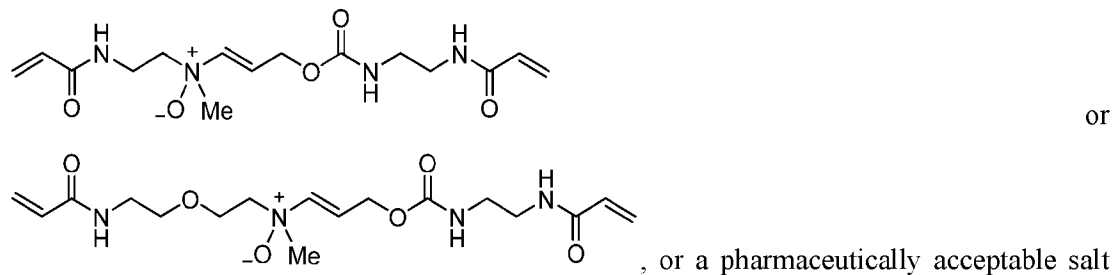
(Ia1) or



(Ia2), or a pharmaceutically acceptable salt or

stereoisomer thereof.

[0061] In some embodiments, the compound of formula I is:



or stereoisomer thereof.

[0062] Another aspect of the present disclosure is directed to a modifiable polymer/hydrogel which is the reaction product of:

- i) a compound of formula I:
-
- (I),
- ii) a polymerizable moiety which is the same as or different from R₄ and/or R₄', and
- iii) an initiator,

wherein:

R₁ is (C₁-C₈) alkyl, (C₃-C₁₀) carbocyclyl, or 4- to 10-membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S, wherein said alkyl, carbocyclyl or heterocyclyl is further optionally substituted, or

R₁ and R₂, together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl, or

R₁ and R₃, together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl;

R₂ is hydrogen, (C₁-C₈) alkyl, chloro, bromo, or iodo;

R₃ is hydrogen, (C₁-C₈) alkyl, chloro, bromo, or iodo;

L₁ is absent or a linker;

L₂ is absent or a linker;

X is a leaving group; and

R₄ and R₄' are independently a polymerizable moiety or a chemical moiety,

provided that at least one of R₄ and R₄' is a polymerizable moiety.

[0063] In some embodiments, L₁ is absent.

[0064] In some embodiments, L₂ is absent.

[0065] In some embodiments, L₁ is a linker.

[0066] In some embodiments, L₂ is a linker.

[0067] In some embodiments, the linker is an alkylene chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}')-$, $-\text{C}\equiv\text{C}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{O}-$, $-\text{C}(\text{NOR}')-$, $-\text{C}(\text{O})\text{N}(\text{R}')-$, $-\text{C}(\text{O})\text{N}(\text{R}')\text{C}(\text{O})-$, $-\text{R}'\text{C}(\text{O})\text{N}(\text{R}')\text{R}'-$, $-\text{C}(\text{O})\text{N}(\text{R}')\text{C}(\text{O})\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{C}(\text{O})-$, $-\text{N}(\text{R}')\text{C}(\text{O})\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R}')-$, $-\text{C}(\text{NR}')-$, $-\text{N}(\text{R}')\text{C}(\text{NR}')-$, $-\text{C}(\text{NR}')\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{C}(\text{NR}')\text{N}(\text{R}')-$, $-\text{OB}(\text{Me})\text{O}-$, $-\text{S}(\text{O})_2-$, $-\text{OS}(\text{O})-$, $-\text{S}(\text{O})\text{O}-$, $-\text{S}(\text{O})-$, $-\text{OS}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{O}-$, $-\text{N}(\text{R}')\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{S}(\text{O})-$, $-\text{S}(\text{O})\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{S}(\text{O})_2\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{S}(\text{O})\text{N}(\text{R}')-$, $-\text{OP}(\text{O})\text{O}(\text{R}')\text{O}-$, $-\text{N}(\text{R}')\text{P}(\text{O})\text{N}(\text{R}')\text{N}(\text{R}')-$, C_3 - C_{12} carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C_1 - C_{24} alkyl, wherein the interrupting and the one or both terminating groups may be the same or different.

[0068] In some embodiments, the alkylene chain is a C_1 - C_{24} alkylene chain. In some embodiments, the alkylene chain is a C_1 - C_{18} alkylene chain. In some embodiments, the alkylene chain is a C_1 - C_{12} alkylene chain. In some embodiments, the alkylene chain is a C_1 - C_{10} alkylene chain. In some embodiments, the alkylene chain is a C_1 - C_8 alkylene chain. In some embodiments, the alkylene chain is a C_1 - C_6 alkylene chain. In some embodiments, the alkylene chain is a C_1 - C_4 alkylene chain. In some embodiments, the alkylene chain is a C_1 - C_2 alkylene chain. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) in at least one of $-\text{N}(\text{R}')-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{C}(\text{O})-$, $-\text{N}(\text{R}')\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R}')-$, $-\text{S}(\text{O})_2-$, $-\text{N}(\text{R}')\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}')-$, 4- to 6-membered heterocyclyl, or a combination thereof. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with $-\text{N}(\text{R}')-$. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with $-\text{C}(\text{O})-$. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with $-\text{C}(\text{O})\text{O}-$. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with $-\text{C}(\text{O})\text{N}(\text{R}')-$. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with $-\text{N}(\text{R}')\text{S}(\text{O})_2-$. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with a 4- to 6-membered heterocyclyl.

[0069] In some embodiments, the linker is a polyethylene glycol chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}')-$, $-\text{C}\equiv\text{C}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{OC}(\text{O})\text{O}-$, $-\text{C}(\text{NOR}')-$, $-\text{C}(\text{O})\text{N}(\text{R}')-$, $-\text{C}(\text{O})\text{N}(\text{R}')\text{C}(\text{O})-$, $-\text{R}'\text{C}(\text{O})\text{N}(\text{R}')\text{R}'-$, $-\text{C}(\text{O})\text{N}(\text{R}')\text{C}(\text{O})\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{C}(\text{O})-$, $-\text{N}(\text{R}')\text{C}(\text{O})\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R}')-$, $-\text{C}(\text{NR}')-$, $-\text{N}(\text{R}')\text{C}(\text{NR}')-$, $-\text{C}(\text{NR}')\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{C}(\text{NR}')\text{N}(\text{R}')-$, $-\text{OB}(\text{Me})\text{O}-$, $-\text{S}(\text{O})_2-$, $-\text{OS}(\text{O})-$, $-\text{S}(\text{O})\text{O}-$, $-\text{S}(\text{O})-$, $-\text{OS}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{O}-$, $-\text{N}(\text{R}')\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{S}(\text{O})-$, $-\text{S}(\text{O})\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{S}(\text{O})_2\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{S}(\text{O})\text{N}(\text{R}')-$, $-\text{OP}(\text{O})\text{O}(\text{R}')\text{O}-$, $-\text{N}(\text{R}')\text{P}(\text{O})\text{N}(\text{R}')\text{N}(\text{R}')-$, C_3 - C_{12} carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C_1 - C_{24} alkyl, wherein the interrupting and the one or both terminating groups may be the same or different.

C(O)N(R')C(O)-, -R'C(O)N(R')R'-, -C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(Me)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, -N(R')S(O)N(R')-, -OP(O)O(R')O-, -N(R')P(O)N(R'R')N(R')-, C₃-C₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C₁-C₂₄ alkyl, wherein the interrupting and the one or both terminating groups may be the same or different.

[0070] In some embodiments, the polyethylene glycol chain has 1 to 20 -(CH₂CH₂-O)- units. In some embodiments, the polyethylene glycol chain has 1 to 15 -(CH₂CH₂-O)- units. In some embodiments, the polyethylene glycol chain has 1 to 10 -(CH₂CH₂-O)- units. In some embodiments, the polyethylene glycol chain has 1 to 6 -(CH₂CH₂-O)- units. In some embodiments, the polyethylene glycol chain has 1 to 2 -(CH₂CH₂-O)- units. In some embodiments, the polyethylene glycol is interrupted by, and/or terminates (at either or both termini) in at least one of -N(R')-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)O-, -OC(O)N(R')-, -S(O)₂-, -N(R')S(O)₂-, -S(O)₂N(R')-, 4- to 6-membered heterocyclyl, or a combination thereof. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with -N(R')-. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with -C(O)-. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with -C(O)O-. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with -C(O)N(R')-. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with -N(R')S(O)₂-. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with 4- to 6-membered heterocyclyl.

[0071] In some embodiments, R₁ is (C₁-C₈) alkyl, (C₃-C₁₀) carbocyclyl, or 4- to 10-membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S, wherein said alkyl, carbocyclyl or heterocyclyl is further optionally substituted. In some embodiments, R₁ is (C₁-C₈) alkyl. In some embodiments, R₁ is methyl.

[0072] In some embodiments, R₁ and R₂, together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl.

[0073] In some embodiments, R₁ and R₃, together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl.

[0074] In some embodiments, R₂ is hydrogen. In some embodiments, R₂ is methyl. In some embodiments, R₂ is chloro. In some embodiments, R₂ is bromo. In some embodiments, R₂ is iodo.

[0075] In some embodiments, R₃ is hydrogen. In some embodiments, R₃ is methyl. In some embodiments, R₃ is chloro. In some embodiments, R₃ is bromo. In some embodiments, R₃ is iodo.

[0076] In some embodiments, X is a leaving group, which as known in the art refers to an atom or group of atoms which breaks away from the rest of the molecule, taking with it the electron pair which used to be the bond between the leaving group and the rest of the molecule. Representative examples of leaving groups include esters, carbonates, carbamates, sulfoxides, sulfonates, sulfates, sulfones, thioesters, and thionoesters. In some embodiments, the leaving group is OR₉, SR₉, -OC(O)R₉, -OC(O)OR₉, -OC(O)NR₉R₉, -OC(S)R₉, -OC(S)OR₉, -OC(S)NR₉R₉, -OS(O)₂R₉, -OS(O)₂OR₉, -OP(O)OR₉OR₉, -OP(O)R₉R₉, -SC(O)R₉, -SC(O)SR₉, or -SC(S)SR₉, wherein each R₉ is independently hydrogen, (C₁-C₆) alkyl, (C₃-C₁₀) carbocyclyl, or 4- to 7-membered heterocyclyl, wherein said alkyl, carbocyclyl, or heterocyclyl is optionally substituted.

[0077] In some embodiments, the polymerizable moiety is the same as R₄ and/or R₄'. In such cases, the modifiable polymer is a homopolymer.

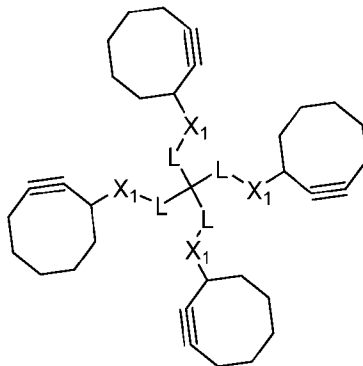
[0078] In some embodiments, the polymerizable moiety is different than R₄ and/or R₄', and the modifiable polymer/hydrogel is a co-polymer, e.g., a random or block co-polymer. In some embodiments, the polymerizable moiety comprises two or more different polymerizable moieties, e.g., vinyl chloride and vinyl alcohol, styrene and acrylamide, or vinyl chloride, styrene, and acrylamide.

[0079] In some embodiments, R₄ and R₄' are a polymerizable moiety. In some embodiments, R₄ and R₄' are acrylamide.

[0080] In some embodiments, R₄ is a polymerizable moiety and R₄' is a chemical moiety. In some embodiments, R₄ is a chemical moiety and R₄' is a polymerizable moiety. In some embodiments, the chemical moiety is a carboxylic acid, amine, sulfonic acid, phenol, catechol, a metal chelator, a PEG chain, or a drug molecule.

[0081] As known in the art, initiators are chemical species that react with a polymerizable monomer to form an intermediate compound that is capable of linking successively with a

large number of other polymerizable monomers. Representative examples of initiators include peroxides (e.g., benzoyl peroxide, di-*tert*-butyl peroxide, methyl ethyl ketone peroxide, acetone peroxide, and peroxydisulfate) and aliphatic azo compounds (e.g., azobisisobutyronitrile (AIBN), azobis(cyclohexanecarbonitrile (ACHN), and diethyldiazene). [0082] Other aspects of the present disclosure are directed to modifiable polymers/hydrogels which are the reaction product of:



i) a 4-arm-cyclooct-2-yn-1-yl,

; and

ii) a dihydroxylamine, $\begin{matrix} R_5 & & R_5 \\ & \diagdown & / \\ & N-L-N & \\ & / & \diagdown \\ OH & & OH \end{matrix}$,

wherein

each X₁ is a leaving group;

each L is a linker; and

each R₅ is (C₁-C₈) alkyl, (C₃-C₁₀) carbocyclyl, or 4- to 10-membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S, wherein said alkyl, carbocyclyl or heterocyclyl is further optionally substituted.

[0083] In some embodiments, the linker is an alkylene chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of -O-, -S-, -N(R')-, -C≡C-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(NOR')-, -C(O)N(R')-, -C(O)N(R')C(O)-, -R'C(O)N(R')R'-, -C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(Me)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, -N(R')S(O)N(R')-, -OP(O)O(R')O-, -N(R')P(O)N(R')N(R')-, C₃-C₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C₁-C₂₄ alkyl, wherein the interrupting and the one or both terminating groups may be the same or different.

[0084] In some embodiments, the alkylene chain is a C₁-C₂₄ alkylene chain. In some embodiments, the alkylene chain is a C₁-C₁₈ alkylene chain. In some embodiments, the alkylene chain is a C₁-C₁₂ alkylene chain. In some embodiments, the alkylene chain is a C₁-C₁₀ alkylene chain. In some embodiments, the alkylene chain is a C₁-C₈ alkylene chain. In some embodiments, the alkylene chain is a C₁-C₆ alkylene chain. In some embodiments, the alkylene chain is a C₁-C₄ alkylene chain. In some embodiments, the alkylene chain is a C₁-C₂ alkylene chain. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) in at least one of -N(R')-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)O-, -OC(O)N(R')-, -S(O)₂-, -N(R')S(O)₂-, -S(O)₂N(R')-, 4- to 6-membered heterocyclyl, or a combination thereof. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with -N(R')-. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with -C(O)-. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with -C(O)O-. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with -C(O)N(R')-. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with -N(R')S(O)₂-. In some embodiments, the alkylene chain is interrupted by, and/or terminates (at either or both termini) with a 4- to 6-membered heterocyclyl.

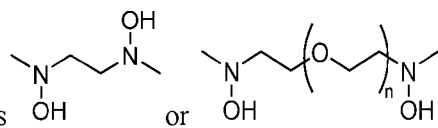
[0085] In some embodiments, the linker is a polyethylene glycol chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of -O-, -S-, -N(R')-, -C≡C-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(NOR')-, -C(O)N(R')-, -C(O)N(R')C(O)-, -R'C(O)N(R')R'-, -C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(Me)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, -N(R')S(O)N(R')-, -OP(O)O(R')O-, -N(R')P(O)N(R')N(R')-, C₃-C₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C₁-C₂₄ alkyl, wherein the interrupting and the one or both terminating groups may be the same or different.

[0086] In some embodiments, the polyethylene glycol chain has 1 to 20 -(CH₂CH₂-O)- units. In some embodiments, the polyethylene glycol chain has 1 to 15 -(CH₂CH₂-O)- units.

In some embodiments, the polyethylene glycol chain has 1 to 10 $-(\text{CH}_2\text{CH}_2\text{-O})-$ units. In some embodiments, the polyethylene glycol chain has 1 to 6 $-(\text{CH}_2\text{CH}_2\text{-O})-$ units. In some embodiments, the polyethylene glycol chain has 1 to 2 $-(\text{CH}_2\text{CH}_2\text{-O})-$ units. In some embodiments, the polyethylene glycol is interrupted by, and/or terminates (at either or both termini) in at least one of $-\text{N}(\text{R}')-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{N}(\text{R}')-$, $-\text{N}(\text{R}')\text{C}(\text{O})-$, $-\text{N}(\text{R}')\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R}')-$, $-\text{S}(\text{O})_2-$, $-\text{N}(\text{R}')\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}')-$, 4- to 6-membered heterocyclyl, or a combination thereof. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with $-\text{N}(\text{R}')-$. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with $-\text{C}(\text{O})-$. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with $-\text{C}(\text{O})\text{O}-$. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with $-\text{C}(\text{O})\text{N}(\text{R}')-$. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with $-\text{N}(\text{R}')\text{S}(\text{O})_2-$. In some embodiments, the polyethylene glycol chain is interrupted by, and/or terminates (at either or both termini) with 4- to 6-membered heterocyclyl.

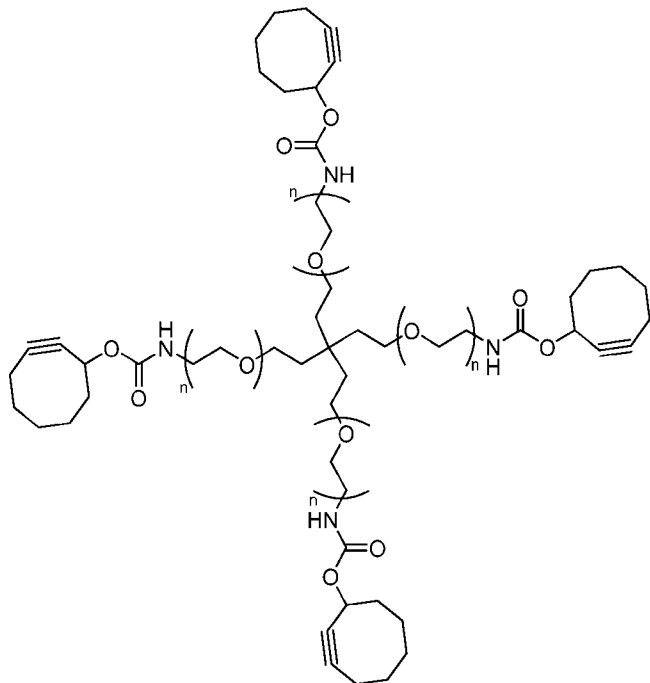
[0087] In some embodiments, R_5 is $(\text{C}_1\text{-C}_8)$ alkyl. In some embodiments, R_5 is methyl.

[0088] In some embodiments, X_1 is a leaving group, which as known in the art refers to an atom or group of atoms which breaks away from the rest of the molecule, taking with it the electron pair which used to be the bond between the leaving group and the rest of the molecule. Representative examples of leaving groups include esters, carbonates, carbamates, sulfoxides, sulfonates, sulfates, sulfones, thioesters, and thionoesters. In some embodiments, the leaving group is OR_9 , SR_9 , $-\text{OC}(\text{O})\text{R}_9$, $-\text{OC}(\text{O})\text{OR}_9$, $-\text{OC}(\text{O})\text{NR}_9\text{R}_9$, $-\text{OC}(\text{S})\text{R}_9$, $-\text{OC}(\text{S})\text{OR}_9$, $-\text{OC}(\text{S})\text{NR}_9\text{R}_9$, $-\text{OS}(\text{O})_2\text{R}_9$, $-\text{OS}(\text{O})_2\text{OR}_9$, $-\text{OP}(\text{O})\text{OR}_9\text{OR}_9$, $-\text{OP}(\text{O})\text{R}_9\text{R}_9$, $-\text{SC}(\text{O})\text{R}_9$, $-\text{SC}(\text{O})\text{SR}_9$, or $-\text{SC}(\text{S})\text{SR}_9$, wherein each R_9 is independently hydrogen, $(\text{C}_1\text{-C}_6)$ alkyl, $(\text{C}_3\text{-C}_{10})$ carbocyclyl, or 4- to 7-membered heterocyclyl, wherein said alkyl, carbocyclyl, or heterocyclyl is optionally substituted.



[0089] In some embodiments, the dihydroxylamine is or stereoisomer thereof, wherein n is an integer from 1-10000. In some embodiments, the dihydroxylamine is about 2 kDa. In some embodiments, the dihydroxylamine is about 1 kDa. In some embodiments, the dihydroxylamine is about 400 Da.

[0090] In some embodiments, the 4-arm-cyclooct-2-yn-1-yl is of formula II:



(II) or stereoisomer thereof, wherein

n is an integer from 1-10000. In some embodiments, the 4-arm-cyclooct-2-yn-1-yl is about 10 kDa.

[0091] In some embodiments, the optional substituent for the hydrogel is independently alkyl, alkenyl, alkynyl, halo, haloalkyl, cycloalkyl, heterocycloalkyl, hydroxy, alkoxy, cycloalkoxy, heterocycloalkoxy, haloalkoxy, aryloxy, heteroaryloxy, aralkyloxy, alkylenyloxy, alkynyloxy, amino, alkylamino, cycloalkylamino, heterocycloalkylamino, arylamino, heteroarylamino, aralkylamino, N-alkyl-N-arylamine, N-alkyl-N-heteroarylamine, N-alkyl-N-aralkylamine, hydroxyalkyl, aminoalkyl, alkylthio, haloalkylthio, alkylsulfonyl, haloalkylsulfonyl, cycloalkylsulfonyl, heterocycloalkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aminosulfonyl, alkylaminosulfonyl, cycloalkylaminosulfonyl, heterocycloalkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, N-alkyl-N-arylaminosulfonyl, N-alkyl-N-heteroarylaminosulfonyl, formyl, alkylcarbonyl, haloalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxy carbonyl, alkylcarbonyloxy, amino, alkylsulfonylamino, haloalkylsulfonylamino, cycloalkylsulfonylamino, heterocycloalkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, aralkylsulfonylamino, alkylcarbonylamino, haloalkylcarbonylamino, cycloalkylcarbonylamino, heterocycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, aralkylsulfonylamino, aminocarbonyl,

alkylaminocarbonyl, cycloalkylaminocarbonyl, heterocycloalkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, N-alkyl-N-heteroarylaminocarbonyl, cyano, nitro, and azido.

[0092] Compounds of the present disclosure may be in the form of a free acid or free base, or a pharmaceutically acceptable salt. A pharmaceutically acceptable salt of the compounds of this disclosure can be formed, for example, by reaction of an appropriate free base of a compound of the disclosure and an appropriate pharmaceutically acceptable acid in a suitable solvent under standard conditions well known in the art. *See, for example, Gould, P. L., "Salt selection for basic drugs," International Journal of Pharmaceutics, 33:201-217 (1986); Bastin, R. J., et al., "Salt Selection and Optimization Procedures for Pharmaceutical New Chemical Entities," Organic Process Research and Development, 4:427-435 (2000); and Berge, S. M., et al., "Pharmaceutical Salts," Journal of Pharmaceutical Sciences, 66:1-19 (1977).*

[0093] Compounds of the present disclosure may have at least one chiral center and thus may be in the form of a stereoisomer, which as used herein, embraces all isomers of individual compounds that differ only in the orientation of their atoms in space. The term stereoisomer includes mirror image isomers (enantiomers which include the (R-) or (S-) configurations of the compounds), mixtures of mirror image isomers (physical mixtures of the enantiomers, and racemates or racemic mixtures) of compounds, geometric (cis/trans or E/Z, R/S) isomers of compounds and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereoisomers). The chiral centers of the compounds may undergo epimerization *in vivo*; thus, for these compounds, administration of the compound in its (R-) form is considered equivalent to administration of the compound in its (S-) form. Accordingly, the compounds of the present disclosure may be made and used in the form of individual isomers and substantially free of other isomers, or in the form of a mixture of various isomers, *e.g.*, racemic mixtures of stereoisomers.

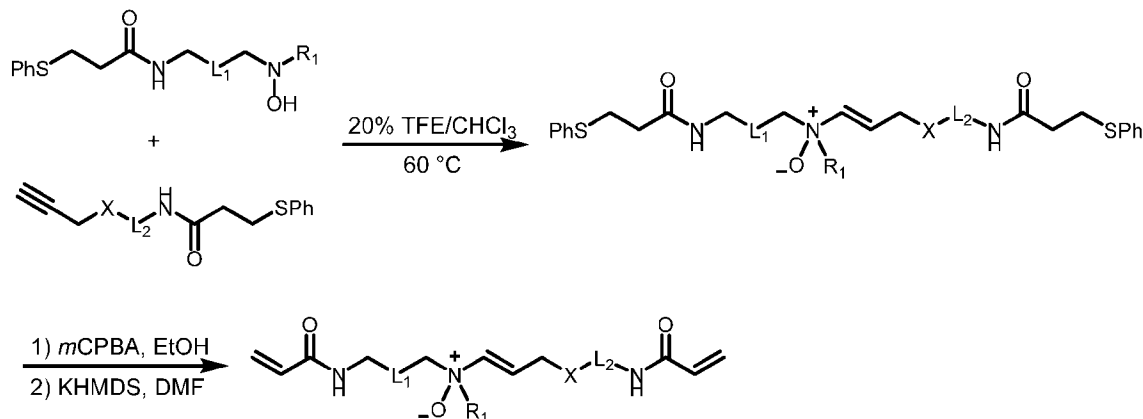
[0094] In some embodiments, the compound of formula I or the hydrogel is an isotopic derivative in that it has at least one desired isotopic substitution of an atom, at an amount above the natural abundance of the isotope, *i.e.*, enriched. In one embodiment, the compound includes deuterium or multiple deuterium atoms. As used herein, the term "compound" embraces isotopic derivatives.

Methods of Synthesis

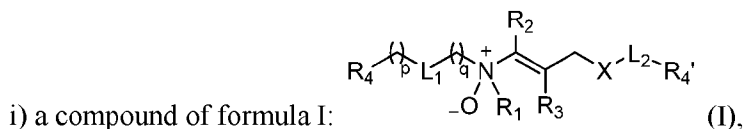
[0095] In another aspect, the present disclosure is directed to a method for making a compound of formula I, a modifiable polymer/hydrogel which is the reaction product of a compound of formula I, a polymerizable moiety, and an initiator, or a modifiable polymer/hydrogel which is the reaction product of a 4-arm-cyclooct-2-yn-1-yl and a dihydroxylamine. Broadly, the compounds and their pharmaceutically acceptable salts and stereoisomers may be prepared by any process known to be applicable to the preparation of chemically related compounds. The compounds of the present disclosure will be better understood in connection with the synthetic schemes that are described in various working examples and which illustrate non-limiting methods by which the compounds may be prepared, e.g. compounds of formula I, modifiable polymers/hydrogels which are the reaction product of a compound of formula I, a polymerizable moiety, and an initiator, and modifiable polymers/hydrogels which are the reaction product of a 4-arm-cyclooct-2-yn-1-yl and a dihydroxylamine.

[0096] The compounds of formula I can be prepared by methods known by those skilled in the art. In one non-limiting example the disclosed compounds can be made by the following schemes.

Scheme 1. Representative synthetic procedure for compounds of formula Ia.



[0097] In another aspect, the present disclosure is directed to methods for preparing modifiable polymers/hydrogels which are the reaction product of:



ii) a polymerizable moiety which is the same as or different from R_4 and/or R_4' , and

iii) an initiator.

[0098] As known in the art, random or block co-polymers can be made by varying the amounts of the “polymerizable moiety” (reactant (ii)) or the sequence in which it/they are added.

[0099] In some embodiments, the reacting is carried out in the presence of a solvent.

[00100] In some embodiments, the solvent is an aprotic solvent. In some embodiments, the aprotic solvent is DCM, CHCl_3 , CCl_4 , DCE, toluene, MeCN, or THF.

[00101] In some embodiments, the solvent is a protic solvent. In some embodiments, the protic solvent is water, MeOH, EtOH, iPrOH, nBuOH, TFE, or HFIP.

[00102] In some embodiments, the solvent is a solvent mixture. In some embodiments, the solvent mixture is a mixture of an aprotic solvent and a protic solvent. In some embodiments, the solvent mixture is 0-100% protic to aprotic. The use of an aqueous solvent results in the production of a modifiable hydrogel and the use of a non-aqueous solvent results in the production of a modifiable polymer.

[00103] In some embodiments, the solvent is a buffered solvent. In some embodiments, the buffered solvent is phosphate-buffered saline. In some embodiments, the pH of the phosphate-buffered saline is about 7.4.

[00104] In some embodiments, the reacting is carried in the solvent with a concentration of is 1-25 wt%. In some embodiments, the concentration is 1, 5, 10, or 15 wt%.

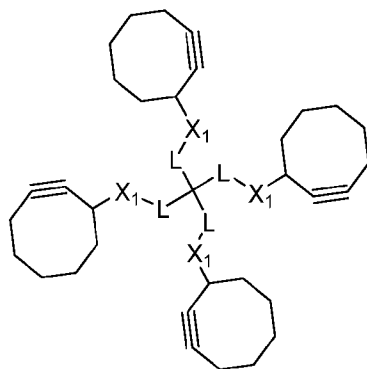
[00105] In some embodiments, the reacting of formula I with the polymer is in a ratio of 1-20 wt%. In some embodiments, the ratio of formula I to polymer is 3, 6, or 12 wt%.

[00106] In some embodiments, the reaction is carried out over a week. In some embodiments, the reaction is carried out over five days. In some embodiments, the reaction is carried out over three days. In some embodiments, the reaction is carried out over a period of 24 hours. In some embodiments, the reaction is carried out over a period of 18 hours. In some embodiments, the reaction is carried out over a period of 12 hours. In some embodiments, the reaction is carried out over a period of 6 hours. In some embodiments, the reaction is carried out over a period of 3 hours. In some embodiments, the reaction is carried out over a period of 2 hours. In some embodiments, the reaction is carried out over a period of 1 hour. In some embodiments, the reaction is carried out over a period of 45 minutes. In some embodiments, the reaction is carried out over a period of 30 minutes. In some embodiments, the reaction is carried out over a period of 15 minutes. In some embodiments, the reaction is carried out over a period of 5 minutes. In some embodiments, the reaction is carried out over a period of 1 minute.

[00107] In some embodiments, the solvent is added after the reaction product is formed. In the initial constructed state, the reaction product would be a modifiable polymer. It would be made into a hydrogel as it swells upon introduction of the solvent, e.g., water.

[00108] In some embodiments, the methods of preparing the hydrogels comprises the following operations or steps: 1) dissolving a polymerizable moiety (e.g., acrylamide) in water at a desired weight per volume and stirring for a period of time; 2) the solution obtained in step 1) is added to a mixture containing a compound of formula I, a catalyst (e.g., tetramethylethylenediamine (TMEDA)), an initiator (e.g., ammonium persulfate (APS)), and calcium sulfate (CaSO_4) and stirred for a period of time; 3) the mixture obtained in step 3 is stored at room temperature for a period of time, forming the hydrogel.

[00109] In another aspect, the present disclosure is directed to methods for preparing modifiable polymers/hydrogels which are the reaction product of one equivalent of a 4-arm-



cyclooct-2-yn-1-yl, , and two equivalents of a

dihydroxylamine, $\text{R}_5\text{-N}(\text{OH})\text{-L-N}(\text{OH})\text{-R}_5$.

[00110] In some embodiments, the reacting is carried out in the presence of a solvent.

[00111] In some embodiments, the solvent is an aprotic solvent. In some embodiments, the aprotic solvent is DCM, CHCl_3 , CCl_4 , DCE, toluene, MeCN, or THF.

[00112] In some embodiments, the solvent is a protic solvent. In some embodiments, the protic solvent is water, MeOH, EtOH, iPrOH, nBuOH, TFE, or HFIP.

[00113] In some embodiments, the solvent is a solvent mixture. In some embodiments, the solvent mixture is a mixture of an aprotic solvent and a protic solvent. In some embodiments, the solvent mixture is 0-100% protic to aprotic. The use of an aqueous solvent results in the production of a modifiable hydrogel and the use of a non-aqueous solvent results in the production of a modifiable polymer.

[00114] In some embodiments, the solvent is a buffered solvent. In some embodiments, the buffered solvent is phosphate-buffered saline. In some embodiments, the pH of the phosphate-buffered saline is about 7.4.

[00115] In some embodiments, the reacting is carried in the solvent with a concentration of is 1-25 wt%. In some embodiments, the concentration is 1, 5, 10, or 15 wt%.

[00116] In some embodiments, the reacting of formula I with the polymer is in a ratio of 1-20 wt%. In some embodiments, the ratio of formula I to polymer is 3, 6, or 12 wt%.

[00117] In some embodiments, the reaction is carried out over a week. In some embodiments, the reaction is carried out over five days. In some embodiments, the reaction is carried out over three days. In some embodiments, the reaction is carried out over a period of 24 hours. In some embodiments, the reaction is carried out over a period of 18 hours. In some embodiments, the reaction is carried out over a period of 12 hours. In some embodiments, the reaction is carried out over a period of 6 hours. In some embodiments, the reaction is carried out over a period of 3 hours. In some embodiments, the reaction is carried out over a period of 2 hours. In some embodiments, the reaction is carried out over a period of 1 hour. In some embodiments, the reaction is carried out over a period of 45 minutes. In some embodiments, the reaction is carried out over a period of 30 minutes. In some embodiments, the reaction is carried out over a period of 15 minutes. In some embodiments, the reaction is carried out over a period of 5 minutes. In some embodiments, the reaction is carried out over a period of 1 minute.

[00118] In some embodiments, the solvent is added after the reaction product is formed. In the initial constructed state, the reaction product would be a modifiable polymer. It would be made into a hydrogel as it swells upon introduction of the solvent, e.g., water.

[00119] Methods of synthesizing hydrogels are known in the art. Varying the properties of the hydrogels, e.g., molecular weight and viscosity, to suit the clinical need at hand, is also within the level of skill in the art. *See*, Freedman *et al.*, *Adv. Mater.*, 2021, 33(17):e2008553 and Ahmed, J. *Adv. Res.*, 2015, 6(2):105-121. For example, a hydrogel of desired viscosity is formed by adding appropriate amounts of water. To obtain a gel that changes viscosity *in vivo*, calcium citrate tetrahydrate can be added to the water component or added after gel formation to obtain gels with higher viscosity. *See*, PCT Publication No. WO 2013/112381. Other parameters that can be varied to create hydrogels with the desired specific properties include: %w/v crosslinker, %w/v monomer, solvent, mol% initiator, reaction time, temperature, and pH.

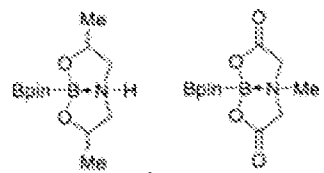
Methods of Use

[00120] As known in the art, hydrogels may be used as a suitable drug delivery system for drugs due to their tunable properties, controllable degradation, and ability to protect labile drugs. *See, Vigata et al., Pharmaceutics*, 2020, *12*(12):1188. Accordingly, in some embodiments, effective amounts of a therapeutically active agent may be added at some point in the preparation of the hydrogels. As known in the art, modifiable non-hydrogel polymers may be used as films and plastics.

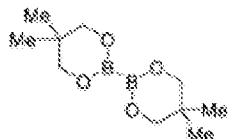
[00121] In some aspects, the present disclosure is directed to methods of degrading modifiable polymers/hydrogels.

[00122] In some embodiments, the present method comprises contacting a modifiable polymer/hydrogel with a diboron reagent.

[00123] In some embodiments, the diboron reagent is a symmetrical diboron reagent. In some embodiments, the diboron reagent is an unsymmetrical diboron reagent. In some



embodiments, the diboron reagent is $B_2(OH)_4$, B_2pin_2 ,



Other representative examples of diboron reagents include bis(catecholato)diboron, bis(hexylene glycolato)diboron, bis[(-)pinanediolato]diboron, bis(diisopropyl-1-tartrate glycolato)diboron, bis(N,N,N',N'-tetramethyl-d-tartaramide glycolato)diboron, and 2,2'-bi-1,3,2-dioxaborinane. Yet other diboron reagents which may be suitable for use in the present disclosure are disclosed in Ali *et al.*, *Studies in Inorganic Chemistry*, "Chapter 1 – Chemistry of the diboron compounds" 22:1-57 (2005); Neeve *et al.*, *Chem. Rev.* *116*(16):9091-9161 (2016); Ding *et al.*, *Molecules* *24*(7):1325 (2019).

[00124] In some embodiments, the diboron reagent is used at a concentration of about 1 pM to about 1 M. In some embodiments, the diboron reagent is used at a concentration of about 1 pM to about 100 mM. In some embodiments, the diboron reagent is used at a concentration of about 1 pM to about 10 mM. In some embodiments, the diboron reagent is used at a concentration of about 1 pM to about 1 mM. In some embodiments, the diboron reagent is used at a concentration of about 1 pM to about 100 μ M. In some embodiments, the diboron reagent is used at a concentration of about 1 pM to about 10 μ M. In some embodiments, the

diboron reagent is used at a concentration of about 1 pM to about 1 μ M. In some embodiments, the diboron reagent is used at a concentration of about 1 pM to about 100 nM. In some embodiments, the diboron reagent is used at a concentration of about 1 pM to about 10 nM. In some embodiments, the diboron reagent is used at a concentration of about 1 pM to about 1 nM. In some embodiments, the diboron reagent is used at a concentration of about 1 pM to about 100 pM. In some embodiments, the diboron reagent is formulated in DMSO.

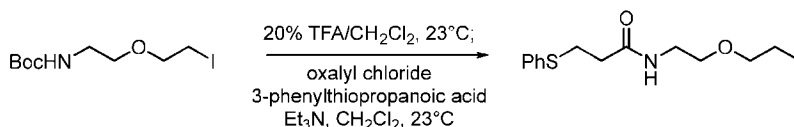
[00125] In some embodiments, the diboron solution contains a calcium chelator. In some embodiments, the calcium chelator is ethylenediaminetetraacetic acid (EDTA) or citric acid.

[00126] In some embodiments, the diboron reagent is formulated, e.g., as a solution, in water or saline. In some embodiments, the solution further comprises a solubilizing additive, e.g., DMSO. In some embodiments, the diboron agent is formulated as a solid.

[00127] These and other aspects of the present disclosure will be further appreciated upon consideration of the following Examples, which are intended to illustrate certain particular embodiments of the disclosure but are not intended to limit its scope, as defined by the claims.

EXAMPLES

[00128] Example 1: Synthesis of (E)-N-(2-(2-acrylamidoethoxy)ethyl)-3-(((2-acrylamidoethyl)carbamoyl)oxy)-N-methylprop-1-en-1-amine oxide (1)



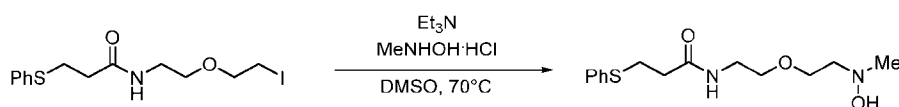
[00129] *N*-(2-(2-Iodoethoxy)ethyl)-3-(phenylthio)propanamide

[00130] A solution of trifluoroacetic acid (TFA) in dichloromethane (DCM, 20% v/v, 200 mL) was added to a round bottom flask charged with *tert*-butyl (2-(2-iodoethoxy)ethyl)carbamate (14.9 g, 47.3 mmol, 1.15 equiv) (Kang *et al.*, Chem., 2022, 8(8):2260-2277). The resulting solution was stirred for 1 hour at room temperature (rt). The solution was concentrated under reduced pressure, followed by azeotropic distillation with toluene (3 $\times$ 15 mL). The crude oil was placed under reduced pressure for 3 hours.

[00131] A separate round bottom flask was charged with 3-phenylthiopropionic acid (7.51 g, 41.2 mmol, 1.00 equiv) and purged with nitrogen. DCM (200 mL) was added via syringe. The solution was then cooled to 0°C in an ice-water bath. Oxalyl chloride (3.70 mL, 43.2

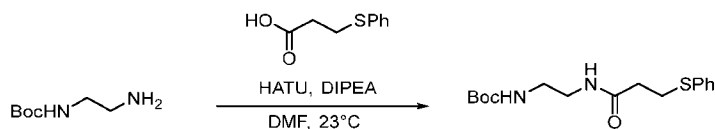
mmol, 1.05 equiv) and *N,N*-dimethylformamide (DMF, 60.4 μ L, 0.780 mmol, 0.020 equiv) were then added dropwise via syringe. The reaction was monitored by reacting an aliquot with methanol and using ^1H NMR. The reaction was complete in 2 hours and the solution of the acid chloride was stored at 0°C until further use.

[00132] DCM (200 mL) was added to the crude oil containing the alkyl iodide and cooled to 0°C in an ice-water bath. Triethylamine (TEA, 12.9 mL, 94.7 mmol, 2.30 equiv) was added dropwise via syringe. The solution of acid chloride was then added dropwise via cannula. After 1 hour, the reaction mixture was diluted with saturated aqueous sodium bicarbonate (250 mL). The aqueous layer was extracted with DCM (3 $\times$ 200 mL), and the combined organic layers were washed with water (300 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography on silica gel (eluent: 20 $\rightarrow$ 30% ethyl acetate in hexanes) to give the title compound as an off-white oil (8.05 g, 52%). ^1H NMR (500 MHz, CDCl_3 , 25°C): δ 7.34 (dd, J = 8.3, 1.3 Hz, 2H), 7.27 (t, J = 7.7 Hz, 2H), 7.20–7.16 (m, 1H), 6.01 (s, 1H), 3.68 (t, J = 6.2 Hz, 2H), 3.53 (dd, J = 5.6, 4.5 Hz, 2H), 3.47–3.42 (m, 2H), 3.25–3.19 (m, 4H), 2.48 (t, J = 7.3 Hz, 2H).



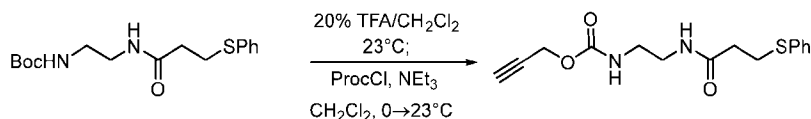
[00133] *N*-(2-(2-(hydroxy(methyl)amino)ethoxy)ethyl)-3-(phenylthio)propanamide

[00134] A round bottom flask was charged with *N*-(2-(2-iodoethoxy)ethyl)-3-(phenylthio)propanamide (1.78 g, 4.69 mmol, 1 equiv) and *N*-methylhydroxylamine hydrochloride (785 mg, 9.40 mmol, 2.00 equiv) then purged with nitrogen. Dimethylsulfoxide (DMSO, 5 mL) and TEA (2.63 mL, 18.8 mmol, 4.00 equiv) was added via syringe. The reaction mixture was heated to 70°C and stirred for 2 hours. The mixture was then cooled to 0°C in an ice-water bath and diluted with saturated aqueous sodium bicarbonate (10 mL). The aqueous layer was extracted with ethyl acetate (3 $\times$ 30 mL), and the combined organic layers were washed with water (4 $\times$ 100 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography on silica gel (eluent: 10 $\rightarrow$ 30% CMA in chloroform) to give the title compound as a light yellow oil (672 mg, 47%). ^1H NMR (500 MHz, CDCl_3 , 25°C): δ 7.33 (dd, J = 8.2, 1.3 Hz, 2H), 7.26 (t, J = 7.7 Hz, 2H), 7.20–7.13 (m, 1H), 6.55 (s, NH), 3.68–3.55 (m, 2H), 3.51 (t, J = 5.1 Hz, 2H), 3.46–3.37 (m, 2H), 3.21 (t, J = 7.4 Hz, 2H), 2.79 (s, 2H), 2.64 (s, 3H), 2.50 (t, J = 7.4 Hz, 2H).



[00135] *tert-Butyl (2-(3-(phenylthio)propanamido)ethyl)carbamate*

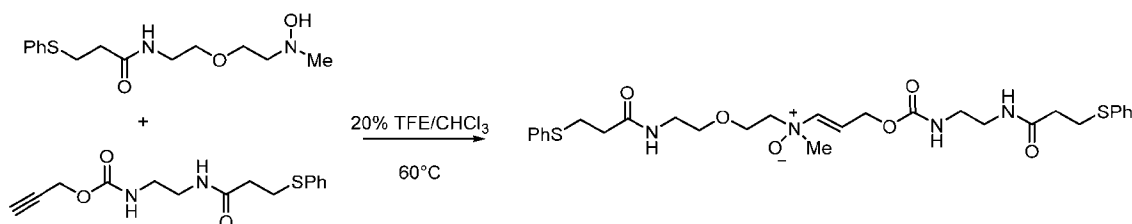
[00136] A round bottom flask was charged with 3-phenylthiopropionic acid (1.09 g, 6.00 mmol, 1 equiv) and 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU, 2.51 g, 6.60 mmol, 1.10 equiv) then purged with nitrogen. DMF (10 mL) was added via syringe followed by diisopropylethylamine (DIPEA, 3.14 mL, 18.0 mmol, 3.00 equiv) and stirred at rt. After 15 min, *N*-Boc-ethylenediamine (1.14 mL, 7.12 mmol, 1.20 equiv) was added via syringe. After 16 hours, the reaction was quenched with water (50 mL), and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water (4 × 300 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (eluent: 30% ethyl acetate in hexanes) to give the title compound as a white solid (2.01 g, 98%). ¹H NMR (500 MHz, CDCl₃, 25 °C): δ 7.34 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.27 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.20–7.16 (m, 1H), 6.17 (s, NH), 4.86 (s, NH), 3.32 (td, *J* = 6.5, 5.5, 4.3 Hz, 2H), 3.24 (d, *J* = 5.4 Hz, 2H), 3.19 (t, *J* = 7.3 Hz, 2H), 2.45 (t, *J* = 7.2 Hz, 2H), 1.41 (s, 9H).



[00137] *Prop-2-yn-1-yl (2-(3-(phenylthio)propanamido)ethyl)carbamate*

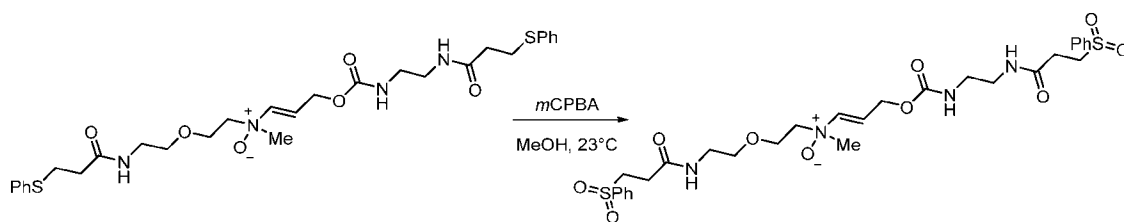
[00138] A solution of TFA in DCM (50% v/v, 3 mL) was added to a round bottom flask charged with *tert*-butyl (2-(3-(phenylthio)propanamido)ethyl)carbamate (2.01 g, 6.20 mmol, 1.00 equiv). After 2 hours, the reaction mixture was concentrated under reduced pressure then placed under reduced pressure for 2 hours. DCM (50 mL) and TEA (2.60 mL, 18.6 mmol, 3.00 equiv) were then sequentially added via syringe to the crude oil. The solution was then cooled to 0°C in an ice-water bath. Propargyl chloroformate (637 μL, 6.53 mmol, 1.10 equiv) was added dropwise via syringe. After complete addition, the reaction mixture was warmed to rt. After 3 hours, the reaction mixture was quenched with saturated aqueous sodium bicarbonate (50 mL). The aqueous layer was extracted with DCM (3 × 50 mL), and the combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting white solid was purified by

flash column chromatography on silica gel (eluent: 20% ethyl acetate in hexanes) to give the title compound as a white solid (1.89 g, 99%). ^1H NMR (500 MHz, CDCl_3 , 25°C): δ 7.37–7.32 (m, 2H), 7.31–7.26 (m, 2H), 7.21–7.16 (m, 1H), 5.96 (s, NH), 5.18 (s, NH), 4.64 (d, J = 2.4 Hz, 2H), 3.34 (dt, J = 18.6, 6.1 Hz, 4H), 3.20 (t, J = 7.2 Hz, 2H), 2.46 (t, J = 7.1 Hz, 2H), 2.43 (t, J = 2.4 Hz, 1H).



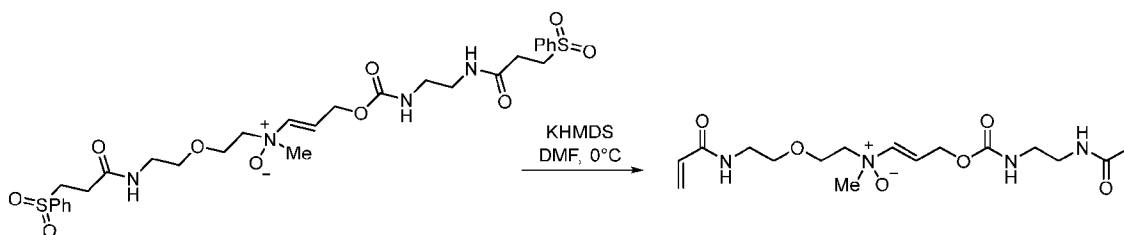
[00139] *(E)-N-methyl-N-(2-(2-(3-(phenylthio)propanamido)ethoxy)ethyl)-3-(((2-(3-(phenylthio)propanamido)ethyl)carbamoyl)oxy)prop-1-en-1-amine oxide*

[00140] A solution of 2,2,2-trifluoroethanol in chloroform (20% v/v, 1 mL) was added to a glass vial charged with *N*-(2-(2-(hydroxy(methyl)amino)ethoxy)ethyl)-3-(phenylthio)propanamide (141 mg, 0.473 mmol, 1.00 equiv) and prop-2-yn-1-yl 2-(3-(phenylthio)propanamido)ethyl carbamate (137 mg, 0.447 mmol, 1.00 equiv). The reaction was heated to 60°C . After 16 hours, the reaction mixture was concentrated under reduced pressure, and purified by flash column chromatography on silica gel (eluent: 10→60% CMA in chloroform) to give the title compound as a yellow oil (116 mg, 42%). ^1H NMR (500 MHz, CD_3OD , 25°C): δ 7.38–7.35 (m, 4H), 7.30 (t, J = 7.8 Hz, 4H), 7.21–7.17 (m, 2H), 6.52 (d, J = 13.4 Hz, 1H), 6.46 (dt, J = 13.2, 5.1 Hz, 1H), 4.64 (dd, J = 5.0, 1.4 Hz, 2H), 3.90 (ddd, J = 11.8, 6.1, 3.2 Hz, 1H), 3.76 (ddd, J = 11.9, 6.4, 3.1 Hz, 1H), 3.56–3.52 (m, 1H), 3.48 (t, J = 5.5 Hz, 2H), 3.38–3.32 (m, 3H), 3.26 (d, J = 5.8 Hz, 2H), 3.24 (s, 3H), 3.21–3.15 (m, 7H), 2.53–2.48 (m, 4H).



[00141] *(E)-N-Methyl-N-(2-(2-(3-(phenylsulfonyl)propanamido)ethoxy)ethyl)-3-(((2-(3-(phenylsulfonyl)propanamido)ethyl)carbamoyl)oxy)prop-1-en-1-amine oxide*

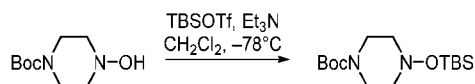
[00142] Methanol (75 mL) was added to a round bottom flask charged with (*E*)-*N*-methyl-*N*-(2-(2-(3-(phenylthio)propanamido)ethoxy)ethyl)-3-(((2-(3-(phenylthio)propanamido)ethyl)carbamoyl)oxy)prop-1-en-1-amine oxide (2.52 g, 4.17 mmol, 1.00 equiv). The solution was cooled to 0°C in an ice-water bath then *meta*-chloroperoxybenzoic acid (4.57 g, 17.5 mmol, 4.20 equiv) was added. After 3 hours, the reaction mixture was concentrated under reduced pressure, and purified by column chromatography on silica gel (eluent: 10→60% CMA in chloroform) to give the title compound as a white solid (1.4 g, 52%). ¹H NMR (500 MHz, CD₃OD, 25°C): δ 7.94 (t, *J* = 1.2 Hz, 2H), 7.93 (t, *J* = 1.3 Hz, 2H), 7.74 (td, *J* = 7.3, 1.3 Hz, 2H), 7.65 (td, *J* = 7.8, 1.8 Hz, 4H), 6.54 (d, *J* = 13.4 Hz, 1H), 6.51–6.43 (m, 1H), 4.67–4.63 (m, 2H), 4.58 (s, 1H), 3.88 (dd, *J* = 10.0, 6.4 Hz, 1H), 3.79–3.73 (m, 1H), 3.61 (t, *J* = 7.1 Hz, 1H), 3.55 (d, *J* = 3.6 Hz, 1H), 3.51 (td, *J* = 7.4, 2.3 Hz, 5H), 3.47–3.44 (m, 2H), 3.27 (t, *J* = 5.5 Hz, 2H), 3.25 (s, 3H), 3.21 (d, *J* = 4.5 Hz, 2H), 3.19–3.16 (m, 2H).



[00143] (*E*)-*N*-(2-(2-Acrylamidoethoxy)ethyl)-3-(((2-acrylamidoethyl)carbamoyl)oxy)-*N*-methylprop-1-en-1-amine oxide

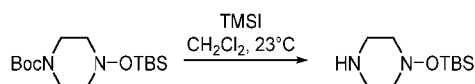
[00144] A round bottom flask was charged with (*E*)-*N*-methyl-*N*-(2-(2-(3-(phenylsulfonyl)propanamido)ethoxy)ethyl)-3-(((2-(3-(phenylsulfonyl)propanamido)ethyl)carbamoyl)oxy)prop-1-en-1-amine oxide (241 mg, 0.360 mmol, 1.00 equiv) and purged with nitrogen. DMF (2 mL) was added via syringe, and the reaction mixture was cooled to 0°C in an ice-water bath. Potassium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran (THF), 720 μL, 0.720 mmol, 2.00 equiv) was then added via syringe. After 30 min, the solvent was concentrated under reduced pressure, and the crude mixture was purified by column chromatography on silica gel (eluent: 10→30% methanol in dichloromethane, 0.2% triethylamine) to give the title compound as an off-white solid (74 mg, 53%). ¹H NMR (500 MHz, CD₃OD, 25°C): δ 6.55 (d, *J* = 13.4 Hz, 1H), 6.50–6.46 (m, 1H), 6.30–6.17 (m, 4H), 5.68–5.63 (m, 2H), 4.73–4.63 (m, 2H), 3.93 (dq, *J* = 9.0, 2.9 Hz, 1H), 3.82–3.77 (m, 1H), 3.61–3.51 (m, 5H), 3.44 (dt, *J* = 9.4, 5.5 Hz, 2H), 3.39–3.35 (m, 2H), 3.27–3.25 (m, 4H).

[00145] Example 2: Synthesis of (*E*)-1-(3-(((2-acrylamidoethyl)carbamoyl)oxy)cyclooct-1-en-1-yl)-4-acryloylpiperazine 1-oxide



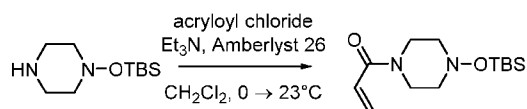
[00146] *tert*-Butyl 4-((*tert*-butyldimethylsilyl)oxy)piperazine-1-carboxylate

[00147] DCM (20 mL) was added to a round bottom flask charged with *N*-Boc-piperazine hydroxylamine (2.99 g, 14.8 mmol, 1.00 equiv). The flask was purged with nitrogen and cooled to -78°C in a dry ice-acetone bath. TEA (6.22 mL, 44.5 mmol, 3.00 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (4.09 mL, 17.8 mmol, 1.20 equiv) were each added sequentially to the solution dropwise via syringe. The resulting mixture was allowed to warm to rt by removing the dry ice-acetone bath. After 1 hour, the solution was diluted with saturated aqueous sodium bicarbonate (50 mL). The aqueous layer was extracted with DCM (3 × 50 mL), and the combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography on silica gel (eluent: 5→15% ethyl acetate in hexanes) to give the title compound as a white solid (2.92 g, 62%). ¹H NMR (500 MHz, CDCl₃, 25°C): δ 3.89 (s, 2H), 2.97 (d, *J* = 12.4 Hz, 4H), 2.51 (td, *J* = 10.9, 3.4 Hz, 2H), 1.43 (s, 9H), 0.88 (s, 9H), 0.08 (s, 6H). ¹³C NMR (125.8 MHz, CDCl₃, 25°C): δ 154.9, 80.0, 57.9, 42.5, 52.1, 28.6, 26.4, 18.1, -5.2.



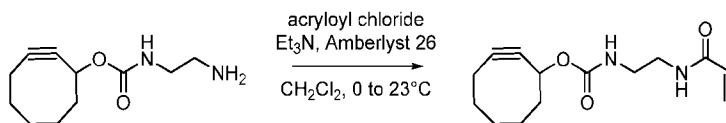
[00148] 1-((*tert*-Butyldimethylsilyl)oxy)piperazine

[00149] DCM (4 mL) was added to a round bottom flask charged with *tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)piperazine-1-carboxylate (350 mg, 1.11 mmol, 1.00 equiv). Trimethylsilyl iodide (630 μL, 4.43 mmol, 4.00 equiv) was then added dropwise via syringe. After 5 min, the crude mixture was quenched with a mixture of saturated aqueous sodium bicarbonate and saturated aqueous sodium thiosulfate (50% v/v, 20 mL). The aqueous layer was extracted with DCM (3 × 10 mL), and the combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting oil was used without further purification.



[00150] 1-((4-((tert-butyl dimethylsilyl)oxy)prop-2-en-1-yl)piperazin-1-yl)prop-2-en-1-one

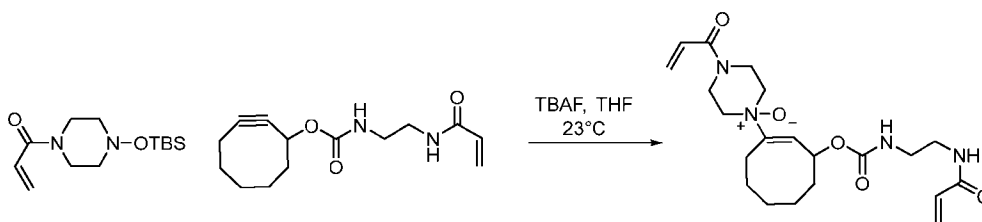
[00151] DCM (20 mL), triethylamine (1.42 mL, 10.2 mmol, 2.00 equiv), and Amberlyst-26 (3.00 g, 60.0 mg per 0.10 mmol of 1-((tert-butyl dimethylsilyl)oxy)piperazine) were sequentially added to a round bottom flask charged with 1-((tert-butyl dimethylsilyl)oxy)piperazine (1.10 g, 5.08 mmol, 1.00 equiv). The flask was then purged with nitrogen and cooled to 0°C in an ice-water bath. Acryloyl chloride (452 µL, 5.59 mmol, 1.10 equiv) was added dropwise via syringe. The reaction mixture was allowed to warm to rt by removing the ice-water bath. After 45 min, the reaction mixture was quenched with methanol (500 µL) then concentrated under reduced pressure. The crude oil was purified by flash column chromatography on silica gel (eluent: 15→30% ethyl acetate in hexanes) to give the title compound as a white foam (976 mg, 71% over two steps). ¹H NMR (500 MHz, CDCl₃, 25°C): δ 6.53 (dd, *J* = 16.8, 10.6 Hz, 1H), 6.26 (dd, *J* = 16.8, 1.9 Hz, 1H), 5.68 (dd, *J* = 10.6, 1.9 Hz, 1H), 4.34 (d, *J* = 13.4 Hz, 1H), 3.86 (d, *J* = 13.4 Hz, 1H), 3.30 (t, *J* = 12.1 Hz, 1H), 3.08 (d, *J* = 30.0 Hz, 3H), 2.58 (td, *J* = 10.7, 3.3 Hz, 2H), 0.89 (s, 9H), 0.09 (s, 6H).



[00152] Cyclooct-2-yn-1-yl (2-acrylamidoethyl)carbamate

[00153] DCM (10 mL), TEA (744 µL, 5.32 mmol, 2.00 equiv), and Amberlyst-26 (800 mg, 60.0 mg per 0.20 mmol of cyclooct-2-yn-1-yl (2-aminoethyl)carbamate) were sequentially added to a round bottom flask charged with cyclooct-2-yn-1-yl (2-aminoethyl)carbamate (560 mg, 2.67 mmol, 1.00 equiv). The flask was then purged with nitrogen and cooled to 0°C in an ice-water bath. Acryloyl chloride (226 µL, 2.79 mmol, 1.05 equiv) was added dropwise via syringe. The reaction mixture was allowed to warm to rt by removing the ice-water bath. After 45 min, the reaction mixture was quenched with methanol (500 µL) then concentrated under reduced pressure. The crude oil was purified by flash column chromatography on silica gel (eluent: 60→100% ethyl acetate in hexanes) to give the title compound as a white foam (471 mg, 67%). ¹H NMR (500 MHz, CDCl₃, 25°C): δ 6.55 (t, *J* = 5.6 Hz, 1H), 6.23 (dd, *J* = 17.1, 1.5 Hz, 1H), 6.09 (dd, *J* = 17.0, 10.3 Hz, 1H), 5.60 (dd, *J* = 10.2, 1.5 Hz, 1H), 5.35 (s, 1H), 5.22 (d, *J* = 3.5 Hz, 1H), 3.45–3.39 (m, 2H), 3.32 (d, *J* = 5.8 Hz, 2H), 2.27–2.19 (m, 1H), 2.13 (dddd, *J* = 24.1, 14.2, 7.6, 3.9 Hz, 2H), 1.95 (ddd, *J* = 14.4, 9.0, 6.6 Hz, 1H), 1.86

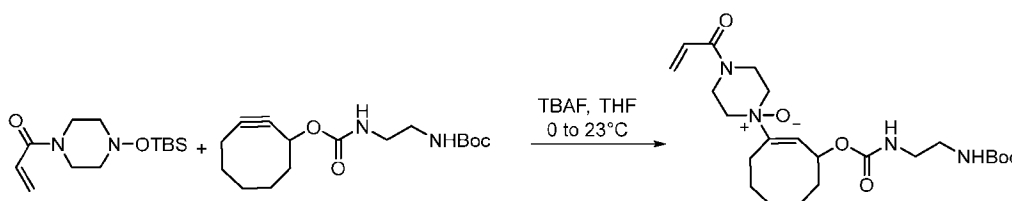
(dt, $J = 15.4, 7.2, 6.1, 2.3$ Hz, 2H), 1.78–1.70 (m, 1H), 1.67–1.57 (m, 2H), 1.54–1.44 (m, 1H). ^{13}C NMR (125.8 MHz, CDCl_3 , 25°C): δ 166.5, 156.8, 131.0, 126.7, 101.9, 91.1, 67.5, 42.0, 40.9, 40.6, 34.4, 29.8, 26.3, 20.9.



[00154] *(E)-1-(3-(((2-Acrylamidoethyl)carbamoyl)oxy)cyclooct-1-en-1-yl)-4-acryloylpiperazine 1-oxide*

[00155] THF (1 mL) and cyclooct-2-yn-1-yl (2-acrylamidoethyl)carbamate (48.9 mg, 185 μmol , 1.00 equiv) were sequentially added to a 4 mL glass vial charged with 1-(4-((*tert*-butyldimethylsilyl)oxy)piperazin-1-yl)prop-2-en-1-one (50.0 mg, 185 μmol , 1.00 equiv). The vial was purged with nitrogen. A solution of tetrabutylammonium fluoride (1.0 M in THF, 203 μL , 203 μmol , 1.10 equiv) was added dropwise via syringe at rt. After 2 hours, the crude mixture was concentrated under reduced pressure, and purified by flash column chromatography on silica gel (eluent: 5→20% methanol in DCM, 0.2% TEA) to give the title compound as a white foam (73 mg, 94%). ^1H NMR (500 MHz, CD_3OD , 25°C): δ 6.82 (dd, $J = 16.8, 10.7$ Hz, 1H), 6.52–6.44 (m, 1H), 6.30–6.18 (m, 3H), 5.82 (dd, $J = 10.6, 1.9$ Hz, 1H), 5.67 (dd, $J = 8.4, 3.7$ Hz, 1H), 5.41 (ddd, $J = 11.8, 7.5, 4.5$ Hz, 1H), 4.61 (d, $J = 12.4$ Hz, 1H), 4.17 (d, $J = 14.0$ Hz, 1H), 4.05 (t, $J = 13.1$ Hz, 1H), 3.85 (dt, $J = 24.5, 11.3$ Hz, 1H), 3.69 (dq, $J = 24.0, 13.0, 12.4$ Hz, 2H), 3.36 (q, $J = 6.4$ Hz, 2H), 3.24 (dd, $J = 7.1, 5.1$ Hz, 3H), 3.11–2.99 (m, 1H), 2.84 (d, $J = 15.9$ Hz, 1H), 2.59 (ddd, $J = 16.0, 12.7, 4.2$ Hz, 1H), 2.01 (ddd, $J = 13.8, 8.8, 4.2$ Hz, 1H), 1.91 (ddd, $J = 14.7, 7.6, 3.3$ Hz, 1H), 1.79–1.51 (m, 6H), 1.34 (t, $J = 7.3$ Hz, 1H). ^{13}C NMR (125.8 MHz, CD_3OD , 25°C): δ 167.0, 166.1, 156.9, 130.7, 128.0, 127.0, 125.4, 124.4, 72.0, 39.9, 38.9, 34.6, 25.4, 24.8, 23.4.

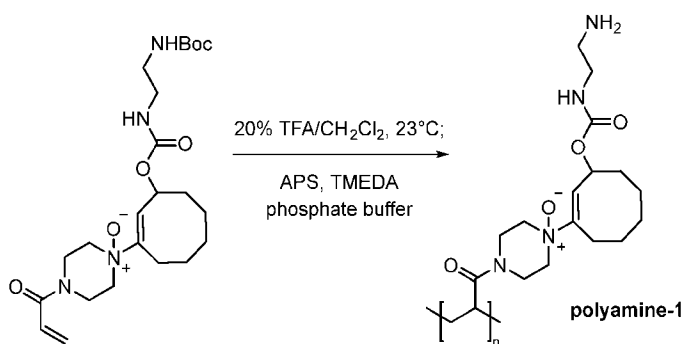
[00156] Example 3: Synthesis of Polyamine-1



[00157] *(E)-4-Acryloyl-1-(3-(((2-((tert-*

butoxycarbonyl)amino)ethyl)carbamoyl)oxy)cyclooct-1-en-1-yl)piperazine 1-oxide

[00158] THF (4 mL) and *tert*-butyl cyclooct-2-yn-1-yl ethane-1,2-diyl dicarbamate (246 mg, 795 μ mol, 1.00 equiv) were sequentially added to a round bottom flask charged with 1-(4-(((*tert*-butyldimethylsilyl)oxy)piperazin-1-yl)prop-2-en-1-one (215 mg, 795 μ mol, 1.00 equiv). The flask was then purged with nitrogen and cooled to 0°C in an ice-water bath. A solution of tetrabutylammonium fluoride (1.0 M in THF, 880 μ L, 880 μ mol, 1.10 equiv) was then added dropwise via syringe and the solution was allowed to warm to rt by removing the ice-water bath. After 2 hours, the crude mixture was concentrated under reduced pressure, and purified by flash column chromatography on silica gel (eluent: 5→15% methanol in dichloromethane, 0.2% triethylamine) to give the title compound as a white foam (291 mg, 79%). ¹H NMR (500 MHz, CD₃OD, 25°C): δ 6.82 (dd, *J* = 16.8, 10.7 Hz, 1H), 6.41 (d, *J* = 7.2 Hz, 1H), 6.30 (dd, *J* = 16.8, 1.9 Hz, 1H), 5.85 (dd, *J* = 10.7, 1.8 Hz, 1H), 5.44–5.32 (m, 1H), 4.76 (s, 1H), 4.36 (s, 1H), 3.95 (d, *J* = 49.5 Hz, 5H), 3.58 (s, 1H), 3.28–3.24 (m, 7H), 3.22–3.09 (m, 4H), 2.89 (dt, *J* = 15.9, 4.2 Hz, 1H), 2.68 (ddd, *J* = 16.4, 12.5, 4.1 Hz, 1H), 2.17 (s, 2H), 2.00 (dddd, *J* = 41.1, 10.0, 7.8, 3.9 Hz, 2H), 1.45 (s, 9H). ¹³C NMR (125.8 MHz, CD₃OD, 25°C): δ 166.1, 128.5, 126.6, 78.7, 71.8, 62.4, 62.0, 58.1, 40.6, 34.1, 29.9, 25.2, 24.5, 23.4, 23.0, 22.8, 19.3, 12.5.



[00159] *Polyamine-1*

A solution of TFA in DCM (20% v/v, 2 mL) was added to a glass vial charged with *(E)-4-acryloyl-1-(3-(((2-((tert-butoxycarbonyl)amino)ethyl)carbamoyl)oxy)cyclooct-1-en-1-yl)piperazine 1-oxide* (104 mg, 220 μ mol, 1.00 equiv). The resulting solution was stirred for 2 hours at rt. The reaction mixture was concentrated under reduced pressure then placed under reduced pressure for 2 hours. Aqueous phosphate buffer solution (100 mM, 110 μ L) and tetramethylethylenediamine (10.6 μ L, 71.0 μ mol, 0.323 equiv) were sequentially added to the crude oil. The reaction mixture was degassed by bubbling with nitrogen for 5 min.

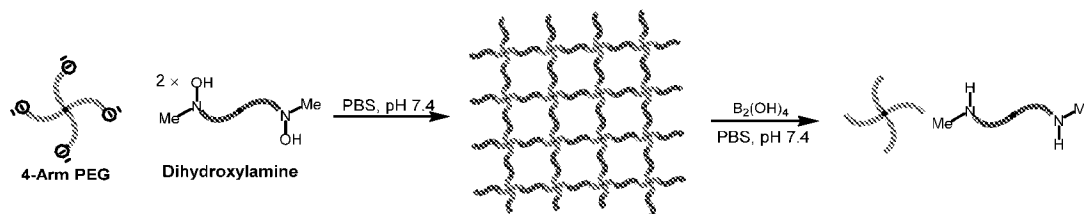
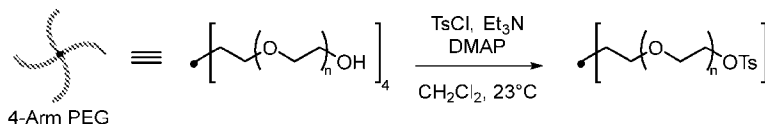
Ammonium persulfate (10.0 mg, 44.0 μ mol, 0.20 equiv) was added in one portion under nitrogen and stirred for 16 hours at rt. The reaction mixture was diluted to a final volume of 500 μ L with water and purified by spin filter (3K MWCO, 4 $\times$ 3800g) to give polyamine-1 with a mass recovery of 52%.

[00160] Example 4: Procedure for the synthesis of chemically degradable polyacrylamide hydrogels

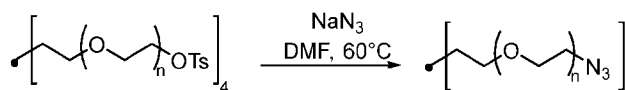
[00161] Chemically degradable hydrogels were fabricated by following previous reports (Freedman *et al.*, Adv. Mater., 2021, 33(17):e2008553) using (*E*)-*N*-(2-(2-acrylamidoethoxy)ethyl)-3-(((2-acrylamidoethyl)carbamoyl)oxy)-*N*-methylprop-1-en-1-amine oxide and (*E*)-1-(3-(((2-acrylamidoethyl)carbamoyl)oxy)cyclooct-1-en-1-yl)-4-acryloylpiperazine 1-oxide as chemical cross-linkers. Polyacrylamide gels were synthesized by mixing acrylamide in water at the desired weight per volume percentage (e.g., 0.03 to 20 w/v%). To the fully dissolved solution was added a desired weight per volume of (*E*)-*N*-(2-(2-acrylamidoethoxy)ethyl)-3-(((2-acrylamidoethyl)carbamoyl)oxy)-*N*-methylprop-1-en-1-amine oxide or (*E*)-1-(3-(((2-acrylamidoethyl)carbamoyl)oxy)cyclooct-1-en-1-yl)-4-acryloylpiperazine 1-oxide. Tetramethylethylenediamine (2% w/v) and ammonium persulfate (6.6% w/v) were added and briefly stirred. The resulting solution was left to gel. Gelation was verified by inversion test (FIG. 1) and remained in the base of the vial. A schematic of the process is shown in FIG. 2. A series of polyacrylamide gels with a varying percentage of cross-linker (0.03 to 0.3 w/v%) were synthesized and cast (FIG. 3A). FIG. 3B confirms that an exemplary polyacrylamide gel (0.12 w/v%) is resistant to stretch loading and unloading.

[00162] Example 5: Procedure for the degradation of polyacrylamide hydrogels

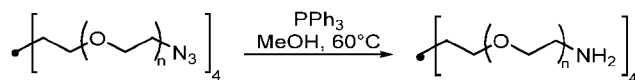
[00163] Chemically degradable gels were submerged in tetrahydroxydiboron (100 mM) in water. Degradation was verified by inversion test (FIG. 4-FIG. 6C) with the degraded gels no longer remaining in the base of the vial.

[00164] Example 6: Synthesis of 4-Arm-PEG-COT and dihydroxyamines**[00165]** *4-Arm PEG-COT***[00166]** *10 kDa 4-Arm PEG-OTs*

[00167] DCM (20 mL) was added to a round bottom flask charged with 10 kDa 4-Arm PEG-OH (Jenkem, 6.00 g, 0.600 mmol, 1.00 equiv), 4-dimethylaminopyridine (36.7 mg, 0.300 mmol, 0.500 equiv) and tosyl chloride (686 mg, 3.60 mmol, 6.00 equiv). TEA (1.01 mL, 7.20 mmol, 12.0 equiv) was then added via syringe and the resulting solution was stirred for 16 hours at rt. The reaction mixture was concentrated under reduced pressure, and the resulting solids were re-dissolved in DCM (10 mL) and diethyl ether (200 mL). The mixture was stirred at rt for 30 min before placing it in a refrigerator (4°C) for 6 hours. The precipitates were filtered and washed with diethyl ether (3 × 100 mL), and dried under reduced pressure to give the title compound as a white solid (5.88 g, 98%).

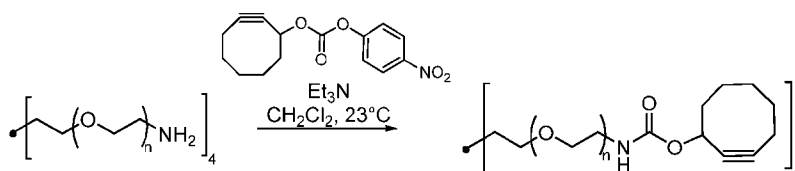
**[00168]** *10 kDa 4-Arm PEG-N₃*

[00169] A round bottom flask was charged with 10 kDa 4-Arm PEG-OTs (1.00 g, 0.100 mmol, 1.00 equiv) and sodium azide (32.5 mg, 0.500 mmol, 5.00 equiv) and purged with nitrogen. DMF (5 mL) was added via syringe and the resulting solution was heated to 60°C and stirred for 16 hours. The crude mixture was concentrated under reduced pressure and diluted with water (30 mL). The aqueous layer was extracted with DCM (3 × 20 mL), and the combined organic layers were washed with brine (60 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting solid was redissolved in DCM (5 mL) and precipitated with diethyl ether (200 mL) at 4°C for 6 hours. The solids filtered and washed with diethyl ether (3 × 100 mL) and dried under reduced pressure to give the title compound as a white solid (721 mg, 72%).



[00170] 10 kDa 4-Arm PEG-NH₂

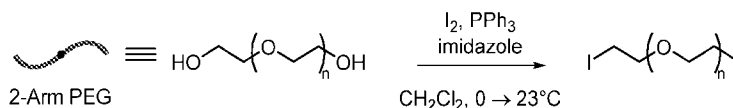
[00171] A round bottom flask was sequentially charged with 4-Arm PEG-N₃ (820 mg, 820 μmol 1.00 equiv) and triphenylphosphine (263 mg, 984 μmol, 12.0 equiv). Methanol (3 mL) was added via a syringe and the reaction was heated to 60°C and stirred for 6 hours. The reaction mixture was allowed to cool to rt then concentrated under reduced pressure. The resulting viscous oil was purified by flash column chromatography on silica gel (eluent: 5→12% methanol in dichloromethane) to give the title compound as a white solid (673 mg, 82%).



[00172] 10 kDa 4-Arm PEG-COT

[00173] DCM (2 mL) was added to a round bottom flask charged with 10 kDa 4-Arm PEG-NH₂ (520 mg, 52.0 μmol, 1.00 equiv). To the resulting solution was added TEA (86.9 μL, 622 μmol, 8.00 equiv) via syringe, then 2-cyclooctynyl-4-nitrophenyl carbonate (180 mg, 311 μmol, 6.00 equiv) in one portion. The reaction mixture was stirred for 4 hours at rt, then concentrated under reduced pressure. The crude oil was purified by flash column chromatography on silica gel (eluent: 2% acetic acid in ethyl acetate then 5→10% methanol in dichloromethane) to give the title compound as an off-white solid (392 mg, 75%).

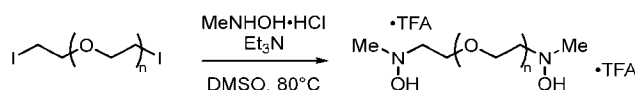
[00174] 2-Arm PEG-NOH



[00175] 400 Da 2-Arm PEG-I

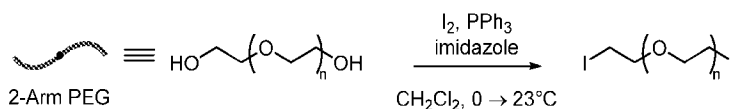
[00176] DCM (15 mL) was added to a round bottom flask charged triphenylphosphine (1.52 g, 3.00 mmol, 3.00 equiv) and imidazole (544 mg, 4.00 mmol, 4.00 equiv). The flask was then purged with nitrogen and cooled to 0°C in an ice-water bath. To the stirring solution was added iodine (1.57 g, 3.00 mmol, 3.00 equiv) dissolved in DCM (5 mL) via syringe and the reaction mixture was allowed to warm to rt by removing the ice-water bath. To the slurry, 400 Da 2-Arm PEG-OH (Jenkem, 800 mg, 2.00 mmol, 1.00 equiv) dissolved in DCM (2 mL) was added dropwise via syringe and the flask was covered with foil and stirred for 3 hours at

rt. The reaction mixture was then concentrated under reduced pressure, diluted with ethyl acetate (20 mL), filtered over a bed of Celite®, and washed with cold ethyl acetate (3 × 20 mL). The solution was concentrated under reduced pressure, then diluted with saturated aqueous sodium bicarbonate, and the aqueous layer was extracted with DCM (3 × 100 mL). The combined organic layers were washed with saturated aqueous sodium thiosulfate (100 mL), then aqueous hydrogen chloride (1N, 100 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (eluent: 5→10% methanol in DCM) to give the title compound and triphenylphosphine oxide as inseparable mixtures. The resulting off-white oil was used as is in the next step.



[00177] 400 Da 2-Arm PEG-NOH·TFA

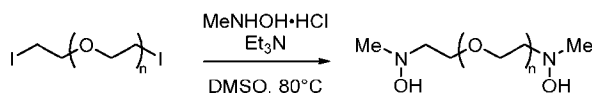
[00178] A round bottom flask was charged with 400 Da 2-Arm PEG-I (800 mg, 2.00 mmol, 1.00 equiv) and *N*-methyl-hydroxylamine hydrochloride salt (669 mg, 8.00 mmol, 4.00 equiv). The reaction flask was purged with nitrogen. DMSO (4 mL) and TEA (2.24 mL, 16.0 mmol, 8.00 equiv) were sequentially added via syringe. The flask was covered with foil and heated to 80°C and stirred for 6 hours. The reaction flask was cooled to 0°C in an ice-water bath and diluted with saturated aqueous sodium bicarbonate (25 mL). The aqueous layer was extracted with DCM (3 × 150 mL). The combined organic layers were washed with brine (4 × 200 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The yellow oil was purified by flash column chromatography on silica gel (eluent: 10→60% CMA in chloroform) to give the title compound as a pale yellow oil (482 mg, 60% over two steps). 400 Da 2-Arm PEG-NOH was then introduced to Isolera Biotage (eluent: 0→100% acetonitrile in water, 0.1% TFA) to provide 400 Da 2-Arm PEG-NOH·TFA as di-trifluoroacetic acid salts. The product was stored as salts to suppress air oxidation of hydroxylamines.



[00179] 1 kDa 2-Arm PEG-I

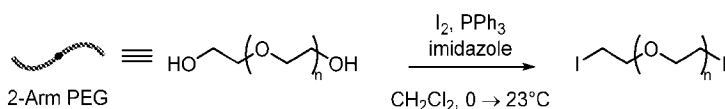
[00180] DCM (20 mL) was added to a round bottom flask charged with triphenylphosphine (1.57 g, 6.00 mmol, 3.00 equiv) and imidazole (544 mg, 8.00 mmol, 4.00 equiv). The flask

was then purged with nitrogen and cooled to 0°C in an ice-water bath. To the stirring solution was added iodine (1.52 g, 6.00 mmol, 3.00 equiv) dissolved in DCM (10 mL) via syringe and the reaction mixture was allowed to warm to rt by removing the ice-water bath. To the slurry, a solution of 1 kDa 2-Arm PEG-OH (Jenkem, 2.00 g, 2.00 mmol, 1.00 equiv) dissolved in DCM (6 mL) was added dropwise via syringe, and the flask was covered with foil, and stirred for 3 hours at rt. The reaction mixture was then concentrated under reduced pressure, diluted with ethyl acetate (50 mL), and filtered over a bed of Celite®, and washed with cold ethyl acetate (3 × 20 mL). The solution was then concentrated under reduced pressure, diluted with saturated aqueous sodium bicarbonate (100 mL), and the aqueous layer was extracted with DCM (3 × 150 mL). The combined organic layers were washed with saturated aqueous sodium thiosulfate (100 mL), then aqueous hydrogen chloride (1N, 100 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (eluent: 2→10% methanol in DCM) to give the title compound as an off-white solid (1.74 g, 87%).



[00181] 1 kDa 2-Arm PEG-NOH

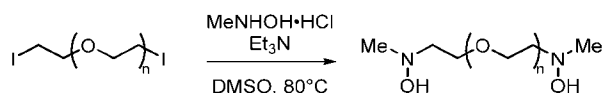
[00182] A round bottom flask was charged with 1 kDa 2-Arm PEG-I (1.00g, 1.00 mmol, 1.00 equiv) and *N*-methyl-hydroxylamine hydrochloride salt (334 mg, 4.00 mmol, 4.00 equiv). The reaction flask was purged with nitrogen. DMSO (4 mL) and TEA (1.12 mL, 8.00 mmol, 8.00 equiv) were sequentially added via syringe. The flask was covered with foil and heated to 80°C and stirred for 6 hours. The reaction flask was cooled to 0°C in an ice-water bath and diluted with saturated aqueous sodium bicarbonate (50 mL). The aqueous layer was extracted with DCM (3 × 150 mL). The combined organic layers were washed with brine (4 × 200 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The yellow oil was purified by flash column chromatography on silica gel (eluent: 10→60% CMA in chloroform) to give the title compound a pale-yellow oil (688 mg, 69%).



[00183] 2 kDa 2-Arm PEG-I

[00184] DCM (50 mL) was added to a round bottom flask charged with triphenylphosphine (3.93 g, 15.0 mmol, 3.00 equiv) and imidazole (1.36 g, 20.0 mmol, 4.00 equiv). The flask

was then purged with nitrogen and cooled to 0°C in an ice-water bath. To the stirring solution was added via syringe a solution of iodine (3.81 g, 15.0 mmol, 3.00 equiv) dissolved in DCM (20 mL). The reaction mixture was allowed to warm to rt by removing the ice-water bath. To the slurry, a solution of 2 kDa 2-Arm PEG-OH (Jenkem, 10.0 g, 5.00 mmol, 1.00 equiv) dissolved in DCM (10 mL) was added dropwise via syringe and the flask was covered with foil and stirred for 3 hours at rt. The reaction mixture was then concentrated under reduced pressure, diluted with ethyl acetate (150 mL), filtered over a bed of Celite®, and washed with cold ethyl acetate (3 × 50 mL). The solution was then concentrated under reduced pressure, diluted with saturated aqueous sodium bicarbonate (200 mL), and the aqueous layer was extracted with DCM (3 × 250 mL). The combined organic layers were washed with saturated aqueous sodium thiosulfate (250 mL), then aqueous hydrogen chloride (1N, 250 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography on silica gel (eluent: 2→10% methanol in DCM) to give the title compound and triphenylphosphine oxide as inseparable mixtures. The resulting off-white solid was used as is in the next step.



[00185] 2 kDa 2-Arm PEG-NOH

[00186] A round bottom flask was charged with 2 kDa 2-Arm PEG-I (10.0 g, 5.00 mmol, 1.00 equiv) and *N*-methyl-hydroxylamine hydrochloride salt (1.67 g, 20.0 mmol, 4.00 equiv). The reaction flask was purged with nitrogen. DMSO (20 mL) and TEA (5.60 mL, 40.0 mmol, 8.00 equiv) were sequentially added via syringe. The flask was covered with foil and heated to 80°C and stirred for 6 hours. The reaction flask was cooled to 0°C in an ice-water bath and diluted with saturated aqueous sodium bicarbonate (200 mL). The aqueous layer was extracted with DCM (3 × 250 mL). The combined organic layers were washed with brine (4 × 300 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The yellow oil was purified by flash column chromatography on silica gel (eluent: 10→60% CMA in chloroform) to give the title compound as a pale-yellow oil (7.29 g, 73% over two steps).

[00187] Example 7: General procedure for gelation of hydrogels containing 4-Arm PEG-COT and 2-Arm PEG-NOH

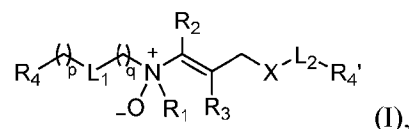
[00188] 4-Arm PEG-COT (1 equiv) was mixed with 2-Arm PEG-NOH (2 equiv) in a glass vial at the desired w/v % (1%, 5%, 10%, 20%). The mixture was sonicated until full dissolution and were left until gelation. For 2-Arm PEG-NOH stored as trifluoroacetic acid salts, 1 N aqueous sodium hydroxide (2 equiv) was used to de-salt the hydroxylamines in-situ for gelation.

[00189] All patent publications and non-patent publications are indicative of the level of skill of those skilled in the art to which this disclosure pertains. All these publications are herein incorporated by reference to the same extent as if each individual publication were specifically and individually indicated as being incorporated by reference.

[00190] Although the disclosure herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present disclosure. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present disclosure as defined by the appended claims.

What is claimed is:

1. A compound having a structure represented by formula I:



or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein:

p is 0 or 1;

q is 0 or 1;

R₁ is (C₁-C₈) alkyl, (C₃-C₁₀) carbocyclyl, or 4- to 10-membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S, wherein said alkyl, carbocyclyl or heterocyclyl is further optionally substituted, or

R₁ and R₂, together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl, or

R₁ and R₃, together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl;

R₂ is hydrogen, (C₁-C₈) alkyl, chloro, bromo, or iodo;

R₃ is hydrogen, (C₁-C₈) alkyl, chloro, bromo, or iodo;

L₁ is absent or a linker;

L₂ is absent or a linker;

X is a leaving group; and

R₄ and R₄' are independently a polymerizable moiety or a chemical moiety, provided that at least one of R₄ and R₄' is a polymerizable moiety.

2. The compound of claim 1, wherein X is an ester, a carbonate, a carbamate, a sulfoxide, a sulfonate, a sulfate, a sulfone, a thioester, or a thionoester.

3. The compound of claim 1 or 2, wherein L₁ is an alkylene chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of -O-, -S-, -N(R')-, -C≡C-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(NOR')-, -C(O)N(R')-, -C(O)N(R')C(O)-, -R'C(O)N(R')R'-, -C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -

C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(Me)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, -N(R')S(O)N(R')-, -OP(O)O(R')O-, -N(R')P(O)N(R'R')N(R')-, C₃-C₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C₁-C₆ alkyl, wherein the interrupting and the one or both terminating groups may be the same or different, or

a polyethylene glycol chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of -O-, -S-, -N(R')-, -C≡C-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(NOR')-, -C(O)N(R')-, -C(O)N(R')C(O)-, -R'C(O)N(R')R'-, -C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(Me)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, -N(R')S(O)N(R')-, -OP(O)O(R')O-, -N(R')P(O)N(R'R')N(R')-, C₃-C₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C₁-C₆ alkyl, wherein the interrupting and the one or both terminating groups may be the same or different.

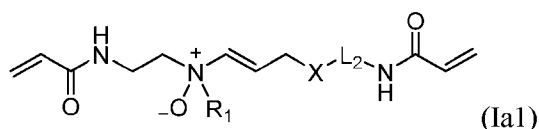
4. The compound of any one of claims 1-3, wherein L₂ is an alkylene chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of -O-, -S-, -N(R')-, -C≡C-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(NOR')-, -C(O)N(R')-, -C(O)N(R')C(O)-, -R'C(O)N(R')R'-, -C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(Me)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, -N(R')S(O)N(R')-, -OP(O)O(R')O-, -N(R')P(O)N(R'R')N(R')-, C₃-C₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C₁-C₆ alkyl, wherein the interrupting and the one or both terminating groups may be the same or different, or

a polyethylene glycol chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of -O-, -S-, -N(R')-, -C≡C-, -C(O)-, -C(O)O-, -OC(O)-, -

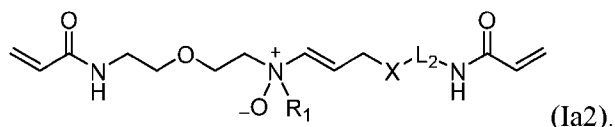
OC(O)O-, -C(NOR')-, -C(O)N(R')-, -C(O)N(R')C(O)-, -R'C(O)N(R')R'-, -C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(Me)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, -N(R')S(O)N(R')-, -OP(O)O(R')O-, -N(R')P(O)N(R'R')N(R')-, C₃-C₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C₁-C₆ alkyl, wherein the interrupting and the one or both terminating groups may be the same or different.

5. The compound of claim 1, wherein R₄ and R₄' are acrylamide.

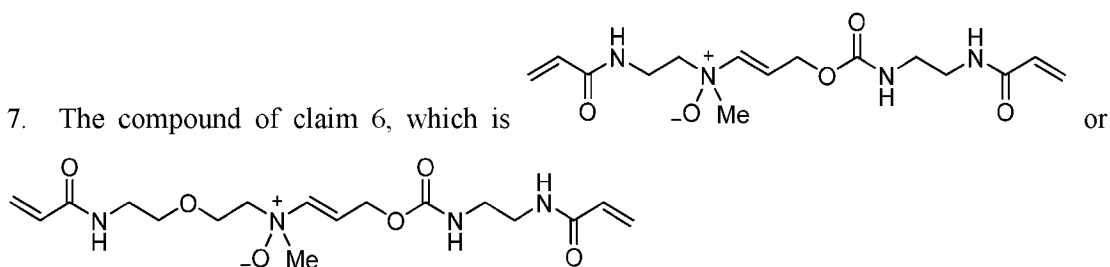
6. The compound of claim 1, which is of formula Ia1 or Ia2:



or



7. The compound of claim 6, which is



8. A polymer or hydrogel which is the reaction product of:

- i) a compound of formula I:
- $$\text{R}_4\text{---L}_1\text{---CH}_2\text{---N}^+\text{(R}_1\text{)}\text{=C(R}_2\text{)---CH}_2\text{---X---L}_2\text{---R}_4'$$
- (I),
- ii) a polymerizable moiety which is the same as or different from R₄ and/or R₄', and
- iii) an initiator,
- wherein:

R₁ is (C₁-C₈) alkyl, (C₃-C₁₀) carbocyclyl, or 4- to 10-membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S, wherein said alkyl, carbocyclyl or heterocyclyl is further optionally substituted, or

R₁ and R₂, together with the atoms to which they are attached form a 4- to 7-membered heterocyclyl, or

R₁ and R₃, together with the atoms to which they are attached form a 5- to 7-membered heterocyclyl;

R₂ is hydrogen, (C₁-C₈) alkyl, chloro, bromo, or iodo;

R₃ is hydrogen, (C₁-C₈) alkyl, chloro, bromo, or iodo;

L₁ is absent or a linker;

L₂ is absent or a linker;

X is a leaving group; and

R₄ and R₄' are independently a polymerizable moiety or a chemical moiety, provided that at least one of R₄ and R₄' is a polymerizable moiety.

9. The polymer or hydrogel of claim 8, wherein X is an ester, a carbonate, a carbamate, a sulfoxide, a sulfonate, a sulfate, a sulfone, a thioester, or a thionoester.

10. The polymer or hydrogel of claim 8 or 9, wherein L₁ is an alkylene chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of -O-, -S-, -N(R')-, -C≡C-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(NOR')-, -C(O)N(R')-, -C(O)N(R')C(O)-, -R'C(O)N(R')R'-, -C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(Me)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, -N(R')S(O)N(R')-, -OP(O)O(R')O-, -N(R')P(O)N(R')N(R')-, C₃-C₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C₁-C₆ alkyl, wherein the interrupting and the one or both terminating groups may be the same or different, or

a polyethylene glycol chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of -O-, -S-, -N(R')-, -C≡C-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(NOR')-, -C(O)N(R')-, -C(O)N(R')C(O)-, -R'C(O)N(R')R'-, -

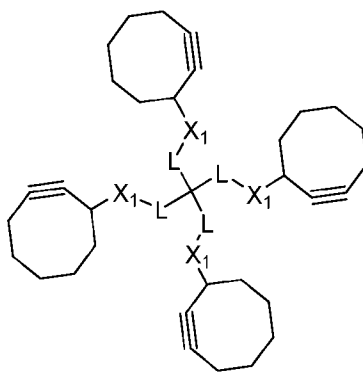
C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(Me)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, -N(R')S(O)N(R')-, -OP(O)O(R')O-, -N(R')P(O)N(R'R')N(R')-, C₃-C₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C₁-C₆ alkyl, wherein the interrupting and the one or both terminating groups may be the same or different.

11. The polymer or hydrogel of any one of claims 8-10, wherein L₂ is an alkylene chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of -O-, -S-, -N(R')-, -C≡C-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(NOR')-, -C(O)N(R')-, -C(O)N(R')C(O)-, -R'C(O)N(R')R'-, -C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(Me)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, -N(R')S(O)N(R')-, -OP(O)O(R')O-, -N(R')P(O)N(R'R')N(R')-, C₃-C₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C₁-C₆ alkyl, wherein the interrupting and the one or both terminating groups may be the same or different, or

a polyethylene glycol chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of -O-, -S-, -N(R')-, -C≡C-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(NOR')-, -C(O)N(R')-, -C(O)N(R')C(O)-, -R'C(O)N(R')R'-, -C(O)N(R')C(O)N(R')-, -N(R')C(O)-, -N(R')C(O)N(R')-, -N(R')C(O)O-, -OC(O)N(R')-, -C(NR')-, -N(R')C(NR')-, -C(NR')N(R')-, -N(R')C(NR')N(R')-, -OB(Me)O-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R')S(O)₂-, -S(O)₂N(R')-, -N(R')S(O)-, -S(O)N(R')-, -N(R')S(O)₂N(R')-, -N(R')S(O)N(R')-, -OP(O)O(R')O-, -N(R')P(O)N(R'R')N(R')-, C₃-C₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C₁-C₆ alkyl, wherein the interrupting and the one or both terminating groups may be the same or different.

12. The polymer or hydrogel of any one of claims 8-11, wherein R₄ is a polymerizable moiety and R₄' is a chemical moiety.
13. The polymer or hydrogel of any one of claims 8-12, wherein the polymerizable moiety is poly(acrylamide).
14. A process of preparing the polymer or hydrogel of any one of claims 8-13, comprising reacting the compound of formula I, a polymerizable moiety, and an initiator, wherein the reacting is carried out in the presence of a solvent.
15. The process of claim 14, wherein the solvent is a non-aqueous solvent.
16. The process of claim 14, wherein the solvent is an aqueous solvent.
17. The process of claim 16, wherein the aqueous solvent is a buffered solvent.
18. The process of claim 17, wherein the buffered solvent is phosphate-buffered saline.
19. The process of claim 18, wherein the pH of the phosphate-buffered saline is about 7.4.
20. The process of any one of claims 17-19, wherein the reacting is carried in the solvent with a concentration of is 1-25 wt%.
21. The process of claim 20, wherein the concentration is 1, 5, 10, or 15 wt%.
22. The process of any one of claims 14-21, wherein the reacting of the compound of formula I with the polymerizable moiety is in a ratio of 1-20 wt%.
23. The process of claim 22, wherein the ratio of the compound of formula I to polymerizable moiety is 3, 6, or 12 wt%.
24. The process of claim of any one of claims 14-23, wherein the polymerizable moiety is the same as R₄ and/or R₄'.

25. The process of claim of any one of claims 14-23, wherein the polymerizable moiety is different than R₄ and/or R₄'.
26. The process of claim of any one of claims 14-23, wherein the polymerizable moiety comprises two or more polymerizable moieties.
27. A method of degrading the polymer or hydrogel of any one of claims 8-13, comprising contacting the compound of formula II with a diboron reagent.
28. The method of claim 27, wherein the diboron reagent is a symmetrical diboron reagent.
29. The method of claim 27, wherein the diboron reagent is an unsymmetrical diboron reagent.
30. A polymer or hydrogel which is the reaction product of:



i) a 4-arm-cyclooct-2-yn-1-yl,

; and

ii) a dihydroxylamine, $\begin{matrix} R_5 & & R_5 \\ & \diagdown & / \\ & N-L-N \\ & | & | \\ & OH & OH \end{matrix}$,

wherein

each X₁ is a leaving group;

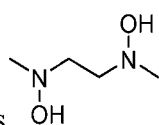
each L is a linker; and

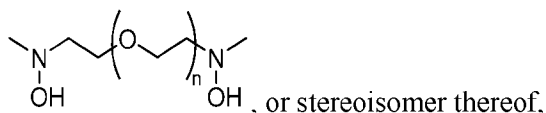
each R₅ is (C₁-C₈) alkyl, (C₃-C₁₀) carbocyclyl, or 4- to 10-membered heterocyclyl comprising 1 to 3 heteroatoms selected from O, N, and S, wherein said alkyl, carbocyclyl or heterocyclyl is further optionally substituted.

31. The polymer or hydrogel of claim 30, wherein each X_1 is an ester, a carbonate, a carbamate, a sulfoxide, a sulfonate, a sulfate, a sulfone, a thioester, or a thionoester.

32. The polymer or hydrogel of claim 30 or 31, wherein each L is an alkylene chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of $-O-$, $-S-$, $-N(R')-$, $-C\equiv C-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(NOR')-$, $-C(O)N(R')-$, $-C(O)N(R')C(O)-$, $-R'C(O)N(R')R'-$, $-C(O)N(R')C(O)N(R')-$, $-N(R')C(O)-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-OC(O)N(R')-$, $-C(NR')-$, $-N(R')C(NR')-$, $-C(NR')N(R')-$, $-N(R')C(NR')N(R')-$, $-OB(Me)O-$, $-S(O)_2-$, $-OS(O)-$, $-S(O)O-$, $-S(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R')S(O)_2-$, $-S(O)_2N(R')-$, $-N(R')S(O)-$, $-S(O)N(R')-$, $-N(R')S(O)_2N(R')-$, $-N(R')S(O)N(R')-$, $-OP(O)O(R')O-$, $-N(R')P(O)N(R'R')N(R')-$, C_3-C_{12} carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C_1-C_6 alkyl, wherein the interrupting and the one or both terminating groups may be the same or different, or

a polyethylene glycol chain, which may be interrupted by, and/or terminate (at either or both termini) in at least one of $-O-$, $-S-$, $-N(R')-$, $-C\equiv C-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(NOR')-$, $-C(O)N(R')-$, $-C(O)N(R')C(O)-$, $-R'C(O)N(R')R'-$, $-C(O)N(R')C(O)N(R')-$, $-N(R')C(O)-$, $-N(R')C(O)N(R')-$, $-N(R')C(O)O-$, $-OC(O)N(R')-$, $-C(NR')-$, $-N(R')C(NR')-$, $-C(NR')N(R')-$, $-N(R')C(NR')N(R')-$, $-OB(Me)O-$, $-S(O)_2-$, $-OS(O)-$, $-S(O)O-$, $-S(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R')S(O)_2-$, $-S(O)_2N(R')-$, $-N(R')S(O)-$, $-S(O)N(R')-$, $-N(R')S(O)_2N(R')-$, $-N(R')S(O)N(R')-$, $-OP(O)O(R')O-$, $-N(R')P(O)N(R'R')N(R')-$, C_3-C_{12} carbocyclyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl or any combination thereof, wherein each R' is independently H or optionally substituted C_1-C_6 alkyl, wherein the interrupting and the one or both terminating groups may be the same or different.

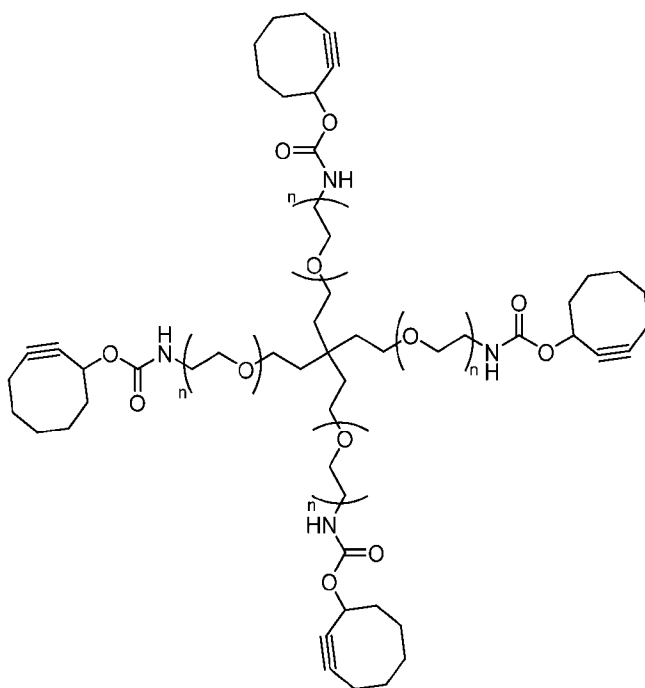
33. The polymer or hydrogel of claim 30, wherein the dihydroxylamine is  or



wherein n is an integer from 1-10000.

34. The polymer or hydrogel of claim 33, wherein the dihydroxylamine is about 2 kDa, about 1 kDa, or about 400Da.

35. The polymer or hydrogel of claim 30, wherein the 4-arm-cyclooct-2-yn-1-yl is of



formula II:

(II) or stereoisomer thereof,

wherein n is an integer from 1-10000.

36. The modifiable polymer or hydrogel of claim 35, wherein the 4-arm-cyclooct-2-yn-1-yl is about 10 kDa.

37. A process of preparing the polymer or hydrogel of claim 30, comprising reacting about one equivalent of the 4-arm-cyclooct-2-yn-1-yl with about two equivalents of the dihydroxylamine.

38. The process of claim 37, wherein the reacting is carried out in the presence of a solvent.

39. The process of claim 38, wherein the solvent is a buffered solvent.

- 40. The process of claim 39, wherein the buffered solvent is phosphate-buffered saline.
- 41. The process of claim 40, wherein the pH of the phosphate-buffered saline is about 7.4.
- 42. A method of degrading the polymer or hydrogel of claim 30, comprising contacting the hydrogel with a diboron reagent.
- 43. The method of claim 42, wherein the diboron reagent is a symmetrical diboron reagent.
- 44. The method of claim 42, wherein the diboron reagent is an unsymmetrical diboron reagent.

1/6

FIG. 1

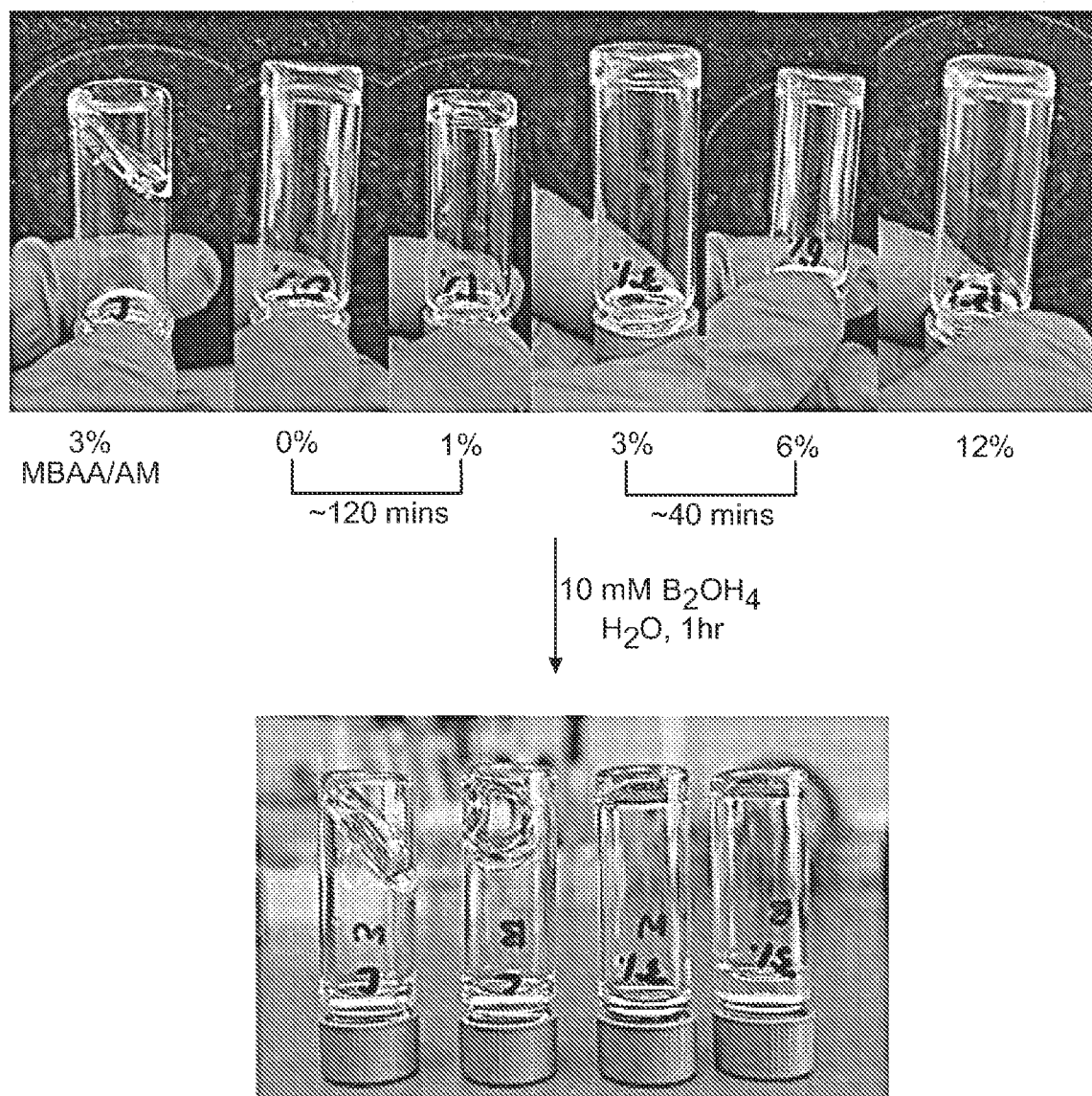
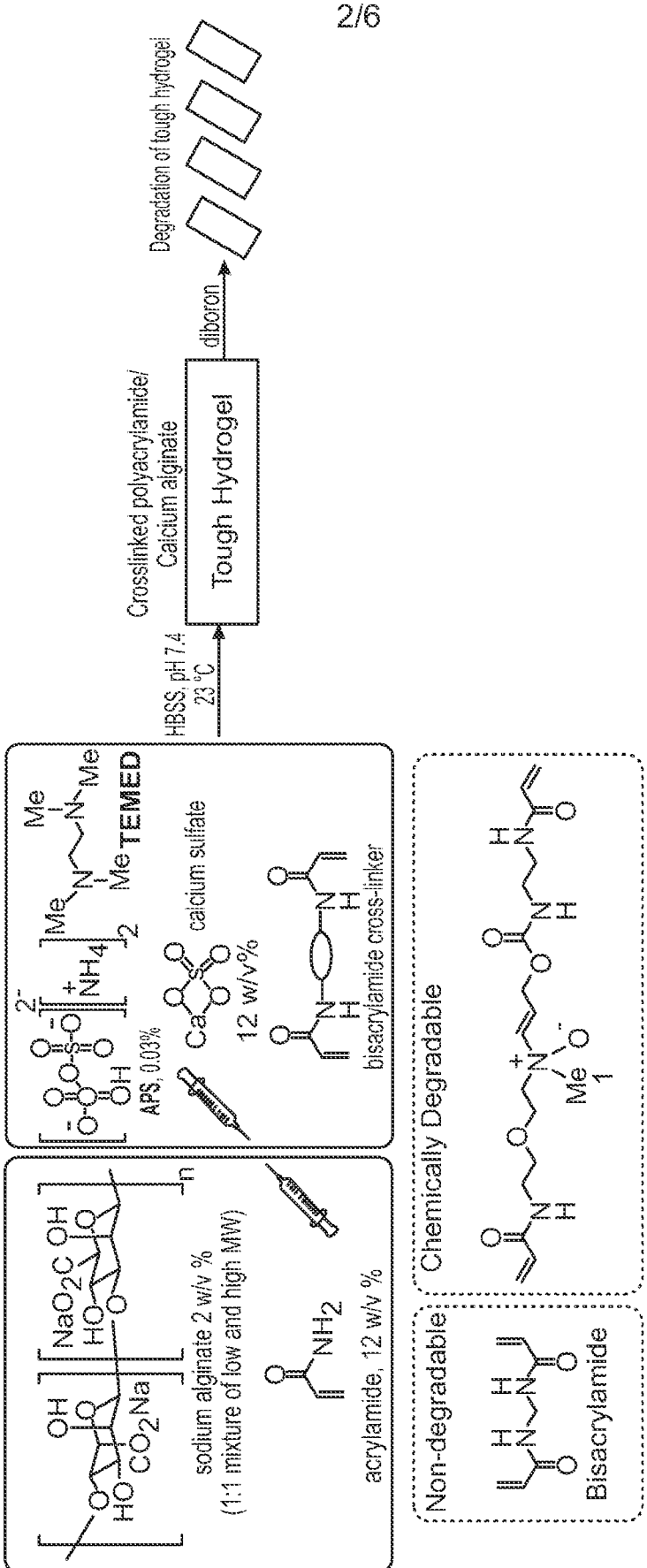


FIG. 2



3/6

FIG. 3A

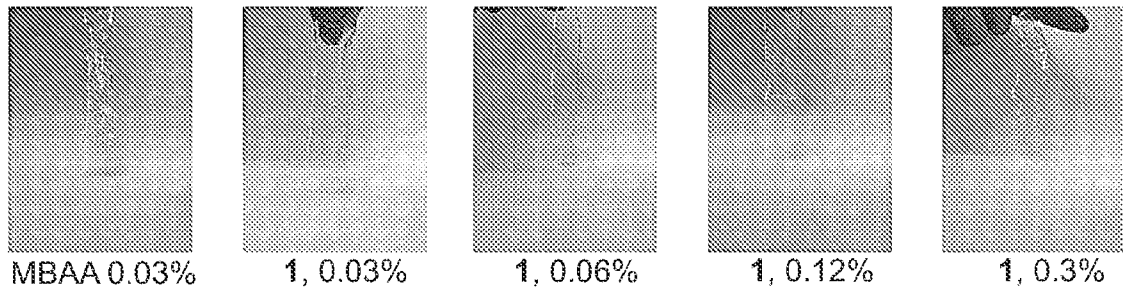


FIG. 3B

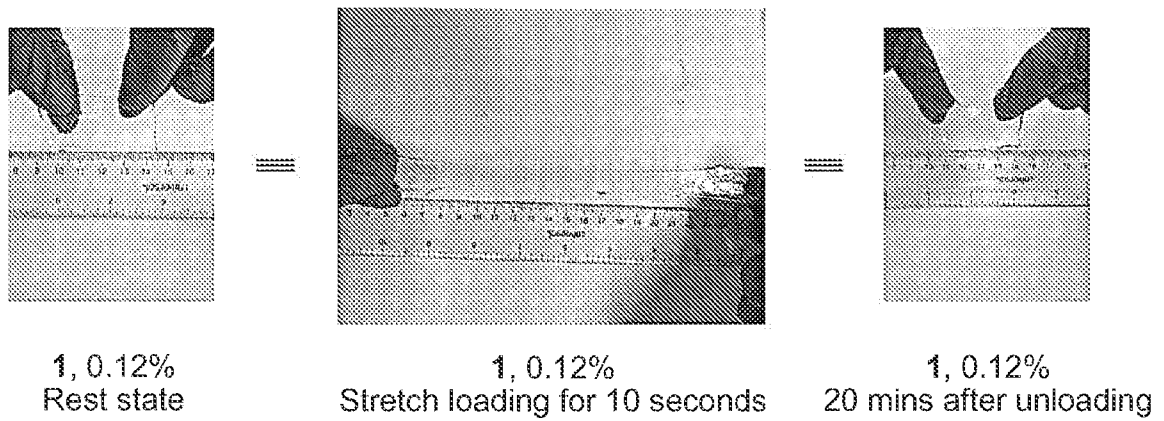
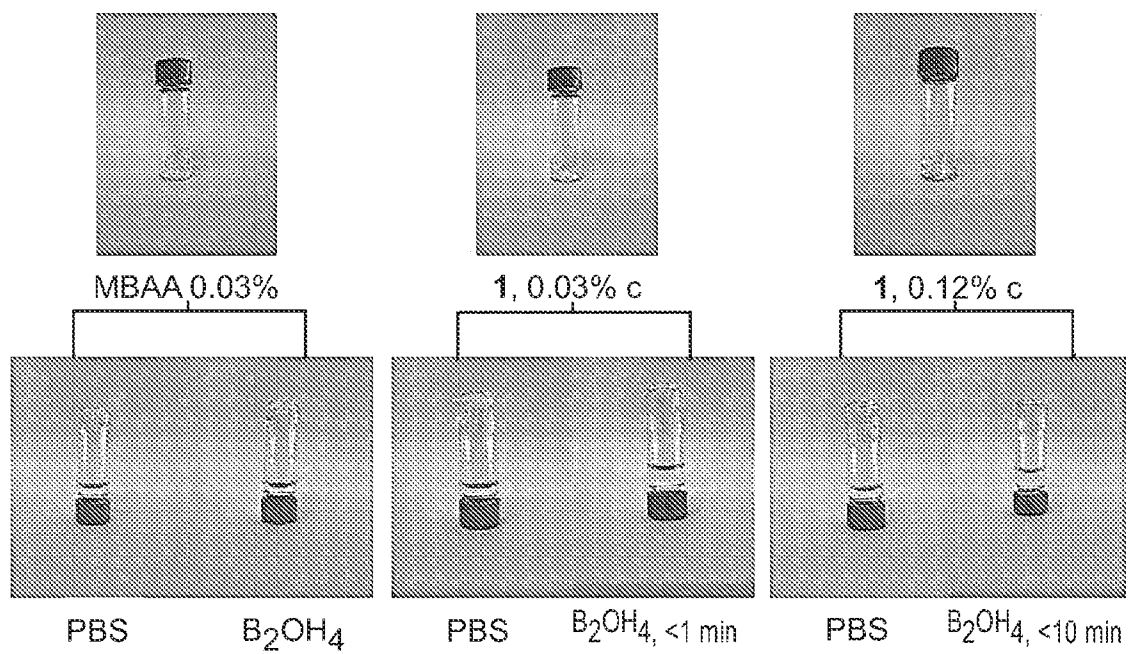


FIG. 4



4/6

FIG. 5A

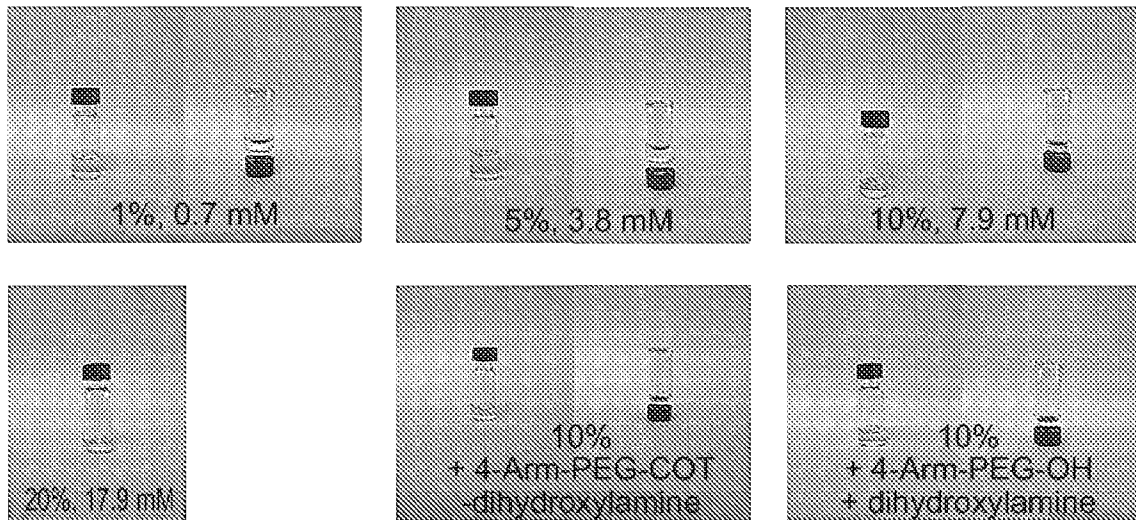
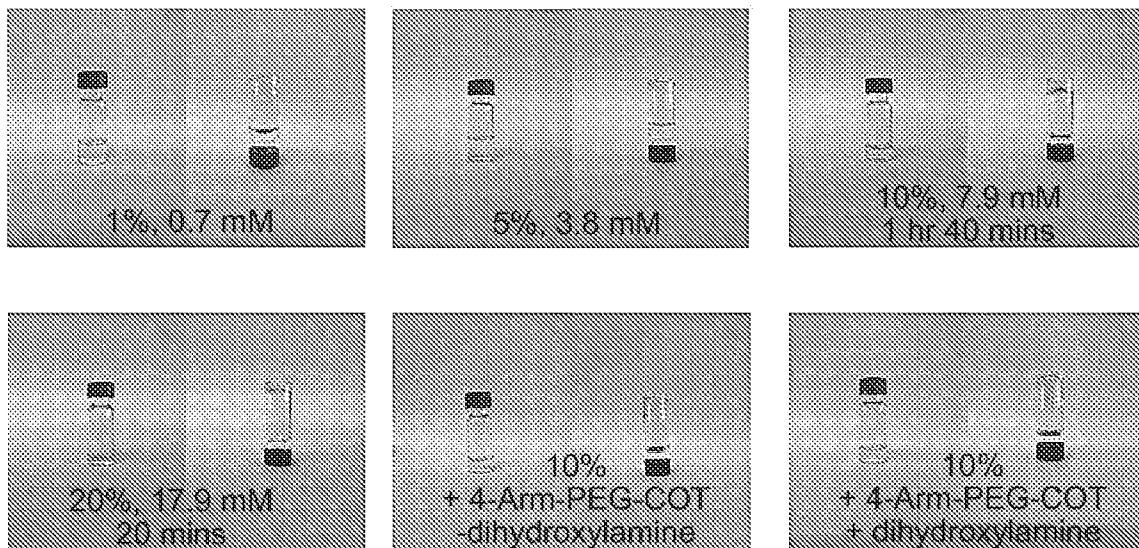


FIG. 5B



5/6

FIG. 5C

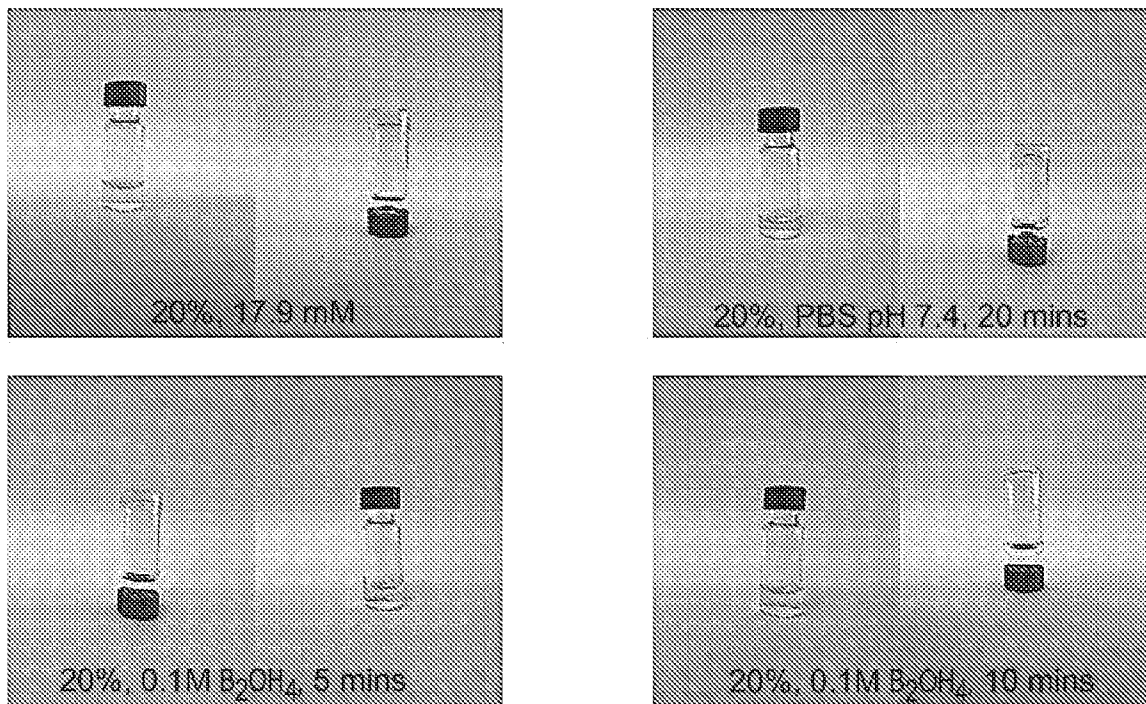
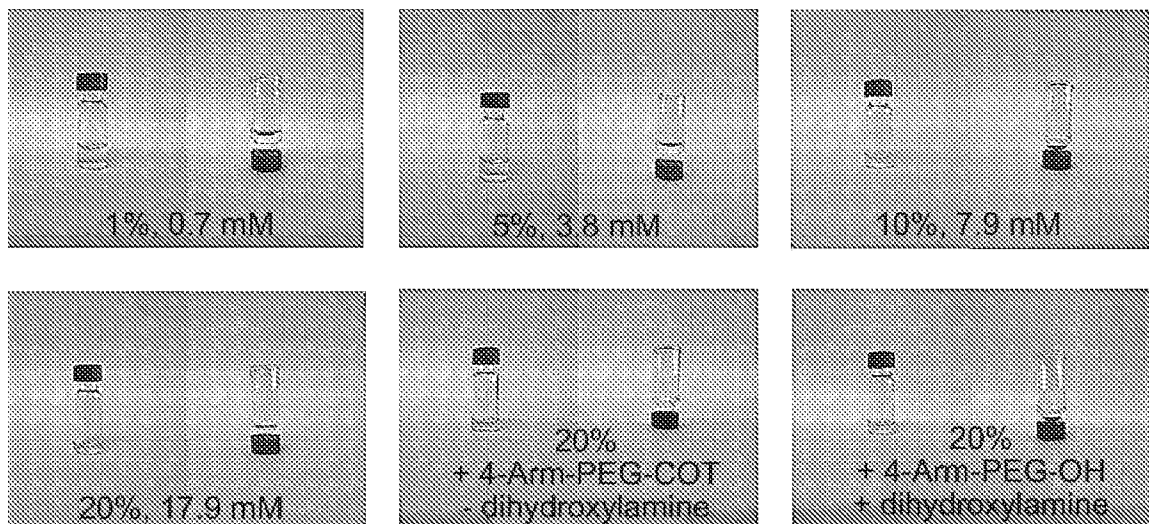


FIG. 6A



6/6

FIG. 6B

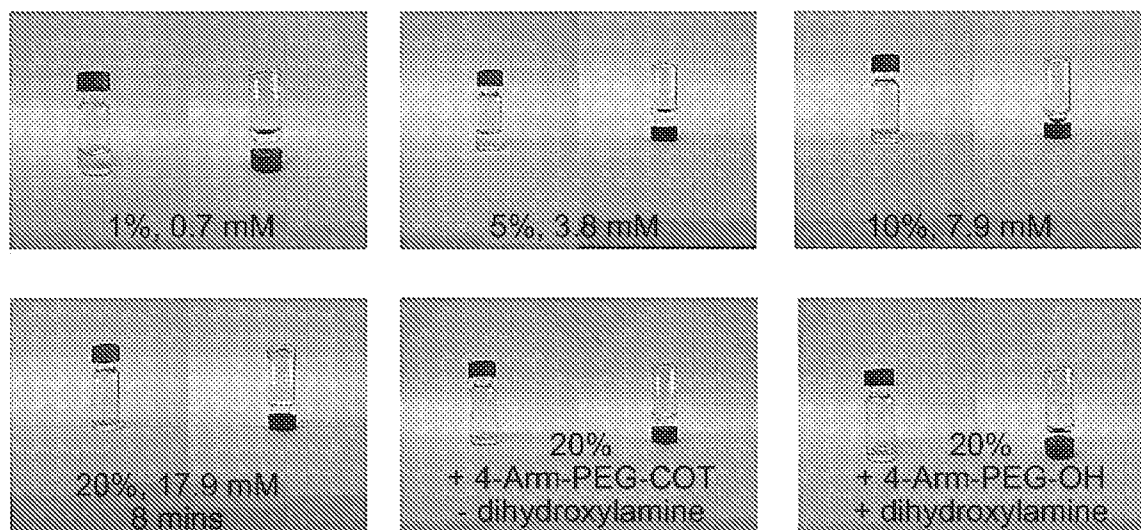


FIG. 6C

