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(54) **POLYMERIC DRUG DELIVERY SYSTEM CONTAINING A MULTI-SUBSTITUTED AROMATIC MOIETY**

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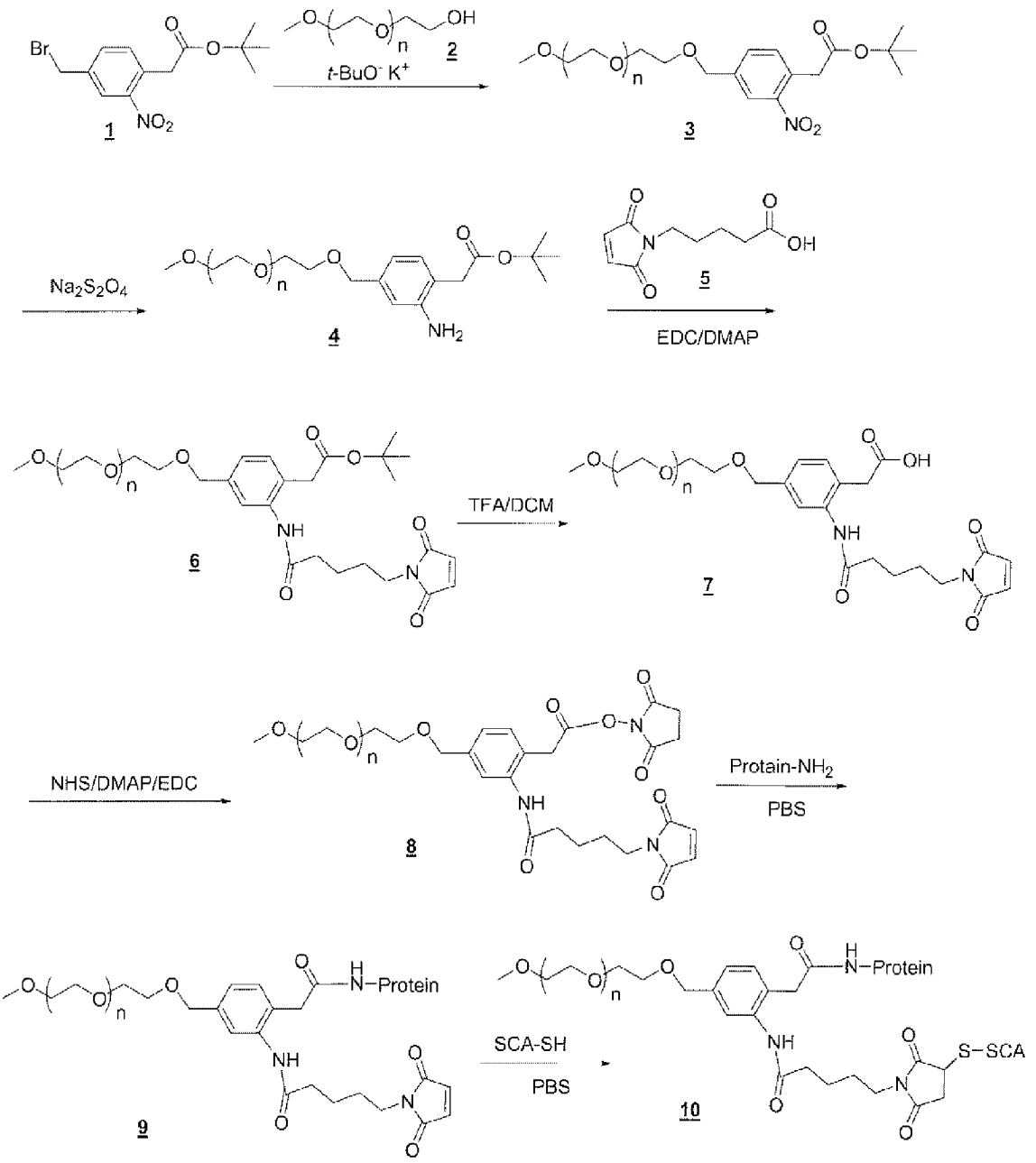
(57) **ABSTRACT**

The present invention provides polymeric delivery systems including a multi-substituted aromatic moiety. Methods of making the polymeric delivery systems and methods of treating mammals using the same are also disclosed.

FIG. 1


Br
NO2
1
OH
n
2
t-BuO⁻ K⁺
3
Na2S2O4
NH2
4
OH
5
EDC/DMAP
6
NH
TFA/DCM
OH
7
NHS/DMAP/EDC
8
Protain-NH2
PBS
H
N–Protein
9
SCA-SH
PBS
S–SCA
10

POLYMERIC DRUG DELIVERY SYSTEM CONTAINING A MULTI-SUBSTITUTED AROMATIC MOIETY

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of priority from U.S. Provisional Patent Application Ser. No. 60/949,168 filed Jul. 11, 2007, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to drug delivery systems. In particular, the invention relates to polymeric-based drug delivery system having a multi-substituted aromatic moiety. The aromatic moiety is conjugated to targeting groups and biologically active moieties such as therapeutic agents, enzymes, proteins and the like.

BACKGROUND OF THE INVENTION

[0003] Over the years, numerous methods have been proposed for administering biologically-effective materials. Medicinal agents are quite often insoluble in aqueous fluid or rapidly degraded in vivo. For example, alkaloids are often difficult to be solubilized and proteins are often prematurely degraded upon administration into the body.

[0004] One of the attempts to solve the obstacles is to include such medicinal agents as part of a soluble transport system. Such transport systems can include permanent conjugate-based systems or prodrugs. In particular, polymeric transport systems can improve the solubility and stability of medicinal agents.

[0005] Multifunctional therapeutics such as proteins can be employed in permanent conjugate-based transport systems including polymers. Proteins employed in such systems maintain biological activities to achieve therapeutic effects. Examples of polymeric conjugates of proteins are described in U.S. Pat. No. 4,179,337, the disclosure of which is incorporated herein by reference. Most of permanent conjugate systems include aliphatic linking moieties between polymers and amino-containing biologically active moieties.

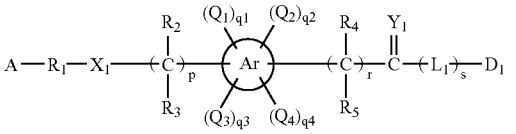
[0006] On the other hand, prodrugs are often biologically inert or substantially inactive forms of a parent or active drug. Among many factors which influence the rate of release of the parent drug, i.e. the rate of hydrolysis, tie release rate is especially modified by the linkages joining the parent drug to the rest of the prodrug system. Care must thus be taken to avoid the prodrugs from being eliminated through the kidney or reticular endothelial system, etc. before a sufficient amount of hydrolysis occurs to release the parent drug. Prodrugs including polymers can improve the circulating half-life of the drug. The prodrug linkages can modify in vivo hydrolysis rate at a rate which eventually generates sufficient amounts of the parent drug after administration thereby providing improved control of the pharmacokinetics of therapeutic moieties like small molecule drugs and the like. Some examples of polymeric prodrugs are described in commonly-assigned U.S. Pat. Nos. 6,180,095 and 6,720,306, the contents of each of which are incorporated herein by reference.

[0007] In spite of the attempts and advances, there still continues to be a need to improve polymeric delivery platforms. The present invention addresses this need and others.

SUMMARY OF THE INVENTION

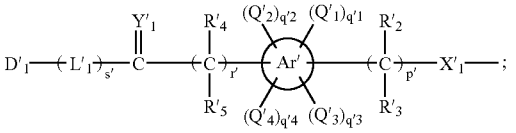
[0008] In one aspect of the invention, there are provided compounds of Formula (I):

(I)



[0009] wherein:

[0010] A is a capping group or



[0011] R_1 is a substantially non-antigenic water-soluble polymer;

[0012] X_1 and X'_1 are independently O, S, SO, SO_2, NR_6 or a bond;

[0013] Ar and Ar' are independently an aryl or heteroaryl moiety;

[0014] Y and Y'_1 are independently O, S, or NR_6;

[0015] L_1 and L'_1 are independently selected bifunctional linkers:

[0016] D_1 and D'_1 are independently selected from among hydrogen, OH, leaving groups, functional groups, targeting groups and biologically active moieties:

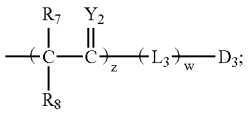
[0017] R_{2-5}, R'_{2-5}, and R_6 are independently selected from among hydrogen, amino substituted amino, azido, carboxy, cyano, halo, hydroxyl, nitro, silyl ether, sulfonyl, mercapto, C_{1-6} alkylmercapto, arylmercapto, substituted arylmercapto, substituted C_{1-6} alkylthio, C_{1-6} alkyls, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-19} branched alkyl, C_{3-8} cycloalkyl, C_{1-6} substituted alkyl, C_{2-6} substituted alkenyl, C_{2-6} substituted alkynyl, C_{3-8} substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_{1-6} heteroalkyl, substituted C_{1-6} heteroalkyl, C_{1-6} alkoxy, aryloxy, C_{1-6} heteroalkoxy, heteroaryloxy, C_{2-6} alkanoyl, arylcarbonyl, C_{2-6} alkoxycarbonyl, aryloxycarbonyl, C_{2-6} alkanoyloxy, arylcarbonyloxy, C_{2-6} substituted alkanoyl, substituted arylcarbonyl, C_{2-6} substituted alkanoyloxy, substituted aryloxycarbonyl, C_{2-6} substituted alkanoyloxy, substituted and arylcarbonyloxy;

[0018] (p), (p'), (r) and (r') are independently zero or a positive integer;

[0019] (q_1), (q'_1), (q_2), (q'_2), (q_3), (q'_3), (q_4) and (q'_4) are independently zero or one;

[0020] (s) and (s') are independently zero or a positive integer;

[0021] Q_{1-4} and Q'_{1-4} are independently selected from among the same moieties which can be used for R_2 or each can be:



[0022] wherein

[0023] R_7 and R_8 are independently selected from the same group as that which defines R_2;

[0024] Y_2 is O, S or NR_6;

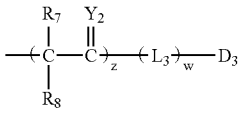
[0025] L_3 is a bifunctional linker;

[0026] (z) is zero or one;

[0027] (w) is zero or a positive integer; and

[0028] D_3 is selected from among hydrogen, OH, leaving groups, functional groups, targeting groups and biologically active moieties such as medicinal agents including small molecular weight compounds,

[0029] provided that the sum of $(q_1)+(q_2)+(q_3)+(q_4)$ is not zero and that at least one Of Q_{1-4} and Q'_{1-4} is



wherein at least one of D_3 is a leaving group, a functional group, a targeting group, a diagnostic agent or a biologically active moiety; and provided that (z) is not zero when (w) is zero.

[0030] In one preferred aspect of the invention, the aromatic portion of the systems is conjugated to at least one target group and at least one biologically active moiety.

[0031] In some preferred aspects, R_1 includes a linear, branched or multi-armed poly(ethylene glycol) residue with molecular weight of from about 5,000 to about 60,000. In certain embodiments, (p) is zero or one and (r) is 0, 1 or 2. In one preferred embodiment, R_{2-5}, R'_{2-5}, R_7 and R_8 are selected from among hydrogen, methyl and ethyl, and each is more preferably hydrogen.

[0032] In another aspect of the invention, there are provided methods of preparing the compounds described herein and methods of treatment using the compounds described herein.

[0033] The polymeric delivery systems described herein include a novel linker which can form a permanent bond such as amide or carbamate bond between polymers and biologically active moieties. For example, the polymeric systems are based on an aromatic structure which is built as part of the PEG backbone permanently and activated as PEG acid ester such as NHS ester. The activated forms can react with an amino group to form the amide bond.

[0034] In another aspect of the invention, the polymeric delivery systems include a releasable bond between the polymers and biologically active moieties. These polymeric systems can release the parent compound in vivo upon chemical hydrolysis or enzymatic metabolism.

[0035] One advantage of the aromatic moiety-based polymeric transport systems described herein is that the polymeric delivery systems have improved stability. Without being bound by any theories, the hydrophobic microenvironment around the covalent linkage between polymers and a moiety such as functional groups, biologically active moieties and targeting groups, protects the covalent linkage from exposure to basic aqueous medium or enzymes which can modify the covalent linkage, thereby stabilizing the covalent linkage. The stability of the polymeric systems also allows long-term storage prior to attaching to targeting groups or biologically active moieties.

[0036] Another advantage of the polymeric systems described herein allows attaching a second agent. Substitution can be easily arranged on the aromatic ring so that artisans in the art can attach a second drug to have a synergistic effect for therapy or a targeting group for selectively targeted delivery.

[0037] A further advantage is that the aromatic moiety allows the polymeric systems to become UV visible. Artisans in the art can easily and efficiently check purity of the polymeric systems and degree of reaction completion. The property, therefore, allows saving costs aid time associated with analytical steps during preparation. The property also allows preparing the polymeric systems described herein in high purity and thereby having uniform pharmacokinetic properties.

[0038] Yet another advantage is that multiple steps previously required to attach a second agent can be avoided. For example, certain bifunctional groups can be directly attached to a second agent and therefore eliminate steps for activating the polymeric systems.

[0039] For purposes of the present invention, the term "residue" shall be understood to mean that portion of a compound, to which it refers, i.e. PEG, etc. that remains after it has undergone a substitution reaction with another compound.

[0040] For purposes of the present invention, the terms "a biologically active moiety" and "a residue of a biologically active moiety" shall be understood to mean that portion of a biologically active compound which remains after the biologically active compound has undergone a substitution reaction in which the transport carrier portion has been attached.

[0041] For purposes of the present invention, the term "polymeric residue" or "PEG residue" shall each be understood to mean that portion of the polymer or PEG which remains after it has undergone a reaction with other compounds, moieties, etc.

[0042] For purposes of the present invention, the term "alkyl" as used herein refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain, and cyclic alkyl groups. The term "alkyl" also includes alkyl-thio-alkyl, alkoxyalkyl, cycloalkylalkyl, heterocycloalkyl, C_{1-6} hydrocarbonyl, groups. Preferably, the alkyl group has 1 to 12 carbons. More preferably, it is a lower alkyl of from about 1 to 7 carbons, yet more preferably about 1 to 4 carbons. The alkyl group can be substituted or unsubstituted. When substituted, the substituted group(s) preferably include halo, oxy, azido, nitro, cyano, alkyl, alkoxy, alkyl-thio, alkyl-thio-alkyl, alkoxyalkyl, alkylamino, trihalomethyl, hydroxyl, mercapto, hydroxy, cyano, alkylsilyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, alkenyl, alkynyl, C_{1-6} hydrocarbonyl, aryl, and amino groups.

[0043] For purposes of the present invention, the term "substituted" as used herein refers to adding or replacing one or more atoms contained within a functional group or compound with one of the moieties from the group of halo, oxy, azido, nitro, cyano, alkyl, alkoxy, alkyl-thio, alkyl-thio-alkyl, alkoxyalkyl, alkylamino, trihalomethyl, hydroxyl, mercapto, hydroxy, cyano, alkylsilyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, alkenyl, alkynyl, C_{1-6} hydrocarbonyl, aryl, and amino groups.

[0044] For purposes of the present invention, the term "alkenyl" refers to groups containing, at least one carbon-carbon double bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkenyl group has about 2 to 12 carbons. More preferably, it is a lower alkenyl of from about 2 to 7 carbons, yet more preferably about 2 to 4 carbons. The alkenyl group can be substituted or unsubstituted. When substituted, the substituted group(s) preferably include halo, oxy, azido, nitro, cyano, alkyl, alkoxy, alkyl-thio, alkyl-thio-alkyl, alkoxyalkyl, alkylamino, trihalomethyl, hydroxyl, mercapto, hydroxy, cyano, alkylsilyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, alkenyl, alkynyl, C_{1-6} hydrocarbonyl, aryl, and amino groups.

[0045] For purposes of the present invention, the term "alkynyl" refers to groups containing at least one carbon-carbon triple bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkynyl group has about 2 to 12 carbons. More preferably, it is a lower alkynyl of from about 2 to 7 carbons, yet more preferably about 2 to 4 carbons. The alkynyl group can be substituted or unsubstituted. When substituted, the substituted group(s) preferably include halo, oxy, azido, nitro, cyano, alkyl, alkoxy, alkyl-thio, alkyl-thio-alkyl, alkoxyalkyl, alkylamino, trihalomethyl, hydroxyl, mercapto, hydroxy, cyano, alkylsilyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, alkenyl, alkynyl, C_{1-6} hydrocarbonyl, aryl, and amino groups. Examples of "alkynyl" include propargyl, propyne, and 3-hexyne.

[0046] For purposes of the present invention, the term "aryl" refers to an aromatic hydrocarbon ring system containing at least one aromatic ring. The aromatic ring can optionally be fused or otherwise attached to otter aromatic hydrocarbon rings or non-aromatic hydrocarbon rings. Examples of aryl groups include, for example, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthalene and biphenyl. Preferred examples of aryl groups include phenyl and naphthyl.

[0047] For purposes of the present invention, the term "cycloalkyl" refers to a C_{3-8} cyclic hydrocarbon. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0048] For purposes of the present invention, the term "cycloalkenyl" refers to a C_{3-8} cyclic hydrocarbon containing at least one carbon-carbon double bond. Examples of cycloalkenyl include cyclopentenyl, cyclopentadienyl, cyclohexenyl, 1,3-cyclohexadienyl, cycloheptenyl, cycloheptatrienyl, and cyclooctenyl.

[0049] For purposes of the present invention, the term "cycloalkylalkyl" refers to an alklyl group substituted with a C_{3-8} cycloalkyl group. Examples of cycloalkylalkyl groups include cyclopropylmethyl and cyclopentylethyl.

[0050] For purposes of the present invention, the term "alkoxy" as used herein refers to an alkyl group of indicated number of carbon atoms attached to the parent molecular moiety through an oxygen bridge. Examples of alkoxy groups include, for example, methoxy, ethoxy, propoxy and isopropoxy.

[0051] For purposes of the present invention, an "alkylaryl" group refers to an aryl group substituted with an alkyl group.

[0052] For purposes of the present invention, an "aralkyl" group refers to an alkyl group substituted with an aryl group.

[0053] For purposes of the present invention, the term "alkoxyalkyl" group refers to an alkyl group substituted with an alkloxy group.

[0054] For purposes of the present invention, the term "alkyl-thio-alkyl" refers to an alkyl-S-alkyl thioether, for example, methylthiomethyl or methylthioethyl.

[0055] For purposes of the present invention, the term "amino" as used herein refers to a nitrogen containing group as is known in the art derived from ammonia by the replacement of one or more hydrogen radicals by organic radicals. For example, the terms "acylamino" and "alkylamino" refer to specific N-substituted organic radicals with acyl and alkyl substituent groups, respectively.

[0056] For purposes of the present invention, the term "alkylcarbonyl" refers to a carbonyl group substituted with alkyl group.

[0057] For purposes of the present invention, the terms "halogen" or "halo" as used herein refer to fluorine, chlorine, bromine, and iodine.

[0058] For purposes of the present invention, the tern "heterocycloalkyl" refers to a non-aromatic ring system containing at least one heteroatom selected from nitrogen, oxygen, and sulfur. The heterocycloalkyl ring can be optionally fused to or otherwise attached to other heterocycloalkyl rings and/or non-aromatic hydrocarbon rings. Preferred heterocycloalkyl groups have from 3 to 7 members. Examples of heterocycloalkyl groups include, for example, piperazine, morpholine, piperidine, tetrahydrofuran, pyrrolidine, and pyrazole. Preferred heterocycloalkyl groups include piperidinyl, piperazinyl, morpholinyl, and pyrolidinyl.

[0059] For purposes of the present invention the term "heteroaryl" refers to an aromatic ring system containing at least one heteroatom selected from nitrogen, oxygen, and sulfur. The heteroaryl ring can be fused or otherwise attached to one or more heteroaryl rings, aromatic or non-aromatic hydrocarbon rings or heterocycloalkyl rings. Examples of heteroaryl groups include, for example, pyridine, furan, thiophene, 5,6,7,8-tetrahydroisoquinoline and pyrimidine. Preferred examples of heteroaryl groups include thienyl, benzothienyl, pyridyl quinolyl pyrazinyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, benzisothiazolyl, triazolyl, tetrazolyl, pyrrolyl, indolyl, pyrazolyl, and benzopyrazolyl.

[0060] For purposes of the present invention, the term "heteroatom" refers to nitrogen, oxygen, and sulfur.

[0061] In some embodiments, substituted alkyls include carboxyalkyls, aminoalkyls, dialkylaminos, hydroxyalkyls and mercaptoalkyls; substituted alkenyls include carboxyalkenyls, aminoalkenyls, dialkenylaminos, hydroxyalkenyls and mercaptoalkenyls; substituted alkynyls include carboxyalkynyls, aminoalkynyls, dialkynylaminos, hydroxyalkynyls and mercaptoalkynyls; substituted cycloalkyls include moieties such as 4-chlorocyclohexyl; aryls include moieties such as napthyl; substituted aryls include moieties such as 3-bromo phenyl; aralkyls include moieties such as tolyl; heteroalkyls include moieties such as ethylthiophene: substituted heteroalkyls include moieties such as 3-methoxy-thiophene; alkoxy includes moieties such as methoxy; and phenoxy includes moieties such as 3-nitrophenoxy. Halo shall be understood to include fluoro, chloro, iodo and bromo.

[0062] For purposes of the present invention, "positive integer" shall be understood to include an integer equal to or greater than 1 and as will be understood by those of ordinary skill to be within the realm of reasonableness by the artisan of ordinary skill, i.e., preferably from 1 to about 10, more preferably 1 or 2 in some embodiments.

[0063] For purposes of the present invention, the term "linked" shall be understood to include covalent (preferably) or noncovalent attachment of one group to another, i.e., as a result of a chemical reaction.

[0064] For purposes of the present invention, the term "bond" shall be understood to mean that an atom is absent and moieties adjacent to the group designated as "bond" are linked directly.

[0065] For purposes of the present invention, it shall be understood to mean that the pharmaceutically active compounds include small molecular weight molecules. Typically, the pharmaceutically active compounds have a molecular-weight of less than about 1,500 daltons and optionally derivatized with amine-, hydroxyl- or thiol-containing moieties to provide a reactive site for conjugation with polymer.

[0066] The terms "effective amounts" and "sufficient amounts" for purposes of the present invention shall mean an amount which achieves a desired effect or therapeutic effect as such effect is understood by those of ordinary skill in the art.

[0067] Broadly speaking, successful treatment (i.e. tumor growth inhibition or inhibition of inflammation) shall be deemed to occur when the desired response is obtained, compared to that observed in the absence of the treatment with the compound described herein. For example, successful treatment, (i.e., tumor growth inhibition or inhibition of inflammation) can be defined by obtaining e.g., 10% or higher (i.e. 20% 30%, 40%) down regulation or up-regulation of genes associated with cancer or inflammation.

[0068] Fuifther, the use of singular terms for convenience in description is in no way intended to be so limitilg. Thus, for example, reference to a composition comprising an enzyme refers to one or more molecules of that enzyme. It is also to be understood that this invention is not limited to the particular configurations, process steps, and materials disclosed herein as such configurations, process steps, and materials may vary somewhat.

[0069] It is also to be understood that the terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limiting, since the scope of the present invention will be limited by the appended claims and equivalents thereof.

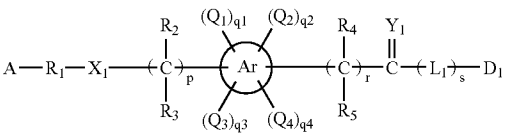
BRIEF DESCRIPTION OF THE DRAWINGS

[0070] FIG. **1** schematically illustrates methods of synthesis described in Examples 1-7.

DETAILED DESCRIPTION OF THE INVENTION

A. Overview

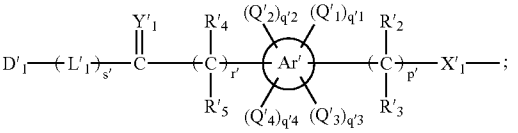
[0071] In one aspect of the present invention, there are provided compounds of Formula (I):



(I)

[0072] wherein:

[0073] A is a capping group or



[0074] R_1 is a substantially non-antigenic water-soluble polymer;

[0075] X_1 and X'_1 are independently O, S, SO, SO_2, NR_6 or a bond;

[0076] Ar and Ar' are independently an aryl or heteroaryl moiety;

[0077] Y_1 and Y'_1 are independently O, S, or NR_6, and preferably Y_1 and Y'_1 are O;

[0078] L_1 and L'_1 are independently selected bifunctional linkers;

[0079] D_1 and D'_1 are independently selected from among hydrogen, OH, leaving groups, functional groups, targeting groups, diagnostic agents and biologically active moieties such as medicinal agents including small molecular weight compounds;

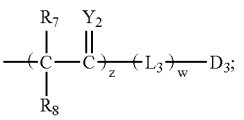
[0080] R_{2-5}, R'_{2-5}, and R_6 are independently selected from among hydrogen, amino, substituted amino, azido, carboxy, cyano, halo, hydroxyl, nitro, silyl ether, sulfonyl, mercapto, C_{1-6} alkylmercapto, arylmercapto, substituted arylmercapto, substituted C_{1-6} alkylthio, C_{1-6} alkyls, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-19} branched alkyl, C_{3-8} cycloalkyl, C_{1-6} substituted alkyl, C_{2-6} alkenyl, C_{2-6} substituted alkynyl, C_{3-8} substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_{1-6} heteroalkyl, substituted C_{1-6}heteroalkyl, C_{1-6} alkoxy, aryloxy, C_{1-6} heteroalkoxy, heteroaryloxy, C_{2-6} alkanoyl, arylcarbonyl, C_{2-6} alkoxycarbonyl, aryloxycarbonyl, C_{2-6} alkanoyloxy, arylcarbonyloxy, C_{2-6} substituted alkanoyl, substituted arylcarbonyl, C_{2-6} substituted alkanoyloxy, substituted aryloxycarbonyl, C_{2-6} substituted alkanoyloxy, substituted and arylcarbonyloxy;

[0081] (p), (p'), (r) and (r') are independently zero or a positive integer, preferably from about 0 to about 10 (e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10), more preferably from about 0 to about 6 (e.g., 0, 1, 2, 3, 4, 5 or 6), and most preferably 0, 1 or 2;

[0082] (q_1), (q'_1), (q_2), (q'_2), (q_3) (q'_3), (q_4) and (q'_4) are independently zero or one;

[0083] (s) and (s') are independently zero or a positive integer, preferably from about 0 to about 6 (e.g., 0, 1, 2, 3, 4, 5 or 6), more preferably zero, 1 or 2, and yet more preferably zero or 1;

[0084] Q_{1-4} and Q'_{1-4} are independently selected from among the same moieties which can be used for R_2 or each can be:



[0085] wherein

[0086] R_7 and R_8 are independently selected from among the same moieties which can be used for R_2;

[0087] Y_2 is O, S or NR_6, and preferably Y_2 is O;

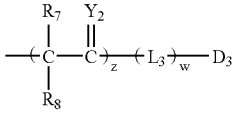
[0088] L_3 is a bifunctional linker;

[0089] (z) is zero or one;

[0090] (w) is zero or a positive integer, preferably from about 0 to about 6 (e.g., 0. 1, 2, 3, 4, 5 or 6), more preferably zero, 1 or 2, and yet more preferably (z) is 0 and (w) is 1; and

[0091] D_3 is selected from among hydrogen, OH, leaving groups, functional groups, targeting groups and biologically active moieties

[0092] provided that the sum of $(q_1)+(q_2)+(q_3)+(q_4)$ is not zero (preferably, the sum of $(q_1)+(q_2)+(q_3)+(q_4)$ or the sum of $(q')+(q'_2)+(q'_3)+(q'_4)$ is 1), and that at least one (e.g., 1, 2, 3, or 4, preferably 1 or 2, and more preferably 1) of Q_{1-4} and Q'_{1-4} is



wherein at least one of D_3 is a leaving group, a functional group, a targeting group, a diagnostic agent or a biologically active moiety; and provided that (z) is not zero when (w) is zero. With this respect, the leaving group is preferably selected from among N-hydroxysuccinimidyl, para-nitrophenoxy, ortho-nitrophenoxy and C_1-C_6 alkyloxy, and the functional group is preferably selected from among maleimidyl, vinyl, and residues of sulfone.

[0093] Within those aspects of the invention, the substituents contemplated for substitution, where said moieties corresponding to R_{2-5}, R'_{2-5}, R_6, R_7 and R_8 are indicated as being possibly substituted can include, for example, acyl, amino, amido, amidine, ara-alkyl, aryl, azido, alkylmercapto, arylmercapto, carbonyl, carboxylate, cyano, ester, ether, formyl, halogen, heteroaryl, heterocycloalkyl, hydroxy, imino, nitro, thiocarbonyl, thioester, thioacetate, thioformate, alkoxy, phosphoryl, phosphonate, phosphinate, silyl, sulfhydryl, sulfate, sulfonate, sulfamoyl, sulfonamide, and sulfonyl.

[0094] In one preferred aspect, the compounds described herein include at least one targeting group and at least one biologically active moiety.

[0095] In some p]referred embodiments, both (p) and (r) are zero or1 one. Alternatively, (p) is 0 and (r) is 2.

[0096] In certain aspects of the invention, when (p) is zero, there are preferably a sufficient number of atoms, e.g., more than five or six atoms, present between X_1/X'_1 and $C(=Y_1)/C(=Y'_1)$, so that a releasable cyclic moiety is not formed. For example, when (p) is zero, the polymeric portion attached to the phenyl ring would not be in an ortho position in relation to D_1, D'_1 or D_3.

[0097] For purposes of the present invention, $C(R_2)(R_3)$ is the same or different when (p) and/or (p') are equal to or greater than 2.

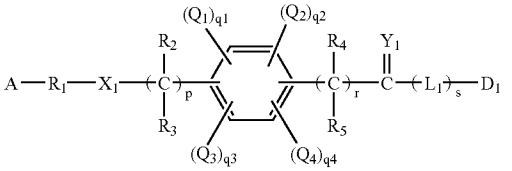
[0098] For purposes of the present invention, $C(R_4)(R_5)$ is the same or different when (r) and/or (r') are equal to or greater than 2.

[0099] For purposes of the present invention, each of L_1, L'_1 and L_3 are the same or different when (s) and (w) are equal to or greater than 2.

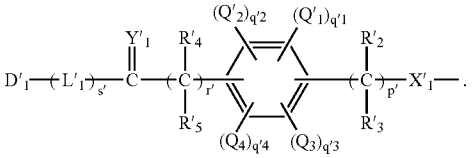
[0100] In another aspect of the invention, the biological moieties include amine containing moieties, hydroxyl containing moieties and thiol containing moieties.

[0101] In yet another aspect, A can be selected from among H, NH_2, OH, CO_2H, C_{1-6} alkoxy, and C_{1-6} alkyls. In some preferred embodiments, A can be methyl, ethyl, methoxy, ethoxy, H, and OH. A is more preferably methyl or methoxy.

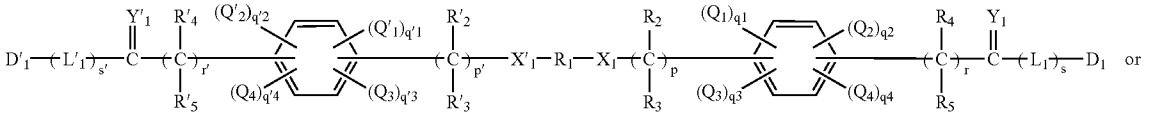
[0102] In one embodiment, compounds described herein have the formula:

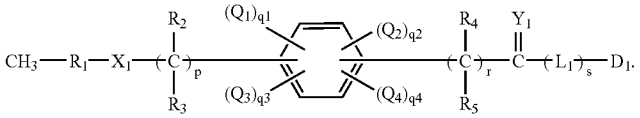


[0103] wherein A is a capping group or

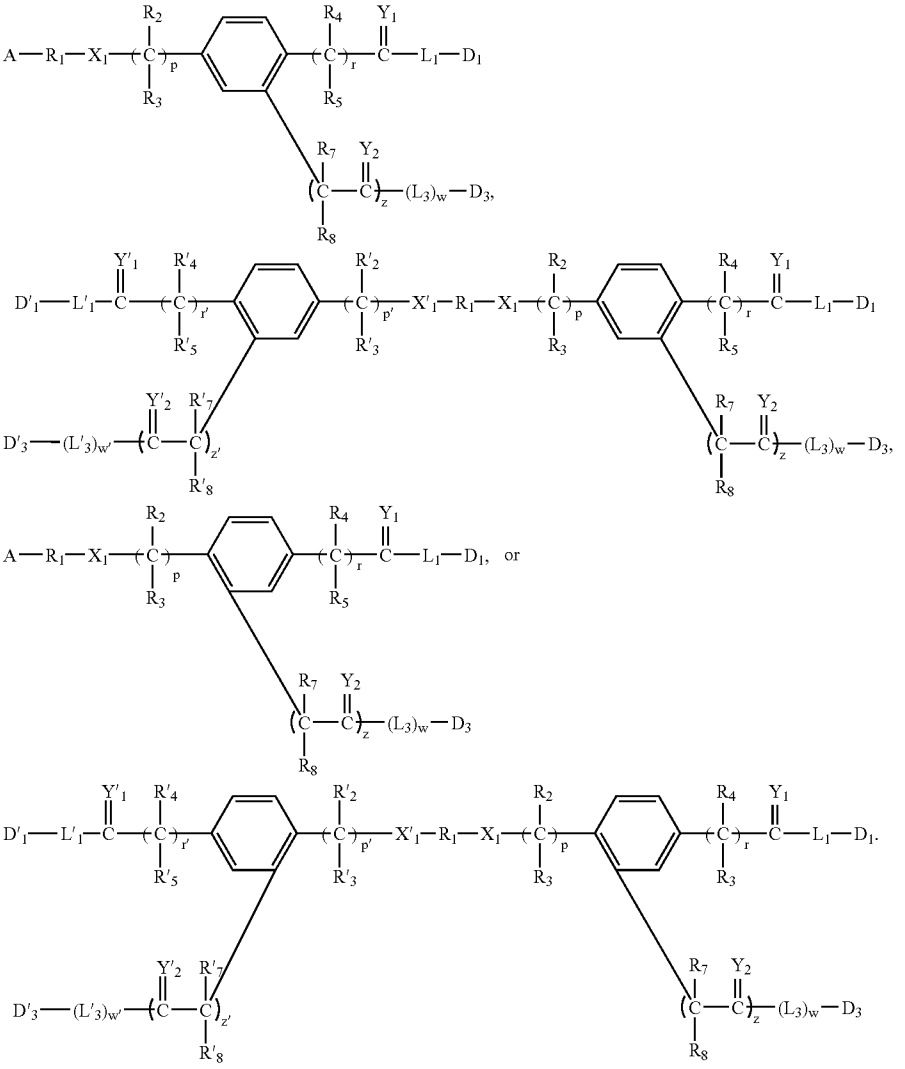


[0104] In certain particular embodiments, compounds described herein have the formula,



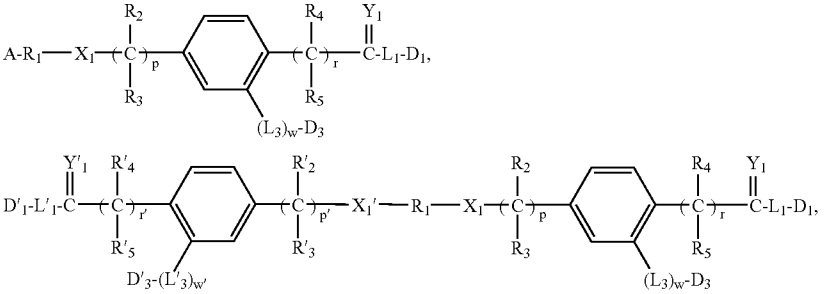


[0105] In one preferred embodiment, the sum of $(q_1)+(q_2)+(q_3)+(q_4)$ or $(q'_1)+(q'_2)+(q'_3)+(q'_4)$ equals to 1. Preferred polymeric compounds call have the formula:



[0106] In a further preferred embodiment, both (p) and (r) are zero or 1; or (p) is zero and (r) is 2.

[0107] More preferably, (z) is 0 and (w) is 1. One particular embodiment can have the formula:



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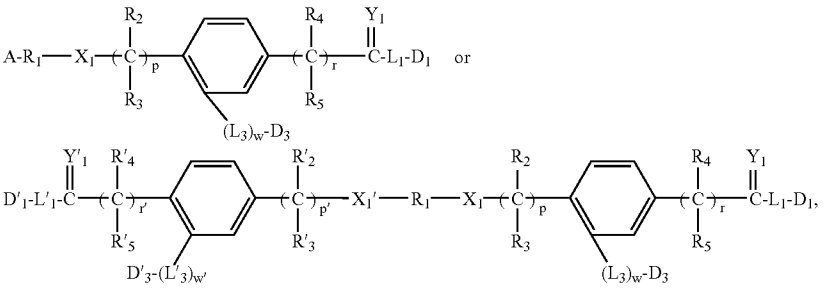
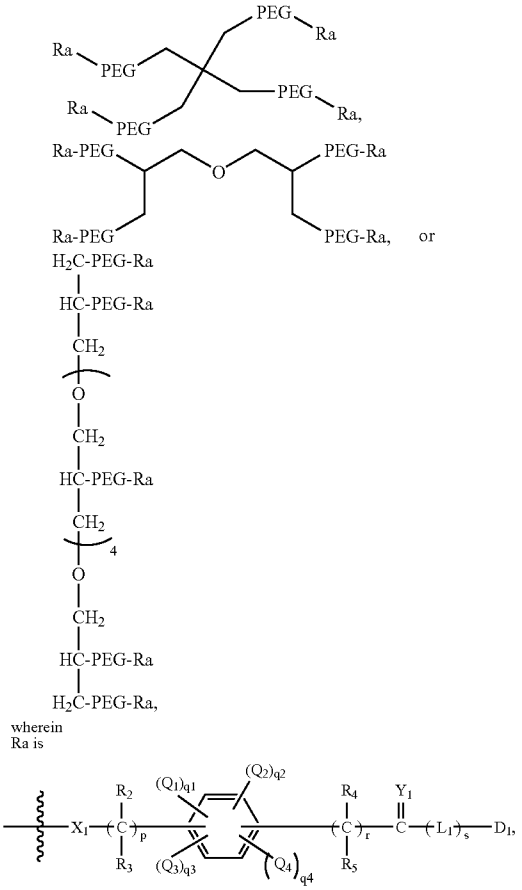


[0108] In another embodiment, R_7 and R_8 include hydrogen or CH_3, preferably hydrogen. In yet another embodiment, X_1 and X'_1 include 0, NH or a bond. In yet another embodiment, Y_1 and Y'_1 include O.

[0109] In yet another preferred embodiment, R_{2-5} and R'_{2-5} include hydrogen or CH_3, more preferably hydrogen.

[0110] In another embodiment, the compounds described herein have the formula:



wherein Ra is

[0111] and at least one of D_1 is a targeting group, a diagnostic agent or a biologically active moiety.

[0112] Preferably the multi-arm polymer includes at least one targeting group and at least one biologically active moiety. The multi-arm polymeric conjugates containing one or more biologically active moieties are contemplated.

B. Substantially Non-Antigenic Water-Soluble Polymers

[0113] Polymers employed in the compounds described herein are preferably water soluble polymers and substantially noon-antigenic such as polyalkylene oxides (PAO's).

[0114] In one aspect of the invention, the compounds described herein include a linear, terminally branched or multi-armed polyalkylene oxide. In some preferred embodiments, the polyalkylene oxide includes polyethylene glycol and polypropylene glycol.

[0115] The polyalkylene oxide has an average molecular weight from about 2,000 to about 100,000 daltons, preferably from about 5,000 to about 60,000 daltons. The polyalkylene oxide can be more preferably from about 5,000 to about 25,000 or alternatively from about 20,000 to about 45,000 daltons (preferably when small molecular weight compounds having an average molecular weight of less than 1,500 daltons (for example, up to 1,200 daltons) are conjugated to the polymer). In some particularly preferred embodiments, the compounds described herein include the polyalkylene oxide having an average molecular weight of from about 12,000 to about 20,000 daltons or from about 30,000 to about 45,000 daltons. In one particular embodiment, polymeric portion has a molecular weight of about 19,000 or 40,000 daltons.

[0116] The polyalkylene oxide includes polyethylene glycols and polypropylene glycols. More preferably, the polyalkylene oxide includes polyethylene glycol (PEG). PEG is generally represented by the structure:

$$—O—(CH_2CH_2O)_n—$$

where (n) represents the degree of polymerization for the polymer, and is dependent on the molecular weight of the polymer. Alternatively, the polyethylene glycol (PEG) residue portion of the invention can be selected from among:

[0117] $—X_{11}—(CH_2CH_2O)_n—CH_2CH_2X_{11}—$,

[0118] $—X_{11}—(CH_2CH_2O)_n—CH_2C(=Y_{11})—X_{11}—$,

[0119] $—X_{11}—C(=Y_{11})—(CH_2)_a'—Y_{12}—(CH_2CH_2O)_n—CH_2CH_2—Y_{12}—(CH_2)_a'—C(=Y_{11})—X_{11}—$, and

[0120] $—X_{11}—(CR_{31}R_{32})_a'—Y_{12}—(CH_2)_b'—O—(CH_2CH_2O)_n—(CH_2)_b'—Y_{12}—(CR_{31}R_{32})_a'—X_{11}—$,

[0121] wherein:

[0122] X_{11} is O, S, SO, SO_2, NR_{33} or a bond;

[0123] Y_{11} and Y_{12} are independently O, S, or NR_{33};

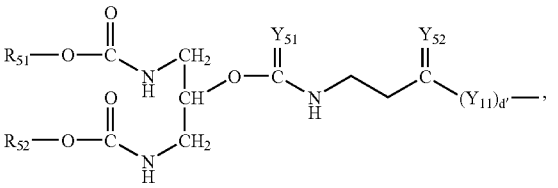
[0124] R_{31-33} are independently the same moieties which can be used for R_2;

[0125] (a') and (b') are independently zero or a positive integer, preferably 0-6 and more preferably 1; and

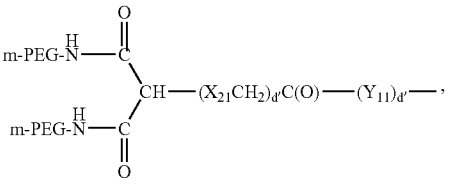
[0126] (n) is an integer from about 10 to about 2300.

[0127] Branched or U-PEG derivatives are described in U.S. Pat. Nos. 5,643,575, 5,919,455, 6,113,906 and 6,566,506, the disclosure of each of which is incorporated herein by reference. A non-limiting list of such polymers corresponds to polymer systems (i)-(vii) with the following structures:

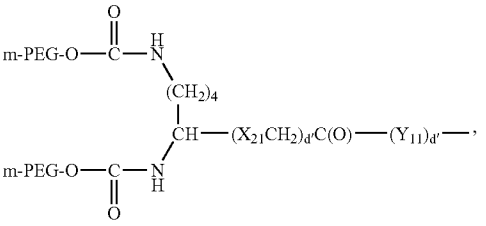
(i)



(ii)



(iii)



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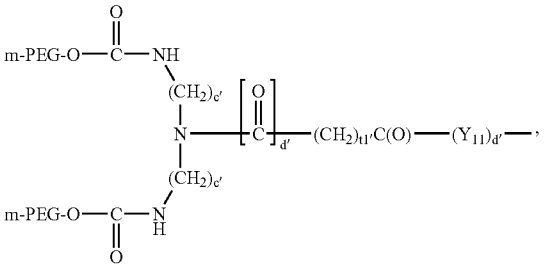

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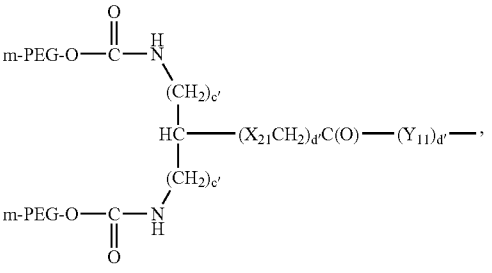

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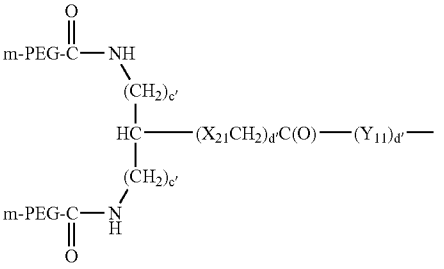
(vii)



[0128] wherein:

[0129] R_{51-52} are polyalkylene oxide;

[0130] Y_{11} and Y_{51-52} are independently O, S or NR_{33};

[0131] X_{21} is O, NR_6, S, SO or SO_2

[0132] (c') and (t1') are independently 0 or a positive integer such as 1, 2, 3, 4 and 5;

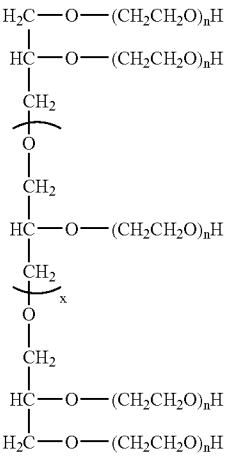
[0133] (d') is 0 or 1:

[0134] mPEG is methoxy PEG

[0135] wherein PEG is previously defined and a total molecular weight of the polymer portion is from about 2,000 to about 100,000 daltons. R_6 and R_{33} are previously defined.

[0136] In yet another aspect, the polymers include multi-arm PEG-OH or "star-PEG" products Such as those described in NOF Corp. Drug Delivery System catalog, Ver. 8, April 2006, the disclosure of which is incorporated herein by reference. See also Shearwater Corporation's 2001 catalog "Polyethylene Glycol and Derivatives for Biomedical Application", the disclosure of which is incorporated herein by reference. The multi-arm polymer conjugates contain four or more polymer arms and preferably four or eight polymer arms.

[0137] For purposes of illustration and not limitation, the multi-arm polyethylene glycol (PEG) residue can be

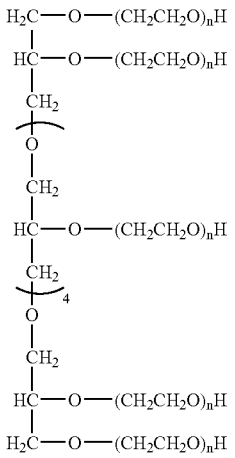


[0138] wherein:

[0139] (x) is zero and a positive integer, i.e. from about 0 to about 28; and

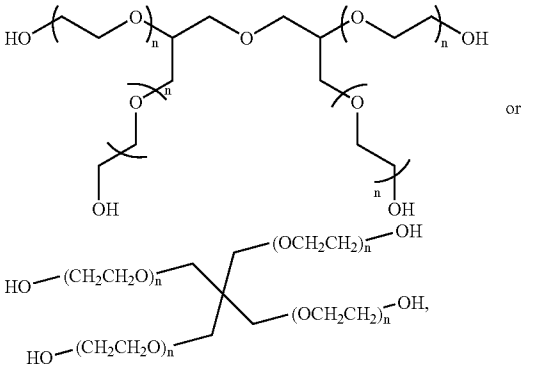
[0140] (n) is the degree of polymerization.

[0141] In one particular embodiment of the present invention, the multi-arm PEG has the structure:



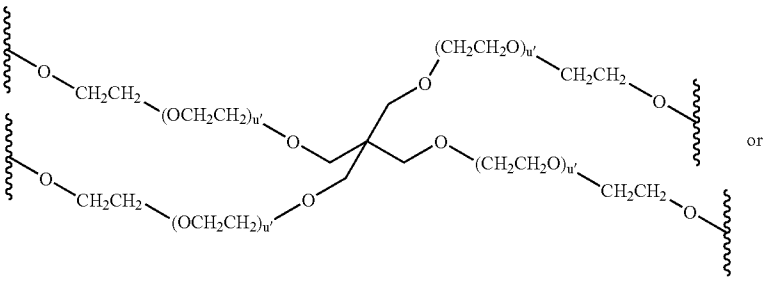
wherein (n)is a positive integer. In one preferred embodiment of the invention, the polymers have a total molecular weight of from about 5,000 Da to about 60,000 Da, and preferably from 20,000 Da to 45,000 Da.

[0142] In yet another particular embodiment, the multi-arm PEG has the structure:

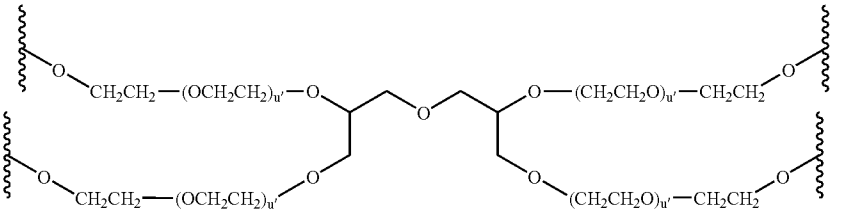


wherein (n) is a positive integer. In one preferred embodiment of the invention, the degree of polymerization for the multi-arm polymer (n) is from about 28 to about 350 to provide polymers having a total molecular weight of from about 5,000 Da to about 60,000 Da, and preferably from 12,000 Da to 45,000 Da. This represents the number of repeating units in the polymer chain and is dependent on the molecular weight of the polymer.

[0143] The polymers can be converted into a suitably activated polymer, using the activation techniques described in U.S. Pat. Nos. 5,127,614 or 5,808,096. Specifically, such PEG can be of the formula:



Star

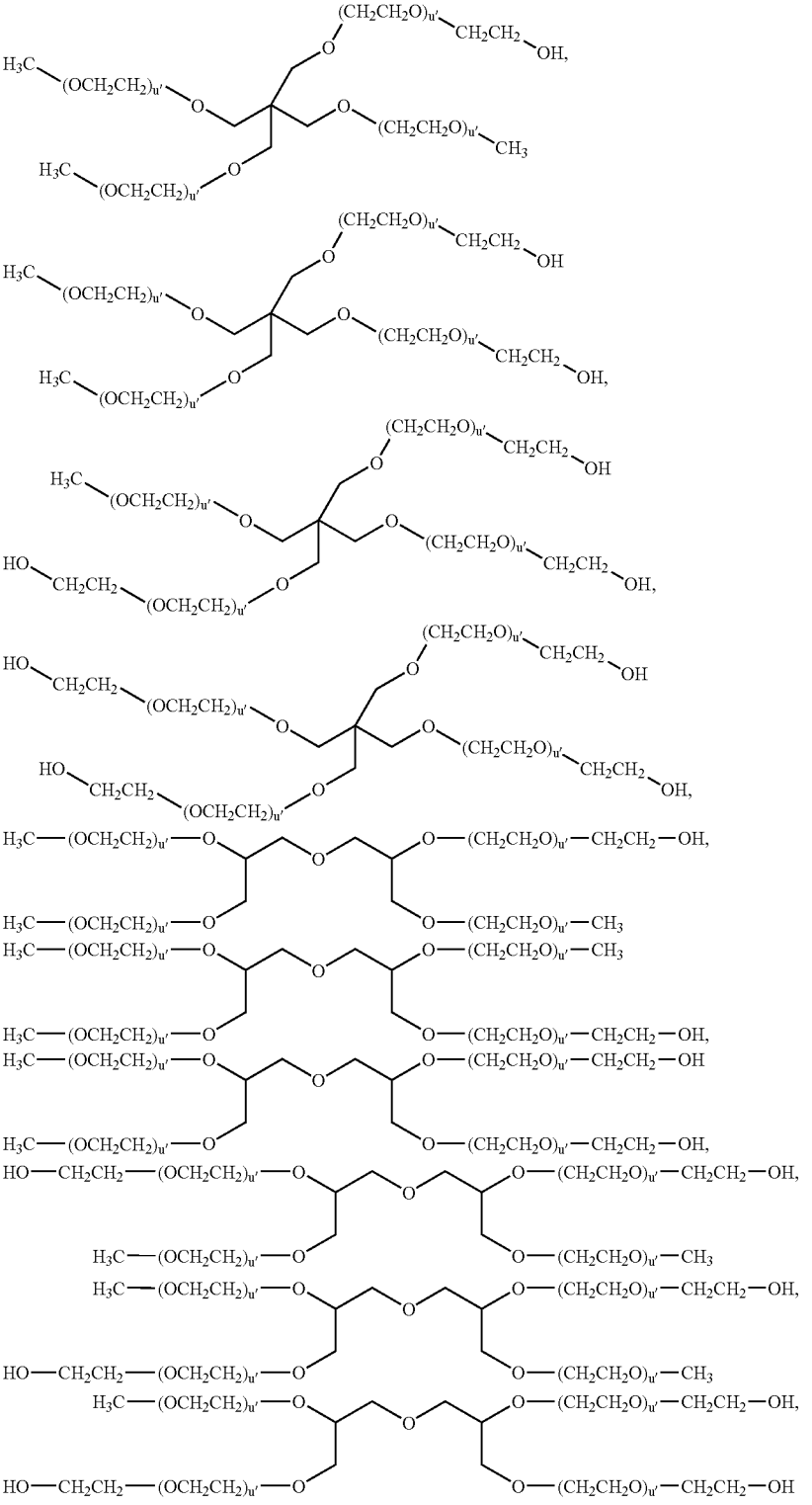


Multi-arm

[0144] wherein:

[0145] (u') is an integer from about 4 to about 455; and up to 3 terminal portions of the residue is/are capped with a methyl or other lower alkyl.

[0146] In some preferred embodiments, all four of the PEG arms can be converted to suitable activating groups, for facilitating attachment to aromatic groups. Such compounds prior to conversion include:



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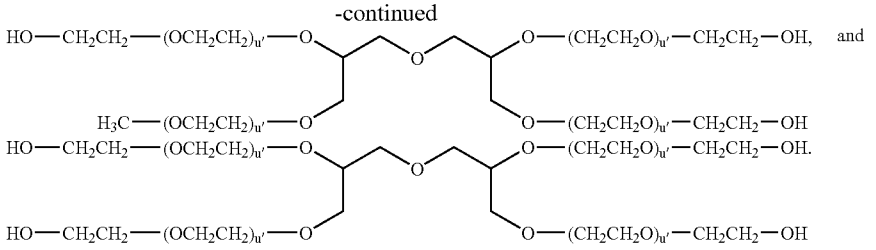


[0147] The polymeric substances included herein are preferably water-soluble at room temperature. A non-limiting list of such polymers include polyalkylene oxide homopolymers such as polyethylene glycol (PEG) or polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof, provided that the water solubility of the block copolymers is maintained.

[0148] In a further embodiment, and as an alternative to PAO-based polymers, one or more effectively non-antigenic materials such as dextran, polyvinyl alcohols, carbohydrate-based polymers, hydroxypropylmethacrylamide (HPMA), polyalkylene oxides, and/or copolymers thereof can be used. See also commonly-assigned U.S. Pat. No. 6,153,655, the contents of which are incorporated herein by reference. It will be understood by those of ordinary skill that the same type of activation is employed as described herein as for PAO's such as PEG. Those of ordinary skill in the art will further realize that the foregoing list is merely illustrative and that all polymeric materials having the qualities described herein are contemplated. For purposes of the present invention, "substantially or effectively non-antigenic" means all materials understood in the art as being nontoxic and not eliciting an appreciable immunogenic response in mammals.

[0149] In some aspects, polymers having terminal amine groups can be employed to make the compounds described herein. The methods of preparing polymers containing terminal airlines in high purity are described in U.S. patent application Ser. Nos. 11/508,507 and 11/537,172, the contents of each of which are incorporated by reference. For example, polymers having azides react with phosphine-based reducing agent such as triphenylphosphine or an alkali metal borohydride reducing agent such as $NaBH_4$. Alternatively, polymers including leaving groups react with protected amine salts such as potassium salt of methyl-tert-butyl imidodicarbonate (KNMeBoc) or the potassium salt of di-tert-butyl imidodicarbonate ($KNBoc_2$) followed by deprotecting the protected amine group. The purity of the polymers containing the terminal amines formed by these processes is greater than about 95% and preferably greater than 99%.

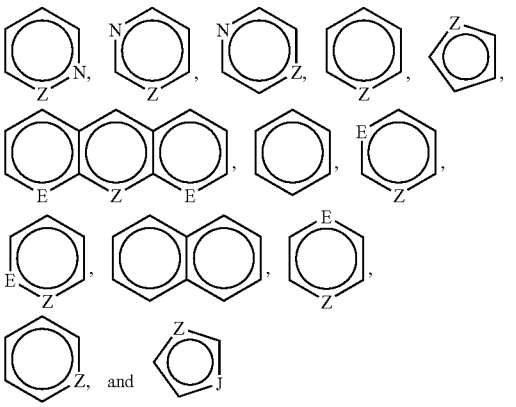
[0150] In alternative aspects, polymers having terminal carboxylic acid groups can be employed in the polymeric delivery systems described herein. Methods of preparing polymers having terminal carboxylic acids in high purity are described in U.S. patent application Ser. No. 11/328,662, the contents of which are incorporated herein by reference. The methods include first preparing a tertiary alkyl ester of a polyalkylene oxide followed by conversion to the carboxylic acid derivative thereof. The first step of the preparation of the PAO carboxylic acids of the process includes forming an intermediate such as t-butyl ester of polyalkylene oxide carboxylic acid. This intermediate is formed by reacting a PAC with a t-butyl haloacetate in the presence of a base such as potassium t-butoxide. Once the t-butyl ester intermediate has been formed, the carboxylic acid derivative of the polyalkylene oxide can be readily provided in purities exceeding 92%, preferably exceeding 97%, more preferably exceeding 99% and most preferably exceeding 99.5% pur-ity.

C. Aromatic Moieties

[0151] Aromatic moieties (Ar) employed in the compounds described herein include a multi-substituted aromatic or heteroaromatic hydrocarbon. A key feature is that the Ar/Ar' group is aromatic in nature. Generally, the π electrons must be shared within a "cloud" both above and below the plane of a cyclic molecule. Furthermore, the number of π electrons must satisfy the Hückle rule (4n+2). Those of ordinary skill will realize that a myriad of moieties will satisfy the aromatic requirement of the moiety and thus are suitable for use herein.

[0152] In one particular embodiment of the invention, the aromatic moieties include

[0153] Other suitable aromatic moieties include:



[0154] wherein J is O, S, or NR_{11}; E and Z are each independently CR_{12} or NR_{13}; and R_{11} R_{12} and R_{13} can be selected from among the same moieties which can be used for R_2.

[0155] Isomers of the five and six-membered rings are also contemplated as well as benzo- and dibenzo-rings such as

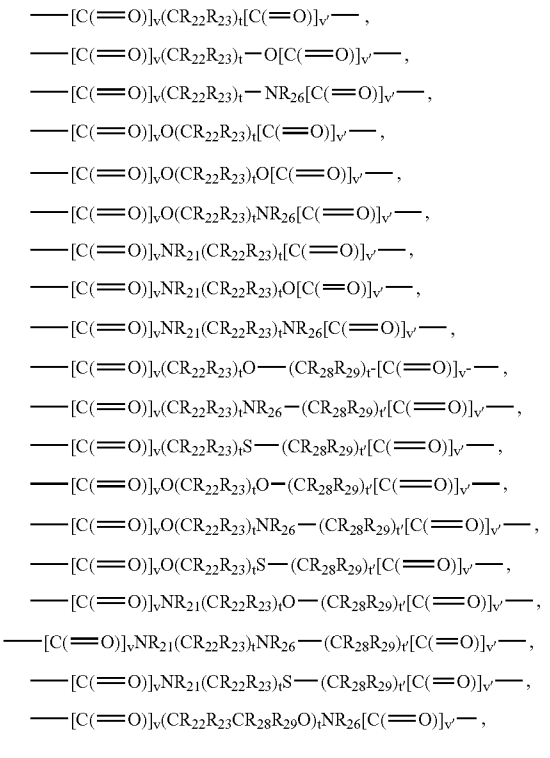
anthracine and napthlene and their related congeners are also contemplated within the scope of the invention.

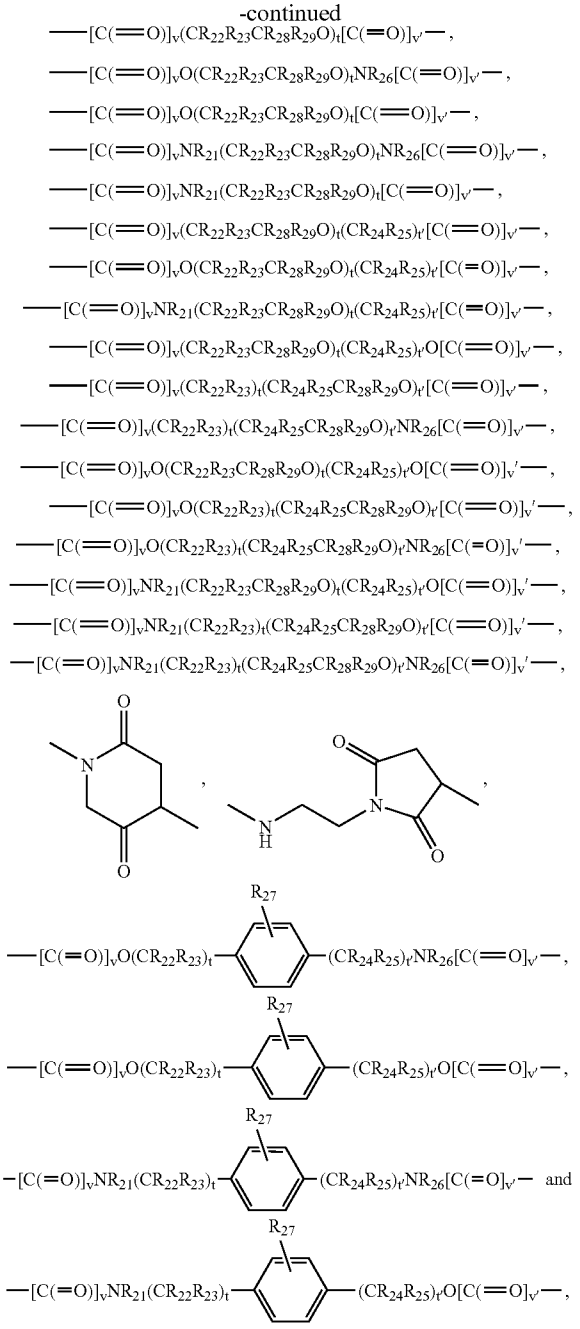
[0156] Furthermore, the aromatic or heteroaromatic moieties may optionally be substituted with halogen(s) and/or side chains. All structures suitable for Ar moieties of the present invention are capable of allowing the substituents on the aromatic group to be aligned within the same plane. Ortho, meta and para substituted aromatic rings can be used.

D. Bifunctional Linkers

[0157] Bifunctional linkers include amino acids, amino acid derivatives and peptides. The amino acids can be among naturally occurring and non-naturally occurring amino acids. Derivatives and analogs of the naturally occurring amino acids, as well as various art-known non-naturally occurring amino acids (D or L), hydrophobic or non-hydrophobic, are also contemplated to be within the scope of the invention. A suitable non-limiting list of the non-naturally occurring amino acids includes 2-aminoadipic acid, 3-aminoadipic acid, beta-alanine, beta-aminopropionic acid, 2-aminobutyric acid, 4-aminobutyric acid, piperidinic acid, 6-aminocaproic acid, 2-aminoheptanoic acid, 2-aminoisobutyric acid, 3-aminoisobutyric acid, 2-aminopimelic acid, 2,4-aminobutyric acid, desmosine, 2,2-diaminopimelic acid 2,3-diaminopropionic acid, N-ethylglycine, N-ethylasparagine, 3-hydroxyproline, 4-hydroxyproline, isodesmosine, alloisoleucine, N-methylglycine, sarcosine, N-methylisoleucine, 6-N-methyl-lysine, N-methylvaline, norvaline, norleucine, and ornithine. Some preferred amino acid residues are selected from glycine, alanine, methionine and sarcosine, and more preferably, glycine.

[0158] Alternatively, L_1, L_1' and L_3 can be selected from among





[0159] wherein:

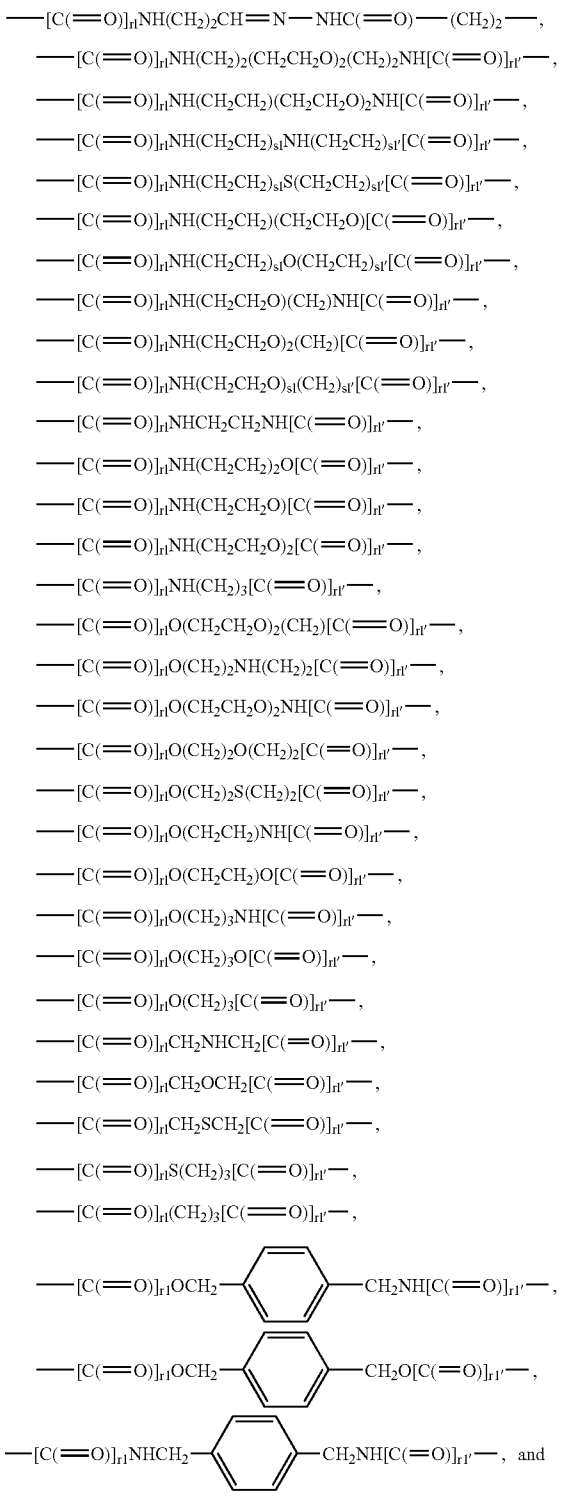
[0160] R_{21-29} are independently selected from the group consisting of hydrogen, C_{1-6}alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cyloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy and C_{1-6} heteroalkoxy;

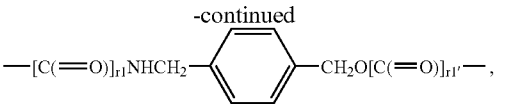
[0161] (t) and (t') are independently zero or a positive integer, preferably from about 0 to about 10 (e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10), more preferably from about 0 to about 6 (e.g., 0, 1, 2, 3, 4, 5 or 6), and yet more preferably 0, 1 or 2; and

[0162] (v) and (v') are independently zero or, 1.

[0163] For purposes of the present invention, $C(R_{24})(R_{25})$ is the same or different when (t) or (t') is equal to or greater than 2.

[0164] Preferably, L_1, L_1' and L_3 can be selected from among:





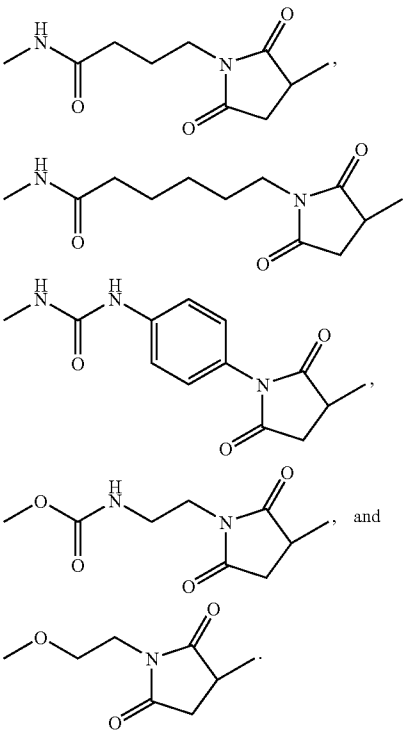
[0165] wherein

[0166] (r1) and (r1') are independently zero or 1; and

[0167] (s1) and (s1') are independently zero or a positive integer, preferably from about 0 to about 4 (e.g., 0, 1, 2, 3, or 4), more preferably 0, 1 or 2,

[0168] provided that both (r1) and (r1') are not zero simultaneously.

[0169] In yet further alternative aspects of the invention, L_1, L'_1 and L_3 include:



[0170] In a further embodiment and as an alternative, L_1, L'_1 and L_3 include structures corresponding to those shown above but having vinyl, residues of sulfone, amino, carboxy, mercapto, hydrazide, carbazate and the like instead of maleimidyl. These bifunctional groups allow a second agent to be directly conjugated and therefore eliminate the need of attaching a functional group for conjugating to a second agent.

E. D_1, D'_1 and D_3 Groups

1. Leaving Groups and Functional Groups

[0171] In some aspects, suitable leaving groups include, without limitations halogen (Br, Cl), activated carbonate, carbonyl imidazole, cyclic imide thione, isocyanate, N-hydroxysuccinimidyl, para-nitrophenoxy, N-hydroxybenzotriazolyl, N-hydroxybenzotriazolyl, imidazole, tosylate, mesylate, tresylate, nosylate, C_1-C_6 alkyloxy, C_1-C_6 alkanoy-

loxy, arylcarbonyloxy, ortho-nitrophenoxy, N-hydroxybenzotriazolyl, pentafluorophenoxy, 1,3,5-trichlorophenoxy, and 1,3,5-trifluorophenoxy or other suitable leaving groups as will be apparent to those of ordinary skill.

[0172] For purposes of the present invention, leaving groups are to be understood as those groups which are capable of reacting with a nucleophile found on the desired target, i.e. a biologically active moiety, a diagnostic agent, a targeting moiety, a bifunctional spacer, intermediate, etc. The targets thus contain a group for displacement, such as OII, NII_2 or SII groups found on proteins, peptides, enzymes, naturally or chemically synthesized therapeutic molecules such as doxorubicin, and spacers such as mono-protected diamines.

[0173] In some preferred embodiments, functional groups to link the polymeric transport systems to biologically active moieties include maleimidyl, vinyl, residues of sulfone, amino, carboxy, mercapto, hydrazide, carbazate and the like which can be further conjugated to a biologically active group.

[0174] In particularly preferred embodiments of the invention, D_1, D'_1 and D_3 can be selected from among OH, methoxy, tert-butoxy, N-hydroxysuccinimidyl and maleimidyl.

2. Biologically Active Moieties

[0175] A wide variety of biologically active moieties can be attached to the activated polymers described herein. The biologically active moieties include pharmaceutically active compounds, enzymes, proteins, oligonucleotides, antibodies, monoclonal antibodies, single chain antibodies and peptides. In addition, the activated polymer of the invention can further contain a biologically active moiety as D_1, D'_1 and D_3 which includes amine-, hydroxyl-, or thiol-containing compounds. A non-limiting list of such suitable compounds includes organic compounds, enzymes, proteins, polypeptides, antibodies, monoclonal antibodies, single chain antibodies or oligonucleotides, etc.

[0176] For purposes of the present invention, it shall be understood to mean that the pharmaceutically active compounds include small molecular weight molecules. Typically, the pharmaceutically active compounds have a molecular weight of less than about 1,500 daltons and optionally derivatized with thiol containing moiety to provide reactive site for conjugation with polymer.

[0177] In some aspects of the invention, biologically active moieties include amine-, hydroxyl-, or thiol-containing compounds. A non-limiting list of such suitable compounds includes organic compounds, enzymes, proteins, polypeptides, antibodies, monoclonal antibodies, single chain antibodies or oligonucleotides, etc. Organic compounds include, without limitations, moieties such as camptothecin and analogs (e.g., SN38 and irinotecan), and related topoisomerase I inhibitors, taxanes and paclitaxel derivatives, nucleosides including AZT, anthracycline compounds including daunorubicin, doxorubicin; p-aminoaniline mustard, melphalan, Ara-C (cytosine arabinoside) and related anti-metabolite compounds, e.g., gemcitabine, etc. Alternatively, biologically active moieties can include cardiovascular agents, anti-neoplastic, anti-infective, anti-fungal such as nystatin and amphotericin B, anti-anxiety agents, gastrointestinal agents, central nervous system-activating agents, analgesic, fertility agents, contraceptive agents, anti-inflammatory agents, steroidal agents, anti-urecemic agents, vasodilating agents, and vasoconstricting agents, etc. It is to be understood that other biologically active materials not specifically mentioned but having suitable amine-, hydroxyl- or thiol-containing groups are also intended and are within the scope of the present invention.

[0178] In another aspect of the invention, the biologically active compounds are suitable for medicinal or diagnostic use in the treatment of animals, e.g., mammals, including humans, for conditions for which such treatment is desired.

[0179] The only limitations on the types of the biologically active moieties suitable for inclusion herein is that there is available at least one amine-, hydroxyl-, or thiol-containing position which can react and link with a carrier portion and that there is not substantial loss of bioactivity in the form of conjugated to the polymeric delivery systems described herein. Alternatively, parent compounds suitable for incorporation into the polymeric transport conjugate compounds of the invention, may be active after hydrolytic release from the linked compound, or not active after hydrolytic release but which will become active after undergoing a further chemical process/reaction. For example, an anticancer drug that is delivered to the bloodstream by the polymeric transport system, may remain inactive until entering a cancer or tumor cell, whereupon it is activated by the cancer or tumor cell chemistry, e.g., by an enzymatic reaction unique to that cell.

[0180] A further aspect of the invention provides the conjugate compounds optionally prepared with a diagnostic tag linked to the polymeric delivery system described herein, wherein the tag is selected for diagnostic or imaging purposes. Thus, a suitable tag is prepared by linking any suitable moiety, e.g., an amino acid residue, to any art-standard emitting isotope, radio-opaque label, magnetic resonance label, or other non-radioactive isotopic labels suitable for magnetic resonance imaging, fluorescence-type labels, labels exhibiting visible colors and/or capable of fluorescing under ultraviolet, infrared or electrochemical stimulation, to allow for imaging tumor tissue during surgical procedures, and so forth. Optionally, the diagnostic tag is incorporated into and/or linked to a conjugated therapeutic moiety, allowing for monitoring of the distribution of a therapeutic biologically active material within an animal or human patient.

[0181] In yet a further aspect of the invention, the inventive tagged conjugates are readily prepared, by art-known methods, with any suitable label, including, e.g., radioisotope labels. Simply by way of example, these include ^{131}Iodine, ^{125}Iodine, ^{99m}Technetiumn and/or ^{111}Indium to produce radioimmunoscintigraphic agents for selective uptake into tumor cells, in vivo. For instance, there are a number of art-known methods of linking peptide to Tc-99m, including, simply by way of example, those shown by U.S. Pat. Nos. 5,328,679; 5,888,474; 5,997,844; and 5,997,845. incorporated by reference herein.

3. Targeting Groups

[0182] In some aspects, the compounds described herein include targeting groups. The targeting groups include receptor ligands, an antibodies or antibody fragments, single chain antibodies, targeting peptides such as cell adhesion peptides and cell penetrating peptides (CPPs), targeting carbohydrate molecules or lectins. Targeting groups enhance binding or uptake of the compounds described herein a target tissue and cell population. For example, a non-limiting list of targeting groups includes vascular endothelial cell growth factor, FGF2, somatostatin and somatostatin analogs, transferrn, melanotropin, ApoE and ApoE peptides, von Willebrand's Factor and von Willebrand's Factor peptides; adenoviral fiber

protein and adenoviral fiber protein peptides; PD1 and PD1 peptides, EGF and EGF peptides, RGD peptides, folate, etc. Other suitable targeting groups include selectin, TAT, penetratin, and Arg_0.

[0183] In a further aspect of the invention, the targeting groups can be optionally labeled with biotin, fluorescent compounds, radio-labeled compounds by art-known methods.

F. Synthesis of the Polymeric Delivery Systems

[0184] Generally, the methods of preparing the compounds described herein include reacting a polymer with an aromatic acid ester to form a polymer-aromatic acid.

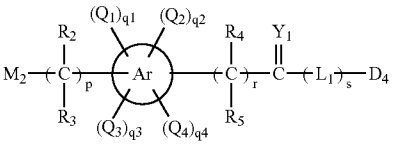
[0185] In one embodiment, the method includes

[0186] reacting a compound of Formula (II) having the structure of:

$$A_1\text{-}R_1\text{—}X_1\text{-}M_1 \quad \text{(II)}$$

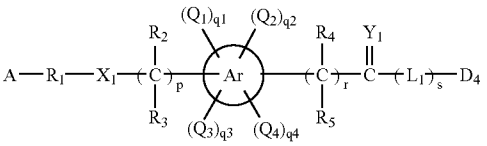
with a compound of Formula (III) having the structure of:

(III)



under conditions effective to form the compound of Formula (IV) having the structure of

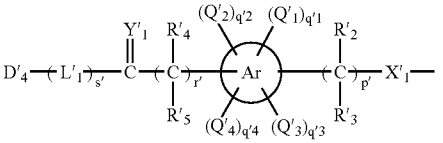
(IV)



[0187] wherein:

[0188] A_1 is a capping group or $M_1\text{-}X'_1$—;

[0189] A is a capping group or



[0190] R_1 is a substantially non-antigenic water-soluble polymer;

[0191] M_1 is —OH, —SH or —NHR_{41};

[0192] M_2 is a leaving group;

[0193] Ar and Ar' are independently an aryl or heteroaryl moiety;

[0194] X_1 and X'_1 are independently O, S, SO, SO_2, NR_6 or a bond;

[0195] Y_1 and Y'_1 are independently O, S, or NR_6;

[0196] L_1 and L'_1 are independently selected bifunctional linkers;

[0197] D_4 and D'_4 are independently selected from among hydrogen, OH, OR_{42}, leaving groups, functional groups, targeting groups, diagnostic agents and biologically active moieties;

[0198] $R_{2\text{-}5}$, $R'_{2\text{-}5}$, R_6 and R_{41} are independently selected from i among hydrogen, amino, substituted amino, azido, carboxy, cyano, halo, hydroxyl, nitro, silyl ether, sulfonyl, mercapto, $C_{1\text{-}6}$ alkylmercapto, arylmercapto, substituted arylmercapto, substituted $C_{1\text{-}6}$ alkylthio, $C_{1\text{-}6}$ alkyls, $C_{2\text{-}6}$ alkenyl $C_{2\text{-}6}$ alkynyl, $C_{3\text{-}19}$ branched alkyl, $C_{3\text{-}8}$ cycloalkyl, $C_{1\text{-}6}$ substituted alkyl, $C_{2\text{-}6}$ substituted alkenyl, $C_{2\text{-}6}$ substituted alkynyl, $C_{3\text{-}8}$ substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, $C_{1\text{-}6}$ heteroalkyl, substituted $C_{1\text{-}6}$ heteroalkyl, $C_{1\text{-}6}$ alkoxy, aryloxy, $C_{1\text{-}6}$ heteroalkoxy, heteroaryloxy, $C_{2\text{-}6}$ alkanoyl, arylcarbonyl, $C_{2\text{-}6}$ alkoxycarbonyl, aryloxycarbonyl, $C_{2\text{-}6}$ alkanoyloxy, arylcarbonyloxy, $C_{2\text{-}6}$ substituted alkanoyl, substituted arylcarbonyl, $C_{2\text{-}6}$ substituted alkanoyloxy, substituted aryloxycarbonyl, $C_{2\text{-}6}$ substituted alkanoyloxy, substituted and arylcarbonyloxy;

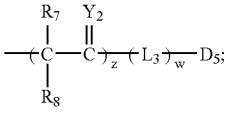
[0199] R_{42} is $C_{1\text{-}6}$ alkyl;

[0200] (p), (p'), (r) and (r') are independently zero or a positive integer, preferably from about 0 to about 10 (e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10), more preferably from about 0 to about 6 (e.g., 0, 1, 2, 3, 4, 5 or 6), and most preferably 0, 1 or 2;

[0201] (q_1), (q'_1), (q_2), (q'_2), (q_3), (q'_3), (q_4) and (q'_4) are independently zero or one:

[0202] (s) and (s') are independently zero or a positive integer, preferably from about 0 to about 6 (e.g., 0, 1, 2, 3, 4, 5 or 6) and more preferably zero, 1 or 2;

[0203] $Q_{1\text{-}4}$ and $Q'_{1\text{-}4}$ are independently selected from among the same moieties which can be used for R_2 or each can be:



[0204] wherein

[0205] R_7 and R_8 are independently selected from the same as used for R_2;

[0206] Y_2 is O, S or NR_6;

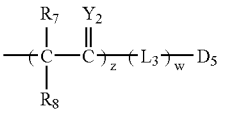
[0207] L_3 is a bifunctional linker;

[0208] (z) is zero or one;

[0209] (w) is zero or a positive integer, preferably from about 0 to about 6 (e.g., 0, 1, 2, 3, 4, 5 or 6), more preferably zero, 1 or 2 (for example, (z) is 0 and (w) is 1 and preferably (z) is 1 and (w) is 1); and

[0210] D_5 is selected from the group consisting of hydrogen, OH, leaving groups, functional groups, targeting groups, diagnostic agents and biologically active moieties;

[0211] provided that the sum of $(q_1)+(q_2)+(q_3)+(q_4)$ is not zero and that at least one of Q_{1-4} and Q'_{1-4} is



wherein at least one of D_5 is a leaving group, a functional group, a targeting group, a diagnostic agent or a biologically active moiety; and

[0212] provided that (z) is not zero when (w) is zero.

[0213] In certain aspects of the invention, when (p) is zero, there are preferably a sufficient number of atoms, e.g., more than five or six atoms, present between X_1/X'_1 and $C(=Y_1)/C(=Y'_1)$, so that a releasable cyclic moiety is not formed. For example, when (p) is zero, the polymeric portion attached to the phenyl ring would not be in an ortho position in relation to D_4, D'_4 or D_5.

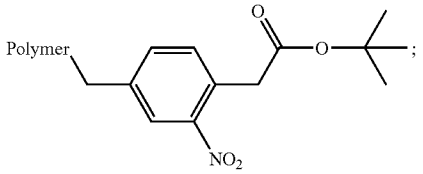
[0214] The leaving group M_1 includes halogen (Br, Cl), activated carbonate, carbonyl imidazole, cyclic imide thione, isocyanate, N-hydroxysuccinimidyl, para-nitrophenoxy, N-hydroxyphtalimide, N-hydroxybenzotriazolyl, imidazole, tosylate, mesylate, tresylate, nosylate, C_1-C_6 alkyloxy, C_1-C_6 alkanoyloxy, arylcarbonyloxy, ortho-nitrophenoxy, N-hydroxybenzotriazolyl, pentafluorophenoxy, 1,3,5-trichlorophenoxy, and 1,3,5-trifluorophenoxy or other suitable leaving groups that is apparent to those of ordinary skill in the art.

[0215] The resulting compounds of Formula (IV) can be then deprotected to form a polymer-aromatic acid. The polymer-aromatic acids are further activated with an amine or a hydroxyl containing compound. Alternatively/additionally, a bifunctional group can be attached to the aromatic moiety to provide a functional group. The functional groups can be further conjugated to a biologically active moiety, or a targeting moiety.

[0216] Alternatively, it is also contemplated that methods can include reacting a polymer containing a leaving group with an aromatic-containing moiety to form a polymer-aromatic acid.

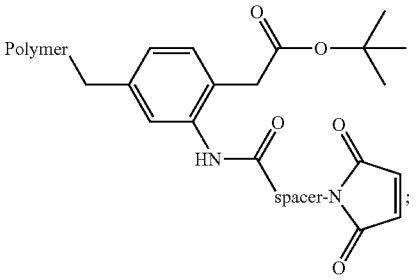
[0217] In one embodiment, the method includes:

[0218] a) reacting a protected aromatic compound with a substantially non-antigenic polymer compound to form a polymer compound of Formula (Ia):



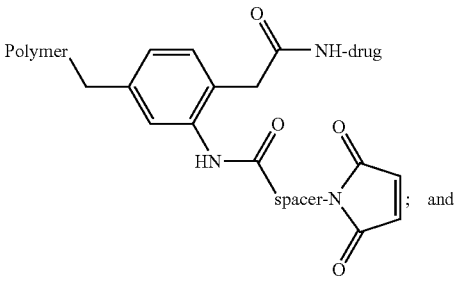
[0219] b) converting the nitro moiety on the compound of Formula (Ia) under a suitable reaction condition to form an amine;

[0220] c) reacting the amine with a suitable bifunctional spacer to form a compound of Formula (Ic):

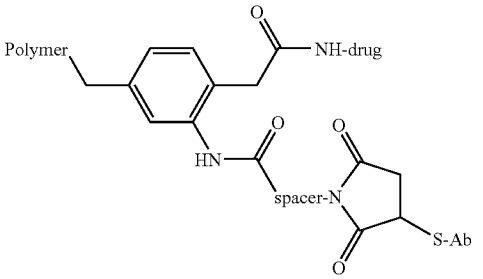


[0221] d) deprotecting the ester of the compound of Formula (Ic) to form an acid;

[0222] e) activating the acid resulting from step (d) and reacting the activated acid with an amine-containing biologically active moiety to form a compound of Formula (Ie):



[0223] f) reacting the compound of Formula (Ie) with a thiol containing moiety to form a compound of Formula (If):



[0224] wherein,

[0225] NH-drug is an amine-containing biologically active moiety;

[0226] Spacer is selected from the same group as defined for L_3;

[0227] Ab is an antibody such as monoclonal antibody, single chain antibody and active fragments thereof, and

[0228] Polymer is a substantially non-antigenic polymer.

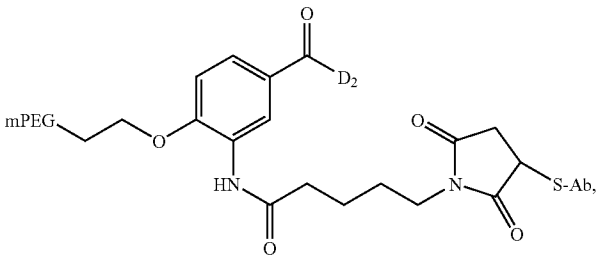
[0229] Attachment of the bifunctional group to the polymer portion is preferably carried out in the presence of a coupling agent. A non-limiting list of suitable coupling agents include 1,3-diisopropylcarbodiimide (DIPC), any suitable dialkyl carbodiimides, 2-halo-1-alkyl-pyridinium halides, (Mukaiyama reagents), 1-(3-dimethylaminopropyl)-3-ethyl car-

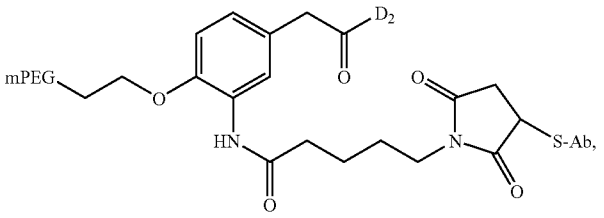
bodiimide (EDC), propane phosphonic acid cyclic anhydride (PPACA) and phenyl dichlorophosphates, etc. which are available, for example from commercial sources such as Sigma-Aldrich Chemical, or synthesized using known techniques.

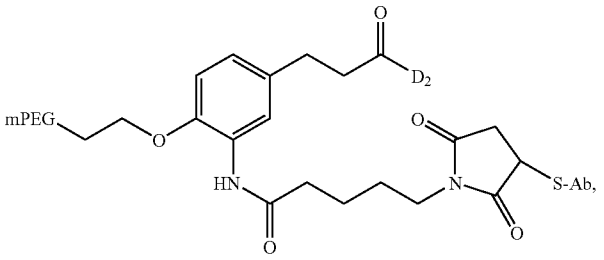
[0230] Preferably, the reactions are carried out in an inert solvent such as methylene chloride, chloroform, DMF or mixtures thereof. The reactions can be preferably conducted in the presence of a base, such as dimethylaminopyridine (DMAP), diisopropylethylamine, pyridine, triethylamine, etc. to neutralize any acids generated. The reactions can be carried out at a temperature from about 0° C. up to about 22° C. (room temperature).

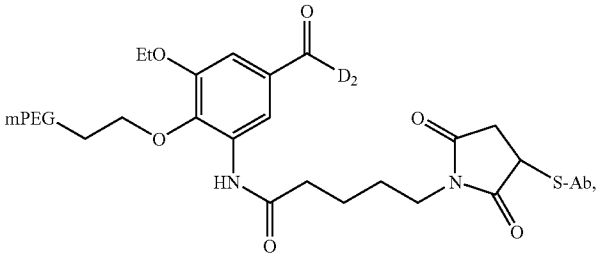
G. Compounds of Formula (I)

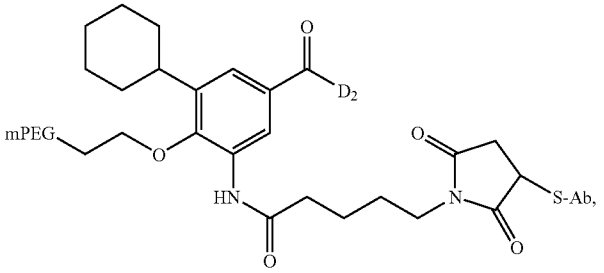
[0231] Some particular embodiments prepared by the methods described herein have the structure:











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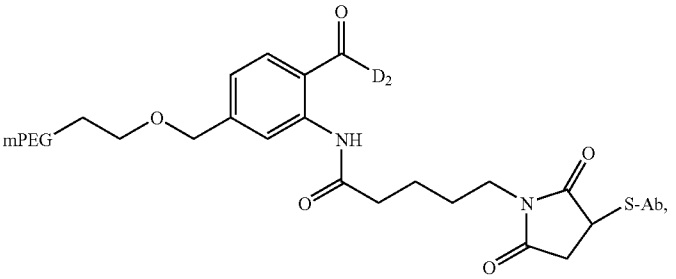

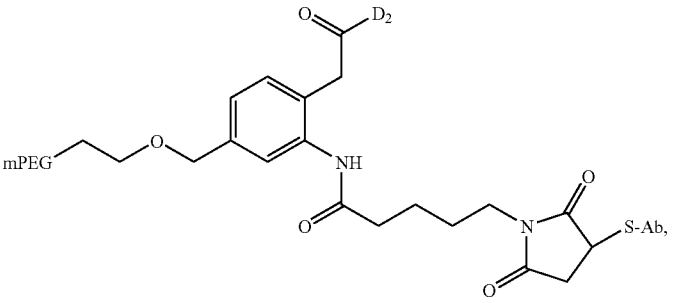

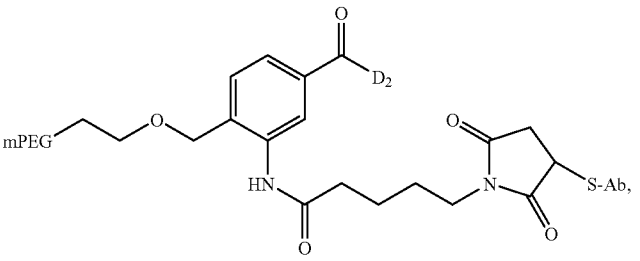

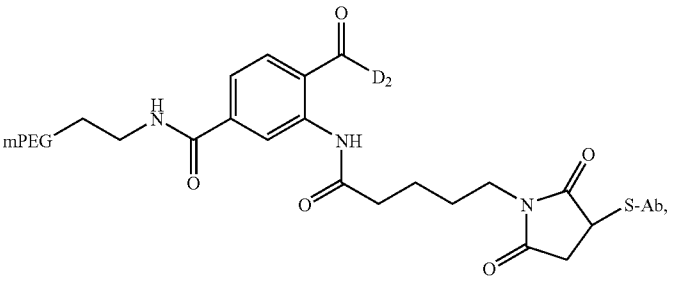

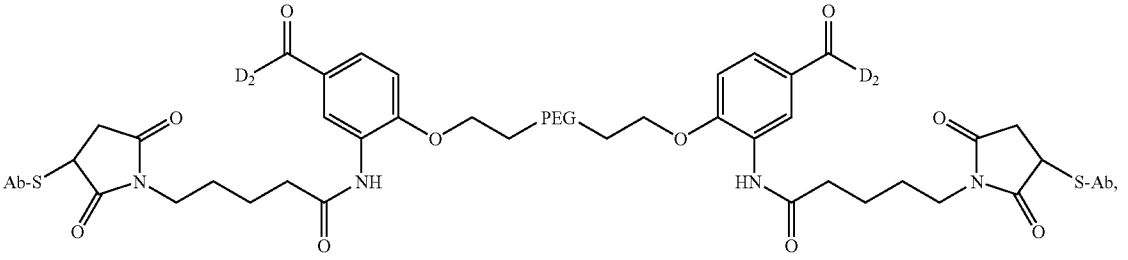

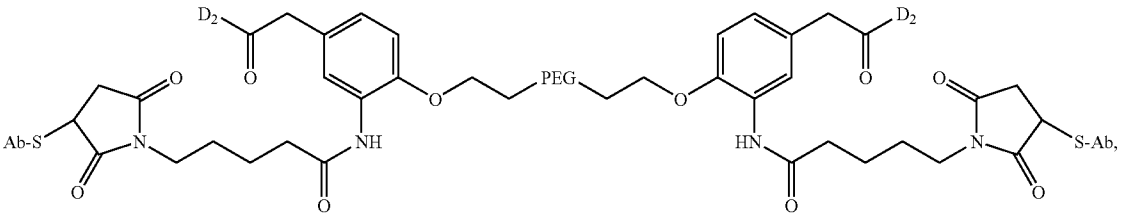

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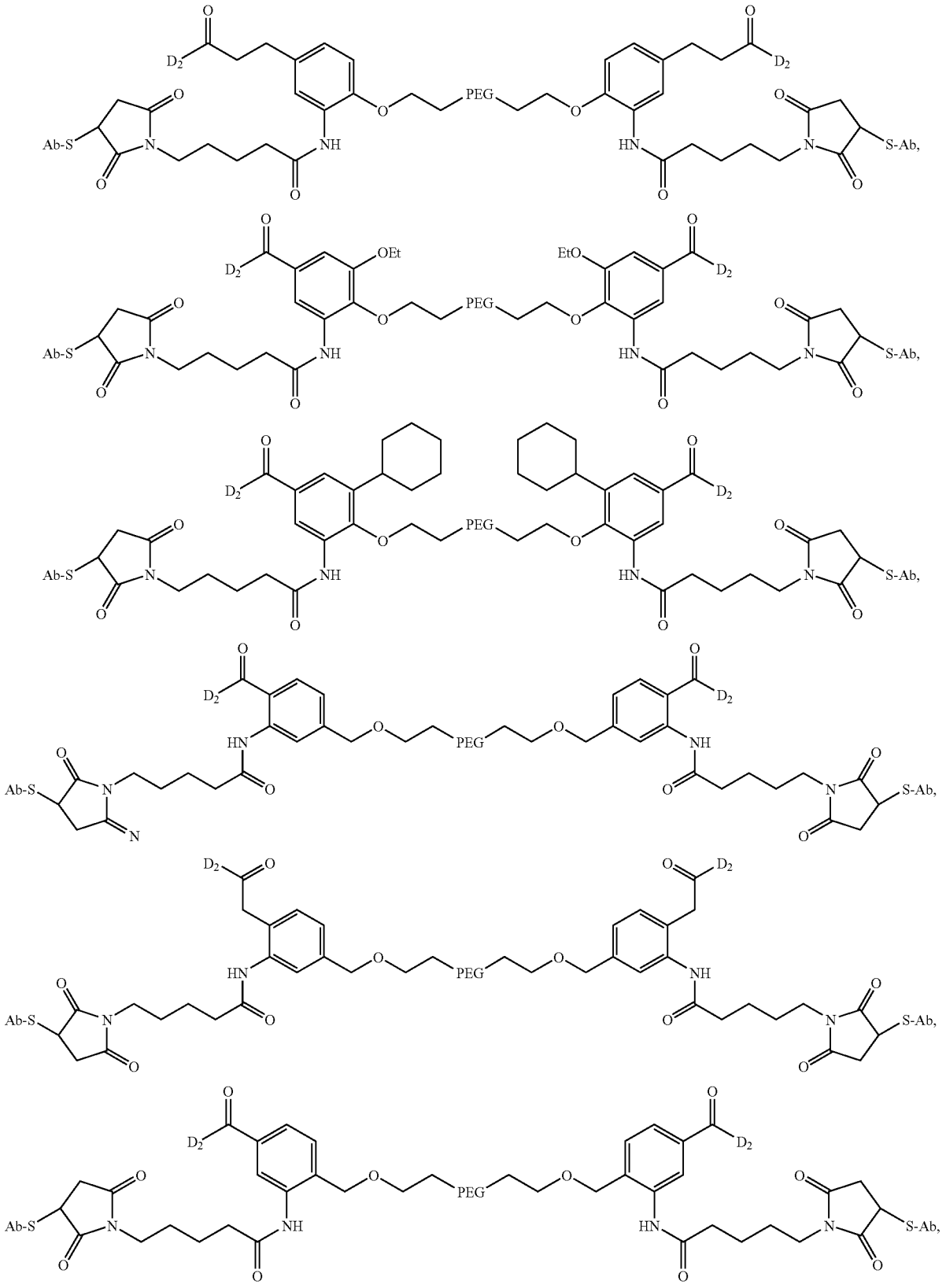

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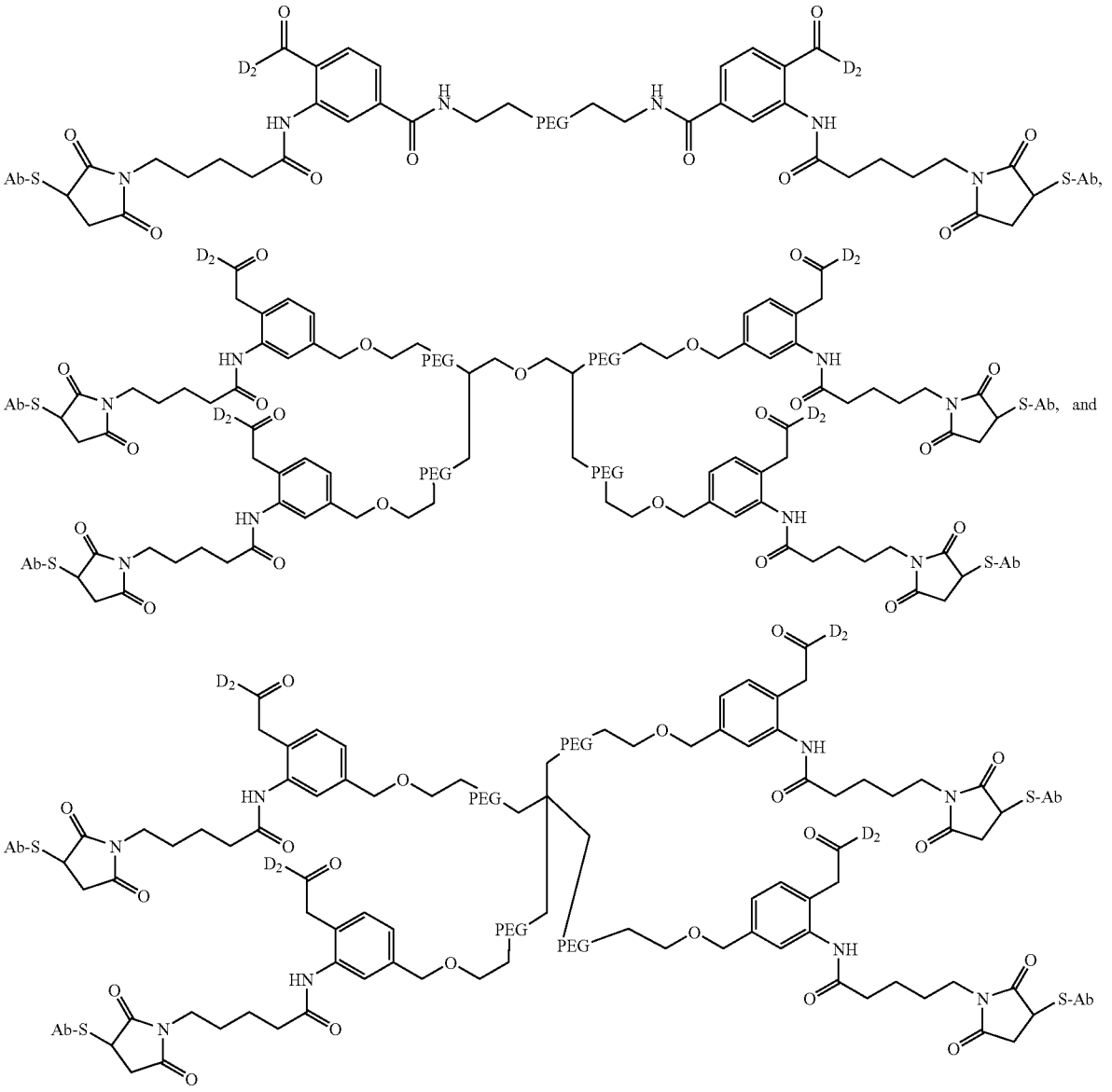


[0232] one or more, preferably all, D_2 is hydrogen, OH, leaving groups, functional groups, targeting groups, diagnostic agents and biologically active moieties;

[0233] Ab is an antibody;

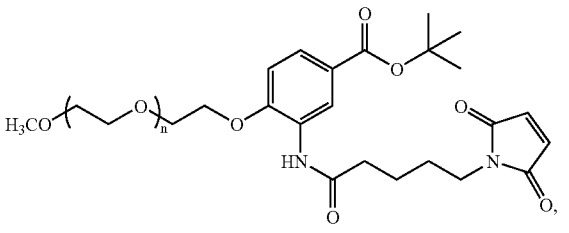
[0234] mPEG has the formula $CH_3O(CH_2(CH_2O)_n$—;

[0235] PEG has the formula —$O(CH_2CH_2O)_n$—, and

[0236] (n) is an integer from about 10 to about 2,300.

[0237] For purposes of the present invention, it will be understood that the "S-Ab" represents antibodies, such as monoclonal antibodies, single chain antibodies, and active fragments thereof

[0238] For example, a non-limiting list of particular embodiments includes:



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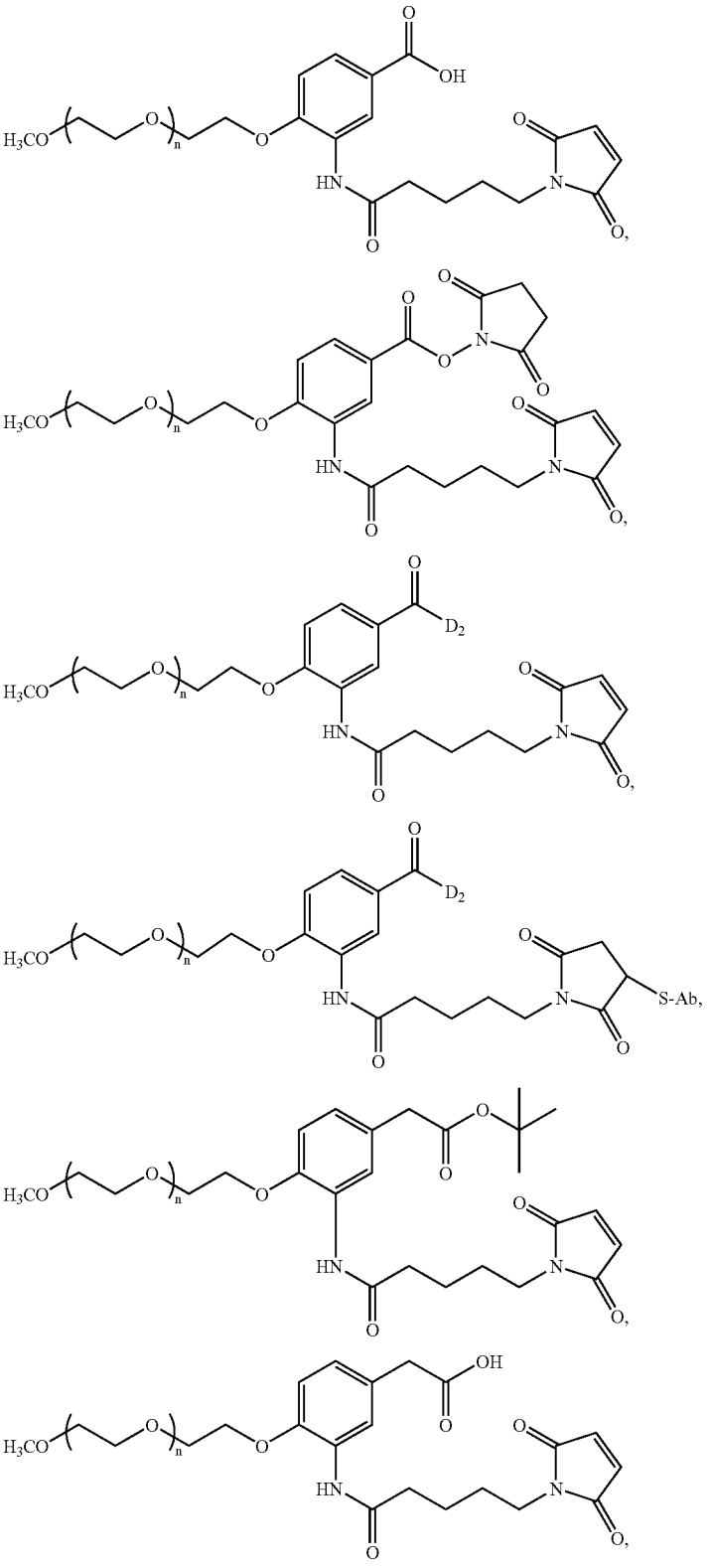

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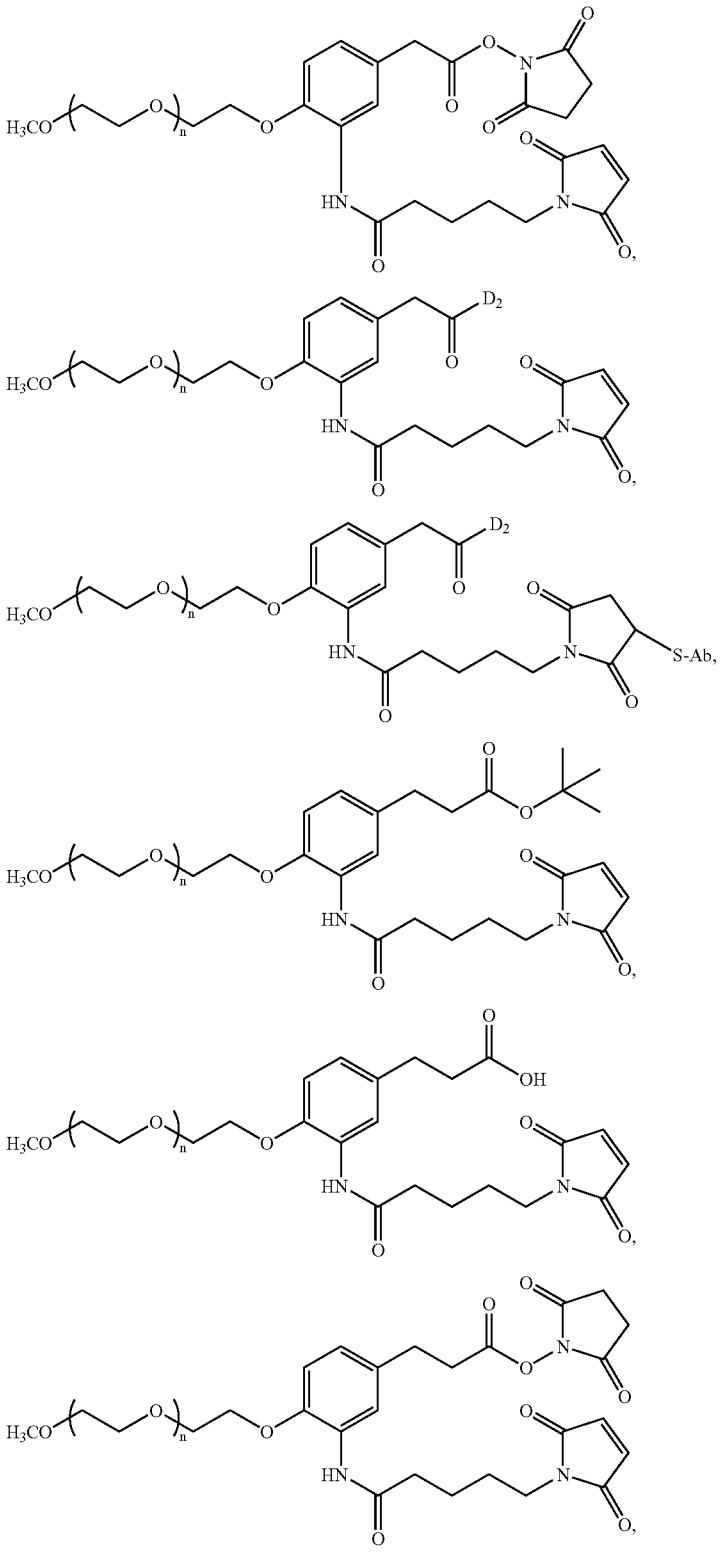

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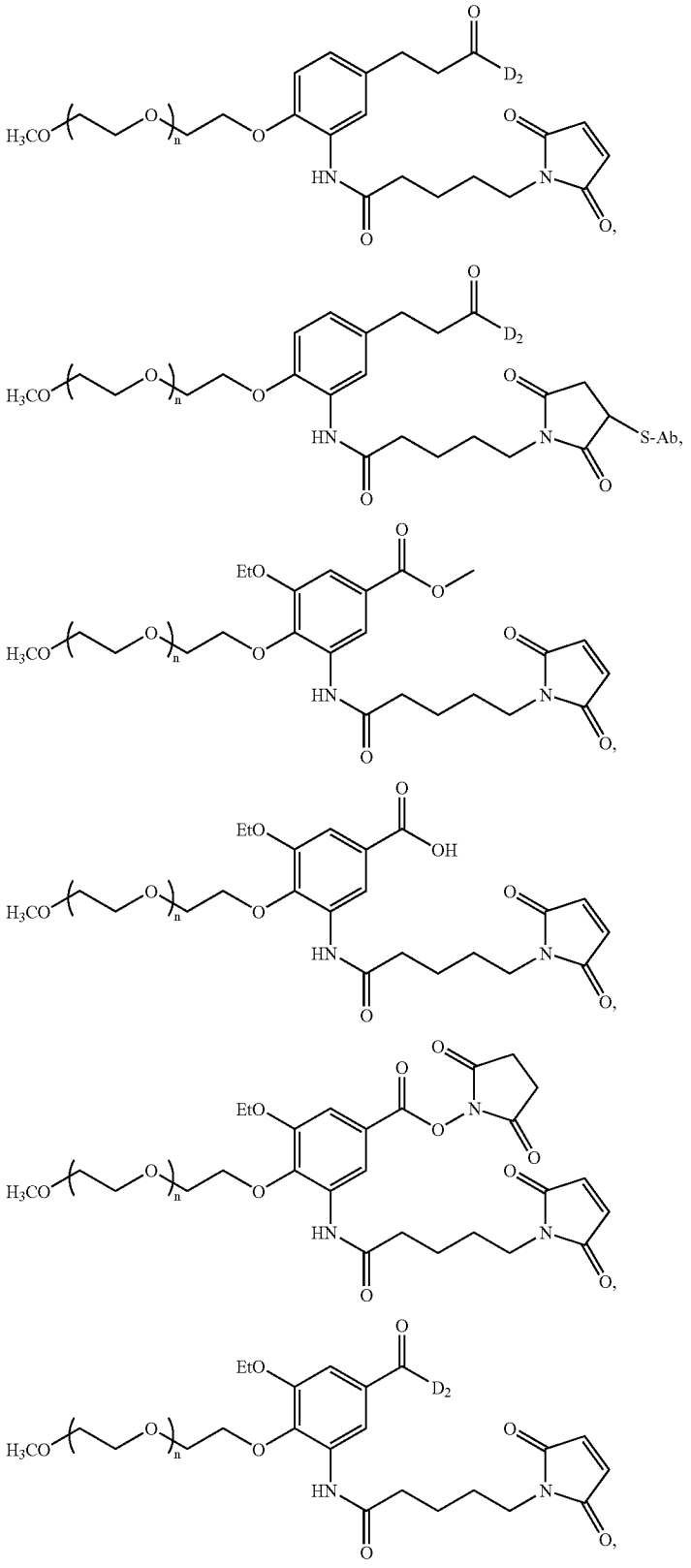

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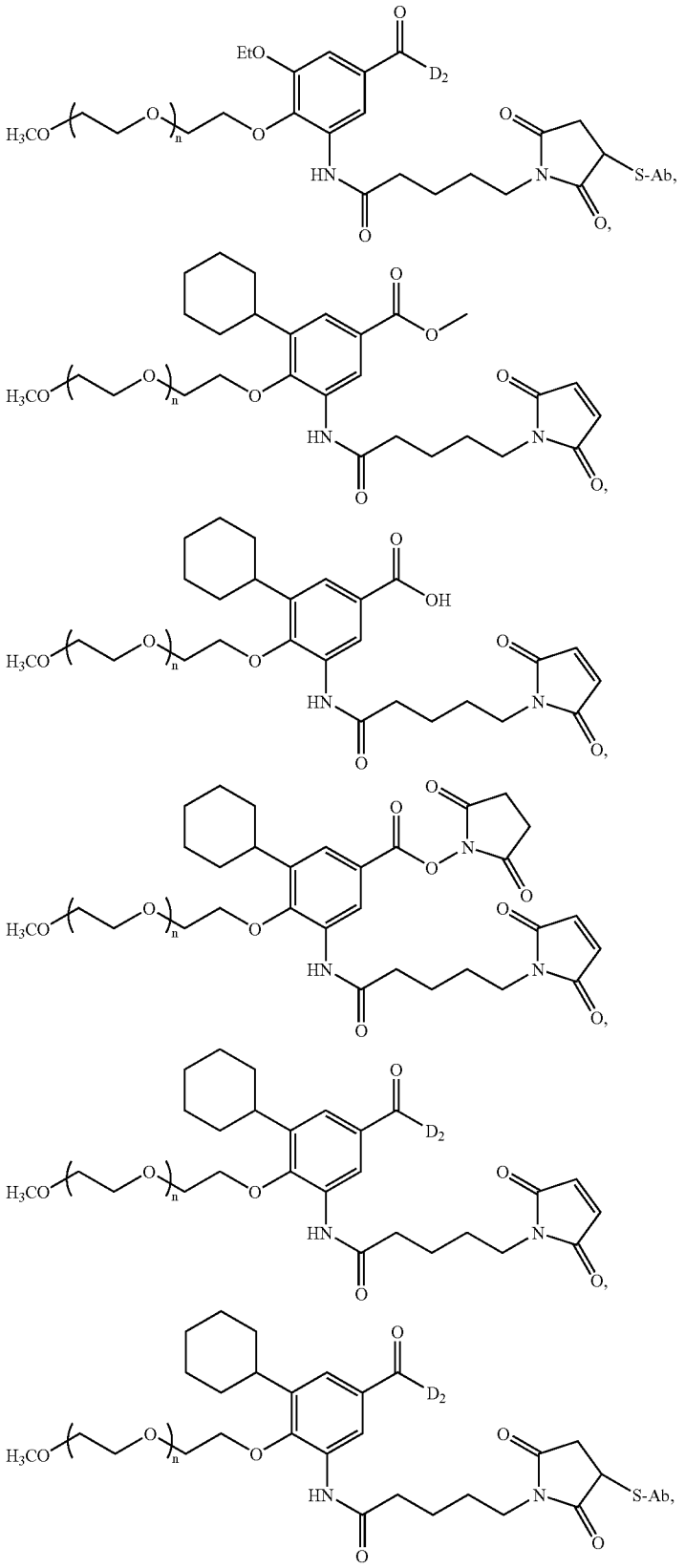

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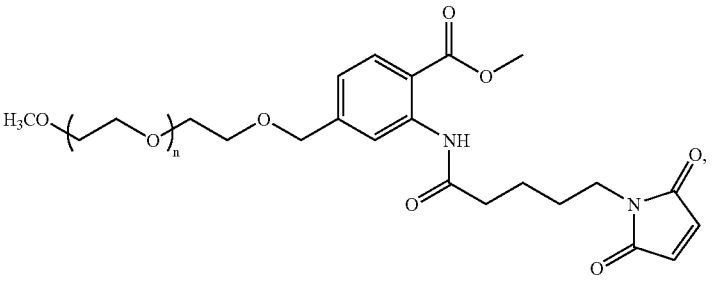

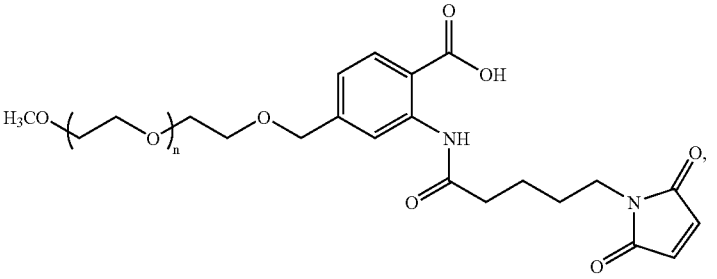

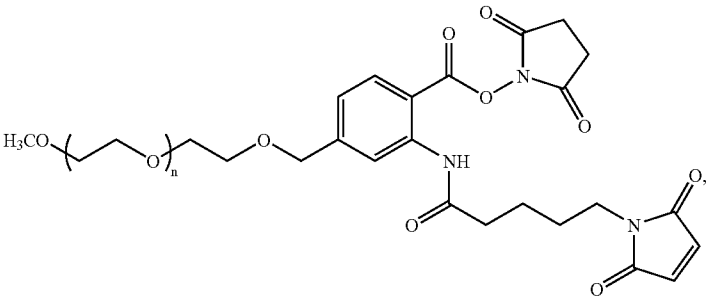

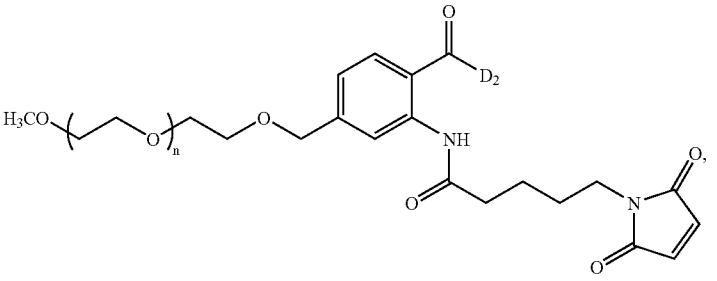

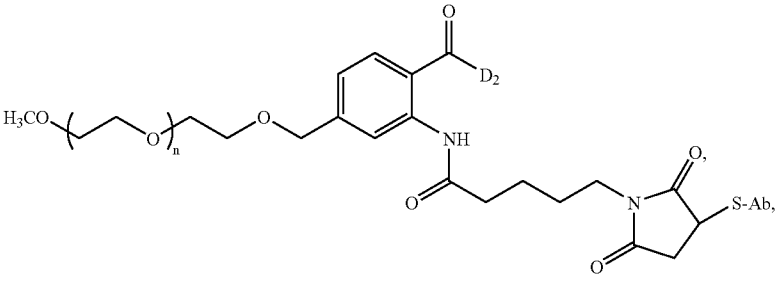

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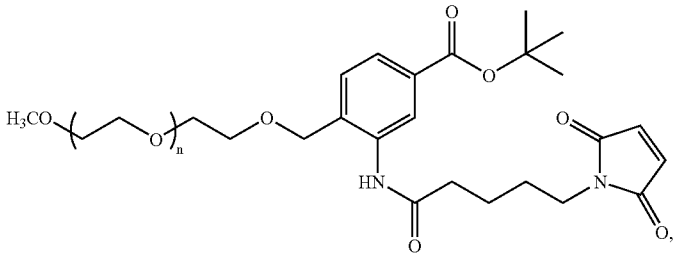

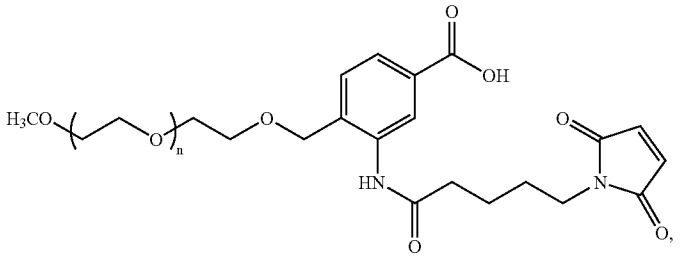

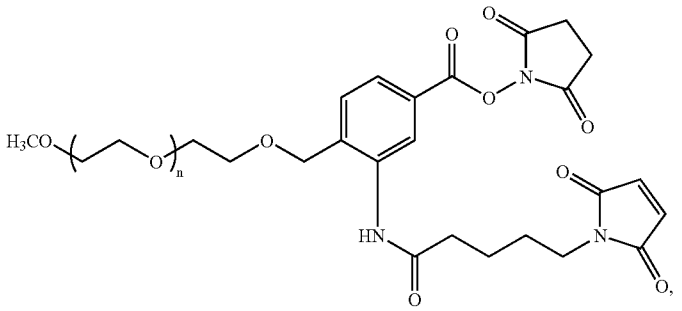

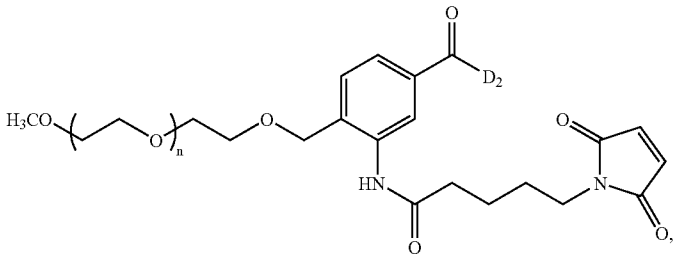

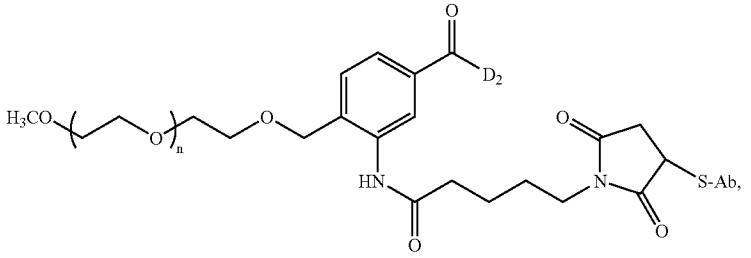

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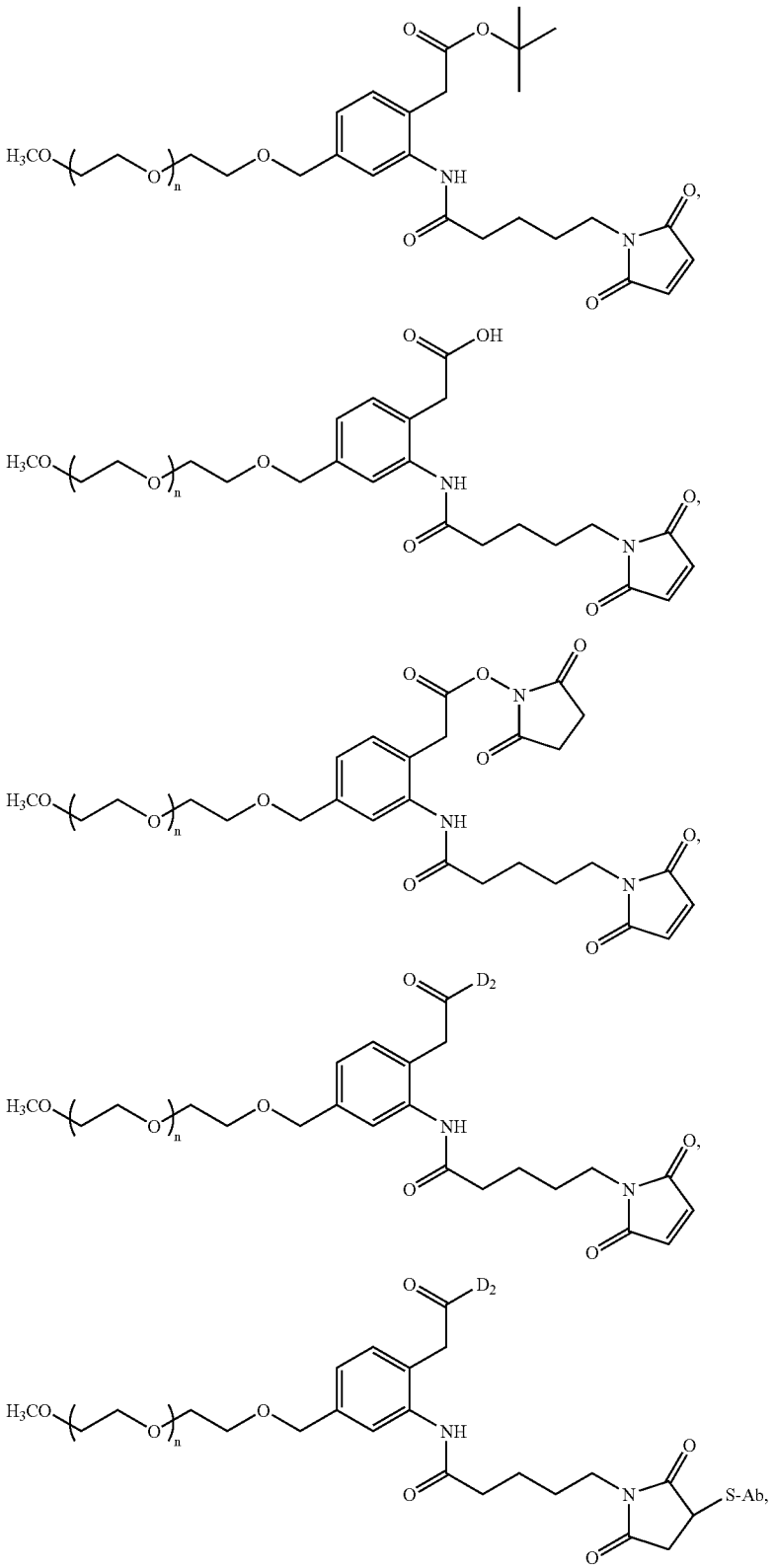

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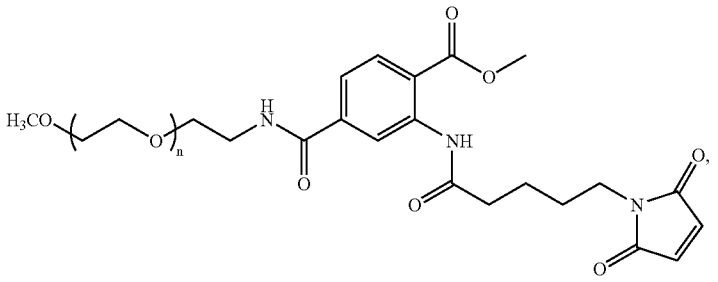
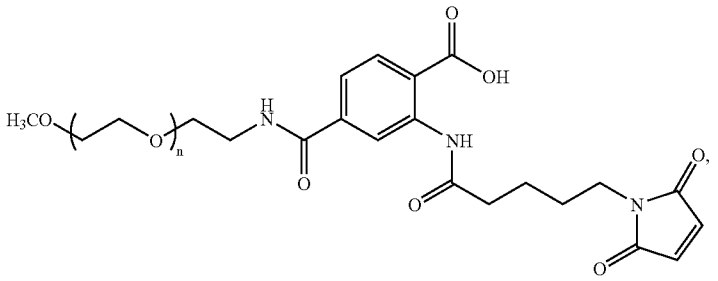
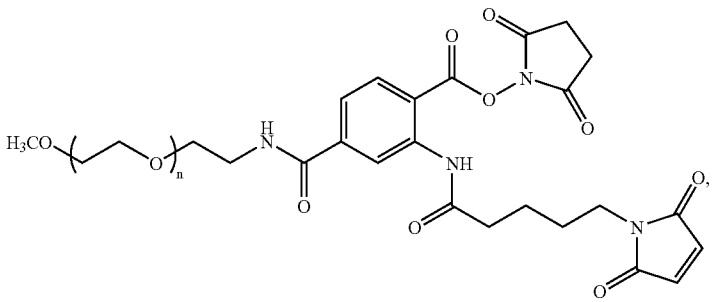
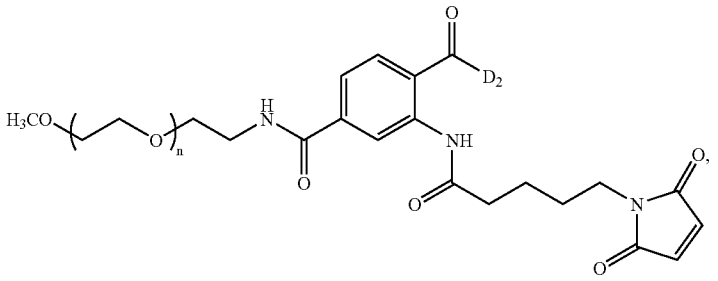
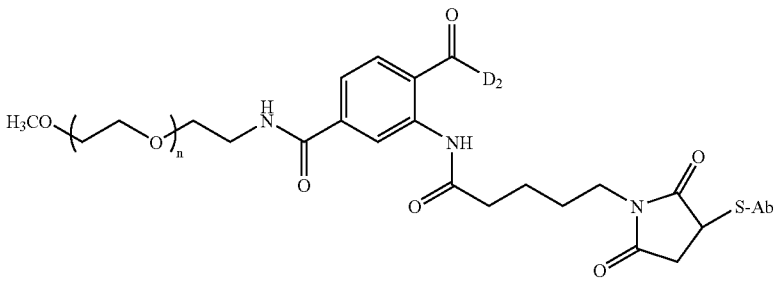








and



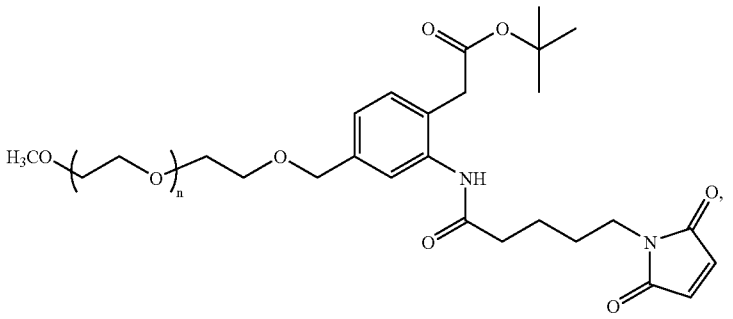
[0239] wherein

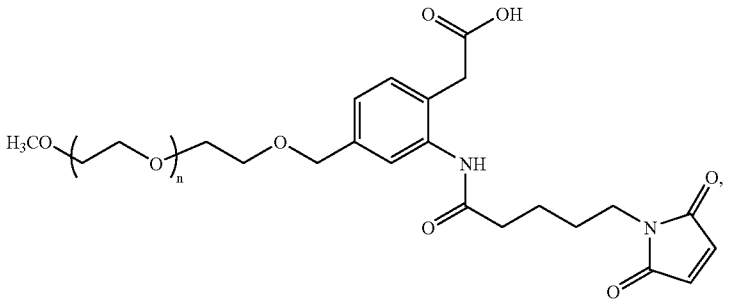
[0240] (n) is all integer from about 10 to about 2300;

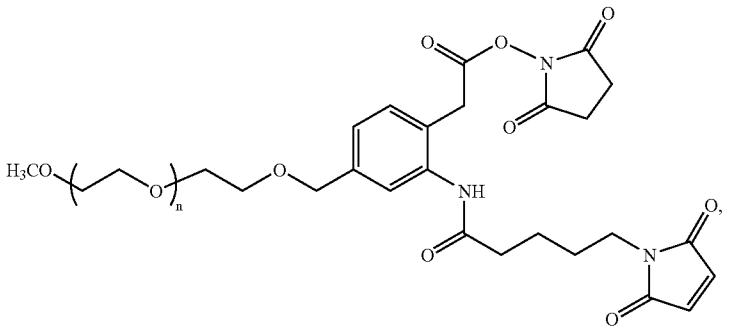
[0241] D_2 is selected from the group consisting of pharmaceutically active compounds, enzymes, proteins, oligonucleotides, antibodies, monoclonal antibodies, single chain antibodies and peptides; and

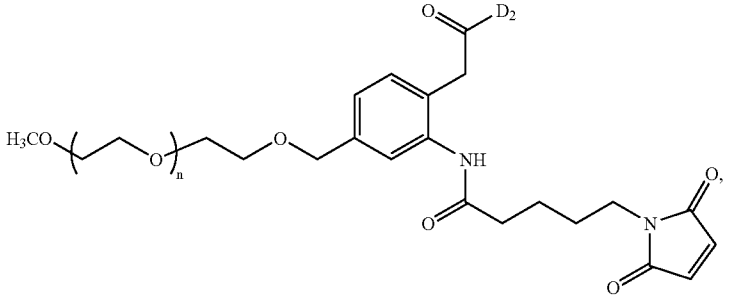
[0242] Ab is an antibody.

[0243] Preferably, the compounds prepared by the methods include:









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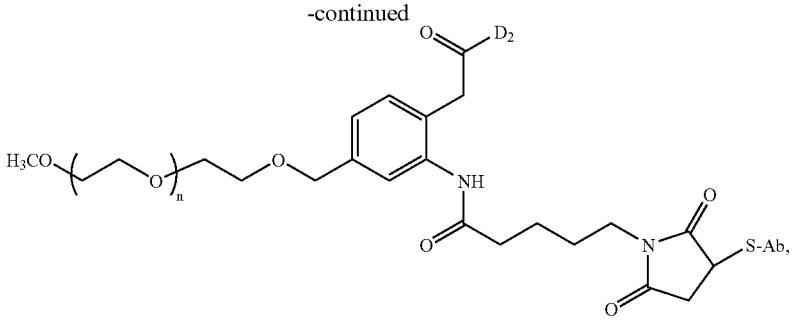


[0244] wherein

[0245] (n) is an integer from about 10 to about 2300;

[0246] D_2 is selected from the group consisting of pharmaceutically active compounds, enzymes, proteins, oligonucleotides, antibodies, monoclonal antibodies, single chain antibodies and peptides; and

[0247] Ab is an antibody.

H. Methods of Treatment

[0248] Another aspect of the present invention provides methods of treatment for various medical conditions in mammals. The methods include administering, to the mammal in need of such treatment, an effective amount of a compound described herein. The polymeric conjugate compounds are useful for, among other things, treating diseases which are similar to those which are treated with the parent compound, e.g. enzyme replacement therapy, neoplastic disease, reducing tumor burden, preventing metastasis of neoplasms and preventing recurrences of tumor/neoplastic growths in mammals.

[0249] The amount of the polymeric conjugate that is administered will depend upon the amount of the parent molecule included therein. Generally, the amount of polymeric conjugate used in the treatment methods is that amount which effectively achieves the desired therapeutic result in mammals. Naturally, the dosages of the various polymeric conjugate compounds will vary somewhat depending upon the parent compound, molecular weight of the polymer, rate of in vivo hydrolysis, etc. Those skilled in the art will determine the optimal dosing of the polymeric transport conjugates selected based on clinical experience and the treatment indication. Actual dosages will be apparent to the artisan without undue experimentation.

[0250] The compounds of the present invention can be included in one or more suitable pharmaceutical compositions for administration to mammals. The pharmaceutical compositions may be in the form of a solution, suspension, tablet, capsule or the like, prepared according to methods well known in the art. It is also contemplated that administration of such compositions may be by the oral and/or parenteral routes depending upon the needs of the artisan. A solution and/or suspension of the composition may be utilized, for example, as a carrier vehicle for injection or infiltration of the composition by any art known methods, e.g., by intravenous, intramuscular, intraperitoneal, subcutaneous injection and the like. Such administration may also be by infusion into a body space or cavity, as well as by inhalation and/or intranasal routes. In preferred aspects of the invention, however, the polymeric conjugates are parenterally administered to mammals in need thereof.

EXAMPLES

[0251] The following examples serve to provide further appreciation of the invention but are not meant in any way to restrict the scope of the invention. The bold-faced numbers recited in the Examples correspond to those shown in FIG. **1**. Abbreviations are used throughout the examples such as, DCM (dichloromethane), DIEA (diisopropylethylamine), DMAP (4-dimethylaminopyridine), DMF (N,N'-dimethylformamide), DSC (disuccinimidyl carbonate), EDC (1-(3-dimethylaminopropyl)-3-ethyl carbodiimide), IPA (isopropanol), NHS (N-hydroxysuccinimide), PEG (polyethylene glycol), SCA-SH (single-chain antibody), and TEA (triethylamine).

General

[0252] All reactions can be conducted under an atmosphere of dry nitrogen. Commercial regents and anhydrous solvents can be used without further purification. NMR spectra can be recorded at a Varian Mercury 300 MHz NMR spectrometer using deuterated solvent indicated. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) and coupling constants (J values) are given in hertz (Hz).

Example 1

Compound 3

[0253] A solution of 5.0 g (1.0 mmole) of $mPEG^{5K}$-OH (compound 2) in 130 ml of toluene is azeotroped for 2 hours, while removing 65 ml of toluene/water. This solution is cooled to 25° C., followed by addition of 2.0 ml (2.0 mmole) of 1.0 molar t-BuOK in t-butanol. This solution is stirred for 30 minutes at 25° C., followed by the addition of 30 ml of anhydrous DMF. To this reaction mixture is added dropwise, a solution of compound 1 (2.0 mmol) in anhydrous DMF. This solution is added at a rate of 10 ml per 20 min. During addition of the 4-(bromomethyl)-phenylacetic acid solution, while the pH of the reaction mixture is monitored. When the pH reaches ~8.0, a 10 ml aliquot of 1.0 molar t-BuOK in t-butanol is added, total volume 7.0 ml over 40 minutes. The reaction mixture is then poured into 700 ml of ether, and the precipitate is collected by filtration and washed with ether. The solid is dissolved in 70 ml of 0.2N HCl solution, and extracted with methylene chloride. The combined methylene

chloride extracts are dried over sodium sulfate, filtered, and the solvent partially removed by rotovap. The product is precipitated out with ether, collected, washed with ether, and recrystallized from 12% DMF/IPA to give the product.

Example 2

Compound 4

[0254] Compound 3 is suspended in a mixture of water and THF and is added $Na_2S_2O_4$. The mixture is stirred overnight at room temperature. The mixture is concentrated in vacuo and the product is extracted with DCM twice. The organic layers are combined and dried over anhydrous Na_2SO_4, filtered, and concentrated to a minimum volume. Anhydrous ether is added to the residual solution to precipitate the product, which is collected by vacuum filtration and dried in the vacuum oven at 45° C. to give the product.

Example 3

Compound 6

[0255] A solution of compound 4 (1.72 mmol), compound 5 (0.80 g, 6.9 mmol), DIEA (1.3 g, 10.3 mmol), and DMAP (50 mg, 0.4 mmol) in 75 ml of dry methylene chloride is cooled to 0° C. in an ice bath, followed by addition of EDC hydrochloride (1.66 g, 8.6 mmol). This mixture is allowed to warm to room temperature overnight. The solvent is partially removed by rotovap. The product is precipitated with ether, and collected and washed with ether to give the crude product, which is dried in the vacuum oven at 45° C. to give the product.

Example 4

Compound 7

[0256] Trifluoroacetic acid (TFA, 2.5 mL) is added to a solution of compound 6 (3.2 mmol) of in 5 mL of methylene chloride followed by stirring at room temperature for 30 minutes. Ether is added until the solid is precipitated. The solid is filtered and washed thoroughly with ether until all the excess TFA is removed. The acid is dried in the vacuum oven at 45° C.

Example 5

Compound 8

[0257] A solution of compound 7 (1.72 mmol), NHS (0.80 g, 6.9 mmol), DTEA (1.3 g, 10.3 mmol), and DMAP (50 mg, 0.4 mmol) in 75 ml of dry methylene chloride is cooled to 0° C. in an ice bath, followed by addition of EDC hydrochloride (1.66 g, 8.6 mmol). This mixture is allowed to warm to room temperature overnight. The solvent is partially removed by rotovap. The product is precipitated with ether, and collected and washed with ether to give the crude product, which is dried in the vacuum oven at 45° C. to give the product.

Example 6

Compound 9

[0258] PEG linker (compound 8) (0.084 mmol) is added to native (L)-asparaginase (0.00027 mmol) in 3 mL of sodium phosphate buffer (0.1 M, pH 7.8) with gentle stirring. The solution is stirred at 30° C. for 30 minutes. A GPC column (Zorbax GF-450) is used to monitor PEG conjugation. At the end of the reaction (as evidenced by the absence of native enzyme), the mixture is diluted with 12 mL of formulation buffer (0.05 M sodium phosphate, 0.85% sodium chloride, pH 7.3) and diafiltered with a Centriprep concentrator (Amicon) to remove the unreacted PEG. Dialfiltration is continued as needed at 4° C. until no more free PEG is detected by mixing equal amount of filtrate and 0.1% PMA (polymethacrylic acid in 0.1 M HCl) to give the product.

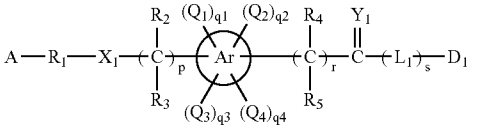
Example 7

Compound 10

[0259] Compound 9 (0.084 mmol) is added to SCA-SH (0.00027 mmol) in 3 mL of sodium phosphate buffer (0.1 M, pH 7.8) with gentle stirring. The solution is stirred at 30° C. for 30 minutes. A GPC column (Zorbax GF-450) is used to monitor PEG conjugation. At the end of the reaction (as evidenced by the absence of native enzyme), the mixture is diluted with 12 mL of formulation buffer (0.05 M sodium phosphate, 0.85% sodium chloride, pH 7.3) and diafiltered with a Centriprep concentrator (Amicon) to remove the unreacted PEG reactant. Dialfiltration is continued as needed at 4° C. until no more free PEG was detected by mixing equal amount of filtrate and 0.1% PMA (polyinethacrylic acid in 0.1 M HCl) to give the product.

We claim:

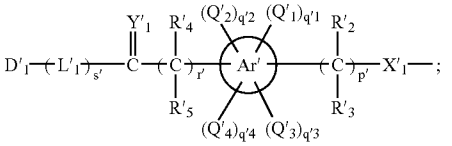
1. A compound of Formula (1):



(I)

wherein:

A is a capping group or



R_1 is a substantially non-antigenic water-soluble polymer;

X_1 and X'_1 are independently O, S, SO, SO_2, NR_6 or a bond;

Ar and Ar' are independently an aryl or heteroaryl moiety;

Y_1 and Y'_1 are independently O, S, or NR_6;

L_1 and L'_1 are independently selected bifunctional linkers;

D_1 and D'_1 are independently selected from the group consisting of hydrogen, OH, leaving groups, functional groups, targeting groups, diagnostic agents and biologically active moieties;

R_{2-5}, R'_{2-5}, and R_6 are independently selected from the group consisting of hydrogen, amino, substituted amino, azido, carboxy, cyano, halo, hydroxyl, nitro, silyl ether, sulfonyl, mercapto, C_{1-6} alkylmercapto, arylmercapto, substituted arylmercapto, substituted C_{1-6} alkylthio, C_{1-6} alkyls, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-19} branched alkyl, C_{3-8} cycloalkyl, C_{1-6} substituted alkyl, C_{2-6} substituted alkenyl, C_{2-6} substituted alkynyl, C_{3-8} substituted cycloalkyl, aryl, substituted aryl, heteroaryl, sub-

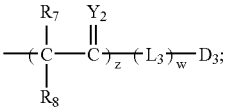
stituted heteroaryl, C_{1-6} heteroalkyl, substituted C_{1-6} heteroalkyl, C_{1-6} alkoxy, aryloxy, C_{1-6} heteroalkoxy, heteroaryloxy, C_{2-6} alkanoyl, arylcarbonyl, C_{2-6} alkoxycarbonyl, aryloxycarbonyl, C_{2-6} alkanoyloxy, arylcarbonyloxy, C_{2-6} substituted alkanoyl, substituted arylcarbonyl, C_{2-6} substituted alkanoyloxy, substituted aryloxycarbonyl, C_{2-6} substituted alkanoyloxy, substituted and arylcarbonyloxy;

(p), (p'), (r) and (r') are independently zero or a positive integer;

(q_1), (q'_1), (q_2), (q'_2), (q_3), (q'_3), (q_4) and (q'_4) are independently zero or one;

(s) and (s') are independently zero or a positive integer;

Q_{1-4} and Q_{1-4} are independently selected from the same moieties which can be used for R_2 or each can be:



wherein

R_7 and R_8 are independently selected from the same group as that which defines R_2;

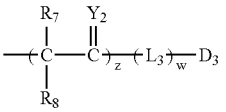
Y_2 is O, S or NR_6;

L_3 is a bifunctional linker;

(z) is zero or one;

(w) is zero or a positive integer; and

D_3 is selected from the group consisting of hydrogen, OH, leaving groups, functional groups, targeting groups, diagnostic agents and biologically active moieties, provided that the sum of $(q_1)+(q_2)+(q_3)+(q_4)$ is not zero and that at least one of Q_{1-4} and Q'_{1-4} is



wherein at least one of D_3 is a leaving group, a functional group, a targeting group, a diagnostic agent or a biologically active moiety; and provided that (z) is not zero when (w) is zero.

2. The compound of claim **1**, wherein the leaving group is selected from the group consisting of halogens, activated carbonates, carbonyl imidazole, cyclic imide thione, isocyanate, N-hydroxybenzotriazolyl, N-hydroxyphtalimide, N-hydroxysuccinimidyl, imidazole, mesylate, nosylate, tosylate, tresylate, C_1-C_6 alkyloxy, C_1-C_6 alkanoyloxy, arylcarbonyloxy, para-nitrophenoxy, ortho-nitrophenoxy, pentafluorophenoxy, 1,3,5-trichlorophenoxy, and 1,3,5-trifluorophenoxy.

3. The compound of claim **1**, wherein the functional group is selected from the group consisting of maleimidyl, vinyl, residues of sulfone, amino, carboxy, mercapto, hydrazide, and carbazate.

4. The compound of claim **17** wherein D_1, D'_1 and D_3 are independently selected from the group consisting of OH, methoxy, tert-butoxy, N-hydroxysuccinimidyl and maleimidyl.

5. The compound of claim **1**, wherein the biologically active moiety is selected from the group consisting of amine-containing moieties, hydroxyl-containing moieties and thiol-containing moieties.

6. The compound of claim **1**, wherein the biologically active moiety is selected from the group consisting of pharmaceutically active compounds, enzymes, proteins, oligonucleotides, antibodies, monoclonal antibodies, single chain antibodies and peptides.

7. The compound of claim **1**, wherein L_1, L'_1 and L_3 are independently selected from the group consisting of:

$$—[C(=O)]_v(CR_{22}R_{23})_t[C(=O)]_{v'}—,$$

$$—[C(=O)]_v(CR_{22}R_{23})_t—O[C(=O)]_{v'}—,$$

$$—[C(=O)]_v(CR_{22}R_{23})_t—NR_{26}[C(=O)]_{v'}—,$$

$$—[C(=O)]_vO(CR_{22}R_{23})_t[C(=O)]_{v'}—,$$

$$—[C(=O)]_vO(CR_{22}R_{23})_tO[C(=O)]_{v'}—,$$

$$—[C(=O)]_v(CR_{22}R_{23})_tNR_{26}[C(=O)]_{v'}—,$$

$$—[C(=O)]_vNR_{21}(CR_{22}R_{23})_t[C(=O]_{v'}—,$$

$$—[C(=O)]_vNR_{21}(CR_{22}R_{23})_tO[C(=O)]_{v'}—,$$

$$—[C(=O)]_vNR_{21}(CR_{22}R_{23})_tNR_{26}[C(=O)_{v'}—,$$

$$—[C(=O)]_v(CR_{22}R_{23})_tO—(CR_{23}R_{29})_t—[C(=O)]_{v'}—,$$

$$—[C(=O)]_v(CR_{22}R_{23})_tNR_{26}—(CR_{28}R_{29})_t—[C(=O)]_{v'}—,$$

$$—[C(=O)]_v(CR_{22}R_{23})_tS—(CR_{28}R_{29})_t—[C(=O)]_{v'}—,$$

$$—[C(=O)]_vO(CR_{22}R_{23})_tO—(CR_{28}R_{29})_t—[C(=O)]_{v'}—,$$

$$—[C(=O)]_vO(CR_{22}R_{23})_tNR_{26}—(CR_{28}R_{29})_t—[C(=O)]_{v'}—,$$

$$—[C(=O)]_v(CR_{22}R_{23})_tS—(CR_{28}R_{29})_t—[C(=O)]_{v'}—,$$

$$—[C(=O)]_vNR_{21}(CR_{22}R_{23})_tO—(CR_{28}R_{29})_t—[C(=O)]_{v'}—,$$

$$—[C(=O)]_vNR_{21}(CR_{22}R_{23})_tNR_{26}—(CR_{28}R_{29})_t—[C(=O)]_{v'}—,$$

$$—[C(=O)]_vNR_{21}(CR_{22}R_{23})_tS—(CR_{28}R_{29})_t—[C(=O)]_{v'}—,$$

$$—[C(=O)]_v(CR_{22}R_{23}CR_{28}R_{29}O)_tNR_{26}[C(=O)]_{v'}—,$$

$$—[C(=O)]_v(CR_{22}R_{23}CR_{28}R_{29}O)_t[C(=O)]_{v'}—,$$

$$—[C(=O)]_vO(CR_{22}R_{23}CR_{28}R_{29}O)_tNR_{26}[C(=O)]_{v'}—,$$

$$—[C(=O)]_vO(CR_{22}R_{23}CR_{28}R_{29}O)_t[C(=O)]_{v'}—,$$

$$—[C(=O)]_vNR_{21}(CR_{22}R_{23}CR_{28}R_{29}O)_tNR_{26}[C(=O)]_{v'}—,$$

$$—[C(=O)]_vNR_{21}(CR_{22}R_{23}CR_{28}R_{29}O)_t[C(=O)]_{v'}—,$$

$$—[C(=O)]_v(CR_{22}R_{23}CR_{28}R_{29}O)_t(CR_{24}R_{25})_t—[C(=O)]_{v'}—,$$

$$—[C(=O)]_vO(CR_{22}R_{23}CR_{28}R_{29}O)_t(CR_{24}R_{25})_t—[C(=O)]_{v'}—,$$

$$—[C(=O)]_vNR_{21}(CR_{22}R_{23}CR_{28}R_{29}O)_t(CR_{24}R_{25})_t—[C(=O)]_{v'}—,$$

$$—[C(=O)]_v(CR_{22}R_{23}CR_{28}R_{29}O)_t(CR_{24}R_{25})_t—O[C(=O)]_{v'}—,$$

$$—[C(=O)]_v(CR_{22}R_{23})_t(CR_{24}R_{25}CR_{28}R_{29}O)_t—[C(=O)]_{v'}—,$$

$$—[C(=O)]_v(CR_{22}R_{23})_tCR_{24}R_{25}CR_{28}R_{29}O)_t—NR_{26}[C(=O)]_{v'}—,$$

$$—[C(=O)]_vO(CR_{22}R_{23}CR_{28}R_{29}O)_t(CR_{24}R_{25})_t—O[C(=O)]_{v'}—,$$

$$—[C(=O)]_vO(CR_{22}R_{23})_t(CR_{24}R_{25}CR_{28}R_{29}O)_t—[C(=O)]_{v'}—,$$

$$—[C(=O)]_vO(CR_{22}R_{23})_t(CR_{24}R_{25}CR_{28}R_{29}O)_t—NR_{26}[C(=O)]_{v'}—,$$

$$—[C(=O)]_vNR(CR_{22}R_{23}CR_{28}R_{29}O)_t(CR_{24}R_{25})_t—O[C(=O)]_{v'}—,$$

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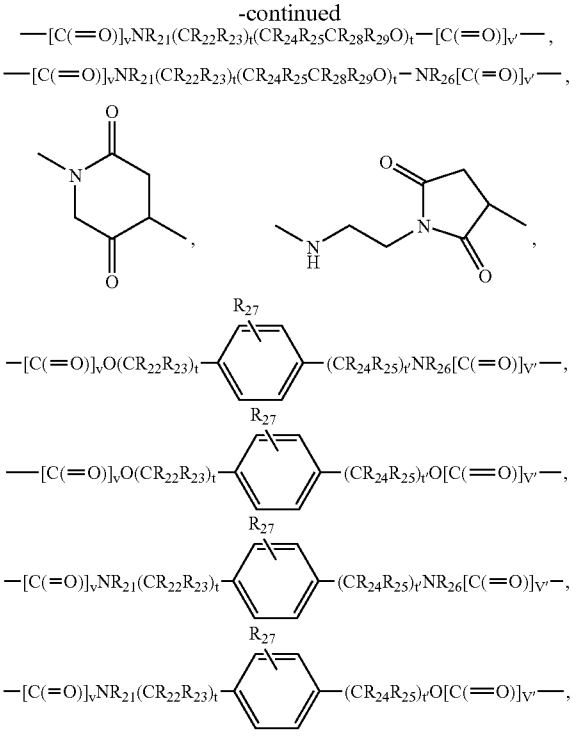


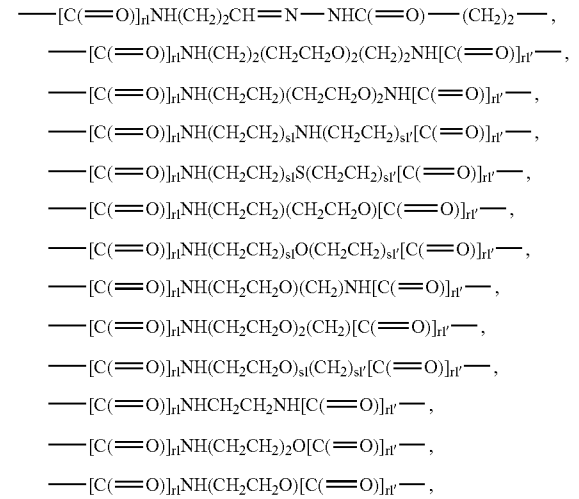
wherein,

R_{21-29} are independently selected fromt the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cyloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, substituted C_{1-6}heteroalkyls, C_{1-6} alkoxy, phenoxy and C_{1-6} heteroalkoxy;

(t) and (t') are independently zero or a positive integer; and

(v) and (v') are independently zero or 1.

8. The compound of claim **1**, wherein L_1, L'_1 and L_3 are independently selected from the group consisting of:



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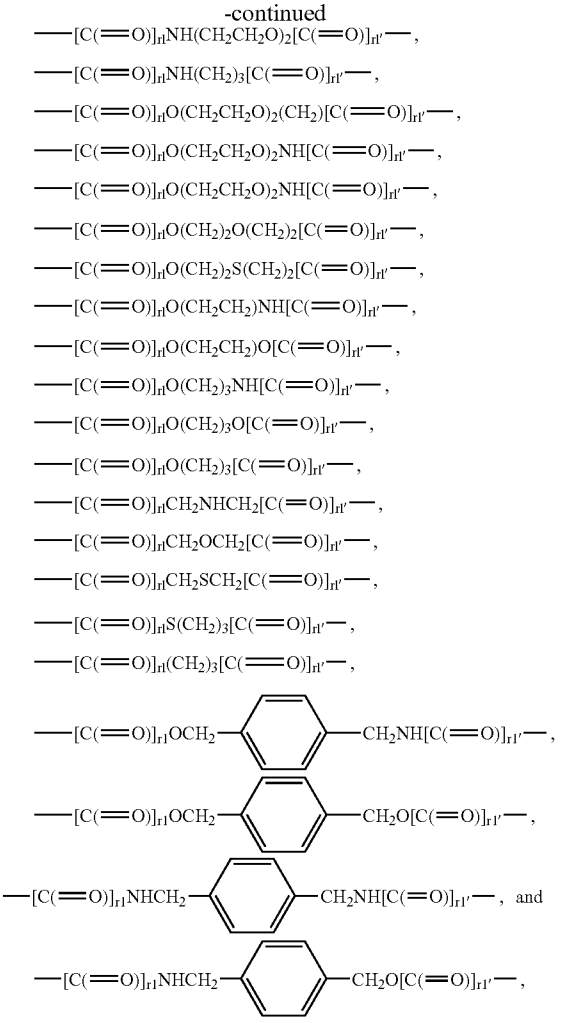


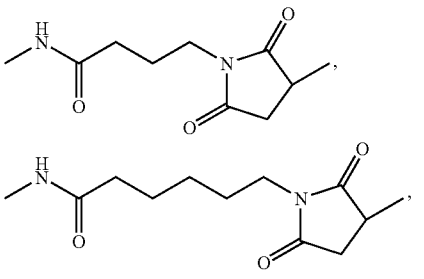
wherein

(r1) and (r1') are independently zero or 1; and

(s1) and (s1') are independently zero or a positive integer, provided that both (r1) and (r1') are not zero simultaneously.

9. The compound of claim **1**, wherein L_1, L'_1 and L_3 are independently selected from the group consisting of amino acids, amino acid derivatives and peptides.

10. The compound of claim **1**, wherein L_3 is selected from the group consisting of:



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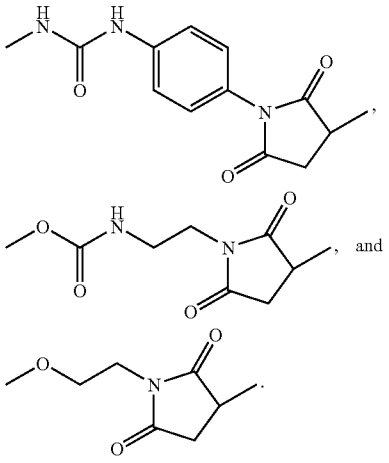
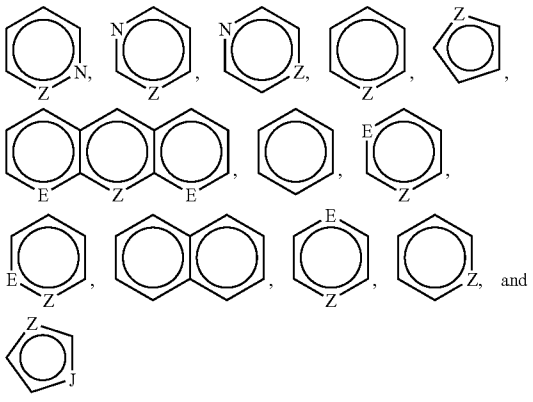


11. The compound of claim **1**, wherein A is selected from the group consisting of H, NH_2, OH, CO_2H, C_{1-6} alkoxy, and C_{1-6} alkyl.

12. The compound of claim **1**, wherein A is methyl or methoxy.

13. The compound of claim **1**, wherein Ar and Ar' are independently selected from the group consisting of:



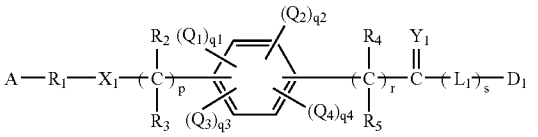
wherein

J is O, S, or NR_{11};

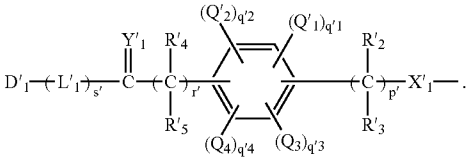
E and Z are independently CR_{12} or NR_{13}; and

R_{11}, R_{12} and R_{13} are independently selected from the same group as that which defines R_2.

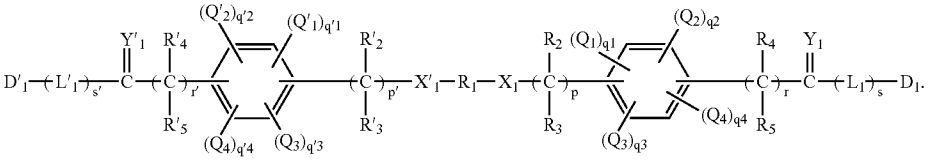
14. The compound of claim **1** having the formula:



wherein A is a capping group or



15. The compound of claim **1**, having the formula:



16. The compound of claim **1**, wherein R_{2-5} and R'_{2-5} are independently hydrogen or CH_3.

17. The compound of claim **1**, wherein R_1 comprises a linear, terminally branched or multi-armed polyalkylene oxide.

18. The compound of claim **17**, wherein the polyalkylene oxide is selected from the group consisting of polyethylene glycol and polypropylene glycol.

19. The compound of claim **17**, wherein the polyalkylene oxide is a polyethylene glycol of the formula, —O—$(CH_2CH_2O)_n$—

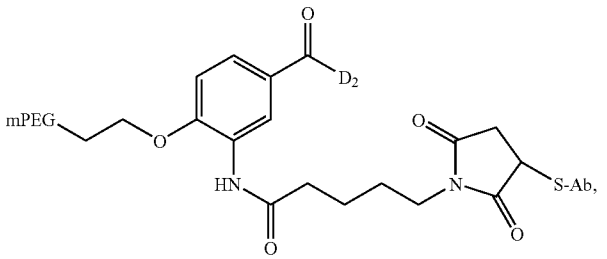
wherein (n) is an integer from about 10 to about 2,300.

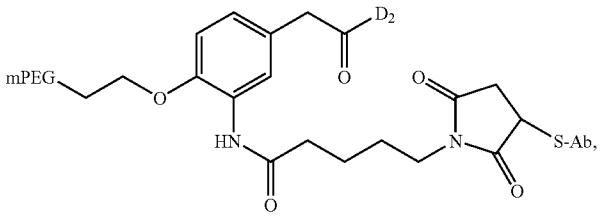
20. The compound of claim **17**, wherein the polyalkylene oxide has an average molecular weight from about 2,000 to about 100,000 Daltons.

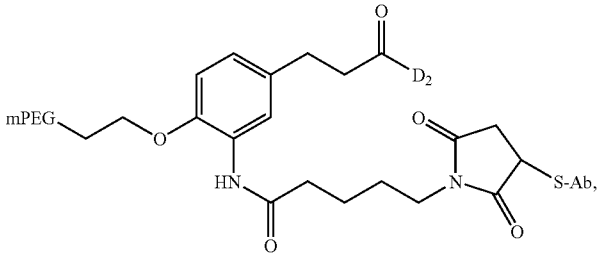
21. The compound of claim **17**, wherein the polyalkylene oxide residue has an average molecular weight of from about 5,000 to about 60,000 daltons.

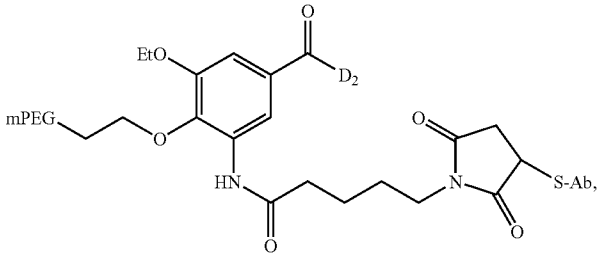
22. The compound of claim **17**, wherein the polyalkylene oxide has an average molecular weight from about 5,000 to about 25,000 Daltons or from about 20,000 to about 45,000 Daltons.

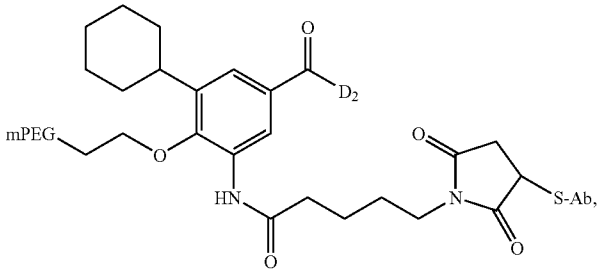
23. A compound of claim **1**, selected from the group consisting of:

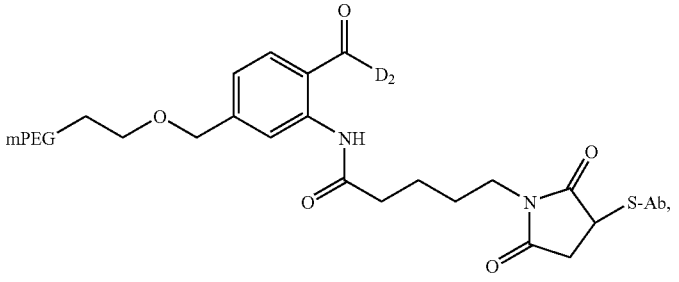












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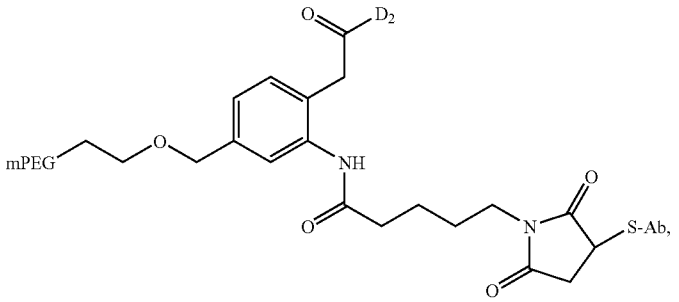

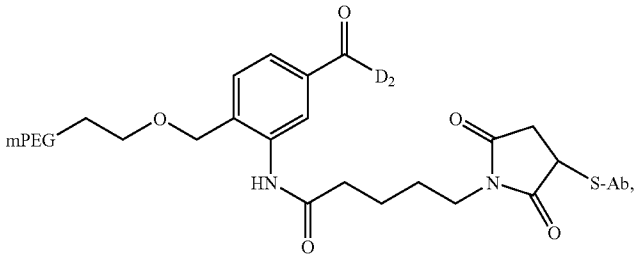

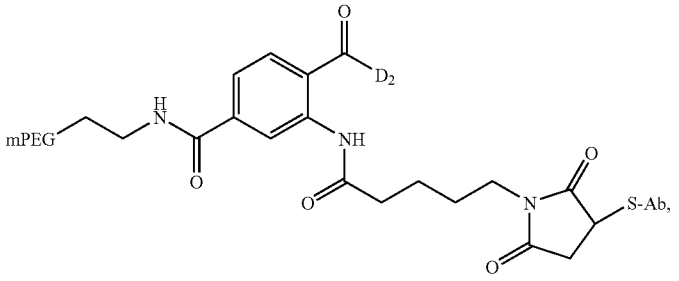

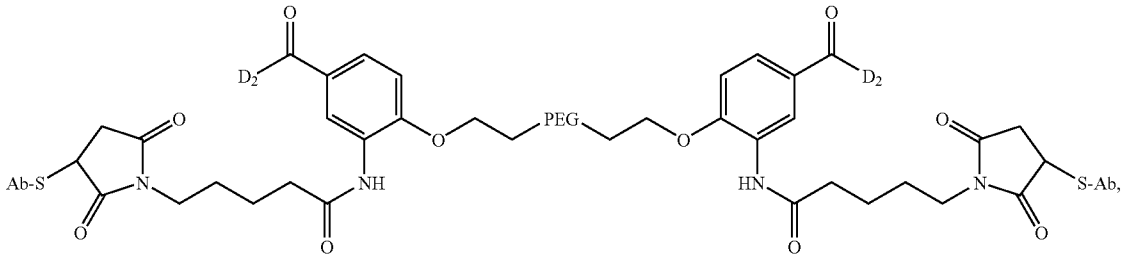

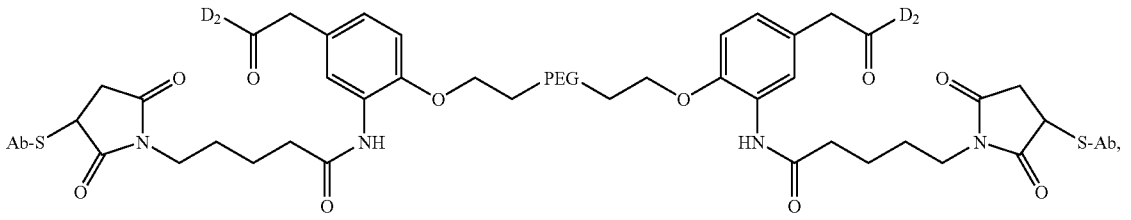

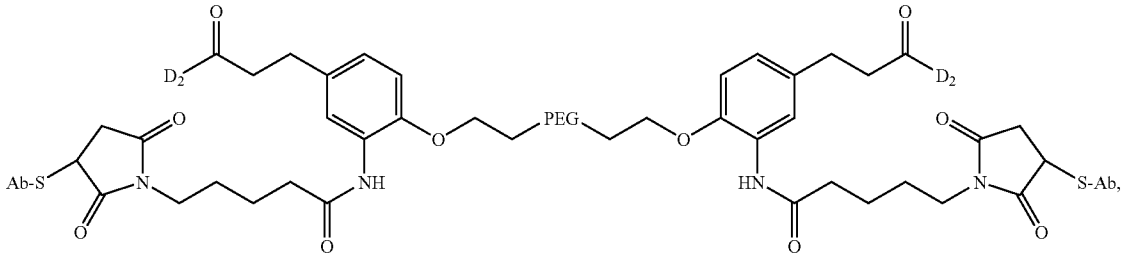

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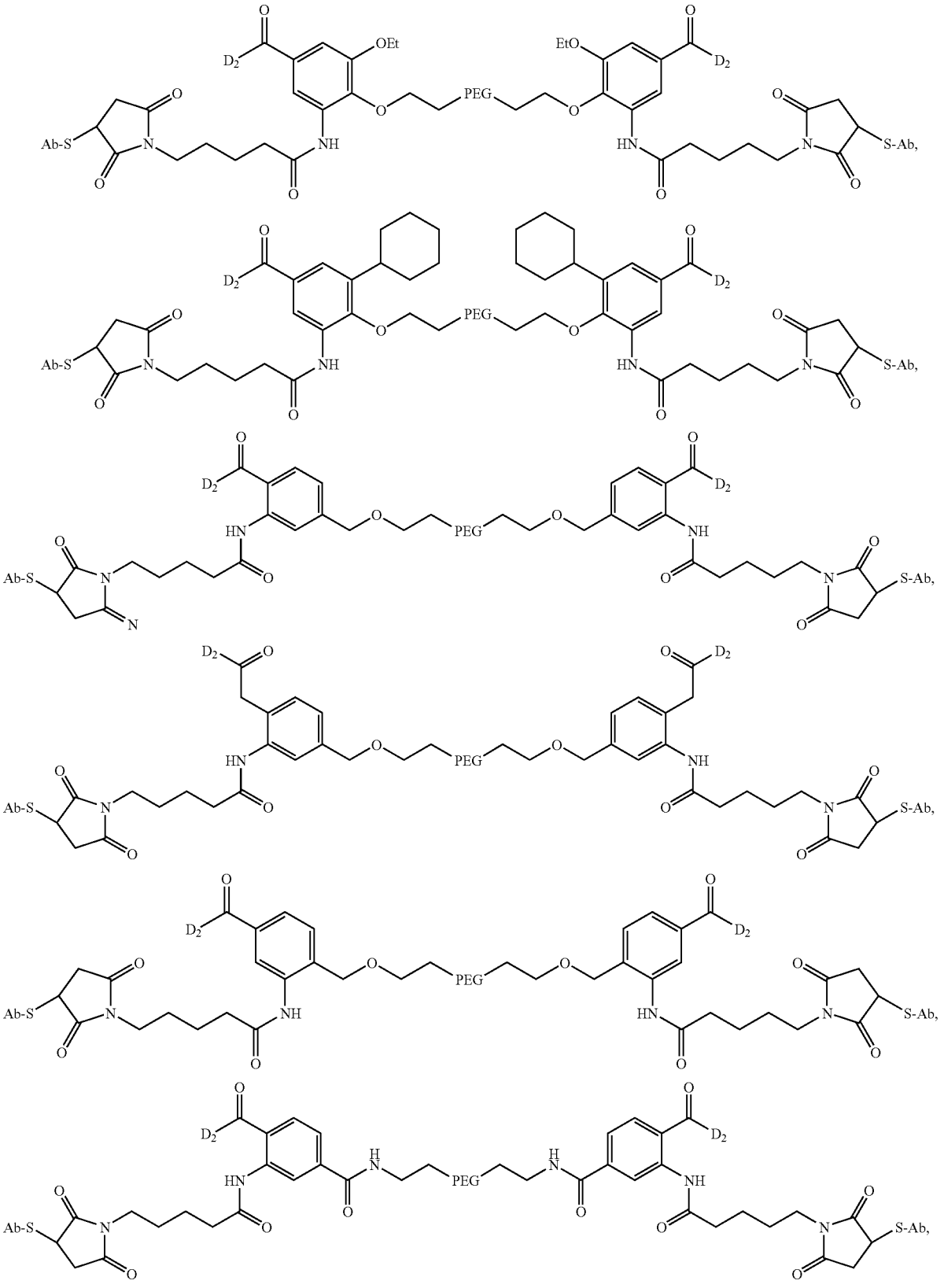

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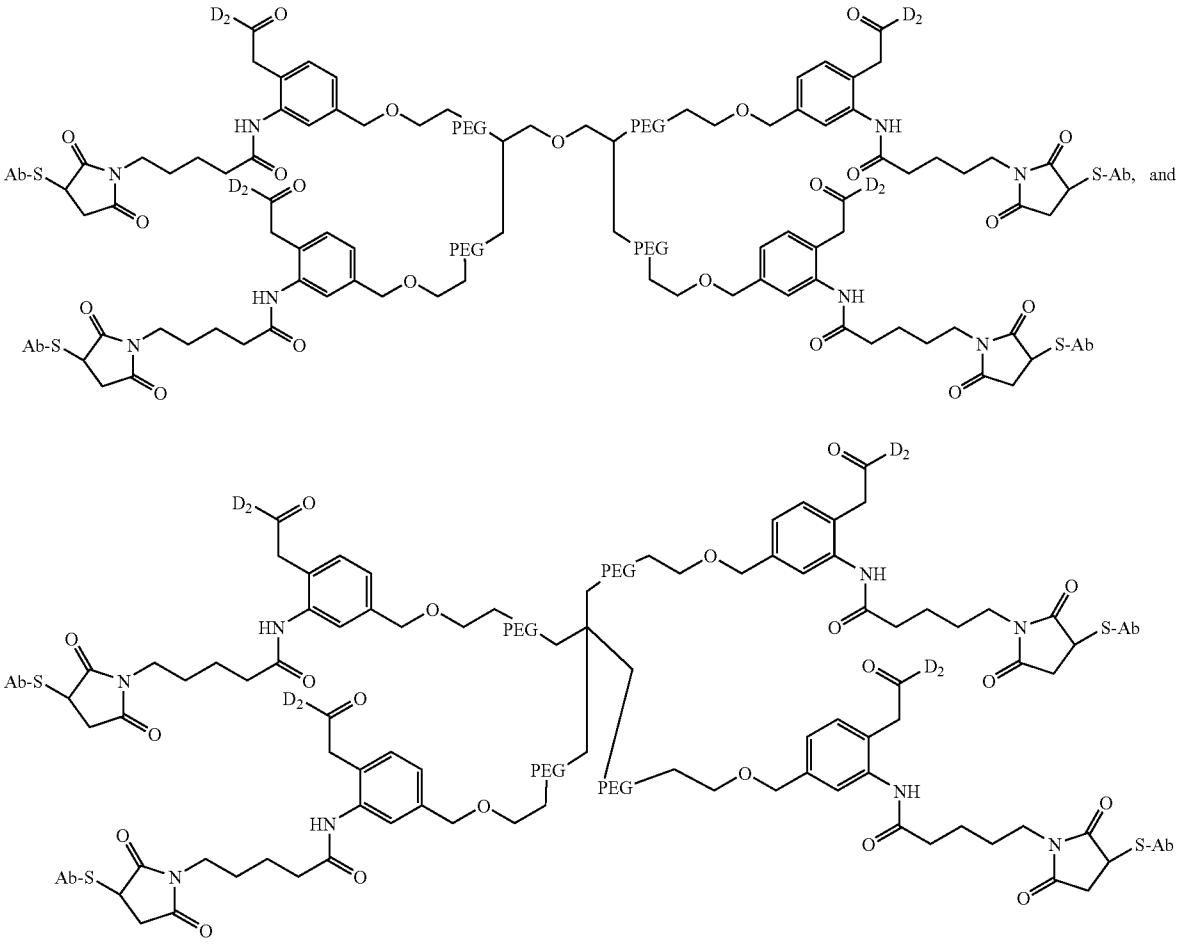


wherein:

D_2 is hydrogen, OH, leaving groups, functional groups, targeting groups, diagnostic agents and biologically active moieties;

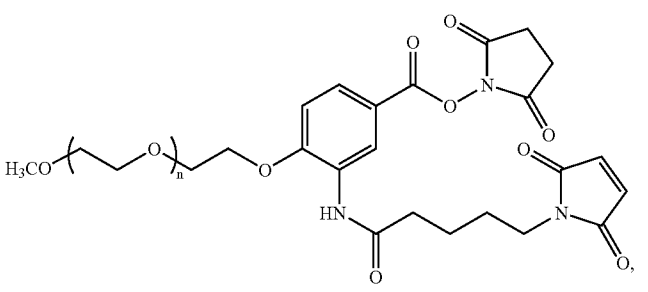
Ab is an antibody;

mPEG has the formula $CH_3O(CH_2CH_2O)_n$—;

PEG has the formula —$O(CH_2CH_2O)_n$—, and

(n) is an integer from about 10 to about 2,300.

24. The compound of claim **23** selected from the group consisting of:



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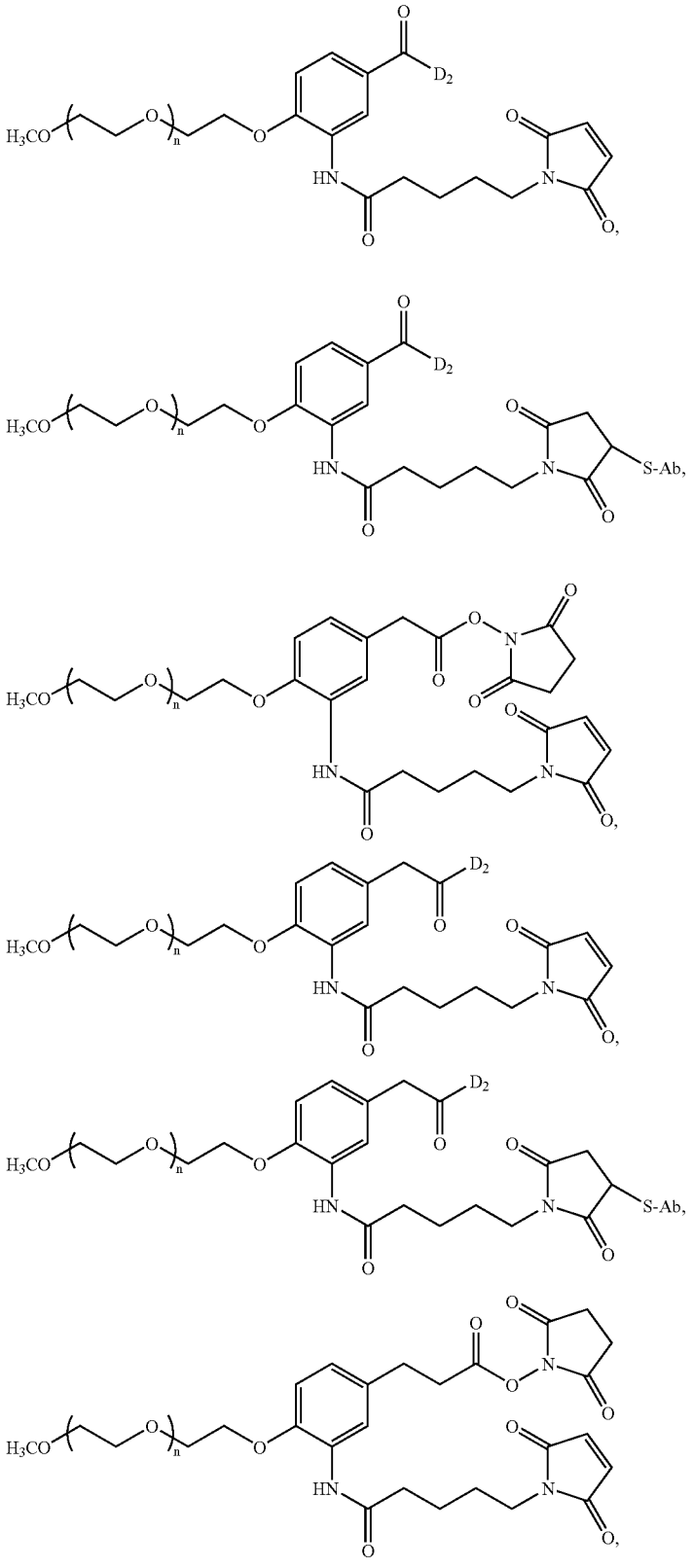

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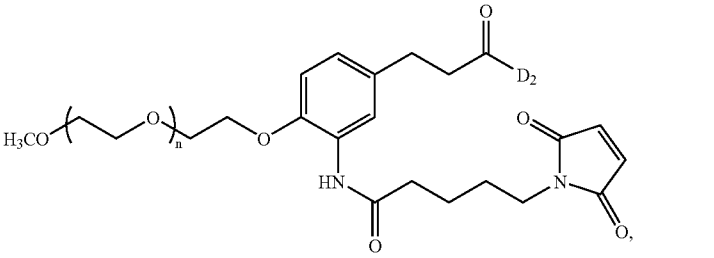

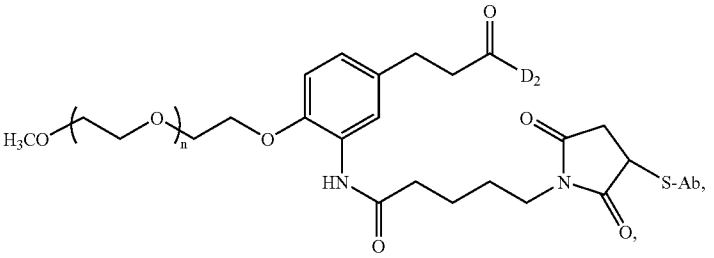

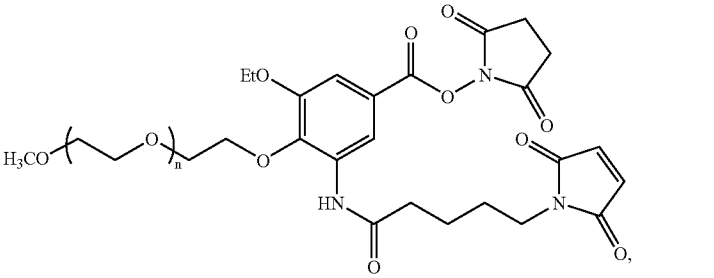

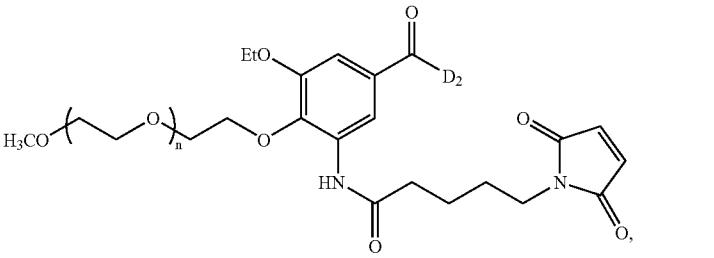

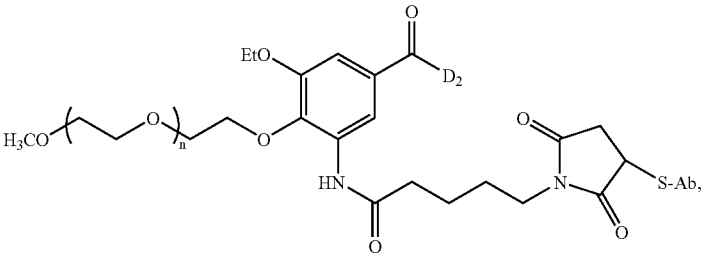

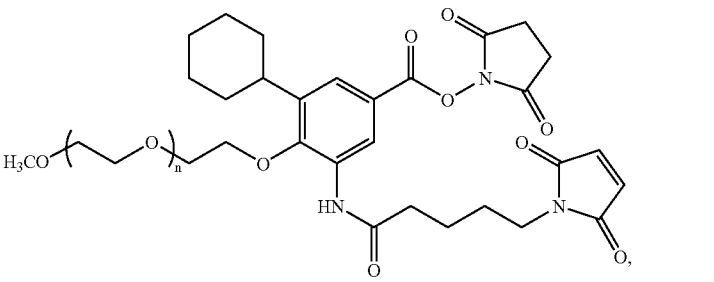

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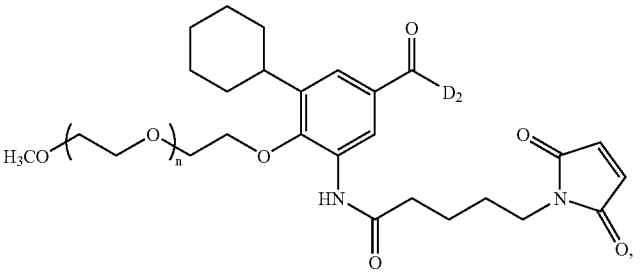

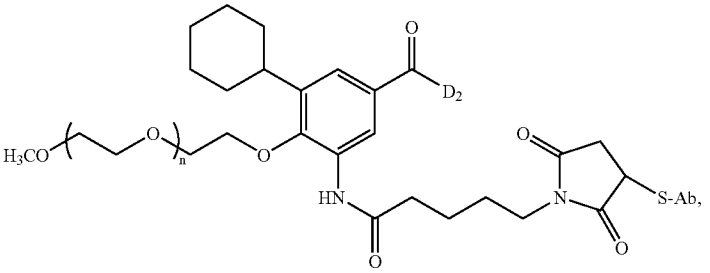

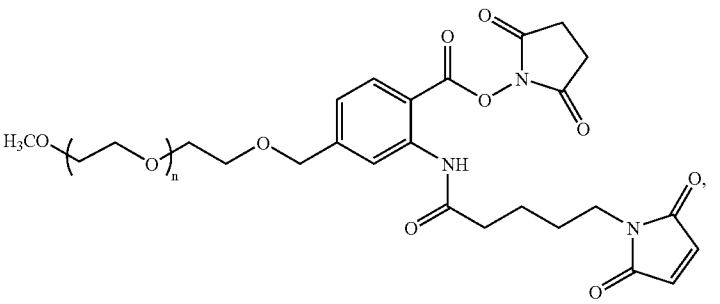

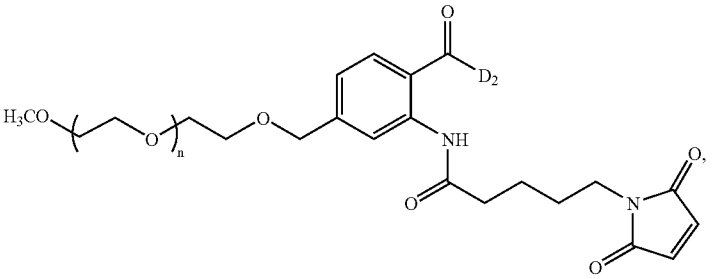

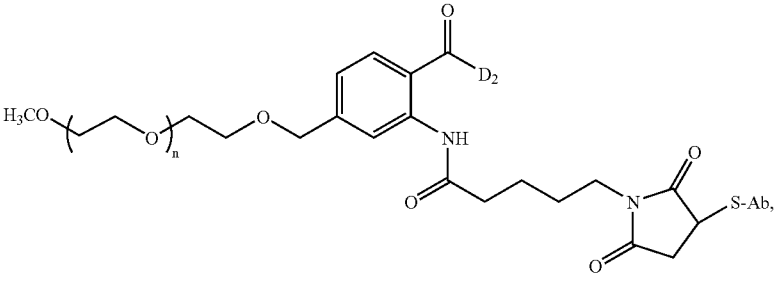

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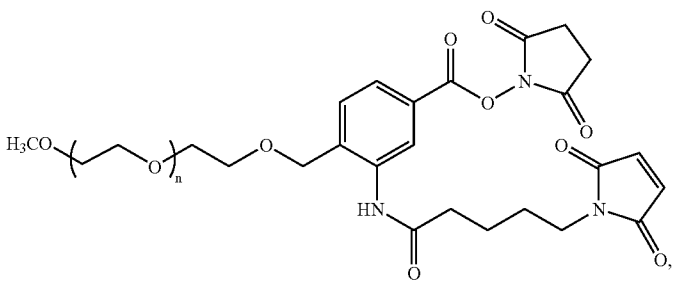

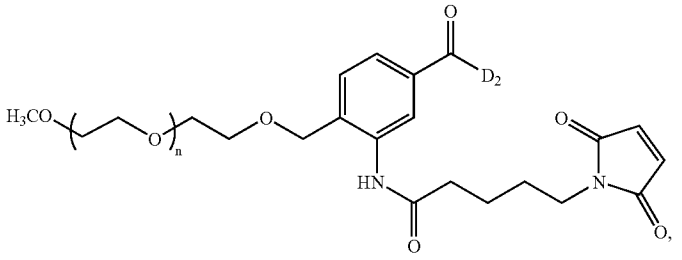

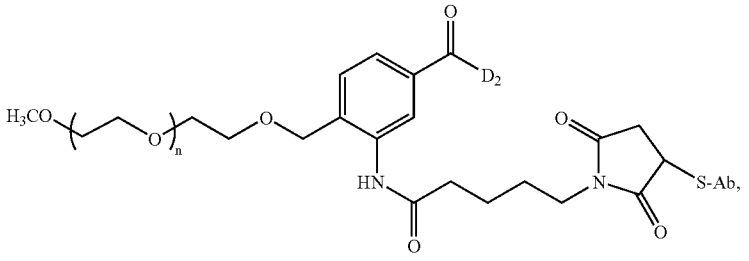

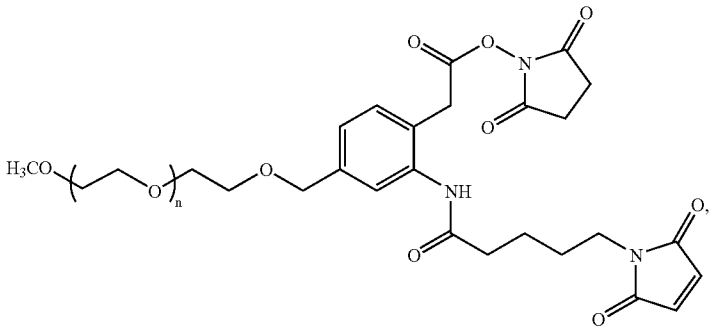

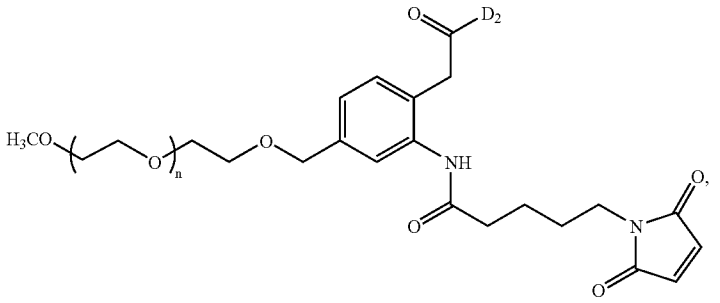

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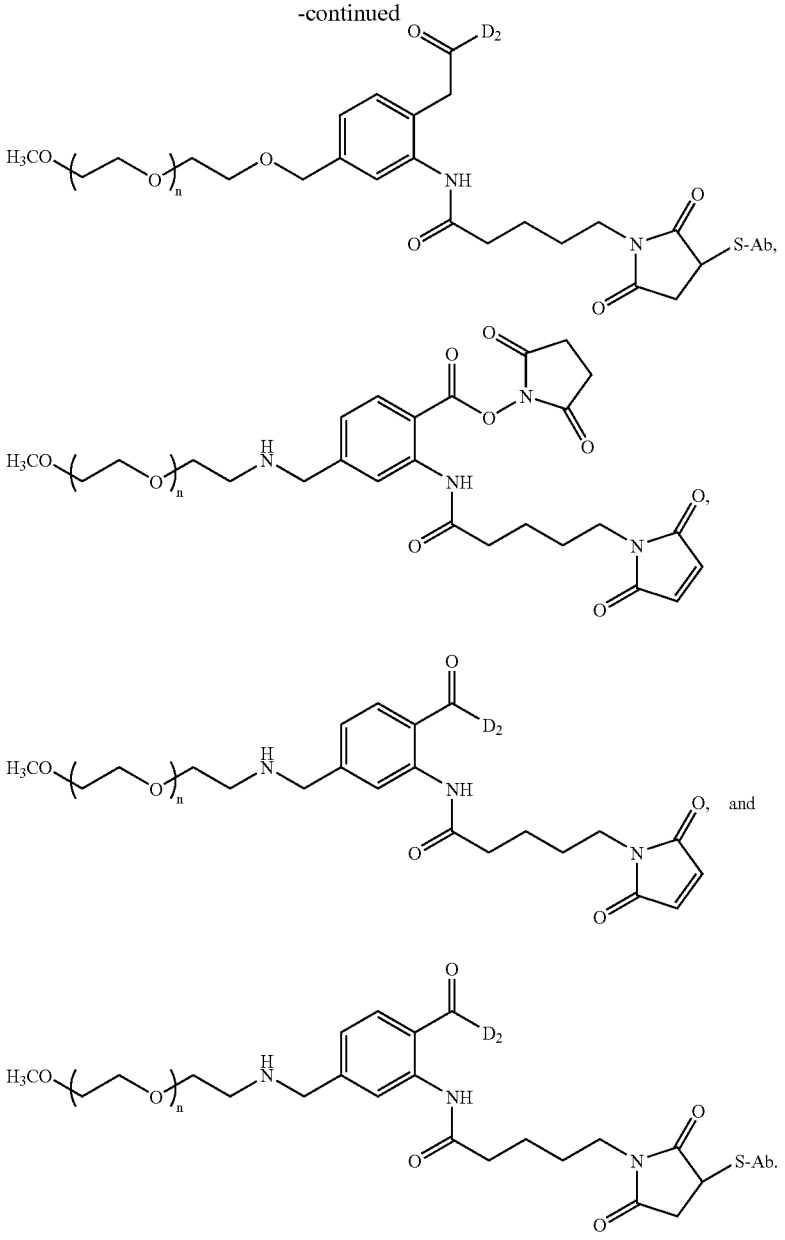
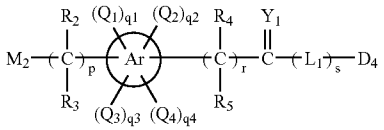


25. A method of preparing a substantially non-antigenic polymer compound having a multisubstituted aromatic moiety comprising:

reacting a compound of Formula (II):

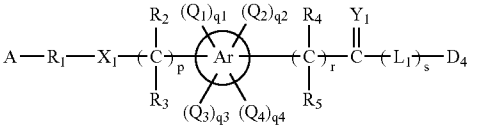
(II)

with a compound of Formula (III):



(III)

under conditions effective to form a compound of Formula (IV):

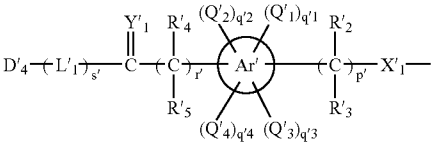


(IV)

wherein:

A is a capping group or M_1-X'_1—;

A is a capping group or



R_1 is a substantially non-antigenic water-soluble polymer;

M_1 is —OH, —SH or —NHR_{41};

M_2 is a leaving group;

Ar and Ar' are independently an aryl or heteroaryl moiety;

X_1 and X'_1 are independently O, S, SO, SO_2, NR_6 or a bond;

Y_1 and Y'_1 are independently O, S, or NR_6;

L_1 and L'_1 are independently selected bifunctional linkers;

D_4 and D'_4 are independently selected from the group consisting of hydrogen, OH, OR_{42}, leaving groups, functional groups, targeting groups, diagnostic agents and biologically active moieties;

R_{2-5}, R'_{2-5}, R_6, and R_{41} are independently selected from the group consisting of hydrogen, amino, substituted amino, azido, carboxy, cyano, halo, hydroxyl, nitro, silyl ether, sulfonyl, mercapto, C_{1-6} alkylmercapto, arylmercapto, substituted arylmercapto, substituted C_{1-6} alkylthio, C_{1-6} alkyls, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-19} branched alkyl, C_{3-8} cycloalkyl, C_{1-6} substituted alkyl, C_{2-6} substituted alkenyl, C_{2-6} substituted alkynyl, C_{3-8} substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_{1-6} heteroalkyl, substituted C_{1-6} heteroalkyl, C_{1-6} alkoxy, aryloxy, C_{1-6} heteroalkoxy, heteroaryloxy, C_{2-6} alkanoyl, arylcarbonyl, C_{2-6} alkoxycarbonyl, aryloxycarbonyl, C_{2-6} alkanoyloxy, arylcarbonyloxy, C_{2-6} substituted alkanoyl, substituted arylcarbonyl, C_{2-6} substituted alkanoyloxy, substituted aryloxycarbonyl, C_{2-6} substituted alkanoyloxy, substituted and arylcarbonyloxy;

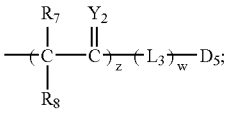
R_{42} is C_{1-6}alkyl;

(p), (p'), (r) and (r') are independently zero or a positive integer;

(q_1), (q'_1), (q_2), (q'_2), (q_3), (q'_3), (q_4) and (q'_4) are independently zero or one;

(s) and (s') are independently zero or a positive integer;

Q_{1-4} and Q_{1-4} are independently selected from the same moieties which can be used for R_2 or each can be:



wherein

R_7 and R_8 are independently selected from the same group as that which defines R_2;

Y_2 is O, S or NR_6;

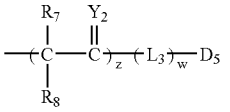
L_3 is a bifunctional linker;

(z) is zero or one;

(w) is zero or a positive integer; and

D_5 is selected from the group consisting of hydrogen, OH, leaving groups, functional groups, targeting groups, diagnostic agents and biologically active moieties;

provided that the sum of $(q_1)+(q_2)+(q_3)+(q_4)$ is not zero and that at least one of Q_{1-4} and Q'_{1-4} is



wherein at least one of D_5 is a leaving group, a functional group, a targeting group, a diagnostic agent or a biologically active moiety; and

provided that (z) is not zero when (w) is zero.

26. A method of treating a mammal, comprising administering an effective amount of a compound of claim **1** to a patient in need thereof, wherein at least one of D_1, D'_1, and D_3 is a biologically active moiety.

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