

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
15 April 2010 (15.04.2010)

PCT

(10) International Publication Number
WO 2010/042600 A2

(51) International Patent Classification:

C07D 319/16 (2006.01) *A61K 31/357* (2006.01)
C07D 319/14 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:

PCT/US2009/059816

(22) International Filing Date:

7 October 2009 (07.10.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/103,806 8 October 2008 (08.10.2008) US

(71) Applicant (for all designated States except US): **THE UAB RESEARCH FOUNDATION** [US/US]; 1530 3rd Avenue South AB 770, Birmingham, AL 35294-0107 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **WANG, Pengfei** [CN/US]; 1613 Deer Valley Circle, Birmingham, AL 35226 (US).

(74) Agents: **ASAM, Michael, R.** et al.; Fish & Richardson P.C., P.O. Box 1022, Minneapolis, MN 55440-1022 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:

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

(54) Title: PHOTO-ACTIVATABLE THERAPEUTIC AGENTS AND METHODS OF USING

(57) Abstract: Novel photo-activatable pro-therapeutic agents and methods for their synthesis and use are described. The photo-activatable pro-therapeutic agents are inactive pro-forms of compounds that can be activated in situ, for example, by providing a pro-therapeutic agent to a subject and photo-activating the pro-therapeutic agent at a selected area of the subject. Also disclosed are methods for administering the photo-activatable pro-therapeutic agents to a subject then activating the pro-therapeutic agents at a selected area of the subject by exposing that area to light.



WO 2010/042600 A2

Photo-activatable Therapeutic Agents and Methods of Using

CROSS-REFERENCE TO PRIORITY APPLICATION

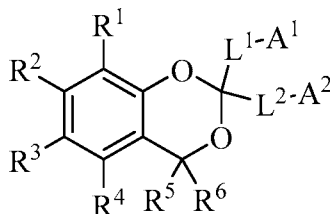
This application claims priority to U.S. Provisional Application No. 61/103,806, filed October 8, 2008, which is incorporated herein by reference in its entirety.

BACKGROUND

Cancer and other diseases and conditions are often treated systemically with chemotherapeutic agents. A downside to systemic treatment using chemotherapeutic agents is that a subject's entire body is impacted by the chemotherapeutic agent, whereas a disease or condition may manifest locally, e.g., a tumor. Further, the side effects can be significant due to the high dosages required for systemic delivery. One alternative is to direct a chemotherapeutic agent to a specific area of a subject's body, e.g., surgically, thereby limiting the overall dose and concomitantly limiting the side effects. Another strategy is to provide inactive forms, i.e., pro-forms, of chemotherapeutic agents that can subsequently be activated (e.g., metabolically or by external influence). When relying on metabolism or external influence as currently practiced, the activation of the chemotherapeutic agent is often difficult to control and the same side effect severity may be observed.

SUMMARY

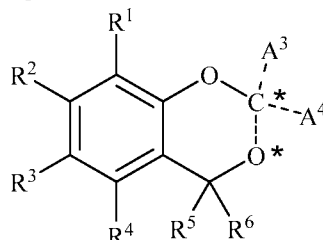
Novel photo-activatable pro-therapeutic agents and methods for making and using them are disclosed. A class of pro-therapeutic agents comprises compounds of the following formula:



and includes pharmaceutically acceptable salts thereof. In this class of compounds, R^1 and R^3 are each independently selected from hydrogen, substituted or unsubstituted hydrocarbon, substituted or unsubstituted hetero-hydrocarbon, halogen, or an electron donating group; R^2 and R^4 are each independently selected from hydrogen, substituted or unsubstituted hydrocarbon, substituted or unsubstituted hetero-hydrocarbon,

halogen, an electron donating group, or an electron withdrawing group; R^5 and R^6 are each independently selected from hydrogen, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, wherein R^5 and R^6 are not simultaneously hydrogen; L^1 is selected from a substituted or unsubstituted hydrocarbon or substituted or unsubstituted hetero-hydrocarbon and L^2 is absent or selected from a substituted or unsubstituted hydrocarbon or substituted or unsubstituted hetero-hydrocarbon; A^1 is a therapeutic agent; and A^2 is hydrogen or a therapeutic agent.

Also disclosed is a method of delivering a therapeutic agent to a selected area in a subject, comprising administering to the subject an effective amount of one or more compounds of the following formula:



and pharmaceutically acceptable salts thereof, and transmitting light to the selected area of the subject. In this class of compounds, R^1 and R^3 are each independently selected from hydrogen, substituted or unsubstituted hydrocarbon, substituted or unsubstituted hetero-hydrocarbon, halogen, or an electron donating group; R^2 and R^4 are each independently selected from hydrogen, substituted or unsubstituted hydrocarbon, substituted or unsubstituted hetero-hydrocarbon, halogen, an electron donating group, or an electron withdrawing group; R^5 and R^6 are each independently selected from hydrogen, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, wherein R^5 and R^6 are not simultaneously hydrogen; $A^3(C^*-O^*)A^4$ is one or more therapeutic agents or pro-therapeutic agents containing a carbonyl group, wherein C^*-O^* is the carbonyl group of the one or more therapeutic agents or pro-therapeutic agents containing a carbonyl group.

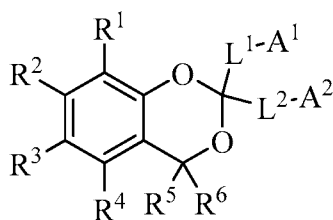
DETAILED DESCRIPTION

Novel photo-activatable pro-therapeutic agents and their uses are disclosed. The pro-therapeutic agents are useful in providing inactive pro-forms of therapeutic agents that can be activated *in situ*, for example, for delivering an inactive pro-form of

a therapeutic agent to a subject and photoactivating the therapeutic agent at a selected area of the subject.

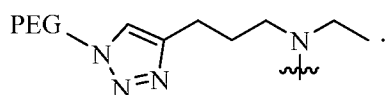
The pro-therapeutic agents described herein are represented by **Compound I**:

5

**I**

or pharmaceutically acceptable salts thereof.

In **Compound I**, R^1 and R^3 are each independently selected from hydrogen, substituted or unsubstituted hydrocarbon, substituted or unsubstituted hetero-hydrocarbon, halogen, or an electron donating group. As an example, one of R^1 or R^3 is a dimethylamino group, a methoxy group, a PEG group, or



In one example, R^1 and R^3 are each methoxy groups. In another example, R^1 is hydrogen and R^3 is a methoxy group.

Also in **Compound I**, R^2 and R^4 are each independently selected from hydrogen, substituted or unsubstituted hydrocarbon, substituted or unsubstituted hetero-hydrocarbon, halogen, an electron donating group, or an electron withdrawing group. In one example, R^2 and R^4 are each hydrogen.

Additionally in **Compound I**, R^5 and R^6 are each independently selected from hydrogen, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, wherein R^5 and R^6 are not simultaneously hydrogen. In one example, R^5 and R^6 are each phenyl.

Also in **Compound I**, L^1 is selected from a substituted or unsubstituted hydrocarbon or substituted or unsubstituted hetero-hydrocarbon and L^2 is absent or selected from a substituted or unsubstituted hydrocarbon or substituted or unsubstituted hetero-hydrocarbon.

Additionally in **Compound I**, A^1 is a therapeutic agent.

Further in **Compound I**, A^2 is hydrogen or a therapeutic agent.

As used herein, the term hydrocarbon includes alkanes, alkenes, alkynes, cycloalkanes, cycloalkenes, and cycloalkynes. Hydrocarbons useful with the compounds and methods described herein include C₁-C₆₀ alkanes, C₂-C₆₀ alkenes, C₂-C₆₀ alkynes, C₃-C₆₀ cycloalkanes, C₃-C₆₀ cycloalkenes, and C₇-C₆₀ cycloalkynes.

5 Additional hydrocarbons useful with the compounds and methods described herein include C₁-C₄₀ alkanes, C₂-C₄₀ alkenes, C₂-C₄₀ alkynes, C₃-C₄₀ cycloalkanes, C₃-C₄₀ cycloalkenes, and C₇-C₄₀ cycloalkynes; C₁-C₃₀ alkanes, C₂-C₃₀ alkenes, C₂-C₃₀ alkynes, C₃-C₃₀ cycloalkanes, C₃-C₃₀ cycloalkenes, and C₇-C₃₀ cycloalkynes; C₁-C₂₀ alkanes, C₂-C₂₀ alkenes, C₂-C₂₀ alkynes, C₃-C₂₀ cycloalkanes, C₃-C₂₀ cycloalkenes, and C₇-C₂₀ cycloalkynes; C₁-C₁₆ alkanes, C₂-C₁₆ alkenes, C₂-C₁₆ alkynes, C₃-C₁₆ cycloalkanes, C₃-C₁₆ cycloalkenes, and C₇-C₁₆ cycloalkynes; C₁-C₁₂ alkanes, C₂-C₁₂ alkenes, C₂-C₁₂ alkynes, C₃-C₁₂ cycloalkanes, C₃-C₁₂ cycloalkenes, and C₇-C₁₂ cycloalkynes; C₁-C₈ alkanes, C₂-C₈ alkenes, C₂-C₈ alkynes, C₃-C₈ cycloalkanes, C₃-C₈ cycloalkenes, and C₇-C₈ cycloalkynes; C₁-C₆ alkanes, C₂-C₆ alkenes, C₂-C₆ alkynes, C₃-C₆ cycloalkanes, and C₃-C₆ cycloalkenes; and C₁-C₄ alkanes, C₂-C₄ alkenes, C₂-C₄ alkynes, C₃-C₄ cycloalkanes, and C₃-C₄ cycloalkenes.

10
15

As used herein, the term hetero-hydrocarbon includes heteroalkanes, heteroalkenes, heteroalkynes, heterocycloalkanes, heterocycloalkenes, and heterocycloalkynes. Hetero-hydrocarbons include substitutions along their main chain of atoms such as O, N, or S. Hydrocarbons useful with the compounds and methods described herein include C₁-C₆₀ heteroalkanes, C₂-C₆₀ heteroalkenes, C₂-C₆₀ heteroalkynes, C₃-C₆₀ heterocycloalkanes, C₃-C₆₀ heterocycloalkenes, and C₇-C₆₀ heterocycloalkynes. Additional hetero-hydrocarbons useful with the compounds and methods described herein include C₁-C₄₀ heteroalkanes, C₂-C₄₀ heteroalkenes, C₂-C₄₀ heteroalkynes, C₃-C₄₀ heterocycloalkanes, C₃-C₄₀ heterocycloalkenes, and C₇-C₄₀ heterocycloalkynes; C₁-C₃₀ heteroalkanes, C₂-C₃₀ heteroalkenes, C₂-C₃₀ heteroalkynes, C₃-C₃₀ heterocycloalkanes, C₃-C₃₀ heterocycloalkenes, and C₇-C₃₀ heterocycloalkynes; C₁-C₂₀ heteroalkanes, C₂-C₂₀ heteroalkenes, C₂-C₂₀ heteroalkynes, C₃-C₂₀ heterocycloalkanes, C₃-C₂₀ heterocycloalkenes, and C₇-C₂₀ heterocycloalkynes; C₁-C₁₆ heteroalkanes, C₂-C₁₆ heteroalkenes, C₂-C₁₆ heteroalkynes, C₃-C₁₆ heterocycloalkanes, C₃-C₁₆ heterocycloalkenes, and C₇-C₁₆ heterocycloalkynes; C₁-C₁₂ heteroalkanes, C₂-C₁₂ heteroalkenes, C₂-C₁₂ heteroalkynes, C₃-C₁₂ heterocycloalkanes, C₃-C₁₂ heterocycloalkenes, and C₇-C₁₂ heterocycloalkynes.

20
25
30

heterocycloalkynes; C₁-C₈ heteroalkanes, C₂-C₈ heteroalkenes, C₂-C₈ heteroalkynes, C₃-C₈ heterocycloalkanes, C₃-C₈ heterocycloalkenes, and C₇-C₈ heterocycloalkynes; C₁-C₆ heteroalkanes, C₂-C₆ heteroalkenes, C₂-C₆ heteroalkynes, C₃-C₆ heterocycloalkanes, and C₃-C₆ heterocycloalkenes; and C₁-C₄ alkanes, C₂-C₄ alkenes, C₂-C₄ alkynes, C₃-C₄ cycloalkanes, and C₃-C₄ heterocycloalkenes.

Aryl and heteroaryl molecules are also useful with the compounds and methods described herein. Aryl molecules include, for example, cyclic hydrocarbons that incorporate one or more planar sets of six carbon atoms that are connected by delocalized electrons numbering the same as if they consisted of alternating single and double covalent bonds. An example of an aryl molecule is benzene. Heteroaryl molecules include substitutions along their main cyclic chain of atoms such as O, N, or S. When heteroatoms are introduced, a set of five atoms, e.g., four carbon and a heteroatom can create an aromatic system. Examples of heteroaryl molecules include, furan, pyrrole, thiophene, imidazole, oxazole, pyridine, and pyrazine. Aryl and heteroaryl molecules can also include additional fused rings, for example, benzofuran, indole, benzothiophene, naphthalene, anthracene, and quinoline.

As used herein, the term electron withdrawing group refers to an atomic group that draws electrons from surrounding atomic groups by a resonance effect or an inductive effect more than a hydrogen atom would if it occupied the same position in the molecule. Electron withdrawing groups useful with the compounds and methods described herein include, for example, halogen (e.g. F, Br, Cl, or I), nitro, cyano, carboxyl, carbonyl, sulfonyl, trifluoromethyl, and trialkylaluminum.

As used herein, the term electron donating group refers to an atomic group that is capable of releasing electrons into surrounding atomic groups by a resonance effect or an inductive effect more than a hydrogen atom would if it occupied the same position in the molecule. Electron donating groups useful with the compounds and methods described herein include, for example, alkoxy, amino, aryl, heteroaryl, hydrocarbon, and hetero-hydrocarbon.

The hydrocarbon, hetero-hydrocarbon, aryl, heteroaryl, electron donating, and electron withdrawing molecules used herein can be substituted or unsubstituted. As used herein, the term substituted includes the addition of a hydrocarbon, hetero-hydrocarbon, aryl, or heteroaryl group (as described herein) to a position attached to the main chain of the hydrocarbon, hetero-hydrocarbon, aryl, or heteroaryl, e.g., the

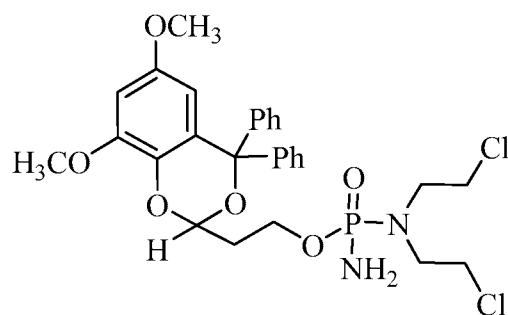
replacement of a hydrogen by one of these molecules. Examples of substitution groups include, but are not limited to, hydroxyl, halogen (e.g., F, Br, Cl, or I), and carboxyl groups. Conversely, as used herein, the term unsubstituted indicates the hydrocarbon, hetero-hydrocarbon, aryl, or heteroaryl group has a full complement of hydrogens, i.e., commensurate with its saturation level, with no substitutions, e.g., linear decane $-(\text{CH}_2)_9-\text{CH}_3$.

Polyethylene glycol (PEG) can be incorporated into the compounds described herein to improve solubility and uptake when administered to a subject. PEG is commonly used in drug development to improve a drug's aqueous solubility, circulation half-life, and other pharmacokinetic properties. PEG is soluble (in organic solvents and water), nontoxic, nonimmunogenic, and eliminated by a combination of renal and hepatic pathways. PEG molecules useful with the photo-activatable protecting groups include substituted or unsubstituted PEG molecules with a molecular weight of greater than about 1,000 Daltons and substituted or unsubstituted PEG molecules with a molecular weight of greater than about 10,000 Daltons. PEG molecules with a molecular weight of 10,000 Daltons or greater show a significantly higher accumulation in tumors than within normal tissue, irrespective of tumor size. Monofunctional PEG molecules, herein referred to as mPEG, are also useful with the photo-activatable protecting groups. The photochemical properties of the compounds described herein are not affected by attaching PEG. Incorporation of PEG into the compounds described herein can be achieved with various synthetic methods. At least some of these methods are known in the art of organic synthesis.

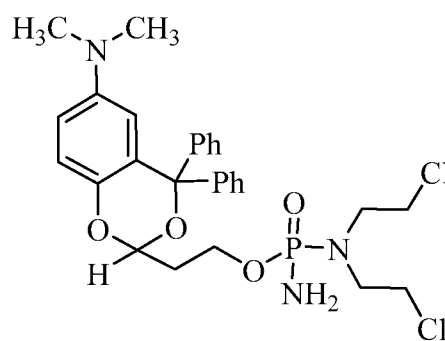
In **Compound I**, adjacent R groups on the phenyl ring, i.e. R^1 , R^2 , R^3 , and R^4 , can be combined to form substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkane, substituted or unsubstituted cycloalkene, substituted or unsubstituted cycloalkyne, substituted or unsubstituted heterocycloalkane, substituted or unsubstituted heterocycloalkene, or substituted or unsubstituted heterocycloalkyne groups. For example, R^1 can be a methanimine group and R^2 can be an ethylene group that combine to form a C_6 heteroaryl group. Other adjacent R groups include the combinations of R^2 and R^3 , and R^3 and R^4 .

Further examples of **Compound I** include:

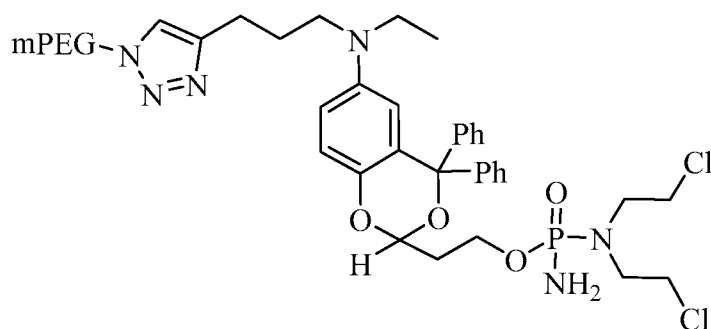
5

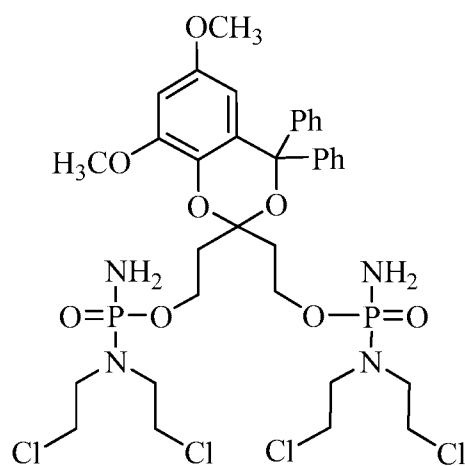
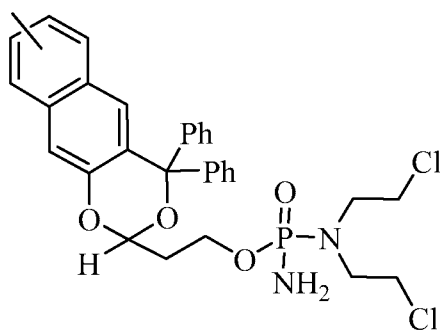
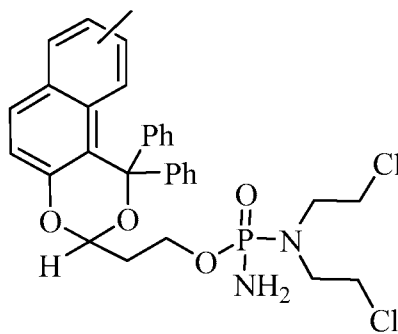
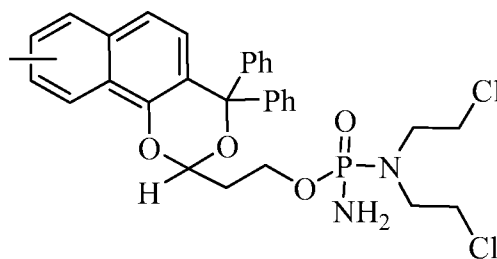
**I-1**

10

**I-2**

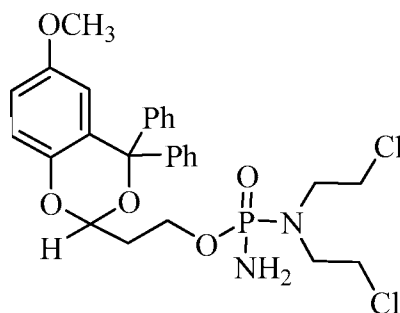
15

**I-3**

**I-4****I-5****I-6****I-7**

5

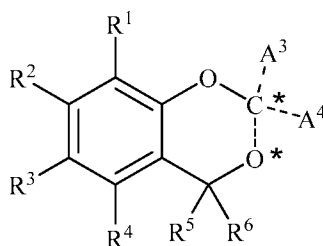
10



I-8

Further described is a method of delivering a therapeutic agent to a selected area in a subject, comprising administering to the subject an effective amount of compounds as represented by **Compound II**:

15



II

20

or pharmaceutically acceptable salts thereof, and transmitting light to the selected area of the subject.

In **Compound II**, R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are as described above for **Compound I**.

25

30

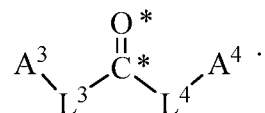
Also in **Compound II**, $A^3(C^*-O^*)A^4$ is one or more therapeutic agents or pro-therapeutic agents containing a carbonyl group, wherein C^*-O^* is the carbonyl group of the one or more therapeutic agents or pro-therapeutic agents (i.e., the C^*-O^* will form the carbonyl group of the one or more therapeutic agents or pro-therapeutic agent upon release of the therapeutic agent or pro-therapeutic agent). In some examples of **Compound II**, $A^3(C^*-O^*)A^4$ is one therapeutic agent (e.g., the carbonyl is in the middle of the therapeutic agent). In some examples of **Compound II**, A^3 and A^4 are each independently therapeutic agents, (e.g., A^3 is a first therapeutic agent and A^4 is a second same or different therapeutic agent).

In **Compound II**, A^3 can include a linker, L^3 , comprising a substituted or unsubstituted hydrocarbon or substituted or unsubstituted hetero-hydrocarbon, with the A^3 —linker molecule being attached through the linker. The A^3 —linker molecule can be a proform of the therapeutic agent (i.e., A^3). Examples of pro-therapeutic agents include $-(CH_2)_2$ —phosphoramidate mustard and $-(CH_2)_2$ —isophosphoramidate mustard. In **Compound II**, A^4 can include a linker, L^4 , comprising oxygen, a substituted or unsubstituted hydrocarbon, or substituted or unsubstituted hetero-hydrocarbon that is connected to A^4 and the carbonyl carbon of A^3 .

As used herein, the terms proform and pro-therapeutic are used interchangeably and are intended to mean a precursor or derivative form of a therapeutic agent that a medical or other practitioner may wish to deliver to a subject in an inactive form that can be activated subsequent to administration. Such proforms may include a property, such as, for example, lower toxicity, increased solubility, or improved transfer rate, as compared to the parent therapeutic agent. When A^3 or A^4 is a proform of a therapeutic agent itself, **Compound II** is in a sense a double-proform as the molecule must first be activated by light and then further activated from the A^3 or A^4 proform into the active parent form. Examples of therapeutic agents useful with the compounds and methods described herein include cancer therapeutic agents. Cancer therapeutic agents include, for example, anthracyclines, bleomycin, calicheamicins, carboplatin, chlorambucil, cisplatin, colchicine, daunorubicin, dactinomycin, diethylstilbestrol, doxorubicin, dynemicins, esperimicins, etoposide, 5-fluorouracil, floxuridine, FR-900482/FR-66979, melphalan, 6-mercaptopurine, methotrexate, mitomycin, nitrogen mustards, paclitaxel, teniposide, 6-thioguanine, vincristine, vinblastine, and derivatives thereof. Examples of nitrogen mustards include phosphoramidate, isophosphoramidate, cyclophosphamide, ifosfamide, and trofosfamide. Further examples of anti-cancer compounds and therapeutic agents are found in The Merck Manual of Diagnosis and Therapy, 15th Ed., Berkow et al., eds., 1987, Rahway, N.J.; Sladek et al. Metabolism and Action of Anti-Cancer Drugs, 1987, Powis et al. eds., Taylor and Francis, New York, N.Y.; and Pratt et al. The Anticancer Drugs, 2nd Ed., 1994, Oxford University Press, New York, N.Y.

When **Compound II** is exposed to light, $A^3(C^*-O^*)A^4$ is released. When A^3 or A^4 includes a linker (i.e., L^3 or L^4), the A^3 —linker molecule connected to the carbonyl

and/or A⁴—linker molecule connected to the carbonyl carbon (C*) is released as shown in the following structure:



5 As used herein, light refers to ultraviolet, visible, or infrared light. Ultraviolet light can be, for example, UVA or UVB light. Ultraviolet light can be provided, for example, from a commercially available 450 W medium pressure mercury lamp. The sun is also a suitable light source. The intensity of the light provided can impact the activation efficiency of the compound. For example, fluorescent lighting may not
10 initiate activation of the compounds or may do so at a much slower rate than sunlight or another light source.

In **Compound II**, adjacent R groups on the phenyl ring, i.e., R¹, R², R³, and R⁴, can be combined to form substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkane, substituted or
15 unsubstituted cycloalkene, substituted or unsubstituted cycloalkyne, substituted or unsubstituted heterocycloalkane, substituted or unsubstituted heterocycloalkene, or substituted or unsubstituted heterocycloalkyne groups. For example, R¹ can be a methanimine group and R² can be an ethylene group that combine to form a C₆ heteroaryl group. Other adjacent R groups include the combinations of R² and R³,
20 and R³ and R⁴.

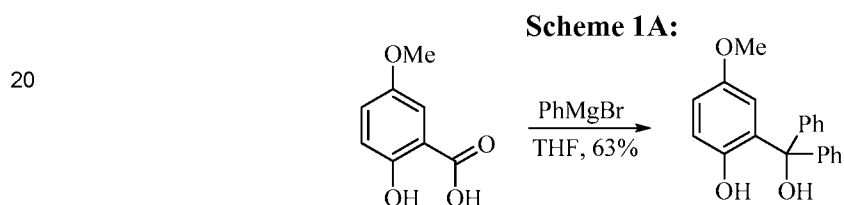
The compounds described herein can be prepared in a variety of ways. The compounds can be synthesized using synthetic methods known in the art of synthetic organic chemistry or variations thereon. The compounds described herein can be prepared from readily available starting materials. Optimum reaction conditions may
25 vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Variations on **Compound I** and **Compound II** include the addition, subtraction, or movement of the various constituents as described for each compound. Similarly, when one or more chiral centers are present in a molecule, the chirality of
30 the molecule can be changed. Additionally, compound synthesis can involve the protection and deprotection of various chemical groups. The use of protection and deprotection, and the selection of appropriate protecting groups can be selected by one skilled in the art. The chemistry of protecting groups can be found, for example,

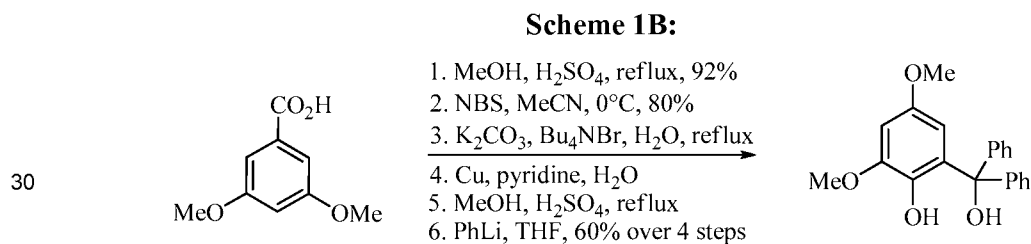
in Wuts and Greene, Protective Groups in Organic Synthesis, 4th Ed., Wiley & Sons, 2006, which is incorporated herein by reference in its entirety.

Reactions to produce the compounds described herein can be carried out in solvents which can be selected by one of skill in the art of organic synthesis. Solvents
 5 can be substantially nonreactive with the starting materials (reactants), the intermediates, or products under the conditions at which the reactions are carried out, i.e., temperature and pressure. Reactions can be carried out in one solvent or a mixture of more than one solvent. Product or intermediate formation can be monitored according to any suitable method known in the art. For example, product
 10 formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ¹H or ¹³C) infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

The compounds described by **Compounds I** and **II** can be made from
 15 photolabile protecting groups (for examples of photolabile protecting groups, see Example 2 below). A method of making the photolabile protecting group used to prepare **Compounds I** and **II** wherein R¹, R², and R⁴ are hydrogen and R³ is methoxy is shown in Scheme 1A.



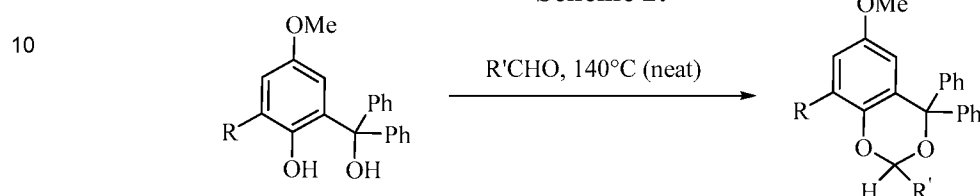
A method of making a photolabile protecting group used to prepare
 25 **Compounds I** and **II** wherein R² and R⁴ are hydrogen and R¹ and R³ are methoxy is shown in Scheme 1B.



The methods shown in Schemes 1A and 1B produce the corresponding photolabile protecting groups in high yields and are amenable to producing multi-gram quantities of the compounds.

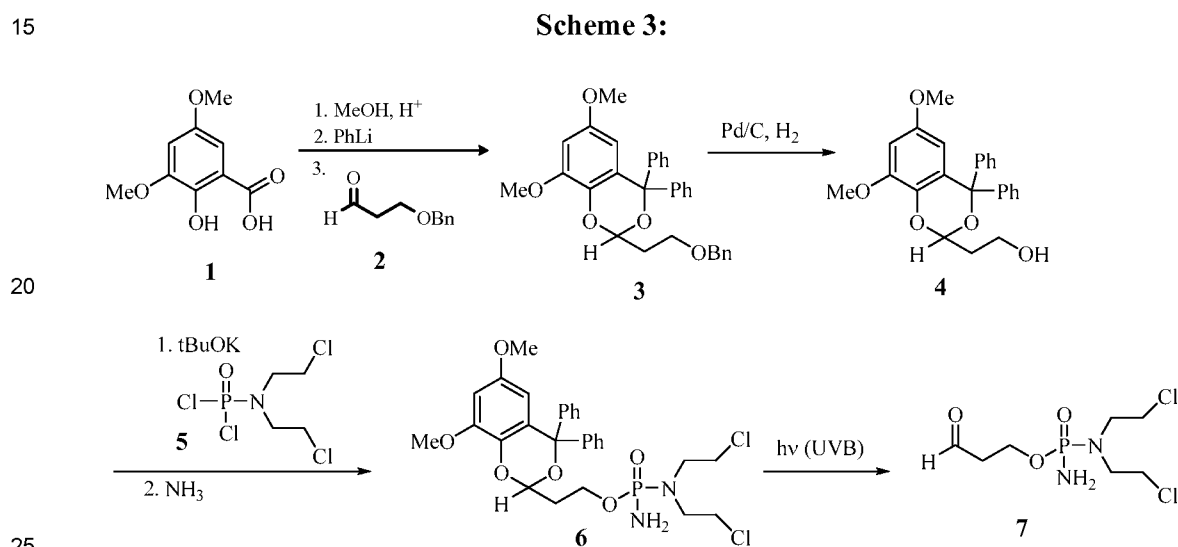
A method of protecting carbonyl compounds with the photolabile protecting groups shown in Schemes 1A and 1B is described below in Scheme 2. In Scheme 2, R is H or OMe. The protection reaction can be performed under neutral conditions without using any additional chemical reagents and/or solvents. Protections performed according to Scheme 2 also exhibit high yields as shown in Example 2.

Scheme 2:



A method for making **Compounds I** and **II** is described by Scheme 3.

Scheme 3:

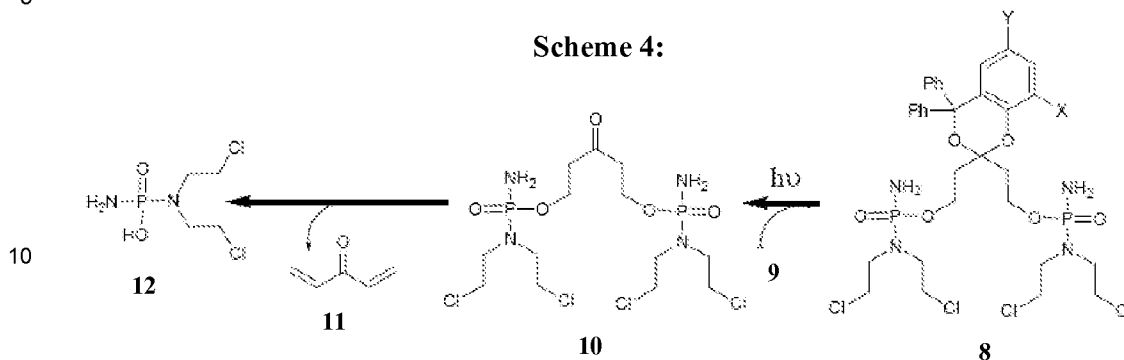


Scheme 3 shows esterifying 2-(hydroxydiphenylmethyl)phenol (**1**; derived from commercially available 3-hydroxypropanal), reducing the resulting ester with phenyl lithium, and treating the resulting compound with a benzyloxy alkyl aldehyde (**2**) under neutral conditions to form **3**, wherein the phenol is substituted as described for **Compounds I** and **II**. The acetal (**3**) is then debenzylated using hydrogenolytic conditions with hydrogen gas and 10% palladium on carbon to form **4**. The alcohol **4** is then treated with potassium *tert*-butoxide and phosphoramidite chloride (**5**) followed by ammonia to form **6**. Photochemical activation using UVA or UVB light releases

aldophosphamide (7), which undergoes spontaneous elimination to produce the phosphamide mustard.

An example of photoactivation of a pro-therapeutic agent containing a first therapeutic agent and second therapeutic agent is shown in Scheme 4.

5



Irradiation of the protherapeutic agent containing a first therapeutic agent and second therapeutic agent (**8**) removes the photolabile protecting group (**9**; not shown) and produces the carbonyl compound (**10**) which can undergo β -elimination to generate two cytotoxic phosphamide mustards (**12**) and dienone (**11**).

The compounds described herein or pharmaceutically acceptable salts thereof can be provided in a pharmaceutical composition. Depending on the intended mode of administration, the pharmaceutical composition can be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, or suspensions, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include an effective amount of the compounds described herein or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, or diluents. By pharmaceutically acceptable is meant a material that is not biologically or otherwise undesirable, which can be administered to an individual along with the selected substrate without causing significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

As used herein, the term carrier encompasses any excipient, diluent, filler, salt, buffer, stabilizer, solubilizer, lipid, or other material well known in the art for use in pharmaceutical formulations. The choice of a carrier for use in a composition will

depend upon the intended route of administration for the composition. The preparation of pharmaceutically acceptable carriers and formulations containing these materials is described in, *e.g.*, Remington's Pharmaceutical Sciences, 21st Edition, ed. University of the Sciences in Philadelphia, Lippincott, Williams & Wilkins, Philadelphia Pa., 2005. Examples of physiologically acceptable carriers include buffers such as phosphate buffers, citrate buffer, and buffers with other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN[®] (ICI, Inc.; Bridgewater, New Jersey), polyethylene glycol (PEG), and PLURONICS[™] (BASF; Florham Park, NJ).

Compositions containing one or more of the compounds described herein or pharmaceutically acceptable salts thereof suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration of the compounds described herein or a pharmaceutically acceptable salt thereof include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds described herein or a pharmaceutically acceptable salt thereof is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (e) solution retarders, as for example, paraffin; (f) absorption accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration of the compounds described herein or pharmaceutically acceptable salts thereof include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers.

Suitable solvents, solubilizing agents, and emulsifiers include, for example, ethyl alcohol; isopropyl alcohol; ethyl carbonate; ethyl acetate; benzyl alcohol; benzyl alcohol; benzyl benzoate, propyleneglycol; 1,3-butyleneglycol; dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil; glycerol; tetrahydrofurfuryl alcohol; polyethyleneglycols; and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting, emulsifying, suspending, sweetening, flavoring, or perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters; microcrystalline cellulose; aluminum metahydroxide; bentonite; agar-agar; tragacanth; mixtures of these substances; and the like.

Compositions of the compounds described herein or pharmaceutically acceptable salts thereof for rectal administrations are optionally suppositories, which can be prepared by mixing the compounds with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and, therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of the compounds described herein or pharmaceutically acceptable salts thereof include ointments, powders, sprays, and inhalants. The compounds described herein or pharmaceutically acceptable salts thereof are admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, ointments, powders, and solutions are also contemplated as being within the scope of the compositions.

The term pharmaceutically acceptable salt as used herein refers to those salts of the compounds described herein that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds described herein. The term salts refers to the relatively non-toxic, inorganic and organic acid salts of the compounds described herein. These salts can be prepared *in situ* during the isolation and purification of the

compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, 5 tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate, methane sulphonate, and laurylsulphonate salts, and the like. These may include cations based on alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to 10 ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (*See* S.M. Berge et al., J. Pharm. Sci. (1977) 66:1-19, which is incorporated herein by reference in its entirety, at least, for compositions taught therein.)

In the method of delivering a **Compound II** to a selected area in a subject, an 15 effective amount of **Compound II** as described above is administered to a subject, then light is transmitted to the selected area of the subject. The effective amount of **Compound II** can be delivered systemically to the subject or delivered to a specific area of the subject, i.e., to the selected area, its vicinity, or its blood supply. The amount of time between the administration step and the transmission of light to the 20 selected area of the subject will depend upon the rate of transfer of the effective amount of **Compound II** to the selected area. An effective amount of **Compound II** is the amount needed for delivery of an effective amount of the therapeutic agent that will be released from **Compound II** to the selected area in the subject. Thus, for systemic delivery, an amount of **Compound II** greater than the amount needed at the 25 selected area of the subject may be provided in order to deliver the effective amount of the therapeutic agent to the selected area (unless **Compound II** is such that all the amount administered to the subject is delivered to the selected area). **Compound I** can be delivered to a selected area in a subject by the same method.

The transmission of light to the selected area of a subject can be accomplished 30 using methods and apparatuses known in the surgical arts. For example, the light can be transmitted through an optical fiber or an optical probe to the selected area. Further, the optical fiber or optical probe can be housed in a needle. The optical fiber, optical probe, or needle housing the optical fiber or optical probe can be guided to the

selected area using CT scan or MRI, which methods are known to those of skill in the surgical arts.

As an example, in the treatment of a cancer tumor, **Compound II** having a cancer therapeutic agent as a first pro-therapeutic agent or as a second pro-therapeutic agent can be administered to a subject having a cancer tumor. Once **Compound II** has been transmitted to the cancer tumor site, the cancer tumor site can be irradiated with light to form the cancer therapeutic agent. Molecules containing PEG groups with molecular weights greater than 10,000 Daltons are known to collect in cancerous tissues, thus, a **Compound II** containing PEG groups may collect in cancer tissue increasing the transfer efficiency of **Compound II** to a tumor site (thereby lowering the overall amount of **Compound II** that is administered to the subject to deliver an effective amount).

Administration of compounds described herein or pharmaceutically acceptable salts thereof can be carried out using therapeutically effective amounts of the compounds described herein or pharmaceutically acceptable salts thereof. The effective amount of the compounds described herein or pharmaceutically acceptable salts thereof may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a mammal of from about 0.05 to about 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. Alternatively, the dosage amount can be from about 0.05 to about 75 mg/kg of body weight of active compound per day, about 0.5 to about 50 mg/kg of body weight of active compound per day, about 0.5 to about 25 mg/kg of body weight of active compound per day, about 1 to about 20 mg/kg of body weight of active compound per day, about 1 to about 10 mg/kg of body weight of active compound per day, about 20 mg/kg of body weight of active compound per day, about 10 mg/kg of body weight of active compound per day, or about 5 mg/kg of body weight of active compound per day. The specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition.

In the methods described herein, the subjects treated can be further treated with one or more additional agents. The one or more additional agents and the compounds described herein or pharmaceutically acceptable salts thereof can be administered in any order, including simultaneous administration, as well as
 5 temporally spaced order of up to several days apart. The methods may also include more than a single administration of the one or more additional agents and/or the compounds described herein or pharmaceutically acceptable salts thereof. The administration of the one or more additional agents and one or more compounds described herein or pharmaceutically acceptable salts thereof may be by the same or
 10 different routes and concurrently or sequentially.

The examples below are intended to further illustrate certain aspects of the methods and compounds described herein, and are not intended to limit the scope of the claims.

EXAMPLES

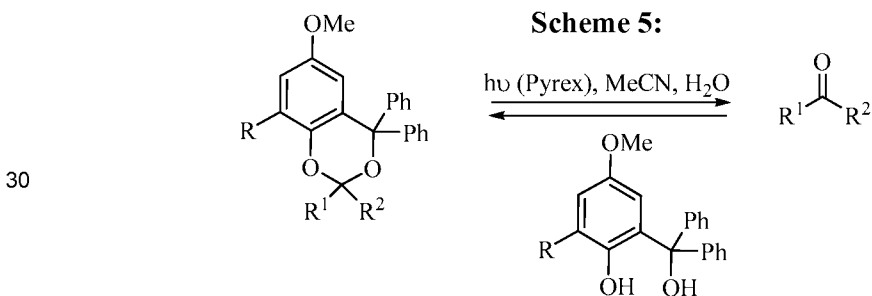
15

Example 1: Irradiation of pro-therapeutics

A photo-activatable pro-therapeutic containing an aldophosphamide was irradiated with UVA or UVB light using a 450 W medium pressure mercury lamp as the light source. The power of the light after filtering was less than 10 W and the
 20 absorbed light was less than 1 W. After irradiating for 10 minutes with the light source, aldophosphamide was released. Aldophosphamide then underwent a spontaneous elimination reaction to produce the phosphamide mustard.

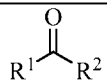
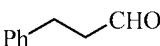
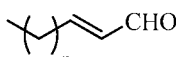
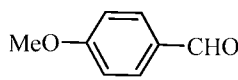
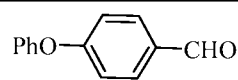
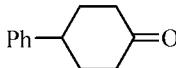
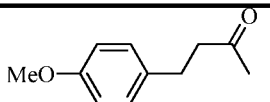
Example 2: Protection and deprotection of various photolabile protecting groups

25 A variety of carbonyl compounds were efficiently protected and photo-released from their protected forms according to the reactions shown in Scheme 5.



The specific carbonyl compounds protected and their deprotection and protection yields according to the reactions of Scheme 5 are shown in Table 1. The photochemical deprotection reactions were complete in less than 80 minutes for compounds wherein R is H and in 30 minutes for compounds wherein R is OMe. The photoreactions can be performed in the presence of water and/or air.

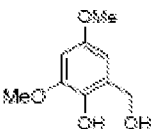
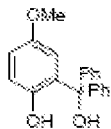
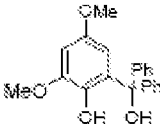
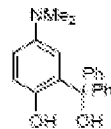
Table 1: Protection/Deprotection Yield Results

R		Deprotection Yield (%)	Protection Yield (%)
H		92	99
OMe		90	99
H		89	91
OMe		-- ^a	-- ^a
H		89	99
OMe		-- ^a	-- ^a
H		-- ^a	-- ^a
OMe		82	93
H		80	97
OMe		86	99
H		86	91
OMe		91	99

^a Not measured

Several acetals were prepared by reacting the photolabile protecting groups shown in Scheme 6 with 3-phenylpropanal. The acetals were then exposed to spring sunlight for 2.5 hours to photorelease the photolabile protecting groups. In each deprotection reaction, 3-phenylpropanal was released in high yields (74–96%). Prior to deprotection, the acetals were stable under normal indoor lighting, which facilitates the handling of the prodrugs.

Scheme 6:

PPG				
protection yields (%)	~ 91	~ 81	~ 93	~ 94
deprotection yields (%)	~ 79%	~ 74	~ 82	~ 96

Example 3: Compound uptake in cell culture

10 The speed and extent to which the compounds are taken up by human prostate cancer (e.g., PC3, LNCaP, DU145) and normal epithelial cells (e.g., PWR-1E) in culture is evaluated. The cells are exposed to different concentrations of the compounds for varying times (e.g., 5 min to 24 hours), lysed, and examined for the presence of the compound in the cytoplasm and nucleus. The concentrations of the

15 compounds are determined by HPLC.

Example 4: Compound stability in cell culture and plasma

 To determine the stability of the compounds in culture, prostate cells (e.g., PC3, LNCaP, DU145, PWR-1E) are exposed to the compounds and then the cells are

20 analyzed to determine if the compounds are intact or if the compounds were activated or otherwise modified. The cells are incubated with several concentrations (e.g., low, medium, and high) of the compounds for varying times. The identity of the compound is then verified or determined (e.g., by HPLC and/or HPLC-MS).

 To determine the stability of the compounds in plasma, several concentrations

25 (e.g., low, medium, and high) of the compounds are incubated at 37°C in mouse and human plasma for various times (e.g., 5 minutes to 8 hours). The identity of the compounds are then verified or determined (e.g., by HPLC and/or HPLC-MS).

 The optimal exposure to UV light to cleave the prodrug into its active form is also studied. The cells are exposed to the compound, then trypsinized and suspended

30 in cell culture media. The cells are exposed in cuvettes to UV light (e.g., 325-375nm) for various times ranging from 5 seconds to 5 minutes. The cells are then evaluated for the concentrations and identity of the activated or modified compounds in the culture media, cytoplasm, and nuclei.

Example 5: Compound cytotoxicity

To determine the *in vitro* toxicity of the compounds, both prostate cancer (e.g., PC3, LNCaP, DU145) and normal epithelial cells (e.g., PWR-1E) are exposed to the compounds for the optimal time required to achieve high uptake. The cells are then
5 exposed to UV light (e.g., 325-375 nm) in order to activate the compound. As a control, additional treated cells are placed in the irradiated area, but shielded from the UV light by glass inserts. The untreated cells are used as a control for the toxicity resulting from UV light exposure. The survival and apoptosis of the cells (both exposed and unexposed) are examined (e.g., by MTT and Annexin V staining assays),
10 and the results for the compound exposed cells are compared to the results for the control cells.

To determine the toxicity of the compounds with chemotherapeutic agents versus the chemotherapeutic agents themselves, the cytotoxicity of these groups against prostate cancer and normal epithelial cells are compared. The cells are
15 exposed to either the compound or to the conventional chemotherapeutic agent and examined for survival (e.g., MTT assay) and apoptosis (e.g., Annexin V + flow cytometry).

Example 6: *In vivo* studies

20 To examine the *in vivo* effects of the compounds, the compounds are administered to normal CD-1 mice and tumor-bearing nude mice. The maximum tolerated dose (MTD) of the compound both prior to and following UV activation is determined.

The normal CD-1 mice are administered varying concentrations of the
25 compound by intravenous injection or oral gavage. If no MTD is found or the MTD is higher than the dosage range relevant to the clinically-relevant dosage range for humans, the mice are treated with 1.5g/kg of the compound, which should yield a clinically-relevant (human equivalent of 25 mg/kg) dose of the compound (e.g., phosphamide mustard). Plasma levels of the compound are examined at several time
30 points (e.g., 10 min to 24 hours) to determine the iv and oral bioavailability of the compound.

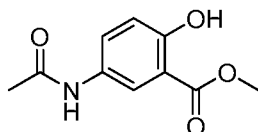
The nude mice bearing prostate cancer xenografts are treated with varying concentrations of the compound. If the compound is found to be orally available, it is

administered by oral gavage. If not, it is administered by iv injection. A subcutaneous xenograft model is used to demonstrate efficacy for the compound. When PC3 xenograft tumors reach approximately 100 mg, the mice are treated with the compound and the tumors exposed to UV light via a light probe for various amounts of time (e.g., 10 seconds to 5 minutes). Mouse tumor growth is monitored for a suitable period of time, e.g., 3 weeks, or until tumor growth necessitates euthanasia. Control groups include mice treated with vehicle only, and those treated with the compound that do not receive the UV light treatment.

Example 7: Synthesis of 2-(6-(*N*-Ethyl-*N*-(4-(1-mPEG-1*H*-1,2,3-triazol-4-yl)butyl)amino-4,4-diphenyl-4*H*-benzo[*d*][1,3]dioxin-2-yl)ethyl-*N,N*-di-(2-chloroethyl)-phosphorodiamidate

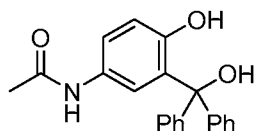
All reagents are commercially available (e.g., from Sigma-Aldrich; St. Louis, MO).

(A) Preparation of methyl 5-acetamido-2-hydroxybenzoate:

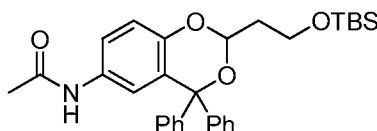


To an ice cooled solution of methyl 5-aminosalicylate (1.0 g, 5.98 mmol) and triethylamine (TEA) (0.834 mL, 5.98 mmol) in dichloromethane (DCM) (80.0 mL), acetyl chloride (0.425 mL, 5.98 mmol) was added dropwise with stirring. After 1h, the reaction was gradually allowed to attain room temperature. After 2h of stirring at room temperature, the reaction was diluted with DCM (80.0 mL), washed with water and brine, and then dried over Na₂SO₄. Removal of the solvent under vacuum followed by recrystallization from DCM furnished **A** (1.16 g, 93% yield).

Characterization of **A**: ¹H NMR (CDCl₃, 300 MHz) δ 10.6 (s, 1 H), 8.01 (d, *J* = 2.7 Hz, 1 H), 7.49 (dd, *J* = 8.9, 2.7 Hz, 1 H), 7.27-7.23 (bs, 1 H), 6.94 (d, *J* = 8.7 Hz, 1 H), 3.93 (s, 3 H), 2.16 (s, 3 H); ¹³C NMR (CDCl₃, 75 MHz) δ 170.1, 168.8, 158.4, 129.5, 128.9, 121.8, 117.5, 112.0, 52.3, 24.0; IR (film) 3279, 2954, 1654, 1491, 1305, 1217, 1186.

(B) Preparation of *N*-(4-hydroxy-3-(hydroxydiphenylmethyl)phenyl)acetamide:

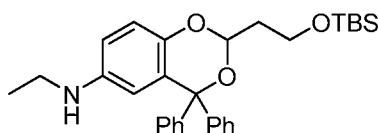
To a solution of A (1.0 g, 4.78 mmol) in THF (100.0 mL) at -78 °C, phenyl lithium (PhLi) (10.79 mL, 14.35 mol) was added with stirring. After 6h, additional PhLi (1.79 mL, 2.39 mmol) was added and the reaction mixture was gradually allowed to attain room temperature. After 36h stirring at room temperature, saturated NH₄Cl solution was added. The solvent was removed in vacuo and the residue was extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with water and brine, and then dried over Na₂SO₄. Removal of the solvent under vacuum followed by silica gel column chromatographic purification of the residue using a mixture of petroleum ether and ethyl acetate (1:1, R_f 0.5) gave **B** (1.41 g, 89% yield). Characterization of **B**: ¹H NMR (CD₃OD, 300 MHz) δ 7.44 (dd, *J* = 8.7, 2.6 Hz, 1 H), 7.18-7.33 (m, 10 H), 6.75 (d, *J* = 8.6 Hz, 1 H), 6.59 (d, *J* = 2.7 Hz, 1 H), 1.96 (s, 3 H); ¹³C NMR (CD₃OD, 75 MHz) δ 172.2, 154.7, 148.0, 134.3, 131.9, 130.0, 129.6, 129.2, 124.8, 123.8, 118.4, 85.1, 24.2; IR (film) 3443, 3310, 3020, 1662, 1551, 1216.

(C) Preparation of 2-(6-acetamido-4,4-diphenyl-4*H*-benzo[d][1,3]dioxin-2-yl)ethyl-(*tert*-butyldimethylsilyl)ether:

A mixture of **B** (900 mg, 2.70 mmol) and 3-(*tert*-butyldimethylsilyloxy)-1-propanal (762 mg, 4.05 mmol) in *p*-xylene (4.0 mL) was heated to 140 °C with stirring in a sealed schlenk tube under an argon atmosphere. After 1.5h, the reaction was allowed to attain room temperature and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatographic purification using a mixture of petroleum ether and ethyl acetate (2:1, R_f 0.3) to produce **C** (1.41 g, 89% yield). Characterization of **C**: ¹H NMR (CDCl₃, 300 MHz) δ 7.48-7.42 (bs, 1 H), 7.37 (dd, *J* = 8.9, 2.6 Hz, 1 H), 7.35-7.27 (m, 5 H), 7.25-7.15 (m, 5 H), 6.84 (d, *J* = 9.0 Hz, 1 H), 6.82 (d, *J* = 2.7 Hz, 1 H), 5.13 (t, *J* = 5.4 Hz, 1 H), 3.82-3.71 (m, 2 H), 2.06 (q, *J*

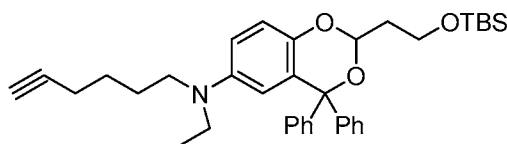
= 5.9 Hz, 2 H), 1.94 (s, 3 H), 0.74 (s, 9 H), -0.06 (s, 6 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 200.4, 168.3, 149.1, 145.9, 143.7, 130.4, 129.0, 128.1, 128.0, 127.8, 127.5, 125.6, 121.6, 121.3, 117.3, 93.1, 84.1, 58.0, 37.9, 25.7, 24.1, 18.0, -5.46, -5.51; IR (film) 3019, 2957, 2930, 1678, 1497, 1393.

5 **(D) Preparation of 2-(6-*N*-ethylamino-4,4-diphenyl-4*H*-benzo[*d*][1,3]dioxin-2-yl)ethyl-(*tert*-butyldimethylsilyl)ether:**



To an ice cooled mixture of LAH (102 mg, 2.70 mmol) in THF (7.0 mL), a solution
 10 of **C** (680 mg, 1.35 mmol) in THF (7.0 mL) was added slowly with stirring and the
 reaction mixture was heated to gentle reflux. After 1h of refluxing, the solution was
 cooled to 0 °C and a 1M aqueous solution of NaOH (10.0 mL) was added. The
 reaction mixture was extracted with ethyl acetate (30 mL x 3), and the combined
 organic layers were washed with water and brine, and dried over Na_2SO_4 . Removal
 15 of the solvent under vacuum followed by silica gel column chromatographic
 purification of the residue using a mixture of petroleum ether and ethyl acetate (10:1
 R_f 0.5) furnished **D** (429 mg, 65% yield). Characterization of **D**: ^1H NMR (CDCl_3 ,
 300 MHz) δ 7.43-7.19 (m, 10 H), 6.77 (d, J = 8.7 Hz, 1 H), 6.48 (dd, J = 8.78, 2.7 Hz,
 1 H), 6.06 (d, J = 3.0 Hz, 1 H), 5.08 (t, J = 5.3 Hz, 1 H), 3.81-3.68 (m, 2 H), 2.92 (qd,
 20 J = 7.1, 1.4 Hz, 2 H), 2.04 (dd, J = 13.7, 6.1 Hz, 2 H), 1.11 (t, J = 7.1 Hz, 3 H), 0.75
 (s, 9 H), -0.064 (d, J = 1.2 Hz, 6 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 146.3, 144.7,
 144.3, 141.8, 129.2, 128.2, 127.9, 127.8, 127.7, 127.2, 125.8, 117.5, 114.0, 113.8,
 92.9, 84.2, 58.2, 39.1, 38.0, 25.8, 18.1, 14.7, 5.5; IR (film) 3404, 3061, 3025, 2958,
 2928, 2856, 1600, 1508, 1228.

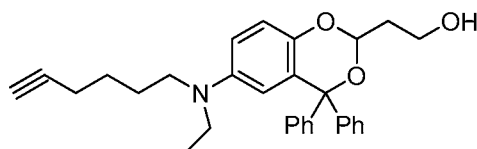
25 **(E) Preparation of 2-(6-(*N*-ethyl-*N*-(hex-5-ynyl)amino)-4,4-diphenyl-4*H*-benzo[*d*][1,3]dioxin-2-yl)ethyl-(*tert*-butyldimethylsilyl)ether:**



To a mixture of **D** (400 mg, 0.817 mmol), K₂CO₃ (564 mg, 4.08 mmol), KI (406 mg, 2.45 mmol), and Bu₄NCl (22 mg, 0.081 mmol) in acetonitrile (20.0 mL), hex-5-ynyl-tosyl ether (412 mg, 1.63 mmol) was added with stirring and the reaction mixture was refluxed for 24h under an argon atmosphere. After cooling to room temperature, the solvent was removed under vacuum and the reaction mixture was diluted with ethyl acetate (80.0 mL), washed with water and brine, and dried over Na₂SO₄. Removal of the solvent under vacuum followed by silica gel column chromatographic purification of the residue using a mixture of petroleum ether and ethyl acetate (10:1, R_f 0.7) gave **E** (428 mg, 92% yield). Characterization of **E**: ¹H NMR (CDCl₃, 300 MHz) δ 7.48-7.45 (m, 2 H), 7.38-7.24 (m, 8 H), 6.86 (d, *J* = 9.0 Hz, 1 H), 6.63 (dd, *J* = 9.0, 2.8 Hz, 1 H), 6.16 (d, *J* = 2.7 Hz, 1 H), 5.17 (t, *J* = 5.3 Hz, 1 H), 3.87-3.68 (m, 2 H), 3.23-3.13 (m, 2 H), 3.12-2.97 (m, 2 H), 2.08-2.02 (m, 4 H), 1.87 (t, *J* = 2.7 Hz, 2 H), 1.58-1.34 (m, 4 H), 0.94 (t, *J* = 6.9 Hz, 1 H), 0.75 (s, 9 H), -0.06 (d, *J* = 1.2 Hz, 6 H); ¹³C NMR (CDCl₃, 75 MHz) δ 146.5, 144.4, 143.9, 141.7, 129.2, 128.0, 127.9, 127.7, 127.6, 127.2, 125.6, 117.3, 114.7, 114.3, 92.8, 84.3, 84.0, 68.5, 58.1, 50.6, 45.7, 38.0, 26.4, 26.0, 25.8, 18.2, 18.0, 12.2, -5.46, -5.50; IR (film) 3309, 3062, 2930, 2857, 1621, 1506, 1242.

(F) Preparation of 2-(6-(*N*-ethyl-*N*-(hex-5-ynyl)amino)-4,4-diphenyl-4*H*-benzo[*d*][1,3]dioxin-2-yl)ethanol:

20

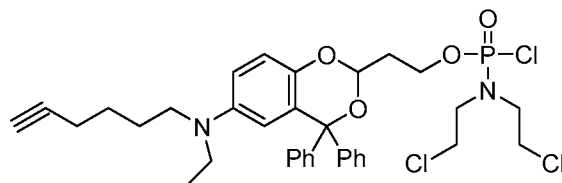


To a solution of **E** (400 mg, 0.702 mmol) in THF (10.0 mL) at room temperature, tetrabutylammonium fluoride solution (1.05 mL, 1.05 mmol) was added with stirring. After 4h of stirring, the solvent was removed under vacuum, diluted with ethyl acetate (60.0 mL), washed with water and brine, and dried over Na₂SO₄. Removal of the solvent under vacuum followed by silica gel column chromatographic purification of the residue using a mixture of petroleum ether and ethyl acetate (2:1, R_f 0.6) gave **F** (304 mg, 95% yield) as a mixture of diastereomers. Characterization of **F**: ¹H NMR (CDCl₃, 300 MHz) δ 7.43-7.34 (m, 5 H), 7.27-7.21 (m, 5 H), 6.80 (d, *J* = 8.7 Hz, 1 H), 6.58 (dd, *J* = 9.0, 3.0 Hz, 1 H), 6.07 (d, *J* = 3.0 Hz, 1 H), 5.14 (t, *J* = 4.7 Hz, 1 H), 3.85-3.79 (m, 2 H), 3.15-3.09 (m, 2 H), 3.07-2.93 (m, 2 H), 2.113-2.04 (m, 4 H), 1.89

30

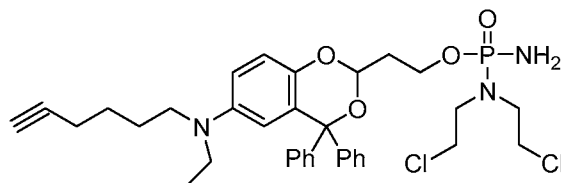
(t, $J = 2.7$ Hz, 1 H), 1.50-1.24 (m, 4 H), 0.95 (t, $J = 7.1$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 146.0, 145.9, 144.1, 144.0, 143.1, 141.9, 129.2, 129.1, 128.03, 128.01, 127.92, 127.88, 127.6, 127.3, 125.2, 125.1, 117.3, 117.2, 114.21, 114.15, 94.4, 84.7, 84.1, 68.4, 58.4, 50.6, 45.7, 36.7, 26.4, 26.0, 18.3, 12.1; IR (film) 3567, 3306, 3010, 2937, 1600, 1508, 1447, 1241, 1067.

(G) Preparation of 2-(6-(*N*-ethyl-*N*-(hex-5-ynyl)amino)-4,4-diphenyl-4*H*-benzo[*d*][1,3]dioxin-2-yl)ethyl-di-(2-chloroethyl)-phosphoramidic chloride:



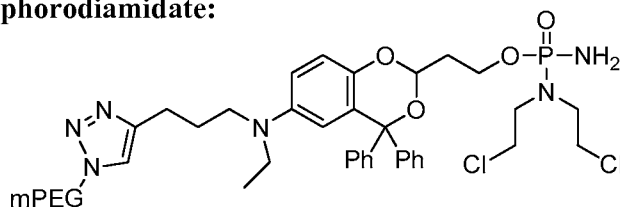
To an ice cooled solution of **F** (200mg, 0.439 mmol) in THF (6.0 mL), a solution of potassium *tert*-butoxide (1.31 mL, 1.31 mmol) was added with stirring. After 2h of stirring at 0 °C, a solution of di-(2-chloroethyl)-phosphoramidic dichloride (455 mg, 1.75 mmol) in THF (4.0 mL) was added. The temperature was maintained at 0 °C for 30 min and then stirred at room temperature for 2h. The solvent was removed under vacuum, saturated NH_4Cl solution was added, and the solution was extracted with ethyl acetate (50.0 mL x 2). The combined organic layers were washed with water and brine, and dried over Na_2SO_4 . Removal of the solvent under vacuum followed by silica gel column chromatographic purification of the residue using a mixture of petroleum ether and ethyl acetate (3:1, R_f 0.6) produced **G** (214 mg, 72% yield) as a mixture of diastereomers. Characterization of **G**: ^1H NMR (CDCl_3 , 300 MHz) δ 7.43-7.31 (m, 5 H), 7.25-7.19 (m, 5 H), 6.80 (d, $J = 8.9$ Hz, 1 H), 6.58 (dd, $J = 9.0, 2.7$ Hz, 1 H), 6.07 (d, $J = 2.4$ Hz, 1 H), 5.08 (dt, $J = 5.0, 1.5$ Hz, 1 H), 4.48-4.32 (m, 2 H), 3.52-3.27 (m, 8 H), 3.18-3.08 (m, 2 H), 3.07-2.92 (m, 2 H), 2.33-2.21 (m, 2 H), 2.11-2.01 (m, 2 H), 1.89 (t, $J = 2.7$ Hz, 1 H), 1.57-1.29 (m, 4 H), 0.94 (t, $J = 6.9$ Hz, 3 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 146.0, 145.9, 144.1, 144.0, 143.1, 141.9, 129.2, 129.1, 128.03, 128.01, 127.92, 127.88, 127.6, 127.3, 125.2, 125.1, 117.3, 117.2, 114.21, 114.15, 91.7, 84.5, 84.4, 84.0, 68.4, 63.7, 63.6, 50.5, 49.69, 49.63, 49.57, 49.51, 45.6, 41.43, 41.40, 41.37, 35.0, 34.8, 34.7, 26.3, 25.8, 18.1, 12.1; IR (film) 3307, 3014, 2969, 1506, 1447, 1269, 1241, 1217.

(H) Preparation of 2-(6-(*N*-ethyl-*N*-(hex-5-ynyl)amino)-4,4-diphenyl-4*H*-benzo[*d*][1,3]dioxin-2-yl)ethyl-*N,N*-di(2-chloroethyl)-phosphorodiamidate:



Ammonia gas was bubbled through a solution of **G** (200 mg, 0.295 mmol) in dioxane with stirring (6.0 mL) at room temperature for 1.5h. The reaction mixture was filtered through celite, concentrated, and purified by silica gel column chromatographic purification using ethyl acetate (R_f 0.8) to furnish **H** (165 mg, 85% yield) as a mixture of diastereomers. Characterization of **H**: ^1H NMR (CDCl_3 , 300 MHz) δ 7.45-7.32 (m, 5 H), 7.28-7.20 (m, 5 H), 6.79 (dd, J = 8.9, 1.3 Hz, 1 H), 6.58 (dd, J = 8.9, 2.5 Hz, 1 H), 6.08 (d, J = 2.5 Hz, 1 H), 5.08 (t, J = 5.1 Hz, 1 H), 4.20-4.03 (m, 2 H), 3.59-3.47 (m, 4 H), 3.37-3.24 (m, 4 H), 3.19-3.08 (m, 2 H), 3.08-2.96 (m, 2 H), 2.78-2.68 (m, 1 H), 2.64-2.54 (m, 1 H), 2.22-2.13 (m, 1 H), 2.11-2.02 (m, 2 H), 1.90 (t, J = 2.6 Hz, 1 H), 1.51-1.31 (m, 4 H), 0.95 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 146.0, 144.3, 144.1, 143.4, 141.8, 129.3, 129.2, 127.95, 127.90, 127.85, 127.6, 127.3, 125.3, 117.3, 114.3, 92.3, 92.2, 84.41, 84.39, 84.0, 68.4, 60.72, 60.66, 50.5, 49.2, 49.13, 49.06, 45.6, 42.3, 35.5, 35.4, 35.3, 26.3, 25.8, 18.1, 12.0; IR (film) 3461, 3307, 3017, 2973, 1506, 1448.

(I) Preparation of 2-(6-(*N*-ethyl-*N*-(4-(1-mPEG-1*H*-1,2,3-triazol-4-yl)butyl)amino)-4,4-diphenyl-4*H*-benzo[*d*][1,3]dioxin-2-yl)ethyl-*N,N*-di(2-chloroethyl)-phosphorodiamidate:



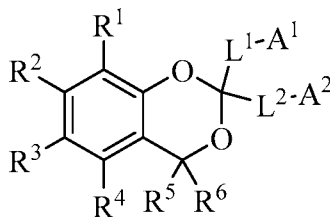
To a solution of **H** (150 mg, 0.227 mmol) and mPEG- N_3 (210 mg, 0.205 mmol) in a mixture of (10:1) acetonitrile and water (10.1 mL) at room temperature, Cu powder (14.3 mg, 0.227 mmol) was added and stirring was continued for 36h. The solvent was removed and the residue was dissolved in chloroform, filtered, and dried over Na_2SO_4 . Removal of the solvent under vacuum followed by silica gel column chromatographic purification using a mixture of DCM and methanol (10:1, R_f 0.4)

produced **I** (317 mg, 92% yield) as a mixture of diastereomers. Characterization of **I**:
¹H NMR (CDCl₃, 300 MHz) δ 7.44-7.32 (m, 5 H), 7.26-7.17 (m, 5 H), 6.78 (dd, *J* =
8.9, 1.4 Hz, 1 H), 6.56 (dd, *J* = 9.0, 3.0 Hz, 1 H), 6.08 (d, *J* = 2.9 Hz, 1 H), 5.08 (dt, *J* =
5.0, 2.0 Hz, 1 H), 4.49 (t, *J* = 5.1 Hz, 2 H), 4.21-4.06 (m, 2 H), 3.85 (t, *J* = 5.5 Hz, 2
5 H), 3.71-3.56 (m, 100 H), 3.58-3.50 (m, 6 H), 3.45-3.25 (m, overlapping s at 3.38, 7
H), 3.19-2.98 (m, 4 H), 2.67 (d, *J* = 4.4 Hz, 1 H), 2.60 (t, *J* = 7.6 Hz, 2 H), 2.51 (d, *J* =
4.4 Hz, 1 H), 2.22 (d, *J* = 6.2 Hz, 1 H), 2.17 (d, *J* = 6.2 Hz, 1 H), 1.61-1.48 (m, 2 H),
1.46-1.29 (m, 2 H), 0.92 (t, *J* = 7.0 Hz, 3 H); ¹³C NMR (CDCl₃, 75 MHz) δ 147.5,
145.99, 145.97, 144.3, 144.1, 143.2, 143.0, 141.8, 129.3, 129.1, 127.9, 127.85,
10 127.80, 127.6, 127.2, 125.24, 125.23, 121.6, 117.21, 117.17, 114.08, 113.98, 113.95,
92.2, 92.1, 84.38, 84.36, 71.7, 70.41, 70.38, 70.34, 70.29, 69.5, 60.7, 60.6, 58.9, 50.7,
50.5, 49.9, 49.13, 49.08, 49.04, 48.99, 45.6, 42.4, 35.49, 35.43, 35.35, 35.27, 26.84,
26.81, 25.4, 12.0; IR (film) 3422, 2977, 1620, 1507, 1449, 1408, 1351, 1297, 1241.

The compounds and methods of the appended claims are not limited in scope
15 by the specific compounds and methods described herein, which are intended as
illustrations of a few aspects of the claims, and any compounds and methods that are
functionally equivalent are within the scope of this disclosure. Various modifications
of the compounds and methods in addition to those shown and described herein are
intended to fall within the scope of the appended claims. Further, while only certain
20 representative compounds, methods, and aspects of these compounds and methods are
specifically described, other compounds and methods are intended to fall within the
scope of the appended claims. Thus a combination of steps, elements, components, or
constituents may be explicitly mentioned herein; however, all other combinations of
steps, elements, components, and constituents are included, even though not explicitly
25 stated.

WHAT IS CLAIMED IS:

1. A compound of the following formula:



or a pharmaceutically acceptable salt thereof, wherein:

R¹ and R³ are each independently selected from hydrogen, substituted or unsubstituted hydrocarbon, substituted or unsubstituted hetero-hydrocarbon, halogen, or an electron donating group;

R² and R⁴ are each independently selected from hydrogen, substituted or unsubstituted hydrocarbon, substituted or unsubstituted hetero-hydrocarbon, halogen, an electron donating group, or an electron withdrawing group;

R⁵ and R⁶ are each independently selected from hydrogen, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, wherein R⁵ and R⁶ are not simultaneously hydrogen;

L¹ is selected from a substituted or unsubstituted hydrocarbon or substituted or unsubstituted hetero-hydrocarbon;

L² is absent or selected from a substituted or unsubstituted hydrocarbon or substituted or unsubstituted hetero-hydrocarbon;

A¹ is a therapeutic agent; and

A² is hydrogen or a therapeutic agent.

2. The compound of claim 1, wherein R¹ and R² are combined to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkane, substituted or unsubstituted cycloalkene, substituted or unsubstituted cycloalkyne, substituted or unsubstituted heterocycloalkane, substituted or unsubstituted heterocycloalkene, or substituted or unsubstituted heterocycloalkyne.

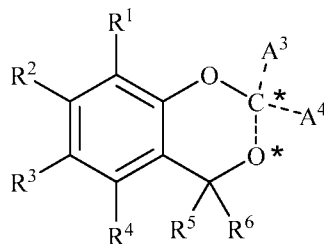
3. The compound of claim 1, wherein R^2 and R^3 are combined to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkane, substituted or unsubstituted cycloalkene, substituted or unsubstituted cycloalkyne, substituted or unsubstituted heterocycloalkane, substituted or unsubstituted heterocycloalkene, or substituted or unsubstituted heterocycloalkyne.
4. The compound of claim 1, wherein R^3 and R^4 are combined to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkane, substituted or unsubstituted cycloalkene, substituted or unsubstituted cycloalkyne, substituted or unsubstituted heterocycloalkane, substituted or unsubstituted heterocycloalkene, or substituted or unsubstituted heterocycloalkyne.
5. The compound of claim 1, wherein R^1 or R^3 is substituted or unsubstituted amino or alkoxy.
6. The compound of claim 1, wherein R^1 or R^3 is methoxy, dimethylamino, PEG, or
- Chemical structure showing a PEG group attached to a triazole ring, which is linked to a butyl chain ending in a dimethylamino group.
7. The compound of claim 6, wherein the PEG has a molecular weight greater than about 1,000 Daltons.
8. The compound of claim 7, wherein the PEG has a molecular weight greater than about 10,000 Daltons.
9. The compound of any of claims 6-8, wherein the PEG is substituted.
10. The compound of claim 9, wherein the PEG is mPEG.
11. The compound of claim 1, wherein R^2 and R^4 are each hydrogen.
12. The compound of claim 1, wherein R^5 and R^6 are each phenyl.
13. The compound of claim 1, wherein the therapeutic agent is a cancer therapeutic agent.

14. The compound of claim 13, wherein the cancer therapeutic agent is selected from the group consisting of calicheamicins and derivatives thereof, esperimicins and derivatives thereof, FR-900482/FR-66979 and derivatives thereof, active metabolites of oxazaphosphorine anticancer drugs and derivatives thereof, acrolein and derivatives thereof, benzaldehyde and derivatives thereof, and isochrysohermidin and derivatives thereof.

15. The compound of claim 14, wherein the cancer therapeutic agent is selected from phosphoramidate, isophosphoramidate, cyclophosphamide, ifosfamide, and trofosfamide.

16. A composition, comprising a compound of any one of claims 1-15 and a pharmaceutically acceptable carrier.

17. A method of delivering a therapeutic agent to a selected area in a subject, comprising administering to the subject an effective amount of a compound of the following formula:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^3 are each independently selected from hydrogen, substituted or unsubstituted hydrocarbon, substituted or unsubstituted hetero-hydrocarbon, halogen, or an electron donating group;

R^2 and R^4 are each independently selected from hydrogen, substituted or unsubstituted hydrocarbon, substituted or unsubstituted hetero-hydrocarbon, halogen, an electron donating group, or an electron withdrawing group;

R^5 and R^6 are each independently selected from hydrogen, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, wherein R^5 and R^6 are not simultaneously hydrogen;

$A^3(C^*-O^*)A^4$ is one or more therapeutic agents or pro-therapeutic agents containing a carbonyl group, wherein C^*-O^* is the carbonyl group of the one or more therapeutic agents or pro-therapeutic agents containing a carbonyl group; and

transmitting light to the selected area of the subject.

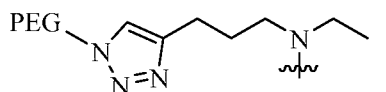
18. The method of claim 17, wherein R^1 and R^2 are combined to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkane, substituted or unsubstituted cycloalkene, substituted or unsubstituted cycloalkyne, substituted or unsubstituted heterocycloalkane, substituted or unsubstituted heterocycloalkene, or substituted or unsubstituted heterocycloalkyne.

19. The method of claim 17, wherein R^2 and R^3 are combined to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkane, substituted or unsubstituted cycloalkene, substituted or unsubstituted cycloalkyne, substituted or unsubstituted heterocycloalkane, substituted or unsubstituted heterocycloalkene, or substituted or unsubstituted heterocycloalkyne.

20. The method of claim 17, wherein R³ and R⁴ are combined to form a substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkane, substituted or unsubstituted cycloalkene, substituted or unsubstituted cycloalkyne, substituted or unsubstituted heterocycloalkane, substituted or unsubstituted heterocycloalkene, or substituted or unsubstituted heterocycloalkyne.

21. The method of claim 17, wherein R¹ or R³ is substituted or unsubstituted amino or alkoxy.

22. The method of claim 17, wherein R¹ or R³ is methoxy, dimethylamino, PEG, or



23. The method of claim 22, wherein the PEG has a molecular weight greater than about 1,000 Daltons.

24. The method of claim 23, wherein the PEG has a molecular weight greater than about 10,000 Daltons.

25. The method of any of claims 22-24, wherein the PEG is substituted.

26. The method of claim 25, wherein the PEG is mPEG.

27. The method of claim 17, wherein R² and R⁴ are each hydrogen.

28. The method of claim 17, wherein R⁵ and R⁶ are each phenyl.

29. The method of claim 17, wherein A³(C^{*}-O^{*})A⁴ is one therapeutic agent.

30. The method of claim 17, wherein A³ and A⁴ are each independently therapeutic agents.

31. The method of claim 17, wherein the therapeutic agent is a cancer therapeutic agent.

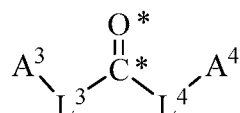
32. The method of claim 17, wherein the pro-therapeutic agent includes a cancer therapeutic agent.

33. The method of claim 31 or 32, wherein the cancer therapeutic agent is selected from the group consisting of calicheamicins and derivatives thereof, esperimicins and derivatives thereof, FR-900482/FR-66979 and derivatives thereof, active metabolites of oxazaphosphorine anticancer drugs and derivatives thereof, acrolein and derivatives thereof, benzaldehyde and derivatives thereof, and isochrysohermidin and derivatives thereof.

34. The method of claim 33, wherein the cancer therapeutic agent is selected from phosphoramidate, isophosphoramidate, cyclophosphamide, ifosfamide, and trofosfamide.

35. The method of claim 17, wherein the pro-therapeutic agent containing a carbonyl group is $-(CH_2)_2$ -phosphoramidate mustard or $-(CH_2)_2$ -isophosphoramidate mustard.

36. The method of claim 17, wherein the pro-therapeutic agent containing a carbonyl group that forms $A^3(C^*-O^*)A^4$ has the following formula:



wherein L^3 and L^4 are each independently selected from substituted or unsubstituted hydrocarbon or substituted or unsubstituted hetero-hydrocarbon .

37. The method of claim 17, wherein the compound is delivered systemically.

38. The method of claim 17, wherein the light is ultraviolet, visible, or infrared light.

39. The method of claim 38, wherein the ultraviolet light is UVA or UVB.

40. The method of any of claims 17-39, wherein an optical fiber or optical probe is used to transmit the light.

41. The method of claim 40, wherein the optical fiber or optical probe is housed in a needle and the needle is positioned near a selected area with cancer.

42. The method of claim 41, wherein the optical fiber or optical probe is guided to the selected area using CT scan or MRI.