Title: OPTICAL MONITORING OF LEUKEMIA

Abstract: The invention relates to compounds, methods and devices for targeting of optical agents to leukemia affected cells or tissues in a subject. Compounds of the invention include conjugates and bioconjugates comprising a targeting moiety and an optical agent. In an aspect of the invention, the targeting moiety is an amino acid sequence which preferentially binds to leukemia cells. In another aspect of the invention, the optical agent is an imaging agent derived from a pyrazine, azulenyl, or azaaazulenyl dye. In a further aspect of the invention, the optical agent may comprise a photosensitizer. Some methods of the invention relate to administration, activation, and/or monitoring of compounds of the invention. In an aspect of the invention, a device includes an electromagnetic radiation source, collector, and detector.
OPTICAL MONITORING OF LEUKEMIA

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit and priority of United States Provisional Patent Application No. 61/241,611 filed on September 11, 2009 entitled Optical Monitoring of Leukemia”, which is hereby incorporated by reference in its entirety.

BACKGROUND

[002] Optical agents currently play a central role in a large number of in vivo, in vitro and ex vivo clinical procedures including important diagnostic and therapeutic procedures. Photodiagnostic and phototherapeutic agents, for example, include a class of molecules capable of absorbing, emitting, or scattering electromagnetic radiation applied to a biological material, particularly in the visible and near infrared regions of the electromagnetic spectrum. This property of optical agents is used in a range of biomedical applications for visualizing, imaging or otherwise characterizing biological materials and/or achieving a desired therapeutic outcome. Recent developments in targeted administration and delivery of optical agents, and advanced systems and methods for applying and detecting electromagnetic radiation in biological environments has considerably expanded the applicability and effectiveness of optical agents for clinical applications.

[003] Important applications of optical agents that absorb and/or emit in the visible and near-infrared (NIR) region of the electromagnetic spectrum include their use in biomedical imaging and visualization. For example, compounds absorbing and/or emitting light in these regions of the electromagnetic spectrum currently are useful for optical tomography, optoacoustic tomography, optical coherence tomography, confocal scanning laser tomography, optical coherence tomography, and fluorescence endoscopy. These techniques have emerged as essential techniques for imaging and visualizing biological processes at the organ, cellular and subcellular (e.g., molecular) levels. Biomedical images are generated, for example, by detecting electromagnetic radiation, nuclear radiation, acoustic waves, electrical fields, and/or magnetic fields transmitted, emitted and/or scattered by components of a biological sample. Modulation of the energy or intensity of the applied radiation yields patterns of transmitted, scattered and/or emitted radiation, acoustic waves, electrical fields or magnetic fields that contain useful anatomical, physiological, and/or biochemical information. A number of applications of biomedical imaging have matured into robust, widely used clinical techniques including planar projection and tomographic X-ray imaging, magnetic resonance imaging, ultrasound imaging, and gamma ray imaging.

[004] Established optical imaging and visualization techniques are based on monitoring spatial variations in a variety of optical parameters including the intensities, polarization states, and frequencies of transmitted, reflected, and emitted electromagnetic radiation. Given that many
biological materials of interest are incompatible with ultraviolet light, research is currently directed to developing and enhancing imaging techniques using visible and near infrared (NIR) radiation (from about 400 nm to about 900 nm). In particular, NIR light (700 nm to 900 nm) is useful for visualizing and imaging deeper regions than visible light because electromagnetic radiation of this wavelength range is capable of substantial penetration (e.g., up to four centimeters) in a range of biological media. Optical imaging and visualization using optical agents has potential to provide a less invasive and safer imaging technology, as compared to X-ray, and other widely used nuclear medicine technologies. Applications of optical imaging for diagnosis and monitoring of the onset, progression and treatment of various disease conditions, including cancer, are well established. (See, e.g., D. A. Benaron and D. K. Stevenson, Optical time-of-flight and absorbance imaging of biologic media, Science, 1993, 259, pp. 1463-1466; R. F. Potter (Series Editor), Medical optical tomography: functional imaging and monitoring, SPIE Optical Engineering Press, Bellingham, 1993; G. J. Tearney et al., In vivo endoscopic optical biopsy with optical coherence tomography, Science, 1997, 276, pp. 2037-2039; B. J. Tromberg et al., Non-invasive measurements of breast tissue optical properties using frequency-domain photon migration, Phil. Trans. Royal Society London B, 1997, 352, pp. 661-668; S. Fantini et al., Assessment of the size, position, and optical properties of breast tumors in vivo by noninvasive optical methods, Appl. Opt, 1998, 37, pp. 1982-1989; A. Pelegrin et al., Photoimmunodiagnosis with antibody-fluorescein conjugates: in vitro and in vivo preclinical studies, J. Cell Pharmacol., 1992, 3, pp. 141-145).

[005] Optical agents for in vivo and in vitro biomedical imaging, anatomical visualization and monitoring organ function are described in International Patent Publication WO/2008/108941; U.S. Patent Nos. 5,672,333; 5,698,397; 6,167,297; 6,228,344; 6,748,259; 6,838,074; 7,011,817; 7,128,896, and 7,201,892. In this context, optical imaging agents are commonly used for enhancing signal-to-noise and resolution of optical images and extending these techniques to a wider range of biological settings and media. In addition, use of optical imaging agents having specific molecular recognition and/or tissue targeting functionality has also been demonstrated as effective for identifying, differentiating and characterizing discrete components of a biological sample at the organ, tissue, cellular, and molecular levels. Further, optical agents have been developed as tracers for real time monitoring of physiological function in a patient, including fluorescence-based monitoring of renal function. (See International Patent Publication WO/US2007/149478). Given their recognized utility, considerable research continues to be directed toward developing improved optical agents for biomedical imaging and visualization.

[006] In addition to their important role in biomedical imaging and visualization, optical agents capable of absorption in the visible and NIR regions have also been extensively developed for clinical applications for phototherapy. The benefits of phototherapy using optical agents are widely acknowledged as this technique has the potential to provide efficacy comparable to radiotherapy, while entirely avoiding exposure of non-target organs and tissue to harmful ionizing radiation. Photodynamic therapy (PDT), in particular, has been used effectively for localized superficial or

[007] Phototherapy is carried out by administration and delivery of a photosensitizer to a therapeutic target tissue (e.g., tumor, lesion, organ, etc.) followed by photoactivation of the photosensitizer by exposure to applied electromagnetic radiation. Phototherapeutic procedures require photosensitizers that are relatively chemically inert and become activated only upon irradiation with light of an appropriate wavelength. Selective tissue injury can be induced with light when photosensitizers bind to the target tissues, either directly or through attachment to a bioactive carrier or targeting moiety. Photosensitizers essentially operate via two different pathways, classified as Types 1 and 2. A primary distinction between these classes of photosensitizers is that the Type 1 process operates via direct energy or electron transfer from the photosensitizer to the cellular components thereby inducing cell death, whereas the Type 2 process involves first the conversion of singlet oxygen from the triplet oxygen found in the cellular environment followed by either direct reaction of singlet oxygen with the cellular components or further generating secondary reactive species (e.g. peroxides, hydroxyl radical, etc.) which will induce cell death.
The Type 1 mechanism proceeds via a multistep process involving activation of the photosensitizer by absorption of electromagnetic radiation followed by direct interaction of the activated photosensitizer, or reactive intermediates derived from the photosensitizer, with the target tissue, for example via energy transfer, electron transfer or reaction with reactive species (e.g., radicals, ions, nitrene, carbene etc.) resulting in tissue damage. The Type 1 mechanism can be schematically represented by the following sequence of reactions:

\[
\text{PHOTOSENSITIZER} \xrightarrow{h\nu} \text{PHOTOSENSITIZER}^\cdot \xrightarrow{} \text{REACTIVE INTERMEDIATES} \xrightarrow{} \text{CELL DEATH} \text{ Collision with Cell Components}
\]

wherein \( h\nu \) indicates applied electromagnetic radiation and \((\text{PHOTOSENSITIZER})^\cdot \) indicates excited state of the photosensitizer. The Type 2 mechanism proceeds via a three-step process involving activation of the photosensitizer by absorption of electromagnetic radiation followed by energy transfer from the activated photosensitizer to oxygen molecules in the environment of the target tissue. This energy transfer process generates excited state oxygen \((^1O_2)\) which subsequently interacts with the target tissue so as to cause tissue damage. The Type 2 mechanism can be schematically represented by the following sequence of reactions:

\[
\text{PHOTOSENSITIZER} \xrightarrow{h\nu} \text{PHOTOSENSITIZER}^\cdot \xrightarrow{3\phi} ^{1}O_2 \text{(Singlet Oxygen)} \xrightarrow{} H_2O \text{ Collision with Cell Components} \xrightarrow{} \text{CELL DEATH} \text{ REACTIVE OXYGEN SPECIES}
\]

wherein \( h\nu \) indicates applied electromagnetic radiation, \((\text{PHOTOSENSITIZER})^\cdot \) indicates photoactivated photosensitizer, \(^3O_2\) is ground state triplet oxygen, and \(^1O_2\) is excited state singlet oxygen.

The biological basis of tissue injury brought about by tumor phototherapeutic agents has been the subject of intensive study. Various biochemical mechanisms for tissue damage have been postulated, which include the following: a) cancer cells up-regulate the expression of low density lipoprotein (LDL) receptors, and phototherapy (PDT) agents bind to LDL and albumin selectively; (b) porphyrin-like substances are selectively taken up by proliferative neovasculature; (c) tumors often contain increased number of lipid bodies and are thus able to bind to hydrophobic photosensitizers; (d) a combination of "leaky" tumor vasculature and reduced lymphatic drainage causes porphyrin accumulation referred to as "EPR" (enhanced permeability and retention) effect;
(e) tumor cells may have increased capabilities for phagocytosis or pinocytosis of porphyrin aggregates; (f) tumor associated macrophages may be largely responsible for the concentration of photosensitizers in tumors; and (g) cancer cells may undergo apoptosis induced by photosensitizers. Among these mechanisms, (f) and (g) are the most general and, of these two alternatives, there is a general consensus that (f) is the most likely mechanism by which the phototherapeutic effect of porphyrin-like compounds is induced.

[011] Much of the research in the past several decades has focused on developing phototherapeutic agents based on the Type 2 (PDT) mechanism. Surprisingly, there has been considerably less attention devoted to Type 1 phototherapeutic agents despite the fact that there are numerous classes of compounds that could potentially be useful for phototherapy that function via this mechanism. Unlike Type 2, the Type 1 process does not require oxygen; and hence Type 1 photosensitizers are expected to be potentially more effective than Type 2 photosensitizers under hypoxic environments typically found in solid tumors. Second, the Type 1 mechanism involves two steps (photoexcitation and direct energy transfer), whereas the Type 2 mechanism involves three steps (photoexcitation, singlet oxygen generation, and energy transfer). Further, studies have recently shown that production of high levels of reactive oxygen species can induce an anti-inflammatory response, which may result in blood vessels to become more "leaky," thereby increasing the risk of metastasis (Hasan et al.). Targeted Type 1 photosensitizers, by their very nature, are not expected to produce reactive oxygen species; rather, the reactive species produced by these photosensitizers will immediately react with the cellular component at the binding site and trigger cell death. Type 2 phototherapeutic agents, however, do have certain advantages over Type 1 agents. For example, Type 2 agents can potentially be catalytic, i.e., the Type 2 photosensitizer is regenerated once the energy transfer to the oxygen has taken place. In contrast, Type 1 process would generally be expected to require stoichiometric amounts of the photosensitizer in some clinical settings. Table B1 provides a summary of the attributes of Type 1 and Type 2 phototherapeutic agents. Given these attributes, it is clear that development of safe and effective Type 1 phototherapeutic agents would be useful to complement the existing therapeutic approaches provided by Type 2 agents, and to enhance the therapeutic portfolio available for clinicians.

**Table B1 - Comparison between Type 1 and Type 2 processes for phototherapy.**

<table>
<thead>
<tr>
<th>TYPE 1 PROCESS</th>
<th>TYPE 2 PROCESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two-step process.</td>
<td>Three-step process.</td>
</tr>
<tr>
<td>Not well explored.</td>
<td>Very well studied.</td>
</tr>
<tr>
<td>Light of any wavelength can be used.</td>
<td>Requires red light for optimal performance.</td>
</tr>
<tr>
<td>Does not require oxygen.</td>
<td>Requires oxygen.</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Large classes of compounds.</td>
<td>Limited classes of compounds.</td>
</tr>
<tr>
<td>Stoichiometric.</td>
<td>Potentially catalytic.</td>
</tr>
<tr>
<td>Intramolecular energy transfer to generate reactive species.</td>
<td>Intermolecular energy transfer to generate reactive oxygen species.</td>
</tr>
<tr>
<td><strong>No products believed to be on the market.</strong></td>
<td>Two products believed to be in use.</td>
</tr>
</tbody>
</table>

[012] Specific optical, chemical and pharmacokinetic properties of optical agents are necessary for their effective use in Type 1 and Type 2 phototherapeutic applications. For example, optical agents for these applications preferably have strong absorption in the visible or NIR regions, and also exhibit low systemic toxicity, low mutagenicity, and rapid clearance from the blood stream. These optical agents must also be compatible with effective administration and delivery to the target tissue, for example by having reasonable solubilities and a low tendency for aggregation in solution. Upon excitation by absorption of visible and NIR electromagnetic radiation, optical agents for Type 1 and 2 phototherapy preferably provide large yields of singlet oxygen (Type 2) or other reactive species, such as free radicals or ions, capable of causing local tissue damage. Both Type 1 and Type 2 photosensitizers typically undergo photoactivation followed by intersystem crossing to their lowest triplet excited state, and therefore, a relatively long triplet lifetime is usually beneficial for providing effective tissue damage. Other useful properties of optical agents for these applications include chemical inertness and stability, insensitivity of optical properties to changes in pH, and compatibility with conjugation to ligands providing targeted delivery via molecular recognition functionality. Multifunctional optical agents have also been developed for phototherapy that are capable of providing both imaging and visual functionality upon excitation at a first range of wavelengths and phototherapeutic functionality upon excitation at a second range of wavelength. (See, US Patent No. 7,235,685 and International Patent Publication WO/2007/1 06436).

[013] Optical agents for phototherapeutic applications preferably exhibit a high degree of selectivity for the target tissue. Selectivity provided by optical agents facilitates effective delivery to a target tissue of interest and provides a means of differentiating different tissue classes during therapy. Selective tissue injury can be induced with light when photosensitizers bind to the target tissues either directly, as in the case of Photofrin, or through attachment to a bioactive carrier, or through in situ biochemical synthesis of the photosensitizer in localized area, as in the case of 2-aminolevulinic acid, which is an intermediate in the biosynthesis of porphyrin. Previous studies have shown that certain dyes localize in tumors and serve as a powerful probe for the detection and treatment of small cancers. (D. A. Belinier et al., Murine pharmacokinetics and antitumor
efficacy of the photodynamic sensitizer 2-[[hexyloxyethyl]-2-devinyl pyropheophorbide-a, J. Photochem. Photobiol., 1993, 20, pp. 55-61; G. A. Wagnieres et al., In vivo fluorescence spectroscopy and imaging for oncological applications, Photochem. Photobiol., 1998, 68, pp. 603-632; J. S. Reynolds et al., Imaging of spontaneous canine mammary tumors using fluorescent contrast agents, Photochem. Photobiol., 1999, 70, pp. 87-94). It is generally recognized, however, that many of these dyes do not localize preferentially in malignant tissues. A number of strategies have been developed for imparting selectivity and/or targeting functionality by incorporation of a molecular recognition component in the optical agent. For example, targeting of fluorescent dyes to tumors has been demonstrated by us and others using dye conjugates with antibodies and peptides for diagnostic imaging of tumors. (See, Achilefu et al., Novel receptor-targeted fluorescent contrast agents for in vivo imaging of tumors, Investigative Radiology, 2000, 35, pp. 479-485; Ballou et al., Tumor labeling in vivo using cyanine conjugated monoclonal antibodies, Cancer Immunology and Immunotherapy, 1995, 41, pp. 257-263; and Licha et al., New contrast agent for optical imaging: acid cleavable conjugates of cyanine dyes with biomolecules, in Biomedical Imaging: Reporters, Dyes and Instrumentation, Proceedings of SPIE, 1999, 3600, pp. 29-35). Therefore, receptor-target mediated phototherapeutic agents provide a promising pathway for achieving site selective activation at various target tissues.

[014] Selectivity for a target tissue may be achieved through a bioconjugate or integrated bioconjugate approach. In the bioconjugate approach, a photosensitizer or imaging moiety is attached to a targeting moiety. In the integrated bioconjugate approach, a photosensitizer or imaging moiety replaces a portion of the targeting moiety. The bioconjugate or integrated bioconjugate may be designed so as to minimize any disruption to the selectivity of the targeting moiety. Targeting moieties may selectively bind to preferred target cell types, tissues, or organs in a subject.

[015] For both photodiagnostic and phototherapeutic applications, optical agents preferably exhibit a high degree of selectivity for the target tissue. Selectivity provided by optical agents facilitates effective delivery to a target tissue of interest and provides a means of differentiating different tissue classes during imaging, visualization and therapy. There is a considerable need for developing optical agents for biomedical applications that have high absorption/emission properties in the visible and NIR regions, high photostability, insensitivity to pH, and wavelength tunability, as well as selectivity for the target tissue.

**SUMMARY**

[016] The invention relates to compounds, methods and devices for targeting of optical agents to leukemia affected cells or tissues in a subject. Compounds of the invention include conjugates and bioconjugates comprising a targeting moiety and an optical agent. In an aspect of the invention, the targeting moiety is an amino acid sequence which preferentially binds to leukemia cells. In another aspect of the invention, the optical agent is an imaging agent derived from a
pyrazine, azulene, or azaazulene dye. In a further aspect of the invention, the optical agent may comprise a photosensitizer. In some aspects, the methods of the invention relate to use, administration, activation, and/or monitoring of compounds of the invention. In an aspect, a compound of the invention is administered to a subject, allowed time to target a leukemia affected cell or tissue in the subject, and the fluorescence intensity of the compound in the subject is measured. In some aspects, devices of the invention include a means for activation, detection and monitoring of compounds of the invention. In an aspect of the invention, a device includes an electromagnetic radiation source, collector, and detector.

[017] In embodiments, compounds of the invention have formulae (FX1) or (FX2):

\[
\text{FX1 or FX2, wherein: } G^4 \text{ is } -N-, -C(B)-, \text{ or } -C(R^4)--; G^5 \text{ is } -N-, -C(B)-, \text{ or } -C(R^5)--; G^6 \text{ is } -N-, -C(B)-, \text{ or } -C(R^6)--; G^7 \text{ is } -N-, -C(B)-, \text{ or } -C(R^7)--; G^8 \text{ is } -N-, -C(B)-, \text{ or } -C(R^8)--; G^9 \text{ is } -N-, -C(B)-, \text{ or } -C(R^9)--; G^{10} \text{ is } -N-, -C(B)-, \text{ or } -C(R^{10})--; G^{11} \text{ is } -N-, -C(B)-, \text{ or } -C(R^{11})--; \text{ wherein at most one of } G^4 \text{ to } G^{11} \text{ is } -N-; \text{ and wherein at least one of } G^4 \text{ to } G^{11} \text{ is } -C(B)-; \text{ each } B \text{ is independently } -\text{CO-} \text{ or } -\text{NR }^{20-}; \text{ each of } R^1 \text{ to } R^{11} \text{ is independently hydrogen, } c_1-c_6 \text{ alkyl, } c_3-c_6 \text{ cycloalkyl, } C_5-C_{10} \text{ aryl, } C_2-C_6 \text{ alkenyl, } C_2-C_6 \text{ alkynyl, } C_5-C_{10} \text{ alkyaryl, } -\text{OR }^{21-}, -\text{SR }^{22-}, -\text{NR }^{23-}R^{24-}, -\text{CONR }^{25-}R^{26-}, -\text{C(O)R }^{27-}, -\text{SOR }^{28-}, -\text{CN, } -\text{NO }_2, -\text{COR }^{29-}, -\text{SO }_2R^{30-}, -\text{SO }_2\text{NR }^{31}R^{32-}, -\text{NR }^{46}\text{COR }^{47-}, -\text{CONR }^{48}(\text{CH }_2)_a\text{OR }^{49-}, \text{ halo, trihalomethyl, or } -\text{PS }_1; \text{ each } PS_1 \text{ is independently a photosensitizer corresponding to a cyanine, an indocyanine, a phthalocyanine, a rhodamine, a phenoxazine, a phenothiazine, a phenoselenazine, a fluorescein, a porphyrin, a benzoporphyrin, a squaraine, a corrin, a croconio, an azo dye, a methine dye, an indolenium dye, a halogen, an anthracylene, an azide, a } C_1-C_{20} \text{ peroxyalkyl, a } C_5-C_{20} \text{ peroxyaryl, a } C_1-C_{20} \text{ sulfenatoalkyl, a } C_5-C_{20} \text{ sulfenatoaryl, a naphthalocyanine, a methylene blue, a chalcogenopyrylium analogue, an azo, a diazo, an oxaza, a diaza, a thioxa, or a dioxa group; each } Y \text{ is independently } -\text{NR }^{33}(\text{CH }_2)_a\text{CO }_2-, -\text{NR }^{34}(\text{CH }_2)_a-, -\text{CH }_2(\text{CH }_2)_a-, -\text{NR }^{35}(\text{C}_6\text{H}_4)\text{CO-}, -\text{NR }^{36}(\text{cyclo-C}_6\text{H}_{10})\text{CO-}, -\text{NR }^{37}(\text{CH }_2)_a\text{NR }^{38-}, -\text{NR }^{39}(\text{C}_6\text{H}_4)\text{NR }^{40-}, -\text{NR }^{41}(\text{cyclo-C}_6\text{H}_{10})\text{NR }^{42-}, -\text{NR }^{43-}, -\text{NR }^{44}(\text{CH }_2)_a\text{CONR }^{45-}, 1.4\text{-diazacyclohexyl, 4-carbonylpiperidinyl, 2-carbonylpyrroldinyl, or 3-carbonylpyrroldinyl}; \text{ each } a \text{ is independently an integer selected from the range of 0 to } 10; \text{ each of } R^{10-} \text{ to } R^{49} \text{ is independently hydrogen, } C_1-C_6 \text{ alkyl, } C_3-C_6 \text{ cycloalkyl, } C_5-C_{10} \text{ aryl, or } C_5-C_{10} \text{ heteroaryl}; \text{ each PEPTIDE is independently an amino acid sequence corresponding to } (S)\text{FXaxaLRS (SEQ ID NO:1); } S(-F)\text{FXaxaLRS (SEQ ID NO:1); } S\text{FF(-F)XaxaLRS (SEQ ID NO:1); } S\text{FF(-Xaa)LRS (SEQ ID NO:1); } S\text{FFXaxa(-L)RS (SEQ ID NO:1); } S\text{FFXaxaL (-R)S (SEQ ID NO:1); or } S\text{FFXaxaL(-S) (SEQ ID NO:1); each } S \text{ is an amino acid corresponding to Serine; each } F \text{ is an amino acid corresponding to Phenylalanine; each } Xaa \text{ is an amino acid corresponding to }

8
Tryptophan, Asparagine, or Tyrosine; each L is an amino acid corresponding to Leucine; each R is an amino acid corresponding to Arginine; wherein each Y is attached to the amino acid sequence at the C- or N-terminal end of the amino acid sequence; or each Y is attached to a side chain of any amino acid of the amino acid sequence; or wherein the side chain of any amino acid of the amino acid sequence is replaced by an optical agent corresponding to a pyrazine, azulene, or azaazulene; or wherein the side chain of any amino acid of the amino acid sequence is replaced by Y; and wherein a dash (−) in the amino acid sequence denotes the position in the amino acid sequence at which Y attaches. In a related embodiment, each Y is independently -NR3(CH2)4CO- or -R39(C6H4)NR40-.

[018] In an embodiment a compound of formula (FX1) or (FX2) is provided wherein the side chain of any amino acid of the amino acid sequence is replaced by Y. In an embodiment a compound of formula (FX1) or (FX2) is provided wherein the side chain of any amino acid of the amino acid sequence is replaced by an optical agent corresponding to an azulene or azaazulene. In an embodiment a compound of formula (FX1) or (FX2) is provided wherein Xaa is Tryptophan. In an embodiment a compound of formula (FX1) or (FX2) is provided wherein each Y is attached to the amino acid sequence at the C- or N-terminal end of the amino acid sequence. In an embodiment a compound of formula (FX1) or (FX2) is provided wherein the side chain of any Serine, Phenylalanine, Leucine, or Arginine of the amino acid sequence is replaced by Y. In an embodiment a compound of formula (FX1) or (FX2) is provided wherein the side chain of any Serine, Phenylalanine, Leucine, or Arginine of the amino acid sequence is replaced by an optical agent corresponding to an azulene or azaazulene. In an embodiment a compound of formula (FX1) or (FX2) is provided wherein only one of G4 to G11 is -C(B)-. In an embodiment a compound of formula (FX1) or (FX2) is provided wherein more than one of G4 to G11 is -C(B)-.

[019] In an embodiment, the invention provides compounds of formula (FX1) or (FX2) wherein the side chain of any amino acid of the sequence is replaced by an optical agent derived from a pyrazine, azulene, or azaazulene. In an aspect, the invention provides compounds being any of formula (FX3), (FX4), (FX5), (FX6), (FX7), (FX8), (FX9), (FX10), or (FX11):

![Diagram of compounds](image-url)
In the context of formulae (FX1) and (FX2), reference to compounds wherein the side chain of any amino acid of the amino acid sequence is replaced by an optical agent corresponding to a pyrazine, azulene, or azaazulene references compounds wherein a pyrazine, azulene or azaazulene derived optical agent is directly linked to the backbone of the amino acid sequence. In an embodiment, for example, the invention provides compounds having formula (FX24), (FX25), (FX26), (FX27), (FX28), (FX29), (FX30), (FX31) or (FX32):
or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein \( R^1 \) - \( R^{11} \), \( S \), \( F \), \( X_a \), \( L \) and \( R \) are defined as described in the context of formulae (FX1) and (FX2).

[021] In an embodiment, the invention provides compounds wherein \( Y \) is attached to the amino acid sequence at the N- or C-terminus of the amino acid sequence. In an aspect, the invention provides compounds being any of formula (FX12), (FX13), (FX14), (FX15), (FX16) or (FX17):
In an embodiment, the invention provides compounds being any of formula (FX18), (FX19), or (FX20):
In an embodiment, the invention provides compounds of formulae (FX1) or (FX2) wherein R - R₀, R₄³ - R₄⁵, a, and PEPTIDE are defined as described in the context of formulae (FX1) and (FX2). In an embodiment, the invention provides a compound being of the formula (FX23):
of formulae (FX1) to (FX20) wherein 

\[
\text{PS}^1 \text{ is a group corresponding to a phenoxazine, a phenothiazine, a phenoselenazine, an indolenium dye, an azide, a C1-C20 peroxyalkyl, a C5-C20 peroxyaryl, a C1-C20 sulfenatoalkyl, a C5-C20 sulfenatoaryl, or an diazo, oxaza, diaza, dithia, thioxa, dioxia, or azo dye.}
\]

[025] In an embodiment, the invention provides compounds of formula (FX1), wherein: each Z is \(-\text{CO}^-\); each of \(R^1\) and \(R^2\) is independently \(\text{Cl}-\text{C}_6\) alkyl, \(\text{C}_5-\text{C}_{10}\) aryl, \(\text{C}_5-\text{C}_6\) cycloalkyl, \(\text{C}_5-\text{C}_{10}\) heteroaryl, \(\text{C}_2-\text{C}_6\) alkenyl, \(\text{C}_2-\text{C}_6\) alkyln, \(\text{C}_5-\text{C}_{10}\) alkyln, \(-\text{OR}^{21}\), \(-\text{SR}^{22}\), \(-\text{NR}^{23}\text{R}^{24}\), or \(-\text{PS}^1\); and each \(R^3\) is independently \(-\text{CONR}^{25}\text{R}^{26}\), \(-\text{C}_0\text{2}\text{R}^{27}\), \(-\text{SOR}^{28}\), \(-\text{CN}\), \(-\text{N}_0\text{2}\), \(-\text{COR}^{29}\), \(-\text{S}_0\text{2}\text{R}^{30}\), \(-\text{S}_0\text{2}\text{NR}^{31}\text{R}^{32}\), or \(-\text{PS}^1\).

[026] In an embodiment, the invention provides compounds of formula (FX1), wherein: each Z is \(-\text{NR}^{30}\); each of \(R^1\) and \(R^2\) is independently \(-\text{CONR}^{25}\text{R}^{26}\), \(-\text{C}_0\text{2}\text{R}^{27}\), \(-\text{SOR}^{28}\), \(-\text{CN}\), \(-\text{N}_0\text{2}\), \(-\text{COR}^{29}\), \(-\text{S}_0\text{2}\text{R}^{30}\), \(-\text{S}_0\text{2}\text{NR}^{31}\text{R}^{32}\), or \(-\text{PS}^1\); and each \(R^3\) is independently \(\text{C}_5-\text{C}_6\) alkyl, \(\text{C}_5-\text{C}_{10}\) aryl, \(\text{C}_5-\text{C}_6\) cycloalkyl, \(\text{C}_5-\text{C}_{10}\) heteroaryl, \(\text{C}_2-\text{C}_6\) alkenyl, \(\text{C}_2-\text{C}_6\) alkyln, \(\text{C}_5-\text{C}_{10}\) alkyln, \(-\text{OR}^{21}\), \(-\text{SR}^{22}\), \(-\text{NR}^{23}\text{R}^{24}\), or \(-\text{PS}^1\).

[027] In an embodiment, the invention provides compounds of formula (FX1) or (FX2), wherein at least one of \(R^1\) to \(R^3\) or at least one of \(R^1\) to \(R^3\) is an electron donating group (EDG). In an aspect, the invention provides compounds of formula (FX1) or (FX2), wherein at least one of \(R^1\) to \(R^3\) or at least one of \(R^1\) to \(R^3\) is \(-\text{OR}^{21}\), \(-\text{SR}^{22}\), \(-\text{NR}^{23}\text{R}^{24}\), \(-\text{CONR}^{25}\text{R}^{26}\), or \(-\text{NR}^{46}\text{COR}^{47}\).

[028] In an embodiment, the invention provides compounds of formula (FX1) or (FX2), wherein at least one of \(R^1\) to \(R^3\) or at least one of \(R^1\) to \(R^3\) is an electron withdrawing group (EWG). In an aspect, the invention provides compounds of formula (FX1) or (FX2), wherein at least one of \(R^1\) to \(R^3\) or at least one of \(R^1\) to \(R^3\) is \(-\text{CN}\), \(-\text{C}_0\text{2}\text{R}^{27}\), \(-\text{COR}^{29}\), \(-\text{S}_0\text{2}\text{R}^{30}\), \(-\text{N}_0\text{2}\), or \(-\text{S}_0\text{2}\text{NR}^{31}\text{R}^{32}\).

[029] In an embodiment, the invention provides compounds of formulas (FX1) to (FX20) wherein at least one of \(R^1\) to \(R^3\) or at least one of \(R^1\) to \(R^3\) is \(-\text{OR}^{21}\), \(-\text{SR}^{22}\), \(-\text{NR}^{23}\text{R}^{24}\), \(-\text{CONR}^{25}\text{R}^{26}\), or \(-\text{NR}^{46}\text{COR}^{47}\); and at least one of \(R^1\) to \(R^3\) or at least one of \(R^1\) to \(R^3\) is \(-\text{CN}\), \(-\text{C}_0\text{2}\text{R}^{27}\), \(-\text{COR}^{29}\), \(-\text{S}_0\text{2}\text{R}^{30}\), \(-\text{N}_0\text{2}\), or \(-\text{S}_0\text{2}\text{NR}^{31}\text{R}^{32}\).

[030] In an aspect, the invention provides compounds of formula (FX1) having \(R\) group substituent pairings \((R^1\text{ and } R^2); (R^2\text{ and } R^3); (R^1\text{ and } R^3)\), wherein one of the identified \(R\) groups in the substituent pairings is \(\text{C}_5-\text{C}_6\) alkyl, \(\text{C}_5-\text{C}_6\) cycloalkyl, \(-\text{OR}^{21}\), \(-\text{SR}^{22}\), \(-\text{NR}^{23}\text{R}^{24}\), or \(-\text{NR}^{46}\text{COR}^{47}\) and the other of the identified \(R\) groups in the substituent pairings is halo, trihalomethyl, \(-\text{CN}\), \(-\text{C}_0\text{2}\text{R}^{27}\), \(-\text{CONR}^{25}\text{R}^{26}\), \(-\text{COR}^{29}\), \(-\text{N}_0\text{2}\), \(-\text{SOR}^{28}\), \(-\text{S}_0\text{2}\text{R}^{30}\), or \(-\text{S}_0\text{2}\text{NR}^{31}\text{R}^{32}\).

[031] In an embodiment, the invention provides compounds of formulas (FX1) to (FX32) wherein the compound binds to a leukemia cell. In an aspect, the invention provides compounds of formulas (FX1) to (FX32) wherein the compound binds to a lymphocytic leukemia cell or a myelogenous leukemia cell. In an aspect, the invention provides compounds of formulas (FX1) to (FX32) wherein the compound binds to an acute lymphocytic leukemia cell, a chronic lymphocytic
leukemia cell, an acute myelogenous leukemia cell, or a chronic myelogenous leukemia cell. In an aspect, the invention provides compounds of formulas (FX1) to (FX32) wherein the compound binds to an MO, M1, M2, M3, M4, M4eo, M5, M6, or M7 acute myelogenous leukemia cell. In an aspect, the invention provides compounds of formulas (FX1) to (FX32) wherein the compound binds to an early pre-B, common, pre-B, mature B-cell, pre-T, or mature T-cell acute lymphocytic leukemia cell.

[032] In an embodiment, the invention provides compounds of formulas (FX1) to (FX32) for use in an optical imaging, diagnostic, monitoring and/or therapeutic biomedical procedure. In an aspect, the invention provides compounds of formulas (FX1) to (FX32) for use in an optical imaging, diagnostic, monitoring and/or therapeutic biomedical procedure comprising: administering to a subject a therapeutically or diagnostically effective amount of the compound under conditions sufficient for contacting a target tissue or cell of the subject with the compound; exposing the administered compound to a therapeutically or diagnostically effective amount of electromagnetic radiation; and detecting electromagnetic radiation emitted from the compound in the subject.

[033] In an aspect, the invention provides compounds of formulas (FX1) to (FX32) for use in an optical imaging, diagnostic, monitoring and/or therapeutic biomedical procedure wherein the procedure comprises exposing the administered compound to electromagnetic radiation having wavelengths selected over the range of 350 nanometers to 900 nanometers. In an aspect, the invention provides compounds of formulas (FX1) to (FX32) for use in an optical imaging, diagnostic, monitoring and/or therapeutic biomedical procedure wherein the procedure comprises collecting the electromagnetic radiation emitted from the compound in the subject. In an aspect, the invention provides compounds of formulas (FX1) to (FX32) for use in an optical imaging, diagnostic, monitoring and/or therapeutic biomedical procedure wherein the electromagnetic radiation is collected proximate an ear, hand, head, forehead, or finger of the subject. In an aspect, the invention provides compounds of formulas (FX1) to (FX32) for use in an optical imaging, diagnostic, monitoring and/or therapeutic biomedical procedure wherein exposing the compound administered to the subject to electromagnetic radiation generates a diagnostically effective amount of fluorescence from the compound. In an aspect, the invention provides compounds of formulas (FX1) to (FX32) for use in an optical imaging, diagnostic, monitoring and/or therapeutic biomedical procedure wherein the fluorescence from the compound has wavelengths selected over the range of 500 nanometers to 1300 nanometers. In an aspect, the invention provides compounds of formulas (FX1) to (FX32) for use in an optical imaging, diagnostic, monitoring and/or therapeutic biomedical procedure comprising generating an image of the fluorescence from the compound.

[034] In an aspect, the invention provides compounds of formulas (FX1) to (FX32) for use in an optical imaging, diagnostic, monitoring and/or therapeutic biomedical procedure wherein the compound is targeted to a leukemia cell. In an aspect, the invention provides compounds of formulas (FX1) to (FX32) for use in an optical imaging, diagnostic, monitoring and/or therapeutic
biomedical procedure wherein the compound is targeted to a lymphocytic leukemia cell or a myelogenous leukemia cell. In an aspect, the invention provides compounds of formulas (FX1) to (FX32) for use in an optical imaging, diagnostic, monitoring and/or therapeutic biomedical procedure wherein the compound is targeted to a lymphocytic leukemia cell, a chronic lymphocytic leukemia cell, an acute myelogenous leukemia cell, or a chronic myelogenous leukemia cell. In an aspect, the invention provides compounds of formulas (FX1) to (FX32) for use in an optical imaging, diagnostic, monitoring and/or therapeutic biomedical procedure wherein the compound is targeted to an acute lymphocytic leukemia cell, an acute myelogenous leukemia cell, or a chronic myelogenous leukemia cell. In an aspect, the invention provides compounds of formulas (FX1) to (FX32) for use in an optical imaging, diagnostic, monitoring and/or therapeutic biomedical procedure wherein the compound is targeted to an acute lymphocytic leukemia cell, an acute myelogenous leukemia cell, or a chronic myelogenous leukemia cell. In an aspect, the invention provides compounds of formulas (FX1) to (FX32) for use in an optical imaging, diagnostic, monitoring and/or therapeutic biomedical procedure wherein the compound is targeted to an acute lymphocytic leukemia cell, an acute myelogenous leukemia cell, or a chronic myelogenous leukemia cell.

[035] In an embodiment, the invention provides a device for monitoring leukemia in a subject, the device comprising: an electromagnetic radiation source for exciting an optical agent administered to a subject, wherein the optical agent selectively binds to leukemia cells in the subject; and a detector for detecting electromagnetic radiation from the optical agent bound to the leukemia cells in the subject, wherein the detector monitors the electromagnetic radiation from the optical agent bound to the leukemia cells in the subject.

[036] In an aspect, the invention provides a device for monitoring leukemia in a subject, the device further comprising: an electromagnetic radiation delivery system in optical communication with the electromagnetic radiation source; an electromagnetic radiation collection system in optical communication with the detector; and a data processing system in optical or electronic communication with the detector. In an aspect, the invention provides a device for monitoring leukemia as described herein further comprising a catheter, endoscope, ear clip, hand band, head band, forehead sensor, surface coil, or finger probe. In an embodiment, for example, the processor is a computer. In an embodiment, the processor is a microprocessor. In an embodiment, the detector is a photodiode, photodiode array, photomultiplier tube, photomultiplier tube array, diode, diode array, CMOS detector, or CCD detector.

[037] In an embodiment, the data processing system of the device uses an algorithm to analyze signals from the detector corresponding to detected electromagnetic radiation to provide diagnostic information relating to the onset, progression and/or stage of a disease state of the subject, such as leukemia. In an aspect, the processor evaluates the signals from the detector using an algorithm to provide diagnostic information relating to the onset, progression and/or stage of a disease state of the subject. In an aspect, the algorithm determines a rate of change of the electromagnetic radiation emitted from the subject, compares the rate of change to a reference
value, and outputs and/or displays diagnostic information relating to onset, progression and/or stage of a disease of the subject, such as leukemia. In an aspect, the algorithm determines an intensity, a power, a rate of change of intensity, a rate of change of power, a temporal intensity profile, and/or a temporal power profile of the electromagnetic radiation emitted from the subject.

In a related aspect, the algorithm compares the intensity, power, rate of change of intensity, rate of change of power, temporal intensity profile, and/or temporal power profile of the electromagnetic radiation emitted from the subject to a reference intensity, power, rate of change of intensity, rate of change of power, temporal intensity profile, and/or temporal power profile. In an embodiment, the algorithm integrates the signal from the detector corresponding to the intensity, power, rate of change of intensity, rate of change of power, temporal intensity profile, and/or temporal power profile of the electromagnetic radiation emitted from the subject. In an embodiment, the algorithm determines a baseline intensity, power, rate of change of intensity, rate of change of power, temporal intensity profile, and/or temporal power profile derived from a subject without an optical agent. In an embodiment, the algorithm determines the power, intensity, rate of change of power, and/or rate of change of intensity of the electromagnetic radiation emitted from the subject at a specific time. In an embodiment, the algorithm determines the reference power, intensity, rate of change of power, and/or rate of change of intensity of the electromagnetic radiation emitted from the subject at a specific time.

[038] In an embodiment, the reference intensity, power, rate of change of intensity, rate of change of power, temporal intensity profile, and/or temporal power profile is derived from the subject, for example at a different time, to evaluate the onset, progression and/or stage of a disease state of the subject, for example leukemia. In an embodiment, the reference intensity, power, rate of change of intensity, rate of change of power, temporal intensity profile, and/or temporal power profile is derived from a healthy subject/person or subjects/persons not having a disease condition of interest, such as leukemia, to evaluate the onset, progression and/or stage of a disease state of the subject. In an embodiment, the reference intensity, power, rate of change of intensity, rate of change of power, temporal intensity profile, and/or temporal power profile is derived from a subject/person or subjects/persons having a disease condition of interest, such as leukemia, to evaluate the onset, progression and/or stage of a disease state of the subject.

[039] In an embodiment, the invention provides a device for monitoring leukemia wherein the optical agent administered to the subject binds to lymphocytic leukemia cells or myelogenous leukemia cells. In an aspect, the invention provides a device for monitoring leukemia wherein the optical agent administered to the subject binds to acute lymphocytic leukemia cells, chronic lymphocytic leukemia cells, acute myelogenous leukemia cells, or chronic myelogenous leukemia cells. In a further aspect, the invention provides a device for monitoring leukemia wherein the optical agent administered to the subject binds to M0, M1, M2, M3, M4, M4eo, M5, M6, or M7 acute myelogenous leukemia cells. In another aspect, the invention provides a device for
monitoring leukemia wherein the optical agent administered to the subject binds to early pre-B, common, pre-B, mature B-cell, pre-T, or mature T-cell acute lymphocytic leukemia cells.

[040] In an embodiment, the invention provides a device which monitors leukemia in a subject by providing a detector which detects radiation from the optical agent in the subject. In an aspect, the device monitors progression or a disease stage of leukemia.

[041] In an embodiment, the invention provides a device for monitoring leukemia wherein the electromagnetic radiation emitted from the optical agent in the subject is fluorescence. In an aspect the invention provides a device for monitoring leukemia wherein the fluorescence emitted from the optical agent has wavelengths selected over the range of 350 nanometers to 900 nanometers. In another aspect the invention provides a device for monitoring leukemia wherein an image of the fluorescence from the compound is generated. In an aspect the invention provides a device for monitoring leukemia wherein the electromagnetic radiation source provides electromagnetic radiation of wavelengths selected over the range of 500 nanometers to 950 nanometers.

[042] In an embodiment the invention provides a device for monitoring leukemia in a subject, the device comprising: an electromagnetic radiation source for exciting an optical agent described herein, for example an optical agent of any of formulae (FX1)-(FX32), administered to a subject, wherein the optical agent selectively binds to leukemia cells in the subject; and a detector for detecting electromagnetic radiation from the optical agent bound to the leukemia cells in the subject, wherein the detector monitors the electromagnetic radiation from the optical agent bound to the leukemia cells in the subject as a function of time.

[043] In an embodiment, the invention provides a device which monitors leukemia in a subject by detecting electromagnetic radiation from an optical agent bound to leukemia cells in the subject, wherein the optical agent is a compound being of the formula (FX1) or (FX2):

\[
\text{R}^1 \quad \text{(FX1)} \quad \text{or} \quad \text{R}^1 \quad \text{(FX2)}, \quad \text{wherein: G}^1 \quad \text{is} \quad -\text{N}, \quad -\text{C(B)}, \quad \text{or} \quad -\text{C(R}^4); \quad G^5 \quad \text{is} \quad -\text{N}, \quad -\text{C(B)}, \quad \text{or} \quad -\text{C(R}^5); \quad G^6 \quad \text{is} \quad -\text{N}, \quad -\text{C(B)}, \quad \text{or} \quad -\text{C(R}^6); \quad G^7 \quad \text{is} \quad -\text{N}, \quad -\text{C(B)}, \quad \text{or} \quad -\text{C(R}^7); \quad G^8 \quad \text{is} \quad -\text{N}, \quad -\text{C(B)}, \quad \text{or} \quad -\text{C(R}^8); \quad G^9 \quad \text{is} \quad -\text{N}, \quad -\text{C(B)}, \quad \text{or} \quad -\text{C(R}^9); \quad G^{10} \quad \text{is} \quad -\text{N}, \quad -\text{C(B)}, \quad \text{or} \quad -\text{C(R}^{10}); \quad G_{\text{m}} \quad \text{is} \quad -\text{N}, \quad -\text{C(B)}, \quad \text{or} \quad -\text{C(R}^\text{m}); \quad \text{wherein at most one of G}^4 \quad \text{to G}^{11} \quad \text{is} \quad -\text{N}; \quad \text{and wherein at least one of G}^4 \quad \text{to G}^{11} \quad \text{is} \quad -\text{C(B)}; \quad \text{each B is independently independently -CO- or -NR}^{20}; \quad \text{each of R}^1 \quad \text{to R}^{11} \quad \text{is independently hydrogen}, \quad \text{C}^1-\text{C}^6 \quad \text{alkyl}, \quad \text{C}^3-\text{C}^6 \quad \text{cycloalkyl}, \quad \text{C}^6-\text{C}_{10} \quad \text{aryl}, \quad \text{C}^5-\text{C}_{10} \quad \text{heteroaryl}, \quad \text{C}^2-\text{C}_{6} \quad \text{alkenyl}, \quad \text{C}^2-\text{C}_{6} \quad \text{alkynyl}, \quad \text{C}^6-\text{C}_{10} \quad \text{alkylaryl}, \quad \text{-OR}^{21}, \quad \text{-SR}^{22}, \quad \text{-NR}^{23-24}, \quad \text{-CONR}^{25-26}, \quad \text{-CO} \quad \text{R}^{27}, \quad \text{-SOR}^{28}, \quad \text{-CN}, \quad \text{-NO}^{29}, \quad \text{-COR}^{29}, \quad \text{-S0} \quad \text{R}^{30}, \quad \text{-S0} \quad \text{NR}^{31}, \quad \text{R}^{32}.\
\]

20
NR^4COR^47, -CONR^48(CH_2)_aOR^49, halo, trihalomethyl, or -PS^1; each PS^1 is independently a photosensitizer corresponding to a cyanine, an indocyanine, a phthalocyanine, a rhodamine, a phenoxazine, a phenothiazine, a phenoselenazine, a fluorescein, a porphyrin, a benzoporphyrin, a squaraine, a corrin, a croconio, an azo dye, a methine dye, an indolenium dye, a halogen, an anthraclyline, an azide, a C_1-C_20 peroxalkyl, a C_5-C_20 peroxyaryl, a C_1-C_20 sulenatoalkyl, a C_5-C_20 sulenatoaryl, a naphthalocyanine, a methylene blue, a chalcogenopyrylium analogue, an azo, a diazo, an oxaza, a diaza, a dithia, a thiao, or a dioxa group; each Y is independently -NR^33(CH_2)_aCO_{2-}, -NR^34(CH_2)_a-, -0(CH_2)_aCO-, -0(CH_2)_a2-, -NR^35(C_6H_4)CO-, -NR^36(cyc/o-C_6H_10)CO-, -NR^37(CH_2)_aNR^38-, -0(CH_2)_aO-, -NR^39(C_6H_4)NR^40-, -NR^41(cyc/o-C_6H_10)NR^42-, -NR^43-, -NR^44(CH_2)_aCONR^45-, 1,4-diazacyclopheXy, 4-carbonylpiperidinyl, 2-carbonylpyrrolidinyl, or 3-carbonylpyrrolidinyl; each a is independently an integer selected from the range of 0 to 10; each of R^0 to R^49 is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 cycloalkyl, C_5-C_10 aryl, or C_5-C_10 heteroaryl; each PEPTIDE is independently an amino acid sequence corresponding to (-S)FFXaaLRS (SEQ ID NO:1); (S-F)FXaaLRS (SEQ ID NO:1); SF(-F)XaaLRS (SEQ ID NO:1); SFF(-Xaa)LRS (SEQ ID NO:1); SFFXaa(-L)RS (SEQ ID NO:1); SFFXaaL(-R)S (SEQ ID NO:1); or SFFXaaLRS(-S) (SEQ ID NO:1); each S is an amino acid corresponding to Serine; each F is an amino acid corresponding to Phenylalanine; each Xaa is an amino acid corresponding to Tryptophan, Asparagine, or Tyrosine; each L is an amino acid corresponding to Leucine; each R is an amino acid corresponding to Arginine; wherein each Y is attached to the amino acid sequence at the C- or N-terminal end of the amino acid sequence; or each Y is attached to a side chain of any amino acid of the amino acid sequence; or wherein the side chain of any amino acid of the amino acid sequence is replaced by an optical agent corresponding to a pyrazine, azulene, or azaaazulene; or wherein the side chain of any amino acid of the amino acid sequence is replaced by Y; and wherein a dash (-) in the amino acid sequence denotes the position in the amino acid sequence at which Y attaches. In a related embodiment, each Y is independently -NR^33(CH_2)_aCO- or -R^49(C_6H_4)NR^40-.

[045] Without wishing to be bound by any particular theory, there can be discussion herein of beliefs or understandings of underlying principles or mechanisms relating to the invention. It is recognized that regardless of the ultimate correctness of any explanation or hypothesis, an embodiment of the invention can nonetheless be operative and useful.

**BRIEF DESCRIPTION OF THE FIGURES**

[046] Figure 1 provides a schematic diagram of a leukemia monitoring device of the present invention.

[047] Figure 2 provides a representative plot showing a detection signal from a subject having a leukemia condition.

[048] Figure 3 provides a synthetic scheme for preparation of pyrazine-SFFX_aaLRS (SEQ ID NO:1) conjugates of the present invention.
Figure 4 provides a plot showing the fluorescence from leukemia cells and non-leukemia cells as a function of concentration for the compound of formula (FX23).

STATEMENTS REGARDING CHEMICAL COMPOUNDS AND NOMENCLATURE

Table C1 - Sequence Information

<table>
<thead>
<tr>
<th>ITEM</th>
<th>SEQUENCE INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEQ ID NO:1</td>
<td>Ser-Phe-Phe-Xaa-Leu-Arg-Ser</td>
</tr>
</tbody>
</table>

In a preferred embodiment relating to the aspect of SEQ ID NO:1, Xaa is Trp, Asn, or Tyr. In a related aspect, Xaa is Trp. In a related aspect, Xaa is Asn. In a related aspect, Xaa is Tyr.

In another preferred embodiment relating to the aspect of SEQ ID NO:1, each amino acid of the amino acid sequence is optionally modified or unmodified. In a related aspect, for example, an amino acid of the amino acid sequence is modified to provide a pyrazine, azulene or azaazulene-containing substituent attached to the side chain of the amino acid. In another aspect, an amino acid of the amino acid sequence is modified to provide a pyrazine, azulene or azaazulene-containing substituent which replaces the side chain of the amino acid. In another related aspect, the amino acid sequence is modified to provide a pyrazine, azulene or azaazulene-containing substituent attached to the amino acid sequence at the C- or N-terminal end of the amino acid sequence.

Any sequence listing, including such submitted as an electronic ASCII text file, is expressly incorporated by reference and considered part of the specification herewith.

As used herein, the symbol convention "-X-", wherein X is an atom or functional group, refers generally to a bonding configuration wherein X is bonded to two other adjacent atoms and/or functional groups. In some embodiments, for example, -X- refers to a linking group or spacer group, including linear and branched groups. In some embodiments, -X- refers to an intra-ring member, for example provided in a cycloalkyl group, aryl group, or heteroaryl group. The designation "-X-" does not specify the type of bond (single, double, triple, etc.) that X forms to adjacent atoms and/or functional groups. In the context of formula (FX2), for example, the symbol -N- in the context of G^4-G^{11} refers to azaazulene-containing compounds having an intra-ring nitrogen atom bonded to adjacent intra-ring carbon atoms. In the context of formula (FX2), for example, the symbol -C(B)- in the context of G^4-G^{11} refers to azulene or azaazulene-containing compounds having an intra-ring carbon atom bonded to adjacent intra-ring carbon atoms and also bound to substituent B. In the context of formula (FX2), for example, the symbol -C(R^n)- wherein n is an integer from 4 to 11, in the context of G^4-G^{11} refers to azulene or azaazulene-containing compounds having an intra-ring carbon atom bonded to two adjacent intra-ring carbon atoms and also bound to substituent R^n.
In an embodiment, a composition or compound of the invention is isolated or purified. In an embodiment, an isolated or purified compound can be at least partially isolated or purified as would be understood in the art. In an embodiment, the composition or compound of the invention has a chemical purity of 95%, optionally for some applications 99%, optionally for some applications 99.9%, optionally for some applications 99.99%, and optionally for some applications 99.999% pure.

Many of the molecules disclosed herein contain one or more ionizable groups. Ionizable groups include groups from which a proton can be removed (e.g., -COOH) or added (e.g., amines) or which can be quaternized (e.g., amines). All possible ionic forms of such molecules and salts thereof are intended to be included individually in the disclosure herein. With regard to salts of the compounds herein, one of ordinary skill in the art can select from among a wide variety of available counterions that are appropriate for preparation of salts of the invention for a given application. In specific applications, the selection of a given anion or cation for preparation of a salt can result in increased or decreased solubility of that salt.

The compounds of this invention can contain one or more chiral centers. Accordingly, this invention is intended to include racemic mixtures, diasteromers, enantiomers, tautomers and mixtures enriched in one or more stereoisomer. The scope of the invention as described and claimed encompasses the racemic forms of the compounds as well as the individual enantiomers and non-racemic mixtures thereof.

As used herein, the term "group" may refer to a functional group of a chemical compound. Groups of the present compounds refer to an atom or a collection of atoms that are a part of the compound. Groups of the present compounds may be attached to other atoms of the compound via one or more covalent bonds. Groups may also be characterized with respect to valence state. The present invention includes groups characterized as monovalent, divalent, trivalent, etc. valence states.

As is customary and well known in the art, hydrogen atoms in formulas (FX1) - (FX32) are not always explicitly shown, for example, hydrogen atoms bonded to the carbon atoms of aromatic, heteroaromatic, and alicyclic rings are not always explicitly shown in formulas (FX1) - (FX32). The structures provided herein, for example in the context of the description of formulas (FX1) - (FX32), are intended to convey to one of reasonable skill in the art the chemical composition of compounds of the methods and compositions of the invention, and as will be understood by one of skill in the art, the structures provided do not indicate the specific bond angles between atoms of these compounds.

As used herein, the term "alkylene" refers to a divalent radical derived from an alkyl group as defined herein. Alkylene groups in some embodiments function as attaching and/or spacer groups in the present compositions. Compounds of the invention may have substituted and unsubstituted C1-C20 alkylene, C1-C40 alkylene and C1-C5 alkylene groups.
As used herein, the term "cycloalkylene" refers to a divalent radical derived from a cycloalkyl group as defined herein. Cycloalkyl groups in some embodiments function as attaching and/or spacer groups in the present compositions. Compounds of the invention may have substituted and unsubstituted C1-C20 cycloalkyl, C1-C10 cycloalkyl and C1-C5 cycloalkyl groups.

As used herein, the term "arylene" refers to a divalent radical derived from an aryl group as defined herein. In some embodiments, an arylene is a divalent group derived from an aryl group by removal of hydrogen atoms from two intra-ring carbon atoms of an aromatic ring of the aryl group. Arylene groups in some embodiments function as attaching and/or spacer groups in the present compositions. Arylene groups in some embodiments function as chromophore, fluorophore, aromatic antenna, dye and/or imaging groups in the present compositions. Compounds of the invention include substituted and unsubstituted C1-C30 arylene, C1-C20 arylene, C1-C10 arylene and C1-C5 arylene groups.

As used herein, the term "heteroarylene" refers to a divalent radical derived from a heteroaryl group as defined herein. In some embodiments, a heteroarylene is a divalent group derived from a heteroaryl group by removal of hydrogen atoms from two intra-ring carbon atoms or intra-ring nitrogen atoms of a heteroaromatic or aromatic ring of the heteroaryl group. Heteroarylene groups in some embodiments function as attaching and/or spacer groups in the present compositions. Heteroarylene groups in some embodiments function as chromophore, aromatic antenna, fluorophore, dye and/or imaging groups in the present compositions. Compounds of the invention include substituted and unsubstituted CrC30 heteroarylene, C1-C20 heteroarylene, C1-C10 heteroarylene and C1-C5 heteroarylene groups.

As used herein, the term "cycloalkylene" refers to a divalent radical derived from a cycloalkyl group as defined herein. Cycloalkylene groups in some embodiments function as attaching and/or spacer groups in the present compositions. Compounds of the invention include substituted and unsubstituted C1-C20 cycloalkylene, C1-C10 cycloalkylene and C1-C5 cycloalkylene groups.

As used herein, the term "alkenylen" refers to a divalent radical derived from an alkenyl group as defined herein. Alkenylene groups in some embodiments function as attaching and/or spacer groups in the present compositions. Compounds of the invention include substituted and unsubstituted C1-C20 alkenylene, C1-C10 alkenylene and C1-C5 alkenylene groups.

As used herein, the term "cycoalkenylen" refers to a divalent radical derived from a cycoalkenyl group as defined herein. Cycoalkenylen groups in some embodiments function as attaching and/or spacer groups in the present compositions. Compounds of the invention include substituted and unsubstituted C1-C20 cycoalkenylen, C1-C10 cycoalkenylen and C1-C5 cycoalkenylen groups.

As used herein, the term "alkynylene" refers to a divalent radical derived from an alkynyl group as defined herein. Alkynylene groups in some embodiments function as attaching and/or
spacer groups in the present compositions. Compounds of the invention include substituted and unsubstituted C1-C20 alkynylene, C1-C10 alkynylene and C1-C5 alkynylene groups.

[068] As used herein, the term "halo" refers to a halogen group such as a fluoro (-F), chloro (-Cl), bromo (-Br), or iodo (-I).

[069] The term "heterocyclic" refers to ring structures containing at least one other kind of atom, in addition to carbon, in the ring. Examples of such atoms include nitrogen, oxygen and sulfur. Examples of heterocyclic rings include, but are not limited to, pyrrolidinyl, piperidyl, imidazolidinyl, tetrahydrofuryl, tetrahydrothienyl, furyl, thiienyl, pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrazinyl, indolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridinyl, benzoxadiazolyl, benzothiadiazolyl, triazolyl and tetrazolyl groups.

[070] The term "carbocyclic" refers to ring structures containing only carbon atoms in the ring. Carbon atoms of carbocyclic rings can be bonded to a wide range of other atoms and functional groups.

[071] The term "alicyclic" refers to a ring that is not an aromatic ring. Alicyclic rings include both carbocyclic and heterocyclic rings.

[072] As used herein, the term "alkoxyalkyl" refers to a substituent of the formula alkyl-O-alkyl.

[073] As used herein, the term "polyhydroxyalkyl" refers to a substituent having from 2 to 12 carbon atoms and from 2 to 5 hydroxyl groups, such as the 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl or 2,3,4,5-tetrahydroxypentyl residue.

[074] As used herein, the term "polyalkoxyalkyl" refers to a substituent of the formula alkyl-(alkoxy)n-alkoxy wherein n is an integer from 1 to 10, preferably 1 to 4, and more preferably for some embodiments 1 to 3.

[075] As used herein, the term "allyl" refers to a substituent of the formula -CH₂CH=CH₂.

[076] Amino acids include, for example, glycine, alanine, valine, leucine, isoleucine, methionine, proline, phenylalanine, tryptophan, asparagine, glutamine, glycine, serine, threonine, serine, rhreonine, asparagine, glutamine, tyrosine, cysteine, lysine, arginine, histidine, aspartic acid and glutamic acid. As used herein, reference to "a side chain residue of a natural α-amino acid" specifically includes the side chains of the above-referenced amino acids.

[077] Alkyl groups include straight-chain, branched and cyclic alkyl groups. Alkyl groups include those having from 1 to 30 carbon atoms. The term cycloalkyl refers to an alkyl group having a ring structure. Alkyl groups include small alkyl groups having 1 to 3 carbon atoms. Alkyl groups include medium length alkyl groups having from 4-10 carbon atoms. Alkyl groups include long alkyl groups having more than 10 carbon atoms, particularly those having 10-30 carbon atoms. Cyclic alkyl groups include those having one or more rings. Cycloalkyl groups include those having a 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-member carbon ring and particularly those having a 3-, 4-, 5-, 6-, or 7-
member ring. The carbon rings in cyclic alkyl groups can also carry alkyl groups. Cycloalkyl groups
can include bicyclic and tricyclic alkyl groups. Alkyl groups are optionally substituted. Substituted
alkyl groups include among others those which are substituted with aryl groups, which in turn can
be optionally substituted. Specific alkyl groups include methyl, ethyl, n-propyl, iso-propyl,
cyclopropyl, n-butyl, s-butyl, t-butyl, cyclobutyl, n-pentyl, branched-pentyl, cyclopentyl, n-hexyl,
branched hexyl, azulenyl and cyclohexyl groups, all of which are optionally substituted. Substituted
alkyl groups include fully halogenated or semihalogenated alkyl groups, such as alkyl groups
having one or more hydrogens replaced with one or more fluorine atoms, chlorine atoms, bromine
atoms and/or iodine atoms. Substituted alkyl groups include fully fluorinated or semifluorinated
alkyl groups, such as alkyl groups having one or more hydrogen atoms replaced with one or more
fluorine atoms. An alkoxy group is an alkyl group that has been modified by linkage to oxygen and
can be represented by the formula R-0- and can also be referred to as an alkyl ether group.
Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, butoxy and
heptoxy. Alkoxy groups include substituted alkoxy groups wherein the alko portion of the groups is
substituted as provided herein in connection with the description of alkyl groups. As used herein
MeO- refers to CH3O-.

[078] Alkenyl groups include straight-chain, branched and cyclic alkenyl groups. Alkenyl groups
include those having 1, 2 or more double bonds and those in which two or more of the double
bonds are conjugated double bonds. Alkenyl groups include those having from 2 to 20 carbon
atoms. Alkenyl groups include small alkenyl groups having 2 to 3 carbon atoms. Alkenyl groups
include medium length alkenyl groups having from 4-10 carbon atoms. Alkenyl groups include long
alkenyl groups having more than 10 carbon atoms, particularly those having 10-20 carbon atoms.
Cyclic alkenyl groups include those having one or more rings. Cyclic alkenyl groups include those
in which a double bond is in the ring or in an alkenyl group attached to a ring. Cyclic alkenyl
groups include those having a 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-member carbon ring and particularly
those having a 3-, 4-, 5-, 6- or 7-member ring. The carbon rings in cyclic alkenyl groups can also
carry alkyl groups. Cyclic alkenyl groups can include bicyclic and tricyclic alkyl groups. Alkenyl
groups are optionally substituted. Substituted alkenyl groups include among others those which
are substituted with alkyl or aryl groups, which groups in turn can be optionally substituted.
Specific alkenyl groups include ethenyl, prop-1-enyl, prop-2-enyl, cycloprop-1-enyl, but-1-enyl, but-
2-enyl, cyclobut-1-enyl, cyclobut-2-enyl, pent-1-enyl, pent-2-enyl, branched pentenyl, cyclopent-1-
enyl, hex-1-enyl, branched hexenyl, cyclohexenyl, all of which are optionally substituted.
Substituted alkenyl groups include fully halogenated or semihalogenated alkenyl groups, such as
alkenyl groups having one or more hydrogens replaced with one or more fluorine atoms, chlorine
atoms, bromine atoms and/or iodine atoms. Substituted alkenyl groups include fully fluorinated or
semifluorinated alkenyl groups, such as alkenyl groups having one or more hydrogen atoms
replaced with one or more fluorine atoms.
Aryl groups include groups having one or more 5-, 6- or 7- member aromatic and/or heterocyclic aromatic rings. The term heteroaryl specifically refers to aryl groups having at least one 5-, 6- or 7- member heterocyclic aromatic rings. Aryl groups can contain one or more fused aromatic and heteroaromatic rings or a combination of one or more aromatic or heteroaromatic rings and one or more nonaromatic rings that may be fused or linked via covalent bonds. Heterocyclic aromatic rings can include one or more N, O, or S atoms in the ring. Heterocyclic aromatic rings can include those with one, two or three N atoms, those with one or two O atoms, and those with one or two S atoms, or combinations of one or two or three N, O or S atoms. Aryl groups are optionally substituted. Substituted aryl groups include among others those which are substituted with alkyl or alkenyl groups, which groups in turn can be optionally substituted. Specific aryl groups include phenyl, biphenyl groups, pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrazinyl, indolyl, imidazolyl, oxazolyl, thiazolyl, pyridinyl, benzoaziazolyl, benzothiadiazolyl, azulienyl, azaaazulienyl and naphthyl groups, all of which are optionally substituted. Substituted aryl groups include fully halogenated or semihalogenated aryl groups, such as aryl groups having one or more hydrogens replaced with one or more fluorine atoms, chlorine atoms, bromine atoms and/or iodine atoms. Substituted aryl groups include fully fluorinated or semifluorinated aryl groups, such as aryl groups having one or more hydrogens replaced with one or more fluorine atoms. Aryl groups include, but are not limited to, aromatic group-containing or heterocyclic aromatic group-containing groups corresponding to any one of the following: benzene, naphthalene, naphthoquinone, diphenylmethane, fluorene, anthracene, anthraquinone, phenanthrene, tetracene, tetracenedione, pyridine, quinoline, isoquinoline, indoles, isoindole, oxazole, thiazole, pyrazine, benzimidazole, benzofuran, dibenzofuran, carbazole, acridine, acridone, phenanthridine, thiophene, benzothiophene, dibenzothiophene, xanthene, xanthone, flavone, coumarin, azulene or anthracycline. As used herein, a group corresponding to the groups listed above expressly includes an aromatic or heterocyclic aromatic radical, including monovalent, divalent and polyvalent radicals, of the aromatic and heterocyclic aromatic groups listed herein are provided in a covalently bonded configuration in the compounds of the invention at any suitable point of attachment. In embodiments, aryl groups contain between 5 and 30 carbon atoms. In embodiments, aryl groups contain one aromatic or heteroaromatic six-membered ring and one or more additional five- or six-membered aromatic or heteroaromatic ring. In embodiments, aryl groups contain between five and eighteen carbon atoms in the rings. Aryl groups optionally have one or more aromatic rings or heterocyclic aromatic rings having one or more electron donating groups, electron withdrawing groups and/or targeting ligands provided as substituents.

Arylalkyl groups are alkyl groups substituted with one or more aryl groups wherein the alkyl groups optionally carry additional substituents and the aryl groups are optionally substituted. Specific alkylaryl groups are phenyl-substituted alkyl groups, e.g., phenylmethyl groups. Alkylaryl groups are alternatively described as aryl groups substituted with one or more alkyl groups wherein the alkyl groups optionally carry additional substituents and the aryl groups are optionally
substituted. Specific alkylaryl groups are alkyl-substituted phenyl groups such as methylphenyl. Substituted arylalkyl groups include fully halogenated or semihalogenated arylalkyl groups, such as arylalkyl groups having one or more alkyl and/or aryl groups having one or more hydrogens replaced with one or more fluorine atoms, chlorine atoms, bromine atoms and/or iodine atoms.

[081] As to any of the groups described herein which contain one or more substituents, it is understood that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these compounds. Optional substitution of alkyl groups includes substitution with one or more alkenyl groups, aryl groups or both, wherein the alkenyl groups or aryl groups are optionally substituted. Optional substitution of alkenyl groups includes substitution with one or more alkyl groups, aryl groups, or both, wherein the alkyl groups or aryl groups are optionally substituted. Optional substitution of aryl groups includes substitution of the aryl ring with one or more alkyl groups, alkenyl groups, or both, wherein the alkyl groups or alkenyl groups are optionally substituted.

[082] Optional substituents for any alkyl, alkenyl and aryl group includes substitution with one or more of the following substituents, among others:

- halogen, including fluorine, chlorine, bromine or iodine;
- pseudohalides, including -CN;
- -COOR where R is a hydrogen or an alkyl group or an aryl group and more specifically where R is a methyl, ethyl, propyl, butyl, or phenyl group all of which groups are optionally substituted;
- -COR where R is a hydrogen or an alkyl group or an aryl group and more specifically where R is a methyl, ethyl, propyl, butyl, or phenyl group all of which groups are optionally substituted;
- -CON(R)₂ where each R, independently of each other R, is a hydrogen or an alkyl group or an aryl group and more specifically where R is a methyl, ethyl, propyl, butyl, or phenyl group all of which groups are optionally substituted; and where R and R can form a ring which can contain one or more double bonds and can contain one or more additional carbon atoms;
- -OCON(R)₂ where each R, independently of each other R, is a hydrogen or an alkyl group or an aryl group and more specifically where R is a methyl, ethyl, propyl, butyl, or phenyl group all of which groups are optionally substituted; and where R and R can form a ring which can contain one or more double bonds and can contain one or more additional carbon atoms;
- -N(R)₂ where each R, independently of each other R, is a hydrogen, or an alkyl group, or an acyl group or an aryl group and more specifically where R is a methyl, ethyl, propyl,
butyl, phenyl or acetyl group, all of which are optionally substituted; and where R and R can form a ring which can contain one or more double bonds and can contain one or more additional carbon atoms;

-SR, where R is hydrogen or an alkyl group or an aryl group and more specifically where R is hydrogen, methyl, ethyl, propyl, butyl, or a phenyl group, which are optionally substituted;

-SO \_2R, or -SOR where R is an alkyl group or an aryl group and more specifically where R is a methyl, ethyl, propyl, butyl, or phenyl group, all of which are optionally substituted;

-OCOOR where R is an alkyl group or an aryl group;

-SO \_2N(R)\_2 where each R, independently of each other R, is a hydrogen, or an alkyl group, or an aryl group all of which are optionally substituted and wherein R and R can form a ring which can contain one or more double bonds and can contain one or more additional carbon atoms;

-OR where R is H, an alkyl group, an aryl group, or an acyl group all of which are optionally substituted. In a particular example R can be an acyl yielding -OCOR where R is a hydrogen or an alkyl group or an aryl group and more specifically where R is methyl, ethyl, propyl, butyl, or phenyl groups all of which groups are optionally substituted.

Specific substituted alkyl groups include haloalkyl groups, particularly trihalomethyl groups and specifically trifluoromethyl groups. Specific substituted aryl groups include mono-, di-, tri, tetra- and pentahalo-substituted phenyl groups; mono-, di-, tri-, tetra-, penta-, hexa-, and heptahalo-substituted naphthalene groups; 3- or 4-halo-substituted phenyl groups, 3- or 4-alkyl-substituted phenyl groups, 3- or 4-alkoxy-substituted phenyl groups, 3- or 4-RCO-substituted phenyl, 5- or 6-halo-substituted naphthalene groups. More specifically, substituted aryl groups include acetylyphenyl groups, particularly 4-acetylyphenyl groups; fluoro phenyl groups, particularly 3-fluorophenyl and 4-fluorophenyl groups; chlorophenyl groups, particularly 3-chlorophenyl and 4-chlorophenyl groups; methylphenyl groups, particularly 4-methylphenyl groups; and methoxyphenyl groups, particularly 4-methoxyphenyl groups.

DETAILED DESCRIPTION

Referring to the drawings, like numerals indicate like elements and the same number appearing in more than one drawing refers to the same element. In general the terms and phrases used herein have their art-recognized meaning, which can be found by reference to standard texts, journal references and contexts known to those skilled in the art. The following definitions are provided to clarify their specific use in the context of the invention.

"Amino acid" generally refers to molecules containing both amine and carboxyl functional groups. Amino acids of the present invention may be alpha-amino acids with the general formula H\_2NCHRCOOH, where R is an organic substituent. "Side chain" in the context of the
present invention refers to the R group substituent in the formula \( \text{H}_2\text{NCHRCOOH} \). For alpha amino acids of the present invention, the amino and carboxylate groups are attached to the same carbon atom. The various alpha amino acids of the present invention may differ in which side chain (R group) is attached to their alpha carbon. The side chain can vary in complexity from a hydrogen atom (in glycine) to a methyl group (in alanine) to a large heterocyclic group (in tryptophan). Table 1 provides 3- and 1-letter abbreviations for some common amino acids. A single letter abbreviation refers to the 1-letter abbreviation. Table 1 further provides 1- and 3-letter abbreviations for some ambiguous and unspecified amino acids.

**Table 1 - Common Amino Acids and Their Abbreviations**

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>3-Letter Abbreviation</th>
<th>1-Letter Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine</td>
<td>Ala</td>
<td>A</td>
</tr>
<tr>
<td>Arginine</td>
<td>Arg</td>
<td>R</td>
</tr>
<tr>
<td>Asparagine</td>
<td>Asn</td>
<td>N</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>Asp</td>
<td>D</td>
</tr>
<tr>
<td>Cysteine</td>
<td>Cys</td>
<td>C</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>Glu</td>
<td>E</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Gln</td>
<td>Q</td>
</tr>
<tr>
<td>Glycine</td>
<td>Gly</td>
<td>G</td>
</tr>
<tr>
<td>Histidine</td>
<td>His</td>
<td>H</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Ile</td>
<td>I</td>
</tr>
<tr>
<td>Leucine</td>
<td>Leu</td>
<td>L</td>
</tr>
<tr>
<td>Lysine</td>
<td>Lys</td>
<td>K</td>
</tr>
<tr>
<td>Methionine</td>
<td>Met</td>
<td>M</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>Phe</td>
<td>F</td>
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<td>Proline</td>
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<td>P</td>
</tr>
<tr>
<td>Serine</td>
<td>Ser</td>
<td>S</td>
</tr>
<tr>
<td>Threonine</td>
<td>Thr</td>
<td>T</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Trp</td>
<td>W</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>Tyr</td>
<td>Y</td>
</tr>
</tbody>
</table>
Valine | Val | V
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ambiguous Amino Acids</strong></td>
<td><strong>3-Letter Abbreviation</strong></td>
<td><strong>1-Letter Abbreviation</strong></td>
</tr>
<tr>
<td>Asparagine or aspartic acid</td>
<td>Asx</td>
<td>B</td>
</tr>
<tr>
<td>Glutamine or glutamic acid</td>
<td>Glx</td>
<td>Z</td>
</tr>
<tr>
<td>Leucine or Isoleucine</td>
<td>Xle</td>
<td>J</td>
</tr>
<tr>
<td>Unspecified or unknown amino acid</td>
<td>Xaa</td>
<td>X</td>
</tr>
</tbody>
</table>

[086] The terms "peptide" and "polypeptide" are used synonymously in the present description, and refer to a class of compounds comprising of amino acid residues chemically bonded together by amide bonds (or peptide bonds), regardless of length, functionality, environment, or associated molecule(s). Peptides and polypeptides are polymeric compounds comprising at least two amino acid residues or modified amino acid residues. Modifications can be naturally occurring or non-naturally occurring, such as modifications generated by chemical synthesis. Modifications to amino acids in peptides include, but are not limited to, phosphorylation, glycosylation, lipification, prenylation, sulfonation, hydroxylation, acetylation, methionine oxidation, alkylation, acylation, carbamylation, iodination and the addition of cofactors. Peptides include proteins and further include compositions generated by degradation of proteins, for example by proteolytic digestion. Peptides and polypeptides can be generated by substantially complete digestion or by partial digestion of proteins. Polypeptides comprising 2 to 100 amino acid units, optionally for some embodiments 2 to 50 amino acid units and, optionally for some embodiments 2 to 20 amino acid units can be used as polypeptide targeting ligands in the invention, for example, where the polypeptide preferentially binds to proteins, peptides or other biomolecules expressed, or otherwise generated by, a target tissue, such as a tumor, precancerous tissue, site of inflammation or other lesion. Typically, the polypeptide is at least four amino acid residues in length and can range up to a full-length protein. Peptides of the present invention may act as a targeting moiety and form a bioconjugate with an optically active moiety. Peptides of a bioconjugate of the present invention may connect to an optically active moiety in several different manners. Connection may occur at the C- or N-terminus of the peptide, at a side chain of any amino acid of the peptide, or the optically active moiety may replace the side chain any amino acid of the peptide. In aspects of the present invention, "integrated" or "integration" refers to modification of a peptide by replacement of, or attachment to, a side chain of any amino acid of the peptide. In bioconjugates of the present invention, for example, an optically active moiety is integrated into a targeting peptide moiety. The symbols (-S), (-F), (-X_{aa}), (-R), and (-L) in the context of the present invention refer to the attachment or integration points of an optically active...
moiety to, or into a peptide, where S, F, X$_{aa}$, R and L are the single letter abbreviations corresponding to amino acids of Table 1. In the present invention, the "C-terminus" or "C-terminal end" refers to the end of a peptide which is terminated by a group corresponding to a carboxyl group. In the present invention, the "N-terminus" or "N-terminal end" refers to the end of a peptide which is terminated by a group corresponding to an amine group.

[087] "Protein" refers to a class of compounds comprising one or more polypeptide chains and/or modified polypeptide chains. Proteins can be modified by naturally occurring processes such as post-translational modifications or co-translational modifications. Exemplary post-translational modifications or co-translational modifications include, but are not limited to, phosphorylation, glycosylation, lipidation, prenylation, sulfonation, hydroxylation, acetylation, methionine oxidation, the addition of cofactors, proteolysis, and assembly of proteins into macromolecular complexes. Modification of proteins can also include non-naturally occurring derivatives, analogues and functional mimetics generated by chemical synthesis. Exemplary derivatives include chemical modifications such as alkylation, acylation, carbamylation, halogenation, iodination or any modification that derivatizes the protein.

[088] As used herein, "polynucleotide" and "oligonucleotide" are used interchangeably and refers to a class of compounds composed of nucleic acid residues chemically bonded together. The invention provides optical agents having an oligonucleotide or polynucleotide targeting ligand which comprises a plurality of nucleic acid residues, such as DNA or RNA residues, and/or modified nucleic acid residues that preferentially binds to proteins, peptides or other biomolecules expressed, or otherwise generated by, a target tissue, such as a tumor, precancerous tissue, site of inflammation or other lesion. Modifications to nucleic acid residues can be naturally occurring or non-naturally occurring, such as modifications generated by chemical synthesis. Oligo- or poly-nucleotide targeting ligands include, for example, oligo- or poly-nucleotides comprising 1 to 100 nucleic acid units, optionally for some embodiments 1 to 50 nucleic acid units and, optionally for some embodiments 1 to 20 nucleic acid units. Polypeptide and oligonucleotide include a polymer of at least two nucleotides joined together by phosphodiester bonds and may consist of either ribonucleotides or deoxyribonucleotides.

[089] The term "aptamer" refers to an oligo- or poly-nucleotide or polypeptide that binds to, or otherwise selectively or preferentially associates with, a specific target molecule. For example, the invention provides optical agents having an aptamer targeting ligand that preferentially binds to proteins, peptides or other biomolecules expressed, or otherwise generated by, a target tissue, such as a tumor, precancerous tissue, site of inflammation or other lesion.

[090] "Peptidomimetic" refers to a molecule having activity, including biological activity, that resembles that of a polypeptide or is substantially the same as a polypeptide. Morphine, for example, is a peptidomimetic of endorphin peptide. In some embodiments, a peptidomimetic is a small protein-like polymer designed to mimic the functionality of a peptide. Peptidomimetics useful

[091] Optical agent" generally refers to compositions, preparations, and/or formulations that absorb, emit, or scatter electromagnetic radiation, for example electromagnetic radiation of wavelength in the range of 350 nanometers to 1300 nanometers, within a biologically relevant environment or condition. In some embodiments, optical agents of the present invention, when excited by electromagnetic radiation, undergo emission via fluorescence or phosphorescence pathways. These pathways are useful for diagnostic imaging, visualization, or disease monitoring. Compounds belonging to this class are commonly referred to as Optical imaging agents’ or Optical contrast agents.’ In some other embodiments, optical agents of the present invention absorb electromagnetic radiation and undergo photochemical reactions such as photofragmentation of one or more photolabile bonds to generate reactive intermediates such as nitrenes, carbenes, free radicals, or ions. This process is useful for a wide range of phototherapy applications, for example in the treatment of cells, tumors or other lesions. Compounds belonging to this class are commonly referred to as "photosensitizers." The term "photosensitizer" refers to a phototherapeutic agent or a component thereof providing for photoactivation. Optical agents include Type 1 and Type 2 phototherapeutic agents. Compounds and compositions of the invention provide optical agents including contrast agents, imaging agents, dyes, detectable agents, and photosensitizers; and conjugates, complexes, and derivatives thereof. Some optical agents provide detectable agents that can be administered to a subject and subsequently detected using a variety of optical techniques, including optical imaging, visualization, and one-, two-, and three-point optical detection. Optical agents include, but are not limited to, phototherapeutic agents (Type 1 and 2), photosensitizers, contrast agents, imaging agents, dyes, detectable agents, photosensitizer agents, photoactivators, and photoreactive agents; and conjugates, bioconjugates, complexes, and derivatives thereof.

[092] Optical agents of the present invention can contain fluorophores. The term "fluorophore" generally refers to a component or moiety of a molecule or group which causes a molecule or group to be fluorescent. Fluorophores can be functional groups in a molecule which absorb electromagnetic radiation of first specific wavelengths and re-emit energy at second specific wavelengths. The amount and wavelengths of the emitted electromagnetic radiation depend on both the fluorophore and the chemical environment of the fluorophore. The term "fluorophore" is abbreviated throughout the present description as "FL". In aspects of the invention, fluorophores
emit energy in the visible (e.g. 350 nm to 750 nm) and NIR regions (e.g., 750 nm - 1300 nm) of the electromagnetic spectrum. As used herein, a "fluorophore" is a compound or functional group of a compound for which absorption of electromagnetic radiation results in subsequent fluorescence. Preferably for some applications incorporation of a fluorophore results in compounds of the invention that absorb electromagnetic radiation and generate fluorescence having wavelengths in the UV region (e.g. 200 nm to 350 nm) or visible region (e.g. 350 nm to 750 nm) of the electromagnetic spectrum. In some embodiments, incorporation of a fluorophore results in compounds having an appreciable quantum yield for fluorescence, such as a quantum yield selected over the range of 0.001 to 1, 0.01 to 1, optionally 0.1 to 1. As used herein, a "chromophore" is a compound or functional group of a compound that results in absorption of electromagnetic radiation, preferably for some applications electromagnetic radiation having wavelengths in the UV region (e.g. 200 nm to 350 nm) or visible region (e.g. 350 nm to 750 nm) of the electromagnetic spectrum.

[093] As used herein, the term "luminescence" refers to the emission of electromagnetic radiation from excited electronic states of atoms or molecules. Luminescence generally refers to electromagnetic radiation emission, such as photoluminescence, chemiluminescence, and electrochemiluminescence, among others. In photoluminescence, including fluorescence and phosphorescence, the excited electronic state is created by the absorption of electromagnetic radiation. Luminescence detection involves detection of one or more properties of the luminescence or associated luminescence process. These properties can include intensity, excitation and/or emission spectrum, polarization, lifetime, and energy transfer, among others. These properties can also include time-independent (steady-state) and/or time-dependent (time-resolved) properties of the luminescence. Representative luminescence techniques include fluorescence intensity (FLINT), fluorescence polarization (FP), fluorescence resonance energy transfer (FRET), fluorescence lifetime (FLT), total internal reflection fluorescence (TIRF), fluorescence correlation spectroscopy (FCS), fluorescence recovery after photobleaching (FRAP), and bioluminescence resonance energy transfer (BRET), among others. By way of example, when an optical agent is used in the present invention, it is desirable that the wavelength of radiation be non-ionizing and be such that it excites the optical agent. This excitation can cause a bond of the molecule to break and can lead to creation of one or more appropriate radical(s). This excitation can also cause the molecule to emit part of the absorbed energy at a different wavelength. Such emission can be detected using fluorometric techniques as described above. One skilled in the art can readily determine the most appropriate treatment and optional detection technique based, at least in part, on the specific phototherapy agent(s) administered and/or the particular use (e.g., tissue to be treated).

[094] Optical condition" refers to one or more of the following: the fluorescence quantum yield, fluorescence intensity, fluorescence excitation wavelength, wavelength distribution or spectrum, emission wavelength, wavelength distribution or spectrum, Stokes shift, color, reflectance,
phosphorescence, chemiluminescence, scattering, and/or other observable and/or measurable spectral property or phenomenon. A detectable optical signal may be, for example, an observable change in absorbance, reflectance, phosphorescence, chemiluminescence, scattering, or other spectral property.

[095] "Phototherapy procedure" refers to a therapeutic procedure involving administration of a phototherapy agent to a patient followed by subsequent excitation by exposure to applied electromagnetic radiation, such as electromagnetic radiation having wavelengths in the visible and/or near IR region of the electromagnetic spectrum. Such wavelengths can be in the range of 350 - 1300 nanometers, so as to generate a therapeutically effective amount of excited phototherapy agent. Phototherapy includes, but is not limited to, photodynamic therapy. As used herein, "phototherapy" includes procedures involving administration of Type 1 and/or Type 2 phototherapy agents, optionally further including administration of one or more additional therapeutic agents.

[096] As used herein, "tumor-specific agent" refers to a compound or composition, such as an optical agent, that preferentially accumulates in a tumor at a higher level than normal tissue regardless of the particular mechanism of uptake in the tumors, for example, receptor mediated or enhanced permeability and retention (EPR). Optical agents of the invention include tumor-specific agents, including tumor specific phototherapy agents, for example having a targeting ligand providing specificity in the administration, delivery and/or binding to tumor tissue.

[097] Methods of this invention comprise the step of administering an "effective amount" of the present diagnostic and therapeutic compositions, formulations and preparations containing the present compounds or compositions, to diagnose, image, monitor, evaluate, treat, reduce, alleviate, ameliorate or regulate a biological condition and/or disease state in a patient. The term "effective amount," as used herein, refers to the amount of the diagnostic and therapeutic formulation, that, when administered to the individual is effective to diagnose, image, monitor, evaluate, treat, reduce alleviate, ameliorate or regulate a biological condition and/or disease state. As is understood in the art, an effective amount of a given composition or formulation will depend at least in part upon the mode of administration (e.g. intravenous, oral, topical administration), any carrier or vehicle employed, and the specific individual to whom the formulation is to be administered (age, weight, condition, sex, etc.). The dosage requirements needed to achieve the "effective amount" vary with the particular formulations employed, the route of administration, and clinical objectives. Based on the results obtained in standard pharmacological test procedures, projected daily dosages of active compound or composition can be determined as is understood in the art.

[098] In an embodiment, an effective amount of a compound or composition of the invention is a therapeutically effective amount. As used herein, the phrase "therapeutically effective" qualifies the amount of compound or composition administered in the therapy. This amount achieves the
goal of ameliorating, suppressing, eradicating, preventing, reducing the risk of, or delaying the onset of a targeted condition. In an embodiment, an effective amount of a compound or composition of the invention is a diagnostically effective amount. As used herein, the phrase "diagnostically effective" qualifies the amount of compound or composition administered in diagnosis, for example of a disease state or other pathological condition. The amount achieves the goal of being detectable while avoiding adverse side effects found with higher doses. In an embodiment, an active ingredient or other component is included in a therapeutically acceptable amount. In an embodiment, an active ingredient or other component is included in a diagnostically acceptable amount.

[099] In an embodiment, the invention provides a medicament which comprises a therapeutically effective amount or diagnostically effective amount of one or more compositions of the invention, such as a compound of any one of formulas (FX1) - (FX32). In an embodiment, the invention provides a method for making a medicament for monitoring of a condition described herein, such as the monitoring of leukemia. In an embodiment, the invention provides a method for making a medicament for diagnosis or aiding in the diagnosis of a condition described herein, such as the diagnosis of leukemia. In an embodiment, the invention provides the use of one or more compositions set forth herein for the making of a medicament for the monitoring of leukemia. In an embodiment, the invention provides the use of one or more compositions set forth herein for the treatment of a disease. Compositions of the invention include formulations and preparations comprising one or more of the present optical agents provided in an aqueous solution, such as a pharmaceutically acceptable formulation or preparation. Optionally, compositions of the invention further comprise one or more pharmaceutically acceptable surfactants, buffers, electrolytes, salts, carriers, binders, coatings, preservatives and/or excipients.

ratio, and effective for their intended use. Prodrugs of the invention can be rapidly transformed in
vivo to a parent compound of a compound described herein, for example, by hydrolysis in blood or
by other cell, tissue, organ, or system processes. Further discussion is provided in T. Higuchi and
V. Stella, Pro-drugs as Novel Delivery Systems, V. 14 of the A.C.S. Symposium Series, and in
Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical

[0101] The invention contemplates pharmaceutically active compounds either chemically
synthesized or formed by in vivo biotransformation to compounds set forth herein.

[0102] In an embodiment, a composition of the invention is isolated or purified. In an
embodiment, an isolated or purified compound may be at least partially isolated or purified as
would be understood in the art.

[0103] "Target tissue" refers to tissue of a subject to which an optical agent is administered or
otherwise contacted, for example during a biomedical procedure such as an optical imaging or
visualization procedure. Target tissue may be contacted with an optical agent of the invention
under in vivo conditions or ex vivo conditions. Target tissues for some applications include cells
that are associated with leukemia. Target tissues in some methods of the invention include
cancerous tissue, precancerous tissue, a tumor, a lesion, a site of inflammation, or vasculature
tissue. Target tissue in some methods of the invention includes a blood cell, a melanoma cell, a
breast lesion, a prostate lesion, a lung cancer cell, a colorectal cancer cell, an atherosclerotic
plaque, a brain lesion, a blood vessel lesion, a lung lesion, a heart lesion, a throat lesion, an ear
lesion, a rectal lesion, a bladder lesion, a stomach lesion, an intestinal lesion, an esophageal
lesion, a liver lesion, a pancreatic lesion, and a solid tumor. Target tissue in some embodiments
refers to a selected organ of the subject or component thereof, such as lung, heart, brain,
stomach, liver, kidneys, gallbladder, pancreas, intestines, rectum, skin, prostate, ovaries, breast,
bladder, blood vessel, throat, ear, or esophagus.

As used herein, "spacer moiety" refers to a component provided between the amino acid
sequence SFFXaaLRS (SEQ ID NO:1) of some compounds of the invention and a pyrazine,
azulene, orazaazulene moiety (optionally substituted). In some embodiments, any Y in formulae
(FX1) - (FX32) is a spacer moiety. Spacer moieties useful for some embodiments are provided
between a pyrazine, azulene, orazaazulene and the amino acid sequence SFFXaaLRS (SEQ ID
NO:1) to enhance the overall chemical, optical, physical and/or pharmacokinetic properties of an
optical agent of the present invention. Useful spacer moieties for compounds of the invention
having formulae (FX1) - (FX32) include, but are not limited to, -NR(CH(2))aC02-, -NR(CH(2))bH2-,
-0(CH(2))aCO-, -0(CH(2))bH2-, R(C6H4)CO-, -NR(cyc/-(CH(2))6H10)CO-, -NR(CH(2))bNR2-, -0(CH(2))aO-,
-NR(C6H4)NR2-, -NR(cyc/-(CH(2))6H10)NR2-, 1,4-diazacyclohexyl, 4-carbonylpiperidinyl, 2-
carbonylpyrroldinyl, or 3-carbonylpyrroldinyl, C1-C10 alkylene, C2-C10 cycloalkylene, C2-C10
alkenylene, C3-C10 cycloalkenylene, C2-C10 alkynylene, ethylene, ethynylene, phenylene, -
(CH₂CH₂O)ₐ⁻ and -(CHOH)ₐ⁻, wherein each a is independently an integer selected from the range of 1 to 100, optionally selected from the range of 1 to 10. The invention includes compounds having formulae (FX1) - (FX32), that do not have a spacer moiety.

[0104] As used herein, "attaching moiety" refers to a component provided to attach a pyrazine, azulene, or azaazulene moiety directly or indirectly to the amino acid sequence SFFXaaLRS (SEQ ID NO:1) in compounds of the invention. In some embodiments, Z in formulae (FX1) - (FX32) is an attaching moiety. Attaching moieties may connect to the amino acid sequence SFFXaaLRS (SEQ ID NO:1) directly or may connect to the amino acid sequence SFFXaaLRS (SEQ ID NO:1) via a spacer moiety. Attaching moieties in some embodiments provide a means of derivatizing the amino acid sequence SFFXaaLRS (SEQ ID NO:1) so as to provide optical agents having useful overall chemical optical, physical and/or pharmakientic properties, including targeting and molecular recognition functionality. Attaching moieties useful in the present invention include, but are not limited to, a single bond, -(CH₂)n-, -(HCCH)n-, -O-, -S-, -SO-, -S0₂-, -S0₂-, -(CHOH)n-, -NR-, -CO-, -COON-, -OCO-, -OCOO-, -CONR-, -NRCO-, -OCONR-, -NRCOO-, -NRCN-, -NRCNSR-, -0(CH₂)n-, -(CH₂)nH, -S(CH₂)n-, -NR(CH₂)n-, -CO(CH₂)n-, -COO(CH₂)n-, -OCONR(CH₂)n-, -NRCO(CH₂)n-, -NRCO(CH₂)n-, -NCN-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCONR(CH₂)n-, -NRCSNR(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, -COO(CH₂)n-, -CONR(CH₂)n-, -CONR(CH₂)n-, -NRCO(CH₂)n-, -NRCSN(CH₂)n-, wherein each n is independently an integer selected from the range of 1 to 10.

[0105] As used herein an "electron withdrawing group" (abbreviated as "EWG") refers to any chemical group that draws electrons or electron density from a center, such as a pyrazine moiety of an optical agent of the invention. Typically, the electron withdrawing group(s) are independently selected from cyano (-CN), carbonyl (-CO), carboxylates (-C0₂R), halo (-F, -Cl, -Br, -I) carbamates (-CONR₂), acyl (-COR), nitro (-NO₂), sulfynil (-SOR), sulfonyl (-SO₂R), -SO₂OR, and -PO₃R₂ wherein in the context of this description, each R is independently selected to enhance biological and/or physicochemical properties of the optical agents of the present invention. In some instances, each R is independently selected from any one of a hydrogen atom, an anionic functional group (e.g., carboxylate, sulfonate, sulfate, phosphonate and phosphate) and a hydrophilic functional group (e.g., hydroxyl, carboxyl, sulfonyl, sulfonato and phosphonato). In other instances, each R is independently selected from any one of a hydrogen atom, - (CH₂)OH, -(CH₂)CO₂H, -(CH₂)₂SO₂H, -(CH₂)₂ISO₂H, -(CH₂)₂NO₂H, -(CH₂)₂NH₂O₃H, -(CH₂)₂PO₃H, -(CH₂)₂PO₃H, -(CH₂)₂PO₃H, -(CH₂)₂PO₃H, -(CH₂)₂PO₃H, -(CH₂)₂PO₃H, -(CH₂)₂PO₃H, -(CH₂)₂PO₃H, -(CH₂)₂PO₃H, wherein each a is independently an integer selected from 1 to 100, optionally from 1 to 10. In one example of this embodiment, the EWG(s) are independently selected from -CN, -C0₂R, -SOR, -OSR, -SO₂OR, -CONR₂, -COR, -NO₂, -SO₂R, -SO₂NR₂, and -PO₃R₂, wherein each R is as described in the context of R² in R¹ in formulae (FX1) and (FX2). In an embodiment, an EWG is located at the terminus of a substituent arm of a pyrazine ring of the present compounds.

38
As used herein, an "electron donating group" (abbreviated as "EDG") refers to any chemical group that releases electrons or electron density to a center, such as a pyrazine moiety of an optical agent of the invention. Typically, the electron donating group(s) are independently selected from C₁₋₁₀ alkyl, CS-C₁₀ alkyl, -(CH₂)ₐOH, -(CH₂)ₐCO₂H, -(CH₂)ₐSO₂H, -(CH₂)ₐSO₃⁻, -(CH₂)ₐOSO₃⁺, -(CH₂)ₐNHSO₃⁺, -(CH₂)ₐNH₂SO₃⁺, -(CH₂)ₐPO₃H₂, -(CH₂)ₐPO₃H⁻, -(CH₂)ₐP(PO₃H)₂, -(CH₂)ₐOP0₃H⁺ and -(CH₂)ₐOP0₃⁻ where n is an integer from 1 to 10. In one example of this embodiment, the EDG(s) are independently CrC₁₀ alkyl, -NR₂, -OR, -NRCOR, or -SR, wherein each R is as described in the context of R¹ to R¹¹ of formulae (FX1) and (FX2). In an embodiment, an EDG is located at the terminus of a substituent arm of a carbocyclic or pyrazine ring of the present compounds.

When used herein, the terms "diagnosis", "diagnostic" and other root word derivatives are as understood in the art and are further intended to include a general monitoring, characterizing and/or identifying a state of health or disease. The term is meant to encompass the concept of prognosis. For example, the diagnosis of cancer can include an initial determination and/or one or more subsequent assessments regardless of the outcome of a previous finding. The term does not necessarily imply a defined level of certainty regarding the prediction of a particular status or outcome.

As defined herein, "administering" means that a compound or formulation thereof of the present invention, such as an optical agent, is provided to a patient or subject, for example in a therapeutically effective amount. The present invention includes methods for a biomedical procedure wherein a therapeutically or diagnostically effective amount of a compound having any one of formulae (FX1) - (FX32) is administered to a patient in need of treatment, for example to a patient undergoing treatment for a diagnosed diseased state including cancer and leukemia.

Alkyl groups include straight-chain, branched and cyclic alkyl groups. Alkyl groups include those having from 1 to 30 carbon atoms. Alkyl groups include small alkyl groups having 1 to 3 carbon atoms. Alkyl groups include medium length alkyl groups having from 4-10 carbon atoms. Alkyl groups include long alkyl groups having more than 10 carbon atoms, particularly those having 10-30 carbon atoms. Cyclic alkyl groups include those having one or more rings. Cyclic alkyl groups include those having a 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-member carbon ring and particularly those having a 3-, 4-, 5-, 6-, or 7-member ring. The carbon rings in cyclic alkyl groups can also carry alkyl groups. Cyclic alkyl groups can include bicyclic and tricyclic alkyl groups.
Alkyl groups are optionally substituted. Substituted alkyl groups include among others those which are substituted with aryl groups, which in turn can be optionally substituted. Specific alkyl groups include methyl, ethyl, n-propyl, iso-propyl, cyclopropyl, n-butyl, s-butyl, t-butyl, cyclobutyl, n-pentyl, branched-pentyl, cyclopentyl, n-hexyl, branched hexyl, and cyclohexyl groups, all of which are optionally substituted. Substituted alkyl groups include fully halogenated or semi-halogenated alkyl groups, such as alkyl groups having one or more hydrogens replaced with one or more fluorine atoms, chlorine atoms, bromine atoms and/or iodine atoms. Substituted alkyl groups include fully fluorinated or semifluorinated alkyl groups, such as alkyl groups having one or more hydrogens replaced with one or more fluorine atoms. An alkoxy group is an alkyl group linked to oxygen and can be represented by the formula R-O. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, butoxy and heptoxy. Alkoxy groups include substituted alkoxy groups wherein the alkyl portion of the groups is substituted as provided herein in connection with the description of alkyl groups.

[0110] Alkenyl groups include straight-chain, branched and cyclic alkenyl groups. Alkenyl groups include those having 1, 2 or more double bonds and those in which two or more of the double bonds are conjugated double bonds. Alkenyl groups include those having from 2 to 20 carbon atoms. Alkenyl groups include small alkenyl groups having 2 to 3 carbon atoms. Alkenyl groups include medium length alkenyl groups having from 4-10 carbon atoms. Alkenyl groups include long alkenyl groups having more than 10 carbon atoms, particularly those having 10-20 carbon atoms. Cyclic alkenyl groups include those having one or more rings. Cyclic alkenyl groups include those in which a double bond is in the ring or in an alkenyl group attached to a ring. Cyclic alkenyl groups include those having a 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-member carbon ring and particularly those having a 3-, 4-, 5-, 6- or 7-member ring. The carbon rings in cyclic alkenyl groups can also carry alkyl groups. Cyclic alkenyl groups can include bicyclic and tricyclic alkenyl groups. Alkenyl groups are optionally substituted. Substituted alkenyl groups include among others those which are substituted with alkyl or aryl groups, which groups in turn can be optionally substituted. Specific alkenyl groups include ethenyl, prop-1-enyl, prop-2-enyl, cycloprop-1-enyl, but-1-enyl, but-2-enyl, cyclobut-1-enyl, cyclobut-2-enyl, pent-1-enyl, pent-2-enyl, branched pentenyl, cyclopent-1-enyl, hex-1-enyl, branched hexenyl, cyclohexenyl, all of which are optionally substituted. Substituted alkenyl groups include fully halogenated or semi-halogenated alkenyl groups, such as alkenyl groups having one or more hydrogens replaced with one or more fluorine atoms, chlorine atoms, bromine atoms and/or iodine atoms. Substituted alkenyl groups include fully fluorinated or semifluorinated alkenyl groups, such as alkenyl groups having one or more hydrogens replaced with one or more fluorine atoms.

[0111] Aryl groups include groups having one or more 5-, 6- or 7- member aromatic or heterocyclic aromatic rings. Aryl groups can contain one or more fused aromatic rings. Heterocyclic aromatic rings can include one or more N, O, or S atoms in the ring. Heterocyclic aromatic rings can include those with one, two or three N, those with one or two O, and those with
one or two S, or combinations of one or two or three N, O or S. Aryl groups are optionally substituted. Substituted aryl groups include among others those which are substituted with alkyl or alkenyl groups, which groups in turn can be optionally substituted. Specific aryl groups include phenyl groups, biphenyl groups, pyridinyl groups, and naphthyl groups, all of which are optionally substituted. Substituted aryl groups include fully halogenated or semihalogenated aryl groups, such as aryl groups having one or more hydrogens replaced with one or more fluorine atoms, chlorine atoms, bromine atoms and/or iodine atoms. Substituted aryl groups include fully fluorinated or semifluorinated aryl groups, such as aryl groups having one or more hydrogens replaced with one or more fluorine atoms. Aryl groups include, but are not limited to, aromatic group-containing or heterocyclic aromatic group-containing groups corresponding to any one of the following benzene, naphthalene, naphthoquinone, diphenylmethane, fluorene, anthracene, anthraquinone, phenanthrene, tetracene, naphthacenedione, pyridine, quinoline, isoquinoline, indoles, isoindole, pyrrole, imidazole, oxazole, thiazole, pyrazole, pyrazine, pyrimidine, purine, benzimidazole, furans, benzoferan, dibenzofuran, carbazole, acridine, acridone, phenanthridine, thiophene, benzothiophene, dibenzothiophene, xanthene, xanthone, flavone, coumarin, azulene or anthracycline. As used herein, a group corresponding to the substituents listed above expressly includes an aromatic or heterocyclic aromatic radical, including monovalent, divalent and polyvalent radicals, of the aromatic and heterocyclic aromatic groups listed above provided in a covalently bonded configuration in the compounds of the present invention. Aryl groups optionally have one or more aromatic rings or heterocyclic aromatic rings having one or more electron donating groups, electron withdrawing groups and/or targeting ligands provided as substituents.

[0112] Arylalkyl groups are aryl groups substituted with one or more aryl groups wherein the alkyl groups optionally carry additional substituents and the aryl groups are optionally substituted. Specific alkylaryl groups are phenyl-substituted alkyl groups, e.g., phenylmethyl groups. Alkylaryl groups are alternatively described as aryl groups substituted with one or more alkyl groups wherein the alkyl groups optionally carry additional substituents and the aryl groups are optionally substituted. Specific alkylaryl groups are alkyl-substituted phenyl groups such as methylphenyl. Substituted alkylaryl groups include fully halogenated or semihalogenated arylalkyl groups, such as arylalkyl groups having one or more alkyl and/or aryl having one or more hydrogens replaced with one or more fluorine atoms, chlorine atoms, bromine atoms and/or iodine atoms.

[0113] Optional substitution of any alkyl, alkenyl and aryl groups includes substitution with one or more of the following substituents: halogens, -CN, -COOR, -COR, -OR, -OCOR, -CON(R)₂, -OCON(R)₂, -N(R)₂, -N(R)₂, -SR, -S0₂R, -S0₂N(R)₂ or -SOR groups. Optional substitution of alkyl groups includes substitution with one or more alkenyl groups, aryl groups or both, wherein the alkenyl groups or aryl groups are optionally substituted. Optional substitution of alkenyl groups includes substitution with one or more alkyl groups, aryl groups, or both, wherein the alkyl groups or aryl groups are optionally substituted. Optional substitution of aryl groups includes substitution...
of the aryl ring with one or more alkyl groups, alkenyl groups, or both, wherein the alkyl groups or alkenyl groups are optionally substituted.

[0114] Optional substituents for alkyl, alkenyl and aryl groups include among others:

-COOR where \( R \) is a hydrogen or an alkyl group or an aryl group and more specifically where \( R \) is methyl, ethyl, propyl, butyl, or phenyl groups all of which are optionally substituted;

-COR where \( R \) is a hydrogen, or an alkyl group or an aryl groups and more specifically where \( R \) is methyl, ethyl, propyl, butyl, or phenyl groups all of which groups are optionally substituted;

-CON(\( R \)) \(_2\) where each \( R \), independently of each other \( R \), is a hydrogen or an alkyl group or an aryl group and more specifically where \( R \) is methyl, ethyl, propyl, butyl, or phenyl groups all of which groups are optionally substituted; \( R \) and \( R \) can form a ring which may contain one or more double bonds;

-OCON(\( R \)) \(_2\) where each \( R \), independently of each other \( R \), is a hydrogen or an alkyl group or an aryl group and more specifically where \( R \) is methyl, ethyl, propyl, butyl, or phenyl groups all of which groups are optionally substituted; \( R \) and \( R \) can form a ring which may contain one or more double bonds;

-N(\( R \)) \(_2\) where each \( R \), independently of each other \( R \), is a hydrogen, or an alkyl group, acyl group or an aryl group and more specifically where \( R \) is methyl, ethyl, propyl, butyl, or phenyl or acetyl groups all of which are optionally substituted; or \( R \) and \( R \) can form a ring which may contain one or more double bonds;

-SR, -SO \(_2\)R, or -S\( OR \) where \( R \) is an alkyl group or an aryl groups and more specifically where \( R \) is methyl, ethyl, propyl, butyl, phenyl groups all of which are optionally substituted; for

-SR, \( R \) can be hydrogen;

-OCOOR where \( R \) is an alkyl group or an aryl groups;

-SO \(_2\)N(\( R \)) \(_2\) where \( R \) is a hydrogen, an alkyl group, or an aryl group and \( R \) and \( R \) can form a ring;

-OR where \( R \) is H, alkyl, aryl, or acyl; for example, \( R \) can be an acyl yielding -OCOR where \( R' \) is a hydrogen or an alkyl group or an aryl group and more specifically where \( R' \) is methyl, ethyl, propyl, butyl, or phenyl groups all of which groups are optionally substituted.

[0115] As used herein, the term "alkylene" refers to a divalent radical derived from an alkyl group as defined herein. Alkylene groups in some embodiments function as attaching and/or
spacer groups in the present compositions. Compounds of the present invention include substituted and unsubstituted C1-C20 alkenylene, C1-C10 alkenylene and C1-C5 alkylene groups.

[0116] As used herein, the term "cycloalkylene" refers to a divalent radical derived from a cycloalkyl group as defined herein. Cycloalkylene groups in some embodiments function as attaching and/or spacer groups in the present compositions. Compounds of the present invention include substituted and unsubstituted C1-C20 cycloalkylene, C1-C10 cycloalkylene and C1-C5 cycloalkylene groups.

[0117] As used herein, the term "alkenylene" refers to a divalent radical derived from an alkenyl group as defined herein. Alkenylene groups in some embodiments function as attaching and/or spacer groups in the present compositions. Compounds of the present invention include substituted and unsubstituted C1-C20 alkenylene, C1-C10 alkenylene and C1-C5 alkenylene groups.

[0118] As used herein, the term "cyloalkenylene" refers to a divalent radical derived from a cyloalkenyl group as defined herein. Cycloalkenylene groups in some embodiments function as attaching and/or spacer groups in the present compositions. Compounds of the present invention include substituted and unsubstituted C1-C20 cyloalkenylene, C1-C10 cyloalkenylene and C1-C5 cyloalkenylene groups.

[0119] As used herein, the term "alkynylene" refers to a divalent radical derived from an alkynyl group as defined herein. Alkynylene groups in some embodiments function as attaching and/or spacer groups in the present compositions. Compounds of the present invention include substituted and unsubstituted C1-C20 alkynylene, C1-C10 alkynylene and C1-C5 alkynylene groups.

[0120] As used herein, the term "halo" refers to a halogen group such as a fluoro (-F), chloro (-Cl), bromo (-Br) or iodo (-I).

[0121] As is customary and well known in the art, hydrogen atoms in formulae (FX1) - (FX32) are not always explicitly shown, for example, hydrogen atoms bonded to the carbon atoms of aromatic and alicyclic rings are not always explicitly shown in formulae (FX1) - (FX32).

[0122] Specific substituted alkyl groups include haloalkyl groups, particularly trihalomethyl groups and specifically trifluoromethyl groups. Specific substituted aryl groups include mono-, di-, tri, tetra- and pentahalo-substituted phenyl groups; mono-, di-, tri, tetra-, penta-, hexa- and heptahalo-substituted naphthalene groups; 3- or 4-halo-substituted phenyl groups, 3- or 4-alkyl-substituted phenyl groups, 3- or 4-alkoxy-substituted phenyl groups, 3- or 4-RCO-substituted phenyl, 5- or 6-halo-substituted naphthalene groups. More specifically, substituted aryl groups include acetylphenyl groups, particularly 4-acetylphenyl groups; fluorophenyl groups, particularly 3-fluorophenyl and 4-fluorophenyl groups; chlorophenyl groups, particularly 3-chlorophenyl and 4-chlorophenyl groups; methylphenyl groups, particularly 4-methylphenyl groups, and methoxyphenyl groups, particularly 4-methoxyphenyl groups.
[0123] As to any of the above groups which contain one or more substituents, it is understood that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these compounds.

[0124] Pharmaceutically acceptable salts comprise pharmaceutically-acceptable anions and/or cations. As used herein, the term "pharmaceutically acceptable salt" can refer to acid addition salts or base addition salts of the compounds in the present disclosure. A pharmaceutically acceptable salt is any salt which retains at least a portion of the activity of the parent compound and does not impart significant deleterious or undesirable effect on a subject to whom it is administered and in the context in which it is administered. Pharmaceutically acceptable salts include metal complexes and salts of both inorganic and organic acids. Pharmaceutically acceptable salts include metal salts such as aluminum, calcium, iron, magnesium, manganese and complex salts. Pharmaceutically acceptable salts include, but are not limited to, acid salts such as acetic, aspartic, alkylsulfonic, arylsulfonic, axetil, benzenesulfonic, benzoic, bicarboonic, bisulfuric, bitartaric, butyric, calcium edetate, camsylic, carbonic, chlorobenzoic, cilexetil, citric, edetic, edisyllic, estolic, esyl, esylic, formic, fumaric, gluceptic, gluconic, glutamic, glycolic, glycolylarsaniclic, hexamic, hexylresorcjnoic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxynaphthoic, isethionic, lactic, lactobionic, maleic, malic, malonic, mandelic, methanesulfonic, methynitric, methylsulfuric, mucic, muconic, napsylic, nitric, oxalic, p-nitromethanesulfonic, pamoic, pantothenic, phosphoric, monohydrogen phosphoric, dihydrogen phosphoric, phthalic, polygalactouronic, propionic, salicylic, stearic, succinic, sulfamic, sulfanlic, sulfonic, sulfuric, tannic, tartaric, teoclic, tolenesulfonic, and the like. Pharmaceutically acceptable salts may be derived from amino acids, including but not limited to cysteine. Other pharmaceutically acceptable salts may be found, for example, in Stahl et al., Handbook of Pharmaceutical Salts: Properties, Selection, and Use, Wiley-VCH; Verlag Helvetica Chimica Acta, Zurich, 2002. (ISBN 3-906390-26-8). Pharmaceutically-acceptable cations include among others, alkali metal cations (e.g., Li⁺, Na⁺, K⁺), alkaline earth metal cations (e.g., Ca²⁺, Mg²⁺), non-toxic heavy metal cations and ammonium (NH₄⁺) and substituted ammonium (N(R')₄⁺, where R' is hydrogen, alkyl, or substituted alkyl, i.e., including, methyl, ethyl, or hydroxyethyl, specifically, trimethyl ammonium, triethyl ammonium, and triethanol ammonium cations). Pharmaceutically-acceptable anions include among other halides (e.g., Cl⁻, Br⁻), sulfate, acetates (e.g., acetate, trifluoroacetate), ascorbates, aspartates, benzoates, citrates, and lactate.

[0125] The compounds of this invention may contain one or more chiral centers. Accordingly, this invention is intended to include racemic mixtures, diasteromers, enantiomers and mixtures enriched in one or more stereoisomer. The scope of the invention as described and claimed encompasses the racemic forms of the compounds as well as the individual enantiomers and non-racemic mixtures thereof.
Before the present methods are described, it is understood that this invention is not limited to the particular methodology, protocols, cell lines, and reagents described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and equivalents thereof known to those skilled in the art, and so forth. As well, the terms "a" (or "an"), "one or more" and "at least one" can be used interchangeably herein. It is also to be noted that the terms "comprising", "including", and "having" can be used interchangeably.

In certain embodiments, the invention encompasses administering optical agents useful in the invention to a patient or subject. A "patient" or "subject", used equivalently herein, refers to an animal. In particular, an animal refers to a mammal, preferably a human. The subject may either: (1) have a condition diagnosable, preventable and/or treatable, in part, by administration of an optical agent of the invention; or (2) is susceptible to a condition that is diagnosable, preventable and/or treatable by administering an optical agent of this invention.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

The invention is further detailed in the following Examples, which are offered by way of illustration and are not intended to limit the scope of the invention in any manner.

Example 1: Optical Monitoring of Leukemia

Example 1a: Optical Monitoring Device and Protocol I

Referring to Figure 1, an example of an in vivo leukemia monitoring assembly includes a source of electromagnetic radiation 10, an electromagnetic radiation detector 70 and a data processing system 80. The electromagnetic radiation source 10 generally includes or is interconnected with an appropriate device or devices 20 for exposing at least a portion of a patient's body to electromagnetic radiation there from 30. Examples of appropriate devices 20 that may be operatively connected to, or be a part of, the electromagnetic radiation source 10 include, but are not limited to, catheters, endoscopes, fiber optics, ear clips, hand bands, head bands, forehead sensors, surface coils, and finger probes. Indeed, any of a number of devices capable of
emitting visible and/or near infrared electromagnetic radiation may be employed in a leukemia
monitoring assembly.

[0132] The electromagnetic radiation detector 70 of the leukemia monitoring assembly may be
any appropriate system capable of collecting and detecting electromagnetic radiation 40 emitted
from a subject 90. The electromagnetic radiation detector 70 may be operatively connected to, for
example, one or more optical collection elements 50. The optical collection elements 50 of the
leukemia monitoring assembly may include, among other elements, lenses, mirrors, filters, and
fiber optics. Electromagnetic radiation detectors 70 suitable for use with the leukemia monitoring
assembly include, but are not limited to, CCD detectors, CMOS detectors, photodiode detectors,
photodiode array detectors, and photomultiplier tube detectors.

[0133] The data processing system 80 of the leukemia monitoring assembly may be any
appropriate system capable of processing data obtained from the electromagnetic radiation
detector 70. For instance, the data processing system 80 may include an amplifier (e.g., to amplify
an electrical signal from the detector), and a processing unit (e.g., to process the electrical signal
from the detector). The data processing system 80 is preferably configured to manipulate collected
electromagnetic radiation data and generate an intensity as a function of time profile and/or a
concentration as a function of time curve indicative of clearance of an optically active bioconjugate
or integrated bioconjugate composition of the present invention from a subject 90. Indeed, the data
processing system 80 may be configured to generate appropriate leukemia disease state data by
comparing differences in amount of normal and impaired cells in the bloodstream, to determine a
rate or an accumulation of the composition in cells, organs or tissues of the subject 90, and/or to
provide tomographic images of cells, organs or tissues having the optically active bioconjugate or
integrated bioconjugate composition associated therewith.

[0134] In one protocol for monitoring of leukemia, an effective amount of a composition including
an optically active bioconjugate or integrated bioconjugate of the invention is administered to the
subject 90. At least a portion of the body of the subject 90 is exposed to visible and/or near
infrared electromagnetic radiation 30 from the electromagnetic radiation source 10. For instance,
the electromagnetic radiation 30 from the electromagnetic radiation source 10 may be delivered
via a fiber optic 20 that is affixed to an ear of the subject 90. The subject 90 may be exposed to the
electromagnetic radiation 30 from the electromagnetic radiation source 10 before or after
administration of the composition to the subject 90. In some cases, it may be beneficial to
generate a background or baseline reading of electromagnetic radiation 40 being emitted from the
body of the subject 90, due to exposure to the electromagnetic radiation 30 from the
electromagnetic radiation source 10, before administering the composition to the subject 90. When
the optically active bioconjugates or integrated bioconjugates of the composition that are in the
body of the subject 90 are exposed to the electromagnetic radiation 30 from the electromagnetic
radiation source 10, the optically active bioconjugates or integrated bioconjugates emit
electromagnetic radiation 40 that is collected by the optical collection elements 50 and detected by
the electromagnetic radiation detector 70. The signal from the electromagnetic radiation detector 70 is then analyzed by the data processing system 80. In an aspect, the optically active bioconjugate or integrated bioconjugate is a compound of formulae (FX1) or (FX2):

\[
\text{[FX1]} \quad \text{or} \quad \text{[FX2], wherein: G}^1 \text{is } -N-, -C(B)-, \text{or } -C(R^4)-; \; G^5 \text{is } -N-, -C(B)-, \text{or } -C(R^5)-; \; G^6 \text{is } -N-, -C(B)-, \text{or } -C(R^6)-; \; G^7 \text{is } -N-, -C(B)-, \text{or } -C(R^7)-; \; G^8 \text{is } -N-, -C(B)-, \text{or } -C(R^8)-; \; G^9 \text{is } -N-, -C(B)-, \text{or } -C(R^9)-; \; G^{10} \text{is } -N-, -C(B)-, \text{or } -C(R^{10})-; \; G^{11} \text{is } -N-, -C(B)-, \text{or } -C(R^{11})-; \text{wherein at most one of G}^4 \text{to G}^{11} \text{is } -N-; \text{and wherein at least one of G}^4 \text{to G}^{11} \text{is } -C(B)-; \text{each B is independently hydrogen, } C_1-C_6 \text{ alkyl, } C_3-C_6 \text{ cycloalkyl, } C_5-C_{10} \text{ aryl, } C_5-C_{10} \text{ heteroaryl, } C_2-C_6 \text{ alkenyl, } C_2-C_6 \text{ alkynyl, } C_2-C_{10} \text{ alkylaryl, } -O-R^21, -S-R^22, -NR^23-R^24, -CONR^25-R^26, -CO-R^27, -SOR^28, -CN, -NOR^29, -COR^30, -SO-R^31-R^32, -NR^46-COR^47, -CONR^48-(CH)_2aOR^49, \text{halo, trihalomethyl, or } -PS^1; \text{each PS}^1 \text{is independently a photosensitizer corresponding to a cyanine, an indocyanine, a phthalocyanine, a rhodamine, a phenoxazine, a phenothiazine, a phenoselenazine, a fluorescein, a porphyrin, a benzoporphyrin, a squaraine, a corrin, a crocoine, an azo dye, a methine dye, an indolenium dye, a halogen, an anthracycline, an azide, a } C_1-C_{20} \text{ peroxyalkyl, a } C_5-C_{20} \text{ peroxyaryl, a } C_1-C_{20} \text{ sulenatoalkyl, a } C_5-C_{20} \text{ sulenatoaryl, a naphthalocyanine, a methylene blue, a chalcogenopyrylium analogue, an azo, a diazo, an oxaza, a diaza, a dithia, a thioxia, or a dioxa group; each } Y \text{ is independently } -NR^30-(CH)_{2a}CO-R^31, -NR^32-(CH)_{2a}CO-R^33, -0(CH)_{2a}CO-R^34, -0(CH)_{2a}CO-R^35, -NR^36-(C_6H_4)CO-R^37, -NR^37-(CH)_{2a}NR^38, -0(CH)_{2a}CO-R^39, -NR^38-(C_6H_4)NR^39, -NR^39-(C_6H_4)NR^40, -NR^40-(C_6H_4)NR^41, -NR^41-(C_6H_4)NR^42, -NR^42-(C_6H_4)NR^43, -NR^43,-NR^44-(CH)_{2a}CONR^45, -1,4-diazacyclohexyl, -4-carbonylpiperidinyl, -2-carbonylpyrrolidinyl, \text{or } 3-carbonylpyrrolidinyl; \text{each a is independently an integer selected from the range of } 0 \text{ to } 10; \text{each of } R^20 \text{ to } R^49 \text{ is independently hydrogen, } C_1-C_6 \text{ alkyl, } C_3-C_6 \text{ cycloalkyl, } C_5-C_{10} \text{ aryl, or } C_5-C_{10} \text{ heteroaryl; each PEPTIDE is independently an amino acid sequence corresponding to (-S)FFXaal_RS (SEQ ID NO:1); S(-F)XaaLRS (SEQ ID NO:1); SF(-F)XaaLRS (SEQ ID NO:1); SFF(-Xaa)LRS (SEQ ID NO:1); SFFXaa(-L)RS (SEQ ID NO:1); SFFXaal(_(-R))S (SEQ ID NO:1); or SFFXaalR(-S) (SEQ ID NO:1); each S is an amino acid corresponding to Serine; each F is an amino acid corresponding to Phenylalanine; each Xaa is an amino acid corresponding to Trytophan, Asparagine, or Tyrosine; each L is an amino acid corresponding to Leucine; each R is an amino acid corresponding to Arginine; wherein each Y is attached to the amino acid sequence at the C- or N-terminal end of the amino acid sequence; or each Y is attached to a side chain of any amino acid of the amino acid sequence; or wherein the side chain of any amino acid of the amino acid sequence is replaced by an optical agent corresponding to a pyrazine, azulene, or azaazulene; or wherein the side chain of any amino acid of the amino acid sequence is replaced.
by Y; and wherein a dash (-) in the amino acid sequence denotes the position in the amino acid sequence at which Y attaches. In a related embodiment, each Y is independently -NR<sup>33</sup>(CH<sub>2</sub>)<sub>a</sub>CO- or -R<sup>39</sup>(C<sub>6</sub>H<sub>4</sub>)NR<sup>40</sup>.

[0136] Referring to Figure 2, initially, administration of the composition to the subject 90 generally enables an electromagnetic radiation signal 100 indicative of the content of the optically active bioconjugate(s) or integrated bioconjugate(s) in the subject 90. The electromagnetic radiation signal 100 tends to decay as a function of time as the optically active bioconjugate(s) or integrated bioconjugate(s) is cleared from the subject 90. In a subject 90 not afflicted with a leukemia condition, the electromagnetic radiation signal 100 will decay to near the baseline level 120 as the optically active bioconjugate(s) or integrated bioconjugate(s) is cleared from the subject 90. In a subject 90 with a leukemia condition, the optically active bioconjugate(s) or integrated bioconjugate(s) will attach to cells, tissues or organs affected with a leukemia condition and will not be cleared by the subject 90 during the time scale of the monitoring. As a result, the electromagnetic radiation signal 100 will not decrease to the baseline level 120, but will remain at an elevated level 110. The difference 130 between this increased electromagnetic radiation signal level 110 and the baseline level 120 is indicative of a leukemia disease state in the subject. As such, the subject 90 may be exposed to the electromagnetic radiation 30 from the electromagnetic radiation source 10 for any amount of time appropriate for providing the desired leukemia monitoring data. Likewise, the electromagnetic radiation collection 50, detection 70, and data processing 80 systems may be allowed to collect and detect electromagnetic radiation 40 for any amount of time appropriate for providing the desired leukemia monitoring data.

Example 1b: Non-Invasive Optical Pharmacokinetic Studies

[0137] Male Sprague-Dawley rats (330-380 g) were anesthetized by Inactin (IP.) or 2% isoflurane gas anesthesia delivered by a small rodent gas anesthesia machine (RC2, Vetequip, Pleasanton, CA). The animals were placed on a heated board where temperature was maintained between 36-38°C. One ear lobe was glued flat to a glass slide positioned approximately 4 mm beneath a fiber optic bundle for recording fluorescence from a test compound passing through the ear. After a 100 second baseline recording, 1 ml of a 2 nM solution was injected into the tail-vein of the rat and the fluorescence signal corresponding to plasma and tissue distribution and subsequent renal clearance of the compound was monitored at the ear. The pharmacokinetic parameters of the compounds were analyzed using WinNonLin pharmacokinetic modeling software (Pharsight, Mountain View, CA).

Example 1c: Optical Monitoring Device and Protocol II

[0138] A nominal 445 nm solid state laser source was employed (Power Technology model LDCU 12/6619). The laser source was directed into one leg of a silica bifurcated fiber optic bundle (Oriel #77565). The common end of this bifurcated bundle was placed approximately 2 mm from the rat ear. The second leg of the bifurcated fiber optic bundle was fitted with a collimating beam
probe (Oriel #77644). A long pass filter (Semrock LP02-488RS-25) and narrow band interference filter (Semrock FF01-560/25-25) were placed in front of a photomultiplier tube (Hamamatsu photosensor module H7827-001).

[0139] Lock-in detection was employed. A chopper (Stanford Research Systems model SR540) was placed after the laser and before the launch into the bifurcated cable. The output of the photosensor was connected to a lock-in amplifier (Stanford Research Systems model SR830). The lock-in output was digitized (National Instruments NI-USB-6211) and the digitized data was acquired by computer using LabVIEW® data acquisition software.

**Example 1d: Optical Monitoring Device and Protocol Using Compound (FX23)**

![Chemical Structure of Compound FX23]

[0140] **Experimental Procedure:** U937 cells were plated at a concentration of 100,000 cells/well in 24 well plate format and allowed to incubate at 37°C in a humidified CO₂ incubator for 2 hours. KB cells were plated at a concentration of 100,000 cells per well in a 24 well plate overnight. Three different dilutions of leukemia-pyrazine conjugates were prepared with 50 μM, 10 μM, and 2 μM concentration of leukemia-pyrazine conjugate of formula (FX23). The conjugates were added to respective wells such that the final concentration of leukemia-pyrazine conjugate of formula (FX23) in each well was 25 μM, 5 μM and 1 μM. All the concentrations were carried out in triplicates. The plate was allowed to incubate at 37°C in a CO₂ incubator for 2 hours. At the end of 2 hours incubation time, cells were washed thrice with 1XDPBS followed by lysis with 300 μL of lysis buffer to insure that all fluorescently tagged cellular components were in the path of the fluorescence excitation light. The lysed cells were transferred to a clear bottom black 96 well plate. The fluorescence of individual wells was monitored at 495 nm excitation wavelength and 595 nm emission wavelength using a commercial fluorescent plate reader (Biotek Synergy 4 Hybrid multiplate reader). The results of the fluorescence measurements are provided in Figure 4.

[0141] **Results and Discussion:** The leukemia peptide SFFX₃aLRS (SEQ ID NO:1) is a hepta peptide that targets the neurolipin receptor present on leukemia cells. The U937 is a monocytic leukemia cell line that expresses neurolipin receptors. The KB cell line is an immortalized nasal pharyngeal cancer cell line that is negative for neurolipin receptor.
Referring to Figure 4, at 25 µM concentration of Leukemia peptide-pyrazine conjugates, the U937 cells show a significant uptake (corresponding to an increase in fluorescence) whereas KB (receptor negative) cells show minimal uptake. The uptake of peptide conjugates essentially remains the same in KB cells at all concentrations whereas the U937 cells show a dose dependent uptake of these conjugates. This suggest that the peptide can be used as a diagnostic agent as well as a targeting vector for delivering drugs and other macro-molecules to the leukemia type cancer cells.

Example 2: Compositions and Methods for Phototherapeutic and Diagnostic Applications

The invention includes phototherapy and diagnostic methods wherein an optical agent comprising a compound of any one of the formulae (FX1) - (FX32) is administered to a patient, for example, wherein a therapeutically or diagnostically effective amount of such a component is administered to a patient in need of treatment. In this aspect, compounds of the invention provide an optical agent capable of selectively targeting and delivery to leukemia cells and tissue and further functions as a diagnostic agent, and optionally, a phototherapeutic agent. Upon administration, the optical agent is allowed to accumulate in a target region of interest (e.g., target tissue, tumor, or organ). To induce fluorescence and/or selective tissue damage, the optical agent is activated by exposure to electromagnetic radiation. In an embodiment, the optical agent is activated after an effective concentration of the optical agent has accumulated in a target tissue. An effective concentration of a compound of the invention depends on the nature of the formulation, method of delivery, target tissue, activation method and toxicity to the surrounding normal non-target tissue. Exposure to electromagnetic radiation and activation of the optical agent may occur during or after administration of the optical agent and accumulation at the target tissue.

In an aspect, the optical agent is a compound of formulae (FX1) or (FX2):

\[
\begin{align*}
\text{R}^2 & \quad \text{R}^3 \quad \text{B} \\
\text{G}^4 & \quad \text{G}^5 \\
\text{G}^6 & \quad \text{G}^7 \\
\text{G}^8 & \quad \text{G}^9 \\
\text{G}^{10} & \quad \text{G}^{11} \\
\text{G}^{12} & \quad \text{G}^{13} \\
\end{align*}
\]

wherein: \( \text{G}^4 \) is \( -\text{N} -, \text{-C(B)} -, \text{-C}(\text{R}^4) - \); \( \text{G}^5 \) is \( -\text{N} -, \text{-C(B)} -, \text{-C}(\text{R}^4) - \); \( \text{G}^6 \) is \( -\text{N} -, \text{-C(B)} -, \text{-C}(\text{R}^5) - \); \( \text{G}^7 \) is \( -\text{N} -, \text{-C(B)} -, \text{-C}(\text{R}^5) - \); \( \text{G}^8 \) is \( -\text{N} -, \text{-C(B)} -, \text{-C}(\text{R}^6) - \); \( \text{G}^9 \) is \( -\text{N} -, \text{-C(B)} -, \text{-C}(\text{R}^6) - \); \( \text{G}^{10} \) is \( -\text{N} -, \text{-C(B)} -, \text{-C}(\text{R}^7) - \); \( \text{G}^{11} \) is \( -\text{N} -, \text{-C(B)} -, \text{-C}(\text{R}^7) - \); \( \text{G}^{12} \) is \( -\text{N} -, \text{-C(B)} -, \text{-C}(\text{R}^8) - \); \( \text{G}^{13} \) is \( -\text{N} -, \text{-C(B)} -, \text{-C}(\text{R}^8) - \); wherein at most one of \( \text{G}^4 \) to \( \text{G}^{11} \) is \( -\text{N} - \); and wherein at least one of \( \text{G}^4 \) to \( \text{G}^{11} \) is \( -\text{C}(\text{B}) - \); each \( \text{B} \) is independently \( -\text{CO} - \) or \( -\text{NR}^{20} - \); each of \( \text{R}^1 \) to \( \text{R}^{11} \) is independently hydrogen, \( \text{C}^1-6 \) alkyl, \( \text{C}^3-6 \) cycloalkyl, \( \text{C}_{6}^{5}-\text{C}_{10}^{5} \) aryI, \( \text{C}_{6}^{5}-\text{C}_{10}^{5} \) heteroaryl, \( \text{C}_{2}^{2}-\text{C}_{6}^{6} \) alklenyl, \( \text{C}_{2}^{2}-\text{C}_{6}^{6} \) alkylcycloalkyl, \( \text{C}_{6}^{5}-\text{C}_{10}^{5} \) alkyllaryl, \( \text{OR}^{21} - \); \( \text{S}^{22} - \text{NR}^{23} - \text{COR}^{24} - \text{CONR}^{25} - \text{C}^{6} \text{O}^{26} - \text{C}^{6} \text{O}^{26} - \text{SOR}^{27} - \text{CN}^{28} - \text{N}^{0}^{29} - \text{COR}^{29} - \text{S}^{0}^{29} - \text{S}^{0}^{29} - \text{NR}^{31} - \text{R}^{32} - \text{N}^{46} - \text{COR}^{47} - \text{CONR}^{48} - \text{C}^{6} \text{O}^{49} - \text{halo}, \text{trihalomethyl}, \text{OR} - \text{PS}^{1} - \); each \( \text{PS}^{1} \) is independently a
photosensitizer corresponding to a cyanine, an indocyanine, a phthalocyanine, a rhodamine, a phenoxyazine, a phenthiazine, a phenoxylenazine, a fluorescein, a porphyrin, a benzoporphyrin, a squaraine, a corrin, a croconium, an azo dye, a methine dye, an indolenium dye, a halogen, an anthracycline, an azide, a C1-C20 peroxyalkyl, a C5-C20 peroxyaryl, a C1-C20 sulfolenoalkyl, a C5-C20 sulfolenatoaryl, a naphthoacyanine, a methylene blue, a chalcogenopyrylum analogue, an azo, a diazo, an oxaza, a diaza, a dithia, a thioxa, or a dioxa group; each Y is independently -NR33(CH2)2CO-, -NR36(CH2)a-, -O(CH2)2CO-, -O(CH2)3a-, -NR38(C6H4)CO-, -NR38(cyclo-C6H10)CO-, -NR37(CH2)aNR38-, -O(CH2)aO-, -NR39(C6H4)NR40-, -NR41(cyclo-C6H10)NR42-, -NR43-, -NR44(C6H4)CONR45-, 1,4-diazacyclohexyl, 4-carbonylpiperidinyl, 2-carbonylpyrrolidinyl, or 3-carbonylpyrrolidinyl; each a is independently an integer selected from the range of 0 to 10; each of R20 to R49 is independently hydrogen, C1-C6 alkyl, C3-C6 cycloalkyl, C5-C10 aryl, or C5-C10 heteroaryl; each PEPTIDE is independently an amino acid sequence corresponding to (-S)FFXaaLRS (SEQ ID NO:1); S(-F)FXaaLRS (SEQ ID NO:1); SF(-F)XaaLRS (SEQ ID NO:1); SFF(-Xaa)LRS (SEQ ID NO:1); SFF(-Xaa)LRS (SEQ ID NO:1); SFFXaa(-L)RS (SEQ ID NO:1); or SFFXaaL(-R)S (SEQ ID NO:1); each S is an amino acid corresponding to Serine; each F is an amino acid corresponding to Phenylalanine; each Xaa is an amino acid corresponding to Tryptophan, Asparagine, or Tyrosine; each L is an amino acid corresponding to Leucine; each R is an amino acid corresponding to Arginine; wherein each Y is attached to the amino acid sequence at the C- or N- terminal end of the amino acid sequence; or each Y is attached to a side chain of any amino acid of the amino acid sequence; or wherein the side chain of any amino acid of the amino acid sequence is replaced by an optical agent corresponding to a pyrazine, azulene, or azaazulene; or wherein the side chain of any amino acid of the amino acid sequence is replaced by Y; and wherein a dash (-) in the amino acid sequence denotes the position in the amino acid sequence at which Y attaches. In a related embodiment, each Y is independently -NR33(CH2)aCO- or -R49(C6H4)NR40-.

[0145] For photoactivation, the target region is illuminated with electromagnetic radiation having wavelengths in the range of about 350 nm to about 1300 nm, preferably for some applications in the range of about 350 nm to about 900 nm. In some embodiments, the wavelengths of the electromagnetic radiation corresponds to a peak in the absorption spectrum of the optical agent, for example are within 20 nanometers of a peak in the absorption spectrum of the optical agent in the visible or NIR regions. In some biomedical procedures the target site is exposed to electromagnetic radiation having sufficient fluence and/or power sufficient to activate the optical agent so as to produce a sufficient amount of fluorescence and/or induce cell death, for example via necrosis or apoptosis processes. In some embodiments, electromagnetic radiation of low energy, power or fluence is needed to activate the optical agent. If the region of interest is, for example, a lesion or tumor on the skin surface, the region can be directly illuminated. Otherwise, endoscopic and/or endoluminal catheters equipped with an electromagnetic radiation source may be employed to provide a photodiagnostic and/or the phototherapeutic effect.
[0146] Appropriate power and intensity of the electromagnetic radiation depends on the size, depth, and the pathology of the target cells or tissues, as is known to one skilled in the art. In an embodiment, the fluence of the electromagnetic radiation is preferably, but not always, kept below 200 mW/cm² to minimize undesirable thermal effects. The intensity, power, and duration of the illumination and the wavelength of the electromagnetic radiation may vary widely depending on the body location, the tissue or cell location, the effect to be achieved, etc. In an embodiment, the power of the applied electromagnetic radiation is preferably selected over the range of 1 - 500 mW/cm² and optionally selected over the range of 1 - 200 mW/cm². In an embodiment, the duration of the exposure to applied electromagnetic radiation selected over the range of 1 second to 60 minutes.

[0147] In an embodiment, the invention provides a method of using an optical agent, the method comprising: (i) administering an effective amount of an optical agent to a subject, the optical agent comprising a compound being of any one of formula (FX1) - (FX32), wherein at least one of R¹ to R¹¹ is -PS¹, or a pharmaceutically acceptable salt or ester thereof; and (ii) exposing the optical agent administered to the patient to electromagnetic radiation.

[0148] In an embodiment, the optical agent is exposed to a therapeutically or diagnostically effective amount of electromagnetic radiation. As used herein, a therapeutically effective amount of electromagnetic radiation is an amount for achieving a desired therapeutic result, for example an amount for generating a therapeutically effective amount of reactive species for damaging or causing cell death of a selected target tissue. In an embodiment, the method further comprises generating one or more reactive species from said compound administered to the patient via the exposure of the optical agent to applied electromagnetic radiation. In an embodiment, for example, the method further comprises the step of cleaving one or more photolabile bonds of the optical agent so as to generate reactive species comprising free radicals. In an embodiment, the method further comprises targeting the optical agent to a selected organ in the patient or to a selected tissue type in the patient. In an embodiment, a therapeutically effective dose of the optical agent is administered to a patient in need of treatment.

[0149] Embodiments of this aspect may comprise a method of carrying out an in vivo therapeutic and/or diagnostic procedure. In an embodiment, the invention comprises a method of carrying out an in vivo phototherapeutic, photoactivation, and/or photosensitizing procedure. The present methods have broad clinical utility which includes, but is not limited to, phototherapy of cells, tumors, inflammatory processes, and impaired vasculature. In embodiments, subjects of the invention may be any mammal, such as a human, and optionally the subject of the present methods is a patient in need of treatment and/or diagnosis. The present methods are also useful in ex vivo and in vitro procedures, including medical therapeutic and diagnostic procedures.

[0150] Methods of the invention may optionally further comprise a number of other steps. In an embodiment, the method further comprises the step of administering the optical agent into a bodily
fluid of the subject. The optical agent may be introduced into the patient by any suitable method, including intravenous, intraperitoneal or subcutaneous injection or infusion, oral administration, transdermal absorption through the skin, or by inhalation. In an embodiment, the method further comprises contacting a target tissue, such as an organ, tissue, tumor, lesion, or cell type, with a compound of any one of formulae (FX1) - (FX32) prior to or during the exposure step. In an embodiment, the method further comprises allowing the compound to accumulate in a target tissue prior to exposure of the optical agent to electromagnetic radiation. In an embodiment, the method further comprises targeting the diagnostic agent to a selected organ, tissue, tumor, lesion, inflammation, or cell type. In an embodiment, the optical agent is administered to the skin, a tumor, surgical site, or a wound site. In an embodiment, for example, the optical agent is administered and/or delivered to a blood vessel, lung, heart, throat, ear, rectum, bladder, stomach, intestines, esophagus, liver, brain, prostrate, breast, or pancreas of the subject.

[0151] As will be understood by one having skill in the art, the optical conditions for the step of exposing the optical agent administered to the patient to electromagnetic radiation will vary considerably with the (i) therapeutic and/or diagnostic objectives, and (ii) the condition of the subject (e.g., height, weight, state of health etc.). In an embodiment, the applied electromagnetic radiation has wavelengths, energy and/or fluence sufficient to achieve a desired therapeutic and/or diagnostic result. In an embodiment, the electromagnetic radiation has wavelengths, energy and/or fluence sufficient to activate the optical agent, for example wavelengths, energy and/or fluence sufficient to result in generation of reactive species, including singlet oxygen and/or free radicals. In an embodiment, the electromagnetic radiation has wavelengths, energy and/or fluence sufficient to result in cleavage of at least one photolabile bond of the optical agent upon absorption. In an embodiment, the electromagnetic radiation exposed to the optical agent has wavelengths corresponding to a maximum in the absorption spectrum of the optical agent, preferably for some applications a maximum in the visible or NIR regions of the electromagnetic spectrum. Optionally, excitation is achieved using electromagnetic radiation substantially free (e.g., less than about 10% of total radiant energy) of ultraviolet radiation, for example, to minimize exposure of the subject to electromagnetic radiation capable of causing unwanted cell or tissue damage. Electromagnetic radiation may be provided to the optical agent using a range of optical sources and/or surgical instrumentation, including a laser, light emitting diodes, fiber optic device, endoscope, catheter, optical filters, or any combination of these.

Example 3: Synthesis of Optical Agent-Peptide Conjugates

[0152] Figure 3 provides a representative synthetic scheme for the production of a pyrazine-peptide conjugate. In Figure 3, C is -OH or -NH(CH$_2$)$_n$C0$_2$H; D is -O-, or -NH(CH$_2$)$_n$C0$_2$-; examples of Coupling Agents include DCC, EDC, DCC/NHS mixtures, EDC/NHS mixtures, EDC/HOBt mixtures, PyBOP, PyBrOP, HATU, and HBTU; and R$^{33}$-R$^{36}$ and PEPTIDE are as defined in the context of (FX1) and (FX2). The specifics of this scheme as applied to pyrazine-peptide and azulene-peptide conjugates are provided in Examples 3a through Example 3e, below.
Example 3a: Synthesis of Pyrazine-Peptide Conjugate of Formula (FX21): Solution Procedure

A typical procedure for the preparation of pyrazine-SFFX<sub>aa</sub>RLS (SEQ ID NO:1) conjugate of formula (FX21) is described. A mixture of 3,5-bis(n-propylamino)-5-N-(2-methoxyethyl)carbamoylpyrazine-carboxylic acid (1 mmol), 1-hydroxybenzotriazole (1.2 mmol), and triethylamine (1.2 mmol) in DMF is stirred at ambient temperature for about 30 minutes. Thereafter, EDC (1.2 mmol) is then added and the entire mixture is stirred at ambient temperature for about 16 hours. The reaction mixture is then poured onto ethyl acetate to precipitate the product. Excess solvent is decanted off and the residue is repeatedly washed with ethyl acetate to remove excess DMF and the crude material is purified by HPLC.

Example 3b: Synthesis of Pyrazine-Peptide Conjugate of Formula (FX21): Automated Procedure

A typical procedure for the preparation of pyrazine-SFFX<sub>aa</sub>RLS (SEQ ID NO:1) conjugate of formula (FX21) using an automated peptide synthesizer is described. It should be noted that other pyrazine fluorophores may be conjugated to the leukemia binding sequence SFFX<sub>aa</sub>RLS (SEQ ID NO:1) by the same procedure. The peptide conjugate is prepared by fluorenylmethoxycarbonyl (Fmoc) solid phase peptide synthesis strategy with a commercial peptide synthesizer from Applied Biosystems (Model 432A SYNERGY Peptide Synthesizer). The first peptide cartridge contains Wang resin pre-loaded with an amide resin on 25-μmol scale. The amino acid cartridges are placed on the peptide synthesizer and the product is synthesized from the C- to the N-terminal position. Coupling of the Fmoc-protected amino acids (75 μmol) to the resin-bound free terminal amine (25 μmol) is carried out with 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU, 75 μmol)/N-hydroxybenzotriazole (HOBt, 75 μmol). Each Fmoc protecting group on solid support is removed with 20% piperidine in dimethylformamide before the subsequent amino acid is coupled to it. The last cartridge contains the pyrazine carboxylic acid derivative of formula (FX33):

wherein R<sup>23</sup> to R<sup>26</sup> are as described in the context of formula (FX1).
After the synthesis is completed, the product is cleaved from the solid support with a cleavage mixture containing trifluoroacetic acid (85%):water (5%):phenol (5%):thioanisole (5%) for 6 hours. The peptide-sulfenamide conjugate is precipitated with t-butyl methyl ether and lyophilized in wateracetonitrile (2:3) mixture. The conjugate is purified by HPLC and analyzed with LC/MS.

Example 3c: Synthesis of Azulene-Peptide Conjugate of Formula (FX22): Solution Procedure

![Diagram of Azulene-Peptide Conjugate]

A typical procedure for the preparation of the azulene-SFFX<sub>aa</sub>RLS (SEQ ID NO:1) conjugate of formula (FX22) is described. A mixture of 1-azulenecarboxylic acid (1 mmol), 1-hydroxybenzotriazole (1.2 mmol), and triethylamine (1.2 mmol) in DMF is stirred at ambient temperature for about 30 minutes. Thereafter, EDC (1.2 mmol) is then added and the entire mixture is stirred at ambient temperature for about 16 hours. The reaction mixture is then poured onto ethyl acetate to precipitate the product. Excess solvent is decanted off and the residue is repeatedly washed with ethyl acetate to remove excess DMF and the crude material is purified by HPLC.

Example 3d: Synthesis of Azulene-Peptide Conjugate of Formula (FX22): Automated Procedure

A typical procedure for the preparation of the azulene-SFFX<sub>aa</sub>RLS (SEQ ID NO:1) conjugate of formula (FX22) using an automated peptide synthesizer is described. It should be noted that other azulene fluorophores may be conjugated to the leukemia binding amino acid sequence SFFX<sub>aa</sub>RLS (SEQ ID NO:1) by the same procedure. The peptide conjugate is prepared by fluorenylmethoxycarbonyl (Fmoc) solid phase peptide synthesis strategy with a commercial peptide synthesizer from Applied Biosystems (Model 432A SYNERGY Peptide Synthesizer). The first peptide cartridge contains Wang resin pre-loaded with an amide resin on 25-µmol scale. The amino acid cartridges are placed on the peptide synthesizer and the product is synthesized from the C- to the N-terminal position. Coupling of the Fmoc-protected amino acids (75 µmol) to the resin-bound free terminal amine (25 µmol) is carried out with 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU, 75 µmol)/N-hydroxybenzotriazole (HOBt, 75 µmol). Each Fmoc protecting group on solid support is removed with 20% piperidine in dimethylformamide before the subsequent amino acid is coupled to it. The last cartridge contains 1-azulenecarboxylic acid.
After the synthesis is completed, the product is cleaved from the solid support with a cleavage mixture containing trifluoroacetic acid (85%):water (5%):phenol (5%):thioanisole (5%) for 6 hours. The peptide-sulfenamide conjugate is precipitated with t-butyl methyl ether and lyophilized in wateracetonitrile (2:3) mixture. The conjugate is purified by HPLC and analyzed with LC/MS.

Example 3e: Synthesis of Pyrazine-Peptide Conjugate of Formula (FX23): Automated Procedure

The leukemia cell binding peptide conjugate pyrazine-SFFYLSR (SEQ ID NO:1) (FX23) was prepared by fluorenylmethyloxycarbonyl (Fmoc) solid phase peptide synthesis strategy with a commercial automated peptide synthesizer. The first peptide cartridge contained Wang resin pre-loaded with an amide resin on 25 µmol scale. The amino acid cartridges each containing S, F, F, Y, L, R, and S amino acids were placed on the peptide synthesizer and the product was synthesized from the C- to the N-terminal sequence. Coupling of the Fmoc-protected amino acids to the resin-bound free terminal amine was carried out with 2-(1H-benzotriazol-1-yl)-1,3,3-tetramethyluronium hexafluorophosphate (HBTU, 75 µmol) / N-hydroxybenzotriazole (HOBr, 75 µmol). Each Fmoc protecting group on solid support was removed with 20% piperidine in dimethylformamide before the subsequent amino acid was coupled to it. The last cartridge contained the pyrazine carboxylic acid derivative (FX24), which was coupled to the peptide automatically, thus avoiding the need for post-synthetic manipulations. After the synthesis, the product was cleaved from the solid support with a cleavage mixture containing trifluoroacetic acid (85%):water (5%):phenol (5%):thioanisole (5%) for 6 hours. The peptide

[0158]  After the synthesis is completed, the product is cleaved from the solid support with a cleavage mixture containing trifluoroacetic acid (85%):water (5%):phenol (5%):thioanisole (5%) for 6 hours. The peptide-sulfenamide conjugate is precipitated with t-butyl methyl ether and lyophilized in wateracetonitrile (2:3) mixture. The conjugate is purified by HPLC and analyzed with LC/MS.

Example 3e: Synthesis of Pyrazine-Peptide Conjugate of Formula (FX23): Automated Procedure

The leukemia cell binding peptide conjugate pyrazine-SFFYLSR (SEQ ID NO:1) (FX23) was prepared by fluorenylmethyloxycarbonyl (Fmoc) solid phase peptide synthesis strategy with a commercial automated peptide synthesizer. The first peptide cartridge contained Wang resin pre-loaded with an amide resin on 25 µmol scale. The amino acid cartridges each containing S, F, F, Y, L, R, and S amino acids were placed on the peptide synthesizer and the product was synthesized from the C- to the N-terminal sequence. Coupling of the Fmoc-protected amino acids to the resin-bound free terminal amine was carried out with 2-(1H-benzotriazol-1-yl)-1,3,3-tetramethyluronium hexafluorophosphate (HBTU, 75 µmol) / N-hydroxybenzotriazole (HOBr, 75 µmol). Each Fmoc protecting group on solid support was removed with 20% piperidine in dimethylformamide before the subsequent amino acid was coupled to it. The last cartridge contained the pyrazine carboxylic acid derivative (FX24), which was coupled to the peptide automatically, thus avoiding the need for post-synthetic manipulations. After the synthesis, the product was cleaved from the solid support with a cleavage mixture containing trifluoroacetic acid (85%):water (5%):phenol (5%):thioanisole (5%) for 6 hours. The peptide
conjugate was precipitated with t-butyl methyl ether, collected by filtration, and purified by HPLC to give 60 mg of the desired pyrazine-peptide conjugate as yellow powder.

Example 4: Pharmaceutical Formulations

4a: Salts and Prodrugs

[0160] The invention contemplates pharmaceutically active compounds either chemically synthesized or formed by in vivo biotransformation to compounds set forth herein.

[0161] Compounds of this invention and compounds useful in the methods of this invention include those of the compounds and formula(s) described herein and pharmaceutically-acceptable salts and esters of those compounds. In embodiments, salts include any salts derived from the acids and bases of the formulas herein which are acceptable for use in human or veterinary applications. In embodiments, the term ester refers to hydrolyzable esters of compounds of the names and formulas herein. In embodiments, salts and esters of the compounds of the formulas herein can include those which have the same or better therapeutic, diagnostic, or pharmaceutical (human or veterinary) general properties as the compounds of the formulas herein. In an embodiment, a composition of the invention is a compound or salt or ester thereof suitable for pharmaceutical formulations.

[0163] Optical agents of the invention can be formulated with pharmaceutically-acceptable anions and/or cations. Pharmaceutically-acceptable cations include among others, alkali metal cations (e.g., Li⁺, Na⁺, K⁺), alkaline earth metal cations (e.g., Ca²⁺, Mg²⁺), non-toxic heavy metal cations and ammonium (NH₄⁺) and substituted ammonium (N(R')₄⁺, where R' is hydrogen, alkyl, or substituted alkyl, i.e., including, methyl, ethyl, or hydroxyethyl, specifically, trimethyl ammonium, triethyl ammonium, and triethanol ammonium cations). Pharmaceutically-acceptable anions include, among others, halides (e.g., F⁻, Cl⁻, Br⁻, At⁻), sulfate, acetates (e.g., acetate, trifluoroacetate), ascorbates, aspartates, benzoates, citrates, and lactate.

[0164] Pharmaceutically acceptable salts comprise pharmaceutically-acceptable anions and/or cations. As used herein, the term "pharmaceutically acceptable salt" can refer to acid addition salts or base addition salts of the compounds in the present disclosure. A pharmaceutically acceptable salt is any salt which retains at least a portion of the activity of the parent compound and does not impart significant deleterious or undesirable effect on a subject to whom it is administered and in the context in which it is administered. Pharmaceutically acceptable salts include metal complexes and salts of both inorganic and organic acids. Pharmaceutically acceptable salts include metal salts such as aluminum, calcium, iron, magnesium, manganese and complex salts. Pharmaceutically acceptable salts include, but are not limited to, acid salts such as acetic, aspartic, alkylsulfonic, arylsulfonic, axetil, benzensulfonic, benzoic, bicarboxic, bisulfuric, bitartaric, butyric, calcium edetate, camsylic, carbonic, chlorobenzoic, cilexetil, citric, edetic, edisyl, estolic, esyl, esylic, formic, fumaric, gluceptic, gluconic, glutamic, glycolic, hexamic, hexylreserinoic, hydrobromic, hydrochloric, hydroiodic, hydroxydehydrobenzoic, isethionic, lactic, lactobionic, maleic, malic, malonic, mandelic, methanesulfonic, mucic, muconic, napsylic, nitric, oxalic, p-nitromethanesulfonic, palmoic, pantosteric, phosphoric, monohydrogen phosphoric, dihydrogen phosphoric, phthalic, polygalactouronic, propionic, salicylic, stearic, succinic, sulfamic, sulfanlic, sulfonic, sulfuric, tannic, tartaric, teolic, tolunesulfonic, polyglutamic, polyaspartic and the like. Pharmaceutically acceptable salts can be derived from amino acids, including, but not limited to, cysteine. Other pharmaceutically acceptable salts can be found, for example, in Stahl et al., Handbook of Pharmaceutical Salts: Properties, Selection, and Use, Wiley-VCH, Verlag Helvetica Chimica Acta, Zurich, 2002. (ISBN 3-906390-26-8).

4b: Efficacy

[0165] Typically, a compound of the invention, or pharmaceutically acceptable salt thereof, is administered to a subject in a diagnostically or therapeutically effective amount. One skilled in the art generally can determine an appropriate dosage.

[0166] Compositions for oral administration can be, for example, prepared in a manner such that a single dose in one or more oral preparations contains at least about 20 mg of the leukemia-targeting agent compound per square meter of subject body surface area, or at least about 50, 100, 150, 200, 300, 400, or 500 mg of the leukemia-targeting agent compound per square meter of
subject body surface area (the average body surface area for a human is, for example, 1.8 square meters). In particular, a single dose of a composition for oral administration can contain from about 20 to about 600 mg, and in certain aspects from about 20 to about 400 mg, in another aspect from about 20 to about 300 mg, and in yet another aspect from about 20 to about 200 mg of the leukemia-targeting agent compound per square meter of subject body surface area. Compositions for parenteral administration can be prepared in a manner such that a single dose contains at least about 20 mg of the leukemia-targeting agent compound per square meter of subject body surface area, or at least about 40, 50, 100, 150, 200, 300, 400, or 500 mg of the leukemia-targeting agent compound per square meter of subject body surface area. In particular, a single dose in one or more parenteral preparations contains from about 20 to about 500 mg, and in certain aspects from about 20 to about 400 mg, and in another aspect from about 20 to about 450 mg, and in yet another aspect from about 20 to about 350 mg of the leukemia-targeting agent per square meter of subject body surface area. It should be recognized that these oral and parenteral dosage ranges represent generally preferred dosage ranges, and are not intended to limit the invention. The dosage regimen actually employed can vary widely, and, therefore, can deviate from the generally preferred dosage regimen. It is contemplated that one skilled in the art will tailor these ranges to the individual subject.

[0167] Toxicity and therapeutic efficacy of such compounds and bioconjugates can be determined by standard pharmaceutical procedures in cell cultures or experimental animals for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀, (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index that can be expressed as the ratio LD₅₀/ED₅₀. Compounds and bioconjugates that exhibit large therapeutic indices are preferred. While compounds and bioconjugates exhibiting toxic side effects can be used, care should be taken to design a delivery system that targets such compounds and bioconjugates to the site affected by the disease or disorder in order to minimize potential damage to unaffected cells and reduce side effects.

[0168] Data obtained from the cell culture assays and animal studies can be used in formulating a range of dosages for use in humans and other mammals. The dosage of such compounds and bioconjugates lies preferably within a range of circulating plasma or other bodily fluid concentrations that include the ED₅₀ and provides clinically efficacious results (i.e., reduction in disease symptoms). The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound and bioconjugate of the present invention, the therapeutically effective amount can be estimated initially from cell culture assays. A dosage can be formulated in animal models to achieve a circulating plasma concentration range that includes the ED₅₀ (the concentration of the test compound that achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful dosages in humans and other mammals. Compound and
bioconjugate levels in plasma can be measured, for example, by high performance liquid chromatography.

[01 69] An amount of a compound or bioconjugate that can be combined with a pharmaceutically acceptable carrier to produce a single dosage form will vary depending upon the patient treated and the particular mode of administration. It will be appreciated by those skilled in the art that the unit content of a compound/bioconjugate contained in an individual dose of each dosage form need not in itself constitute a therapeutically effective amount, as the necessary therapeutically effective amount could be reached by administration of a number of individual doses. The selection of dosage depends upon the dosage form utilized, the condition being treated, and the particular purpose to be achieved according to the determination of those skilled in the art.

[01 70] The dosage and dosage regime for treating a disease or condition can be selected in accordance with a variety of factors, including the type, age, weight, sex, diet and/or medical condition of the patient, the route of administration, pharmacological considerations such as activity, efficacy, pharmacokinetic and/or toxicology profiles of the particular compound/bioconjugate employed, whether a compound/bioconjugate delivery system is utilized, and/or whether the compound/bioconjugate is administered as a pro-drug or part of a drug combination. Thus, the dosage regime actually employed can vary widely from subject to subject, or disease to disease and different routes of administration can be employed in different clinical settings.

[01 71] The identified compounds/bioconjugates monitor, treat, inhibit, control and/or prevent, or at least partially arrest or partially prevent, diseases and conditions of interest and can be administered to a subject at therapeutically effective amounts and optionally diagnostically effective amounts. Compositions/formulations of the present invention comprise a therapeutically effective amount (which can optionally include a diagnostically effective amount) of at least one compound or bioconjugate of the present invention. Subjects receiving treatment that includes a compound/bioconjugate of the invention are preferably animals (e.g., mammals, reptiles and/or avians), more preferably humans, horses, cows, dogs, cats, sheep, pigs, and/or chickens, and most preferably humans.

4c: Administration

[01 72] The preferred composition depends on the route of administration. Any route of administration can be used as long as the target of the compound or pharmaceutically acceptable salt is available via that route. Suitable routes of administration include, for example, oral, intravenous, parenteral, inhalation, rectal, nasal, topical (e.g., transdermal and intraocular), intravesical, intrathecal, enteral, pulmonary, intralymphatic, intracavitary, vaginal, transurethral, intradermal, aural, intramammary, buccal, orthotopic, intratracheal, intralesional, percutaneous, endoscopical, transmucosal, sublingual, and intestinal administration.
In an embodiment, the invention provides a method for treating a medical condition comprising administering to a subject (e.g. patient) in need thereof, a therapeutically effective amount of a composition of the invention, such as a compound of any one of formulas (FX1) - (FX32). In an embodiment, the invention provides a method for diagnosing or aiding in the diagnosis of a medical condition comprising administering to a subject in need thereof, a diagnostically effective amount of a composition of the invention. In an embodiment, the medical condition is leukemia or cancer, or various other diseases, injuries, and disorders, including cardiovascular disorders such as atherosclerosis and vascular restenosis, inflammatory diseases, ophthalmic diseases and dermatological diseases.

The diagnostic and therapeutic formulations of this invention can be administered alone, but can be administered with a pharmaceutical carrier selected upon the basis of the chosen route of administration and standard pharmaceutical practice.

Any suitable form of administration can be employed in connection with the diagnostic and therapeutic formulations of the invention. The diagnostic and therapeutic formulations of this invention can be administered intravenously, in oral dosage forms, intraperitoneally, subcutaneously, or intramuscularly, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

The present compositions, preparations and formulations can be formulated into diagnostic or therapeutic compositions for enteral, parenteral, topical, aerosol, inhalation, or cutaneous administration. Topical or cutaneous delivery of the compositions, preparations and formulations can also include aerosol formulation, creams, gels, solutions, etc. The present compositions, preparations and formulations are administered in doses effective to achieve the desired diagnostic and/or therapeutic effect. Such doses can vary widely depending upon the particular compositions employed in the composition, the organs or tissues to be examined, the equipment employed in the clinical procedure, the efficacy of the treatment achieved, and the like. These compositions, preparations and formulations contain an effective amount of the composition(s), along with conventional pharmaceutical carriers and excipients appropriate for the type of administration contemplated. These compositions, preparations and formulations can also optionally include stabilizing agents and skin penetration enhancing agents.

(i) \textit{Parenteral Administration}

Compounds and bioconjugates of the present invention can be formulated for parenteral administration by injection (e.g., by bolus injection or continuous infusion). Formulations for injection can be presented in unit dosage form in ampoules or in multi-dose containers with an optional preservative added. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass, plastic or the like. The formulation can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents.
For example, a parenteral preparation can be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent (e.g., as a solution in 1,3-butanediol). Among the acceptable vehicles and solvents that can be employed are water, Ringer’s solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid can be used in the parenteral preparation.

Alternatively, compounds and bioconjugates of the present invention can be formulated in powder form for constitution with a suitable vehicle, such as sterile pyrogen-free water, before use. For example, a compound/bioconjugate suitable for parenteral administration can include a sterile isotonic saline solution containing between 0.1 percent and 90 percent weight per volume of the compound/bioconjugate. By way of example, a solution can contain from about 5 percent to about 20 percent, more preferably from about 5 percent to about 17 percent, more preferably from about 8 to about 14 percent, and still more preferably about 10 percent weight per volume of the compound/bioconjugate. The solution or powder preparation can also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Other methods of parenteral delivery of compounds/bioconjugates will be known to the skilled artisan and are within the scope of the invention.

(ii) Oral Administration

For oral administration, a compound/bioconjugate of the invention can be formulated to take the form of tablets or capsules prepared by conventional means with one or more pharmaceutically acceptable carriers (e.g., excipients such as binding agents, fillers, lubricants and disintegrants).

(iii) Controlled-Release Administration

Controlled-release (or sustained-release) preparations can be formulated to extend the activity of a compound/bioconjugate and reduce dosage frequency. Controlled-release preparations can also be used to effect the time of onset of action or other characteristics, such as blood levels of the compound/bioconjugate, and consequently affect the occurrence of side effects.

Controlled-release preparations can be designed to initially release an amount of a compound/bioconjugate that produces the desired therapeutic effect, and gradually and continually release other amounts of the compound/bioconjugate to maintain the level of therapeutic effect over an extended period of time. In order to maintain a near-constant level of a compound/bioconjugate in the body, the compound/bioconjugate can be released from the dosage form at a rate that will replace the amount of compound/bioconjugate being metabolized and/or excreted from the body. The controlled-release of a compound/bioconjugate can be stimulated by
various inducers, e.g., change in pH, change in temperature, enzymes, water, and/or other physiological conditions or molecules.

[0183] Controlled-release systems can include, for example, an infusion pump which can be used to administer the compound/bioconjugate in a manner similar to that used for delivering insulin or chemotherapy to the body generally, or to specific organs or tumors. Typically, using such a system, the compound/bioconjugate is administered in combination with a biodegradable, biocompatible polymeric implant that releases the compound/bioconjugate over a controlled period of time at a selected site. Examples of polymeric materials include polyanhydrides, polyorthoesters, polyglycolic acid, polyactic acid, polyethylene vinyl acetate, (PEG) polyethylene glycol and copolymers and combinations thereof. In addition, a controlled release system can be placed in proximity of a therapeutic target (e.g., organ, tissue, or group of cells), thus requiring only a fraction of a systemic dosage.

[0184] Compounds/bioconjugates of the invention can be administered by other controlled-release means or delivery devices that are well known to those of ordinary skill in the art. These include, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or the like, or a combination of any of the above to provide the desired release profile in varying proportions. Other methods of controlled-release delivery of compounds/bioconjugates will be known to the skilled artisan and are within the scope of the invention.

(iv) Inhalation Administration

[0185] Compounds/bioconjugates of the invention can be administered directly to the lung of a patient/subject by inhalation. For administration by inhalation, a compound/bioconjugate can be conveniently delivered to the lung by a number of different devices. For example, a Metered Dose Inhaler ("MDI") which utilizes canisters that contain a suitable low boiling point propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas can be used to deliver a compound/bioconjugate directly to the lung. MDI devices are available from a number of suppliers such as 3M Corporation, Aventis, Boehringer Ingleheim, Forest Laboratories, GlaxoSmithKline, Merck & Co. and Vectura.

[0186] Alternatively, a Dry Powder Inhaler (DPI) device can be used to administer a compound/bioconjugate to the lung. DPI devices typically use a mechanism such as a burst of gas to create a cloud of dry powder inside a container, which can then be inhaled by the patient. DPI devices are also well known in the art and can be purchased from a number of vendors which include, for example, GlaxoSmithKline, Nektar Therapeutics, Innovata and Vectura. A popular variation is the multiple dose DPI ("MDDPI") system, which allows for the delivery of more than one therapeutic dose. MDDPI devices are available from companies such as AstraZeneca, GlaxoSmithKline, TEVA, Merck & Co., SkyePharma and Vectura. For example, capsules and cartridges of gelatin for use in an inhaler or insufflator can be formulated containing a powder mix.
of the compound/bioconjugate and a suitable powder base such as lactose or starch for these systems.

[0187] Another type of device that can be used to deliver a compound/bioconjugate to the lung is a liquid spray device supplied, for example, by Aradigm Corporation. Liquid spray systems use extremely small nozzle holes to aerosolize liquid compound/bioconjugate formulations that can then be directly inhaled into the lung. For example, a nebulizer device can be used to deliver a compound/bioconjugate to the lung. Nebulizers create aerosols from liquid compound/bioconjugate formulations by using, for example, ultrasonic energy to form fine particles that can be readily inhaled. Examples of nebulizers include devices supplied by Aventis and Battelle.

[0188] In another example, an electrohydrodynamic ("EHD") aerosol device can be used to deliver a compound/bioconjugate to the lung. EHD aerosol devices use electrical energy to aerosolize liquid compound/bioconjugate solutions or suspensions. The electrochemical properties of the compound/bioconjugate formulation are important parameters to optimize when delivering this compound/bioconjugate to the lung with an EHD aerosol device. Such optimization is routinely performed by one of skill in the art. Other methods of intra-pulmonary delivery of compounds/bioconjugates will be known to the skilled artisan and are within the scope of the invention.

[0189] Liquid compound/bioconjugate formulations suitable for use with nebulizers and liquid spray devices and EHD aerosol devices will typically include the compound/bioconjugate with a pharmaceutically acceptable carrier. In one exemplary embodiment, the pharmaceutically acceptable carrier is a liquid such as alcohol, water, polyethylene glycol or a perfluorocarbon. Optionally, another material can be added to alter the aerosol properties of the solution or suspension of the compound/bioconjugate. For example, this material can be a liquid such as an alcohol, glycol, polyglycol or a fatty acid. Other methods of formulating liquid compound/bioconjugate solutions or suspensions suitable for use in aerosol devices are known to those of skill in the art.

(v) Depot Administration

[0190] A compound/bioconjugate of the invention can be formulated as a depot preparation. Such long-acting formulations can be administered by implantation (e.g., subcutaneously or intramuscularly) or by intramuscular injection. Accordingly, the compound/bioconjugate can be formulated with suitable polymeric or hydrophobic materials such as an emulsion in an acceptable oil or ion exchange resin, or as sparingly soluble derivatives such as a sparingly soluble salt. Other methods of depot delivery of compounds/bioconjugates will be known to the skilled artisan and are within the scope of the invention.

(vi) Topical Administration
[0191] For topical application, a compound/bioconjugate can be combined with a pharmaceutically acceptable carrier so that an effective dosage is delivered, based on the desired activity ranging from an effective dosage, for example, of 1.0 µM to 1.0 mM in one aspect of the invention, a topical formulation of a compound/bioconjugate can be applied to the skin. The pharmaceutically acceptable carrier can be in the form of, for example, and not by way of limitation, an ointment, cream, gel, paste, foam, aerosol, suppository, pad or gelled stick.

[0192] A topical formulation can include a therapeutically effective amount of a compound/bioconjugate in an ophthalmologically acceptable excipient such as buffered saline, mineral oil, vegetable oils such as corn or arachis oil, petroleum jelly, Miglyol 182, alcohol solutions, or liposomes or liposome-like products. Any of these formulations of such compounds/bioconjugates can include preservatives, antioxidants, antibiotics, immunosuppressants, and other biologically or pharmaceutically effective agents that do not exert a significant detrimental effect on the compound/bioconjugate. Other methods of topical delivery of compounds/bioconjugates will be known to the skilled artisan and are within the scope of the invention.

(vii) Rectal Administration

[0193] Compounds/bioconjugates of the invention can be formulated in rectal formulations such as suppositories or retention enemas that include conventional suppository bases such as cocoa butter or other glycerides and/or binders and/or carriers such as triglycerides, microcrystalline cellulose, gum tragacanth or gelatin. Rectal formulations can contain a compound/bioconjugate in the range of 0.5% to 10% by weight, for example. Other methods of rectal delivery of compounds/bioconjugates will be known to the skilled artisan and are within the scope of the invention.

(viii) Other Systems of Administration

[0194] Various other delivery systems are known in the art and can be used to administer the compounds/bioconjugates of the invention. Moreover, these and other delivery systems can be combined and/or modified to promote optimization of the administration of compounds/bioconjugates of the present invention. Exemplary formulations that include compounds/bioconjugates of the present invention are described elsewhere herein (the compounds/bioconjugates of the present invention are indicated as the active ingredient, but those of skill in the art will recognize that pro-drugs and compound combinations are also meant to be encompassed by this term).

4d: Formulation

[0195] Compositions of the invention includes formulations and preparations comprising one or more of the present optical agents provided in an aqueous solution, such as a pharmaceutically acceptable formulation or preparation. Optionally, compositions of the invention further comprise
one or more pharmaceutically acceptable surfactants, buffers, electrolytes, salts, carriers, binders, coatings, preservatives and/or excipients.

[0196] In an embodiment, the invention provides a pharmaceutical formulation having an active ingredient comprising composition of the invention, such as a compound of any one of formulae (FX1) - (FX32). In an embodiment, the invention provides a method of synthesizing a composition of the invention or a pharmaceutical formulation thereof, such as a compound of any one of formulae (FX1) - (FX32). In an embodiment, a pharmaceutical formulation comprises one or more excipients, carriers, diluents, and/or other components as would be understood in the art. Preferably, the components meet the standards of the National Formulary ("NF"), United States Pharmacopoeia ("USP"; United States Pharmacopeial Convention Inc., Rockville, Maryland), or Handbook of Pharmaceutical Manufacturing Formulations (Sarfraz K. Niazi, all volumes, ISBN: 9780849317521, ISBN 10: 0849317525; CRC Press, 2004). See, e.g., United States Pharmacopeia and National Formulary (USP 30-NF 25), Rockville, MD: United States Pharmacopeial Convention; 2007; and 2008, and each of any earlier editions; The Handbook of Pharmaceutical Excipients, published jointly by the American Pharmacists Association and the Pharmaceutical Press (Pharmaceutical Press (2005) (ISBN-10: 0853696187, ISBN-13: 978-0853696186); Merck Index, Merck & Co., Rahway, N.J.; and Gilman et al., (eds) (1996); Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press. In embodiments, the formulation base of the formulations of the invention comprises physiologically acceptable excipients, namely, at least one binder and optionally other physiologically acceptable excipients. Physiologically acceptable excipients are those known to be usable in the pharmaceutical technology sectors and adjacent areas, particularly, those listed in relevant pharmacopoeias (e.g. DAB, Ph. Eur., BP, NF, USP), as well as other excipients whose properties do not impair a physiological use.

[0197] In an embodiment, an effective amount of a composition of the invention is a therapeutically effective amount. As used herein, the phrase "therapeutically effective" qualifies the amount of compound administered in the therapy. This amount achieves the goal of ameliorating, suppressing, eradicating, preventing, reducing the risk of, or delaying the onset of a targeted condition, such as leukemia, cancer or inflammation. In an embodiment, a therapeutically effective amount is an amount of a compound administered to a target tissue for attenuating or preventing tumor growth, proliferation and/or metastasis. In an embodiment, an effective amount of a composition of the invention is a diagnostically effective amount. As used herein, the phrase "diagnostically effective" qualifies the amount of compound administered in diagnosis or prognosis. The amount achieves the goal of being optically detectable while avoiding adverse side effects that may be observed with higher doses. In an embodiment, for example, an active ingredient or other component is included in a therapeutically acceptable amount. In an embodiment, an active ingredient or other component is included in a diagnostically effective amount. A diagnostically
effective amount of electromagnetic radiation refers to an amount upon exposure to an optical agent of the present invention resulting in optical detection and/or imaging.

[0198] Compounds of this invention and compounds useful in the methods of this invention include those of the compounds and formula(s) described herein and pharmaceutically-acceptable salts and esters of those compounds. In embodiments, salts include any salts derived from the acids of the formulas herein which acceptable for use in human or veterinary applications. In embodiments, the term "esters" refers to hydrolyzable esters of compounds of the names and structural formulas herein. In embodiments, salts and esters of the compounds of the formulas herein can include those which have the same or better therapeutic, diagnostic, or pharmaceutical (human or veterinary) general properties as the compounds of the formulas herein. In an embodiment, a composition of the invention is a compound or salt or ester thereof suitable for pharmaceutical formulations.

[0199] In an embodiment, the invention provides a method for treating a medical condition comprising administering to a subject (e.g. patient) in need thereof, a therapeutically effective amount of a composition of the invention, such as a compound of any one of formulae (FX1) - (FX32). In an embodiment, the medical condition is leukemia, cancer, or various other diseases, injuries, and disorders, including cardiovascular disorders such as coronary thrombosis, atherosclerosis and vascular restenosis, and inflammatory diseases such as osteoporosis and rheumatoid arthritis.

[0200] Formulations for enteral administration may vary widely, as is well known in the art. In general, such formulations are liquids, which include an effective amount of the inventive agent in aqueous solution or suspension. Such enteral compositions may optionally include buffers, surfactants, thixotropic agents, and the like. Compositions for oral administration may also contain flavoring agents and other ingredients for enhancing their organoleptic qualities.

[0201] In one embodiment, the optically functional leukemia targeting bioconjugates are formulated as nanoparticles or microparticles. Use of such nanoparticle or microparticle formulations may be beneficial for some applications to enhance delivery, localization, target specificity, administration, etc. of the optically functional leukemia targeting bioconjugates. Potentially useful nanoparticles and microparticles include, but are not limited to, micelles, liposomes, microemulsions, nanoemulsions, vesicles, tubular micelles, cylindrical micelles, bilayers, folded sheets structures, globular aggregates, swollen micelles, inclusion complex, encapsulated droplets, microcapsules, nanocapsules or the like. As will be understood by those having skill in the art, the optically functional leukemia targeting bioconjugates can be located inside the nanoparticle or microparticle, within a membrane or wall of the nanoparticle or microparticle, or outside of (but bonded to or otherwise associated with) the nanoparticle or microparticle. The agent formulated in nanoparticles or microparticles may be administered by any of the routes previously described. In a formulation applied topically, the optical agent is slowly
released over time. In an injectable formulation, the liposome, micelle, capsule, etc., circulates in the bloodstream and is delivered to the desired site (e.g., target tissue).

[0202] Preparation and loading of nanoparticles and microparticles are well known in the art. As one example, liposomes may be prepared from dipalmitoyl phosphatidylcholine (DPPC) or egg phosphatidylcholine (PC) because this lipid has a low heat transition. Liposomes are made using standard procedures as known to one skilled in the art (e.g., Braun-Falco et al., (Eds.), Griesbach Conference, Liposome Dermatics, Springer-Verlag, Berlin (1992), pp. 69 81; 91 117 which is expressly incorporated by reference herein). Polyacrylactone, poly(glycolic) acid, poly(lactic) acid, polyanhydride or lipids may be formulated as microspheres. As an illustrative example, the optically functional leukemia targeting bioconjugate may be mixed with polyvinyl alcohol (PVA), the mixture then dried and coated with ethylene vinyl acetate, then cooled again with PVA. In a liposome, the optically functional leukemia targeting bioconjugate may be within one or both lipid bilayers, in the aqueous between the bilayers, or with the center or core. Liposomes may be modified with other molecules and lipids to form a cationic liposome. Liposomes may also be modified with lipids to render their surface more hydrophilic which increases their circulation time in the bloodstream. The thus-modified liposome has been termed a "stealth" liposome, or a long-lived liposome, as described in U.S. Pat. No. 6,258,378, and in Stealth Liposomes, Lasic and Martin (Eds.) 1995 CRC Press, London, which are expressly incorporated by reference herein. Encapsulation methods include detergent dialysis, freeze drying, film forming, injection, as known to one skilled in the art and disclosed in, for example, U.S. Pat. No. 6,406,713 which is expressly incorporated by reference herein in its entirety.

[0203] In an embodiment, the invention provides a medicament which comprises a therapeutically effective amount of one or more compositions of the invention, such as a compound of any one of formulae (FX1) - (FX32). In an embodiment, the invention provides a medicament which comprises a diagnostically effective amount of one or more compositions of the invention. In an embodiment, the invention provides a method for making a medicament for treatment of a condition described herein. In an embodiment, the invention provides a method for making a medicament for diagnosis or aiding in the diagnosis of a condition described herein. In an embodiment, the invention provides the use of one or more compositions set forth herein for the making of a medicament.

[0204] Compounds of the invention can have prodrug forms. Prodrugs of the compounds of the invention are useful in embodiments including compositions and methods. Any compound that will be converted in vivo to provide a biologically, pharmaceutically, diagnostically, or therapeutically active form of a compound of the invention is a prodrug. Various examples and forms of prodrugs are well known in the art. Examples of prodrugs are found, inter alia, in Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985), Methods in Enzymology, Vol. 42, at pp. 309-396, edited by K. Widder, et. al. (Academic Press, 1985); A Textbook of Drug Design and Development, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H.

[0205] The invention contemplates pharmaceutically active compounds either chemically synthesized or formed by in vivo biotransformation to compounds set forth herein.

[0206] In an embodiment, a composition of the invention is isolated or purified. In an embodiment, an isolated or purified compound may be at least partially isolated or purified as would be understood in the art.

[0207] Typically, a compound of the present invention, or pharmaceutically acceptable salt thereof, is administered to a subject in a diagnostically or therapeutically effective amount. One skilled in the art generally can determine an appropriate dosage. Factors affecting a particular dosage regimen (including the amount of compound delivered, frequency of administration, and whether administration is continuous or intermittent) include, for example, the type, age, weight, sex, diet, and condition of the subject; the type of pathological condition and its severity; and the nature of the desired effect. Pharmacological considerations include optically functional leukemia targeting bioconjugate compound activity, efficacy, pharmacokinetic, and toxicology profiles of the particular optically functional leukemia targeting bioconjugate compound used; the route of administration and whether a drug delivery system is utilized; and whether the optically functional leukemia targeting bioconjugate is administered as part of a combination therapy (e.g., whether the agent is administered in combination with one or more active compounds, other agents, radiation, and the like).

[0208] Compositions for oral administration may be, for example, prepared in a manner such that a single dose in one or more oral preparations contains at least about 20 mg of the optically functional leukemia targeting bioconjugate per square meter of subject body surface area, or at least about 50, 100, 150, 200, 300, 400, or 500 mg of the optically functional leukemia targeting bioconjugate per square meter of subject body surface area (the average body surface area for a human is, for example, 1.8 square meters). In particular, a single dose of a composition for oral
administration can contain from about 20 to about 600 mg, and in certain aspects from about 20 to about 400 mg, in another aspect from about 20 to about 300 mg, and in yet another aspect from about 20 to about 200 mg of the optically functional leukemia targeting bioconjugate per square meter of subject body surface area. Compositions for parenteral administration can be prepared in a manner such that a single dose contains at least about 20 mg of the optically functional leukemia targeting bioconjugate per square meter of subject body surface area, or at least about 40, 50, 100, 150, 200, 300, 400, or 500 mg of the optically functional leukemia targeting bioconjugate per square meter of subject body surface area. In particular, a single dose in one or more parenteral preparations contains from about 20 to about 500 mg, and in certain aspects from about 20 to about 400, and in another aspect from about 20 to about 400 mg, and in yet another aspect from about 20 to about 350 mg of the optically functional leukemia targeting bioconjugate per square meter of subject body surface area. It should be recognized that these oral and parenteral dosage ranges represent generally preferred dosage ranges, and are not intended to limit the invention. The dosage regimen actually employed can vary widely, and, therefore, can deviate from the generally preferred dosage regimen. It is contemplated that one skilled in the art will tailor these ranges to the individual subject.

[0209] In an embodiment, a therapeutically or diagnostically effective amount of the optical agent is provided to the subject. For example, parenteral or intravenous administration advantageously contains a sterile aqueous solution or suspension of the optical agent having a concentration of a compound of any one of formulae (FX1) - (FX32) ranging from about 1 nM to about 0.5M. Preferred parenteral or intravenous formulations for some applications have a concentration of the compound of any one of formulae (FX1) - (FX32) selected over the range of 1 \( \mu \)M to 10 \( \mu \)M. Such solutions also may contain pharmaceutically acceptable buffers, emulsifiers, surfactants, and, optionally, electrolytes such as sodium chloride. In an embodiment, the dose of the compound of any one of formulae (FX1) - (FX32) may vary from 0.1 to 500 mg/kg body weight, preferably from 0.5 to 2 mg/kg body weight.

[0210] As indicated above, it is contemplated that the optically functional leukemia targeting bioconjugate compounds and pharmaceutically acceptable salts of the present invention may be used as part of a combination therapy. The term "combination therapy" means the administration of two or more compounds directed to the target condition. The treatments of the combination generally may be co-administered in a simultaneous manner. Two compounds can be co-administered as, for example: (a) a single formulation (e.g., a single capsule) having a fixed ratio of active ingredients; or (b) multiple, separate formulations (e.g., multiple capsules) for each compound. The treatments of the combination may alternatively (or additionally) be administered at different times.

[0211] It is further contemplated that the optically functional leukemia targeting bioconjugate compounds and salts of this invention can be used in the form of a kit that is suitable for use in performing the methods described herein, packaged in a container. The kit can contain the
optically functional leukemia targeting bioconjugate compound or compounds and, optionally, appropriate diluents, devices or device components suitable for administration and instructions for use in accordance with the methods of the present invention. The devices can include parenteral injection devices, such as syringes or transdermal patch or the like. Device components can include cartridges for use in injection devices and the like. In one aspect, the kit includes a first dosage form including a optically functional leukemia targeting bioconjugate compound or salt of this invention and a second dosage form including another active ingredient in quantities sufficient to carry out the methods of the present invention. The first dosage form and the second dosage form together can include a therapeutically effective amount of the compounds for treating the targeted condition(s).

[0212] This invention also is directed, in part, to pharmaceutical compositions including a therapeutically effective amount of a compound or salt of this invention, as well as processes for making such compositions. Such compositions generally include one or more pharmaceutically acceptable carriers (e.g., excipients, vehicles, auxiliaries, adjuvants, diluents) and may include other active ingredients. Formulation of these compositions may be achieved by various methods known in the art. A general discussion of these methods may be found in, for example, Hoover, John E., Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA: 1975). See also, Lachman, L., eds., Pharmaceutical Dosage Forms (Marcel Decker, New York, N. Y., 1980).

[0213] The preferred composition depends on the route of administration. Any route of administration may be used as long as the target of the compound or pharmaceutically acceptable salt is available via that route. Suitable routes of administration include, for example, oral, parenteral, inhalation, rectal, nasal, topical (e.g., transdermal and intraocular), intravesical, intrathecal, enteral, pulmonary, intralymphatic, intracavitial, vaginal, transurethral, intradermal, aural, intramammary, buccal, orthotopic, intratracheal, intralesional, percutaneous, endoscopic, transmucosal, sublingual, and intestinal administration.

[0214] Pharmaceutically acceptable carriers that may be used in conjunction with the compounds of the invention are well known to those of ordinary skill in the art. Carriers can be selected based on a number of factors including, for example, the particular optically functional leukemia targeting bioconjugate compound(s) or pharmaceutically acceptable salt(s) used; the compound's concentration, stability, and intended bioavailability; the condition being treated; the subject's age, size, and general condition; the route of administration; etc. A general discussion related to carriers may be found in, for example, J.G. Nairn, Remington's Pharmaceutical Science, pp. 1492-1517 (A. Gennaro, ed., Mack Publishing Co., Easton, Pa. (1985)).

[0215] Solid dosage forms for oral administration include, for example, capsules, tablets, gelcaps, pills, dragees, troches, powders, granules, and lozenges. In such solid dosage forms, the compounds or pharmaceutically acceptable salts thereof can be combined with one or more pharmaceutically acceptable carriers. The compounds and pharmaceutically acceptable salts
thereof can be mixed with carriers including, but not limited to, lactose, sucrose, starch powder, corn starch, potato starch, magnesium carbonate, microcrystalline cellulose, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, sodium carbonate, agar, mannitol, sorbitol, sodium saccharin, gelatin, acacia gum, alginic acid, sodium alginate, tragacanth, colloidal silicon dioxide, croscarmellose sodium, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation, as can be provided in a dispersion of the compound or salt in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms also can include buffering agents, such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills additionally can, for example, include a coating (e.g., an enteric coating) to delay disintegration and absorption. The concentration of the optically functional leukemia targeting bioconjugate compound in a solid oral dosage form can be from about 5 to about 50%, and in certain aspects from about 8 to about 40%, and in another aspect from about 10 to about 30%) by weight based on the total weight of the composition.

[0216] Liquid dosage forms of the compounds of the present invention for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (e.g., water). Such compositions also can include adjuvants, such as wetting, emulsifying, suspending, flavoring (e.g., sweetening), and/or perfuming agents. The concentration of the optically functional leukemia targeting bioconjugate compound in the liquid dosage form can be from about 0.01 to about 5 mg, and in certain aspects from about 0.01 to about 1 mg, and in another aspect from about 0.01 to about 0.5 mg per ml of the composition. Low concentrations of the compounds of the present invention in liquid dosage form can be prepared in the case that the optically functional leukemia targeting bioconjugate compound is more soluble at low concentrations. Techniques for making oral dosage forms useful in the present invention are generally described in, for example, Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors (1979)). See also, Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981). See also, Ansel, Introduction to Pharmaceutical Dosage Forms (2nd Edition (1976)).

[0217] In some aspects of the present invention, tablets or powders for oral administration can be prepared by dissolving the optically functional leukemia targeting bioconjugate compound in a pharmaceutically acceptable solvent capable of dissolving the compound to form a solution and then evaporating when the solution is dried under vacuum. A carrier can also be added to the solution before drying. The resulting solution can be dried under vacuum to form a glass. The glass can then mixed with a binder to form a powder. This powder may be mixed with fillers or other conventional tableting agents, and then processed to form a tablet. Alternatively, the powder may be added to a liquid carrier to form a solution, emulsion, suspension, or the like.
In some aspects, solutions for oral administration are prepared by dissolving the optically functional leukemia targeting bioconjugate compound in a pharmaceutically acceptable solvent capable of dissolving the compound to form a solution. An appropriate volume of a carrier is added to the solution while stirring to form a pharmaceutically acceptable solution for oral administration.

"Parenteral administration" includes subcutaneous injections, intravenous injections, intraarterial injections, intraorbital injections, intracapsular injections, intraspinal injections, intraperitoneal injections, intramuscular injections, intrasternal injections, and infusion. Dosage forms suitable for parenteral administration include solutions, suspensions, dispersions, emulsions, and any other dosage form that can be administered parenterally.

Injectable preparations (e.g., sterile injectable aqueous or oleaginous suspensions) can be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents. Acceptable vehicles for parenteral use include both aqueous and nonaqueous pharmaceutically-acceptable solvents. Suitable pharmaceutically-acceptable aqueous solvents include, for example, water, saline solutions, dextrose solutions (e.g., such as DW5), electrolyte solutions, etc.

Suitable pharmaceutically-acceptable nonaqueous solvents include, but are not limited to, the following (as well as mixtures thereof): alcohols (these include, for example, o-glycerol formal, β-glycerol formal, 1, 3-butylene glycol, aliphatic or aromatic alcohols having from 2 to about 30 carbons (e.g., methanol, ethanol, propanol, isopropanol, butanol, t-butanol, hexanol, octanol, amylene hydrate, benzyl alcohol, glycerin (glycerol), glycol, hexylene glycol, tetrahydrofuranyl alcohol, cetyl alcohol, and stearyl alcohol), fatty acid esters of fatty alcohols (e.g., polyalkylene glycols, such as polypropylene glycol and polyethylene glycol), sorbitan, sucrose, and cholesterol); amides (these include, for example, dimethylacetamide (DMA), benzyl benzoate DMA, dimethylformamide, N-hydroxyethylO-lactamide, N, N-dimethylacetamide-amides, 2-pyrrolidinone, 1-methyl-2-pyrrolidinone, and polyvinylpyrrolidone); esters (these include, for example, acetate esters (e.g., monoacetin, diacetin, and triacetin), aliphatic and aromatic esters (e.g., ethyl caprylate or octanoate, alkyl oleate, benzyl benzoate, or benzyl acetate), dimethylsulfoxide (DMSO), esters of glycerin (e.g., mono, di, and tri-glyceryl citrates and tartrates), ethyl benzoate, ethyl acetate, ethyl carbonate, ethyl lactate, ethyl oleate, fatty acid esters of sorbitan, glyceryl monostearate, glyceride esters (e.g., mono, di, or tri-glycerides), fatty acid esters (e.g., isopropyl myristate), fatty acid derived PEG esters (e.g., PEG-hydroxyleate and PEG-hydroxystearate), N-methyl pyrrolidinone, pluronic 60, polyoxyethylene sorbitol oleic polyesters (e.g., poly(ethoxylated)_{30-60} sorbitol poly(oleate)_{2-4}, poly(oxyethylene)_{15-20} monooleolate, poly(oxyethylene)_{15-20} mono 12-hydroxystearate, and poly(oxyethylene)_{15-20} mono ricinoleate), polyoxyethylene sorbitan esters (e.g., polyoxyethylene-sorbitan monooleate, polyoxyethylene-sorbitan monopalmitate, polyoxyethylene-sorbitan monolaurate, polyoxyethylene-sorbitan monostearate, and POLYSORBATE 20, 40, 60, and 80 (from ICI Americas, Wilmington, DE)), polyvinylpyrrolidone,
alkyleneoxy modified fatty acid esters (e.g., polyoxyl 40 hydrogenated castor oil and polyoxyethylated castor oils, such as CREMOPHOR EL solution or CREMOPHOR RH 40 solution), saccharide fatty acid esters (i.e., the condensation product of a monosaccharide (e.g., pentoses, such as ribose, ribulose, arabinose, xylose, lyxose, and xylulose; hexoses, such as glucose, fructose, galactose, mannose, and sorbose; trioses; tetrose; heptoses; and octoses), disaccharide (e.g., sucrose, maltose, lactose, and trehalose), oligosaccharide, or a mixture thereof with one or more fatty acids (e.g., saturated fatty acids, such as caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, and stearic acid; and unsaturated fatty acids, such as palmitoleic acid, oleic acid, elaidic acid, erucic acid, and linoleic acid), and steroidal esters; ethers (these are typically alkyl, aryl, and cyclic ethers having from 2 to about 30 carbons. Examples include diethyl ether, tetrahydrofuran, dimethyl isosorbide, diethylene glycol monoethyl ether), and glycofurol (tetrahydrofurfuranyl alcohol polyethylene glycol ether); ketones (these typically have from about 3 to about 30 carbons. Examples include acetone, methyl ethyl ketone, methyl isobutyl ketone; hydrocarbons (these are typically aliphatic, cycloaliphatic, and aromatic hydrocarbons having from about 4 to about 30 carbons). Examples include benzene, cyclohexane, dichloromethane, dioxolanes, hexane, n-decane, n-dodecane, n-hexane, sulfolane, tetramethylenesulfone, tetramethylenesulfoxide, toluene, dimethylsulfoxide (DMSO); and tetramethylene sulfoxide; oils (these include oils of mineral, vegetable, animal, essential, or synthetic origin). These include mineral oils, such as aliphatic and wax-based hydrocarbons, aromatic hydrocarbons, mixed aliphatic and aromatic based hydrocarbons, and refined paraffin oil; vegetable oils, such as linseed, tung, safflower, soybean, castor, cottonseed, groundnut, rapeseed, coconut, palm, olive, corn, corn germ, sesame, persic, and peanut oil; glycerides, such as mono-, di-, and triglycerides; animal oils, such as fish, marine, sperm, cod-liver, haliver, squaine, squalane, and shark liver oil; oleic oils; and polyoxyethylated castor oil); alkyl, alkenyl, or aryl halides (these include alkyl or aryl halides having from 1 to about 30 carbons and one or more halogen substituents. Examples include methylene chloride); monoethanolamine; petroleum benzin; trolamine; omega-3 polyunsaturated fatty acids (e.g., alpha-linolenic acid, eicosapentaenoic acid, docosapentaenoic acid, or docosahexaenoic acid); polyglycol ester of 12-hydroxystearic acid and polyethylene glycol (SOLUTOL HS-15, from BASF, Ludwigshafen, Germany); polyoxyethylene glycerol; sodium laurate; sodium oleate; and sorbitan monooleate. Other pharmaceutically acceptable solvents for use in the invention are well known to those of ordinary skill in the art. General discussion relating to such solvents may be found in, for example, The Chemotherapy Source Book (Williams & Wilkins Publishing), The Handbook of Pharmaceutical Excipients, (American Pharmaceutical Association, Washington, D.C., and The Pharmaceutical Society of Great Britain, London, England, 1968), Modern Pharmaceutics 3d ed., (G. Banker et. al., eds., Marcel Dekker, Inc., New York, New York (1995)), The Pharmacological Basis of Therapeutics, (Goodman & Gilman, McGraw Hill Publishing), Pharmaceutical Dosage Forms, (H. Lieberman et. al., eds., Marcel Dekker, Inc., New York, New York (1980)), Remington’s Pharmaceutical Sciences, 19th ed., (A. Gennaro, ed., Mack Publishing, Easton, PA, (1995)), The

Solvents useful in the present invention include, but are not limited to, those known to stabilize the optically functional leukemia targeting bioconjugate compounds or pharmaceutically acceptable salts thereof. These typically include, for example, oils rich in triglycerides, such as safflower oil, soybean oil, and mixtures thereof; and alkyleneoxy-modified fatty acid esters, such as polyoxy 40 hydrogenated castor oil and polyoxyethylated castor oils (e.g., CREMOPHOR solution or CREMOPHOR RH 40 solution). Commercially available triglycerides include INTRALIPID emulsified soybean oil (Kabi-Pharmacia Inc., Stockholm, Sweden), NUTRALIPID emulsion (McGaw, Irvine, California), LIPOSYN II 20% emulsion (a 20% fat emulsion solution containing 100 mg safflower oil, 100 mg soybean oil, 12 mg egg phosphatides, and 25 mg glycerin per ml of solution; Abbott Laboratories, Chicago, IL), LIPOSYN III 2% emulsion (a 2% fat emulsion solution containing 100 mg safflower oil, 100 mg soybean oil, 12 mg egg phosphatides, and 25 mg glycerin per ml of solution; Abbott Laboratories, Chicago, IL), natural or synthetic glycerol derivatives containing the docosahexaenoxy group at levels of from about 25 to about 100% (by weight based on the total fatty acid content) (DHASCO from Martek Biosciences Corp., Columbia, MD; DHA MAGURO from Daito Enterprises, Los Angeles, CA; SOYACAL; and TRAVEMULSION). Ethanol in particular is a useful solvent for dissolving a optically functional leukemia targeting bioconjugate compound or pharmaceutically acceptable salt thereof to form solutions, emulsions, and the like.

Additional components can be included in the compositions of this invention for various purposes generally known in the pharmaceutical industry. These components tend to impart properties that, for example, enhance retention of the optically functional leukemia targeting bioconjugate compound or salt at the site of administration, protect the stability of the composition, control the pH, and facilitate processing of the optically functional leukemia targeting bioconjugate compound or salt into pharmaceutical formulations, and the like. Specific examples of such components include cryoprotective agents; agents for preventing reprecipitation of the optically functional leukemia targeting bioconjugate compound or salt surface; active, wetting, or emulsifying agents (e.g., lecithin, polysorbate-80, TWEEN 80, pluronic 60, and polyoxyethylene stearate); preservatives (e.g., ethyl-p-hydroxybenzoate); microbial preservatives (e.g., benzyl alcohol, phenol, m-cresol, chlorobutanol, sorbic acid, thimerosal, and paraben); agents for adjusting pH or buffering agents (e.g., acids, bases, sodium acetate, sorbitan monolaureate, etc.); agents for adjusting osmolarity (e.g., glycerin); thickeners (e.g., aluminum monostearate, stearic acid, cetyl alcohol, stearyl alcohol, guar gum, methyl cellulose, hydroxypropylcellulose, tristearin, cetyl wax esters, polyethylene glycol, etc.); colorants; dyes; flow aids; non-volatile silicones (e.g., cyclomethicone); clays (e.g., bentonites); adhesives; bulking agents; flavorings; sweeteners; adsorbents; fillers (e.g., sugars such as lactose, sucrose, mannitol, sorbitol, cellulose, calcium
phosphate, etc.); diluents (e.g., water, saline, electrolyte solutions, etc.); binders (e.g., gelatin; gum tragacanth; methyl cellulose; hydroxypropyl methylcellulose; sodium carboxymethyl cellulose; polyvinylpyrrolidone; sugars; polymers; acacia; starches, such as maize starch, wheat starch, rice starch, and potato starch; etc.); disintegrating agents (e.g., starches, such as maize starch, wheat starch, rice starch, potato starch, and carboxymethyl starch; cross-linked polyvinyl pyrrolidone; agar; alginic acid or a salt thereof, such as sodium alginate; croscarmellose sodium; cospovidone; etc.); lubricants (e.g., silica; talc; stearic acid and salts thereof, such as magnesium stearate; polyethylene glycol; etc.); coating agents (e.g., concentrated sugar solutions including gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, titanium dioxide, etc.); and antioxidants (e.g., sodium metabisulfite, sodium bisulfite, sodium sulfite, dextrose, phenols, thiophenols, etc.). Techniques and compositions for making parenteral dosage forms are generally known in the art. Formulations for parenteral administration may be prepared from one or more sterile powders and/or granules having a compound or salt of this invention and one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The powder or granule typically is added to an appropriate volume of a solvent (typically while agitating (e.g., stirring) the solvent) that is capable of dissolving the powder or granule. Particular solvents useful in the invention include, for example, water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers.

[0224] Emulsions for parenteral administration can be prepared by, for example, dissolving a compound or salt of this invention in any pharmaceutically acceptable solvent capable of dissolving the compound to form a solution; and adding an appropriate volume of a carrier, which is an emulsion, to the solution while stirring to form the emulsion. Solutions for parenteral administration can be prepared by, for example, dissolving a compound or salt of this invention in any pharmaceutically acceptable solvent capable of dissolving the compound to form a solution; and adding an appropriate volume of a carrier to the solution while stirring to form the solution.

[0225] Suppositories for rectal administration can be prepared by, for example, mixing the drug with a suitable nonirritating excipient that is solid at ordinary temperatures, but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter; synthetic mono-, di-, or triglycerides; fatty acids; and/or polyethylene glycols.

[0226] "Topical administration" includes the use of transdermal administration, such as transdermal patches or iontophoresis devices.

[0227] If desired, the emulsions or solutions described above for oral or parenteral administration can be packaged in IV bags, vials, or other conventional containers in concentrated form, and then diluted with a pharmaceutically acceptable liquid (e.g., saline) to form an acceptable optically functional leukemia targeting bioconjugate concentration before use.

76
Other adjuvants and modes of administration well known in the pharmaceutical art may also be used. Pharmaceutically acceptable salts comprise pharmaceutically-acceptable anions and/or cations. Pharmaceutically-acceptable cations include among others, alkali metal cations (e.g., Li⁺, Na⁺, K⁺), alkaline earth metal cations (e.g., Ca²⁺, Mg²⁺), non-toxic heavy metal cations and ammonium (NH₄⁺) and substituted ammonium (N(R')₄⁺, where R' is hydrogen, alkyl, or substituted alkyl, i.e., including, methyl, ethyl, or hydroxyethyl, specifically, trimethyl ammonium, triethyl ammonium, and triethanol ammonium cations). Pharmaceutically-acceptable anions include among other halides (e.g., Cl⁻, Br⁻), sulfate, acetates (e.g., acetate, trifluoroacetate), ascorbates, aspartates, benzoates, citrates, and lactate.

It is understood that this invention is not limited to the particular compounds, methodology, protocols, and reagents described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the invention which will be limited only by the appended claims.

Compositions of the invention includes formulations and preparations comprising one or more of the present compounds provided in an aqueous solution, such as a pharmaceutically acceptable formulation or preparation. Optionally, compositions of the invention further comprise one or more pharmaceutically acceptable surfactants, buffers, electrolytes, salts, carriers, binders, coatings, preservatives and/or excipients.

(i) Binding Agents

Binding agents include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof. Suitable forms of microcrystalline cellulose include, for example, the materials sold as AVICEL-PH-101, AVICEL-PH-103 and AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pennsylvania, USA). An exemplary suitable binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581 by FMC Corporation.

(ii) Fillers

Fillers include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), lactose, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

(iii) Lubricants
Lubricants include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, electromagnetic radiation mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, Maryland, USA), a coagulated aerosol of synthetic silica (marketed by Deaussa Co. of Piana, Texas, USA), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Massachusetts, USA), and mixtures thereof.

Disintegrants

Disintegrants include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polyacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

Tablets or capsules can optionally be coated by methods well known in the art. If binders and/or fillers are used with a compound/bioconjugate of the invention, they are typically formulated as about 50 to about 99 weight percent of the compound/bioconjugate. In one aspect, about 0.5 to about 15 weight percent of disintegrant, and particularly about 1 to about 5 weight percent of disintegrant, can be used in combination with the compound. A lubricant can optionally be added, typically in an amount of less than about 1 weight percent of the compound/bioconjugate. Techniques and pharmaceutically acceptable additives for making solid oral dosage forms are described in Marshall, SOLID ORAL DOSAGE FORMS, Modern Pharmaceutics (Banker and Rhodes, Eds.), 7:359-427 (1979). Other formulations are known in the art.

Liquid preparations for oral administration can take the form of solutions, syrups or suspensions. Alternatively, the liquid preparations can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and/or preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations can also contain buffer salts, flavoring, coloring, perfuming and sweetening agents as appropriate. Preparations for oral administration can also be formulated to achieve controlled release of the compound/bioconjugate. Oral formulations preferably contain 10% to 95% compound/bioconjugate. In addition, a compound/bioconjugate of the present invention can be formulated for buccal administration in the form of tablets or lozenges formulated in a conventional manner. Other methods of oral delivery of compounds/bioconjugates of the invention will be known to the skilled artisan and are within the scope of the invention.
Formulation 1

[0237] Hard gelatin capsules are prepared using the following ingredients:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>(mg/capsule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>250.0</td>
</tr>
<tr>
<td>Starch</td>
<td>305.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5.0</td>
</tr>
</tbody>
</table>

[0238] The above ingredients are mixed and filled into hard gelatin capsules in 560 mg quantities.

Formulation 2

[0239] A tablet formula is prepared using the following ingredients:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>(mg/tablet)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>250.0</td>
</tr>
<tr>
<td>Cellulose, microcrystalline</td>
<td>400.0</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>10.0</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>5.0</td>
</tr>
</tbody>
</table>

[0240] The components are blended and compressed to form tablets, each weighing 665 mg.

Formulation 3

[0241] A dry powder inhaler formulation is prepared containing the following components:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>5</td>
</tr>
<tr>
<td>Lactose</td>
<td>95</td>
</tr>
</tbody>
</table>

[0242] The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.
Formulation 4

[0243] Tablets, each containing 60 mg of active ingredient, are prepared as follows:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>milligrams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>60.0</td>
</tr>
<tr>
<td>Starch</td>
<td>45.0</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>35.0</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone (as 10% solution in water)</td>
<td>4.0</td>
</tr>
<tr>
<td>Sodium carboxymethyl starch</td>
<td>4.5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5</td>
</tr>
<tr>
<td>Talc</td>
<td>1.0</td>
</tr>
<tr>
<td>Total</td>
<td>150.0</td>
</tr>
</tbody>
</table>

[0244] The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a 16 mesh U.S. sieve. The granules as produced are dried at 50-60 °C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

[0245] Capsules, each containing 80 mg of active ingredient are made as follows:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>milligrams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>80.0</td>
</tr>
<tr>
<td>Starch</td>
<td>109.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.0</td>
</tr>
<tr>
<td>Total</td>
<td>190.0</td>
</tr>
</tbody>
</table>
The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 190 mg quantities.

**Formulation 6**

Suppositories, each containing 225 mg of active ingredient, are made as follows:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>milligrams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>225</td>
</tr>
<tr>
<td>Saturated fatty acid glycerides to</td>
<td>2000</td>
</tr>
</tbody>
</table>

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

**Formulation 7**

Suspensions, each containing 50 mg of active ingredient per 5.0 ml dose are made as follows:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>milligrams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>50.0 mg</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>4.0 mg</td>
</tr>
<tr>
<td>Sodium carboxymethyl cellulose (11%)</td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose (89%) 50.0 mg</td>
<td></td>
</tr>
<tr>
<td>Sucrose</td>
<td>1.75 g</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>10.0 mg</td>
</tr>
<tr>
<td>Flavor</td>
<td>q.v.</td>
</tr>
<tr>
<td>Color</td>
<td>q.v.</td>
</tr>
<tr>
<td>Purified water to</td>
<td>5.0 ml</td>
</tr>
</tbody>
</table>

The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with...
some of the water and added with stirring. Sufficient water is then added to produce the required volume.

**Formulation 8**

[0251] Capsules, each containing 150 mg of active ingredient, are made as follows:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>milligrams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>150.0</td>
</tr>
<tr>
<td>Starch</td>
<td>407.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>560.0</strong></td>
</tr>
</tbody>
</table>

[0252] The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 560 mg quantities.

4e: Kits

[0253] Various embodiments of the present invention include kits. Such kits can include a compound/bioconjugate of the present invention, optionally one or more ingredients for preparing a pharmaceutically acceptable formulation of the compound/bioconjugate, and instructions for use (e.g., administration). When supplied as a kit, different components of a compound/bioconjugate formulation can be packaged in separate containers and admixed immediately before use. Such packaging of the components separately can, if desired, be presented in a pack or dispenser device which can contain one or more unit dosage forms containing the compound/bioconjugate. The pack can, for example, comprise metal or plastic foil such as a blister pack. Such packaging of the components separately can also, in certain instances, permit long-term storage without losing activity of the components. In addition, if more than one route of administration is intended or more than one schedule for administration is intended, the different components can be packaged separately and not mixed prior to use. In various embodiments, the different components can be packaged in one combination for administration together.

[0254] It is further contemplated that the leukemia-targeting agent compounds and salts of this invention can be used in the form of a kit that is suitable for use in performing the methods described herein, packaged in a container. The kit can contain the leukemia-targeting agent compound or compounds and, optionally, appropriate diluents, devices or device components suitable for administration and instructions for use in accordance with the methods of the invention. The devices can include parenteral injection devices, such as syringes or transdermal patch or the like. Device components can include cartridges for use in injection devices and the
like. In one aspect, the kit includes a first dosage form including a leukemia-targeting agent compound or salt of this invention and a second dosage form including another active ingredient in quantities sufficient to carry out the methods of the invention. The first dosage form and the second dosage form together can include a therapeutically effective amount of the compounds for treating the targeted condition(s).

[0255] In certain embodiments, kits can be supplied with instructional materials. Instructions can be printed on paper or other substrate, and/or can be supplied as an electronic-readable medium, such as a floppy disc, mini-CD-ROM, CD-ROM, DVD-ROM, Zip disc, videotape, audio tape, and the like. Detailed instructions cannot be physically associated with the kit; instead, a user can be directed to an Internet web site specified by the manufacturer or distributor of the kit, or supplied as electronic mail.

[0256] If desired, the emulsions or solutions described above for oral or parenteral administration can be packaged in IV bags, vials, or other conventional containers in concentrated form, and then diluted with a pharmaceutically acceptable liquid (e.g., saline) to form an acceptable leukemia-targeting agent compound concentration before use.

[0257] Kits can include reagents in separate containers such as, for example, sterile water or saline to be added to a lyophilized active component packaged separately. For example, sealed glass ampules can contain lyophilized superoxide dismutase mimetics and in a separate ampule, sterile water, sterile saline or sterile each of which has been packaged under a neutral non-reacting gas, such as nitrogen. Ampules can consist of any suitable material, such as glass, organic polymers, such as polycarbonate, polystyrene, ceramic, metal or any other material typically employed to hold reagents. Other examples of suitable containers include bottles that can be fabricated from similar substances as ampules, and envelopes that can consist of foil-lined interiors, such as aluminum or an alloy. Other containers include test tubes, vials, flasks, bottles, syringes, and the like. Containers can have a sterile access port, such as a bottle having a stopper that can be pierced by a hypodermic injection needle. Other containers can have two compartments that are separated by a readily removable membrane that upon removal permits the components to mix. Removable membranes can be glass, plastic, rubber, and the like.

STATEMENTS REGARDING INCORPORATION BY REFERENCE AND VARIATIONS

[0258] All references throughout this application, for example patent documents including issued or granted patents or equivalents; patent application publications; and non-patent literature documents or other source material; are hereby incorporated by reference herein in their entireties, as though individually incorporated by reference, to the extent each reference is at least partially not inconsistent with the disclosure in this application (for example, a reference that is partially inconsistent is incorporated by reference except for the partially inconsistent portion of the reference).
[0259] The terms and expressions which have been employed herein are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the invention has been specifically disclosed by preferred embodiments, exemplary embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims. The specific embodiments provided herein are examples of useful embodiments of the invention and it will be apparent to one skilled in the art that the invention may be carried out using a large number of variations of the devices, device components, methods steps set forth in the present description. As will be obvious to one of skill in the art, methods and devices useful for the present methods can include a large number of optional composition and processing elements and steps.

[0260] It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and equivalents thereof known to those skilled in the art, and so forth. As well, the terms "a" (or "an"), "one or more" and "at least one" can be used interchangeably herein. It is also to be noted that the terms "comprising", "including", and "having" can be used interchangeably. The expression "of any of claims XX-YY" (wherein XX and YY refer to claim numbers) is intended to provide a multiple dependent claim in the alternative form, and in some embodiments is interchangeable with the expression "as in any one of claims XX-YY."

[0261] When a group of substituents is disclosed herein, it is understood that all individual members of that group and all subgroups, including any isomers, enantiomers, and diastereomers of the group members, are disclosed separately. When a Markush group or other grouping is used herein, all individual members of the group and all combinations and subcombinations possible of the group are intended to be individually included in the disclosure. When a compound is described herein such that a particular isomer, enantiomer or diastereomer of the compound is not specified, for example, in a formula or in a chemical name, that description is intended to include each isomers and enantiomer of the compound described individual or in any combination. Additionally, unless otherwise specified, all isotopic variants of compounds disclosed herein are intended to be encompassed by the disclosure. For example, it will be understood that any one or more hydrogens in a molecule disclosed can be replaced with deuterium or tritium. Isotopic variants of a molecule are generally useful as standards in assays for the molecule and in chemical and biological research related to the molecule or its use. Methods for making such isotopic variants are known in the art. Specific names of compounds are intended to be
exemplary, as it is known that one of ordinary skill in the art can name the same compounds differently.

[0262] Many of the molecules disclosed herein contain one or more ionizable groups [groups from which a proton can be removed (e.g., -COOH) or added (e.g., amines) or which can be quaternized (e.g., amines)]. All possible ionic forms of such molecules and salts thereof are intended to be included individually in the disclosure herein. With regard to salts of the compounds herein, one of ordinary skill in the art can select from among a wide variety of available counterions those that are appropriate for preparation of salts of this invention for a given application. In specific applications, the selection of a given anion or cation for preparation of a salt may result in increased or decreased solubility of that salt.

[0263] Every formulation or combination of components described or exemplified herein can be used to practice the invention, unless otherwise stated.

[0264] Some of the present compositions, preparations and formulations can be used both as a diagnostic agent as well as a therapeutic agent concomitantly. For example, an effective amount of the present compositions, preparations and formulations in a pharmaceutically acceptable formulation is administered to a patient. Administration is followed by a procedure that combines photodiagnosis and therapy. For example, a composition comprising compounds for combined photodiagnosis and therapy is administered to a patient and its concentration, localization, or other parameters is determined at the target site of interest. More than one measurement may be taken to determine the location of the target site. The time it takes for the compound to accumulate at the target site depends upon factors such as pharmacokinetics, and may range from about thirty minutes to two days. Once the site is identified, the photodiagnostic part of the procedure may be done either immediately after determining the site or before the agent is cleared from the site. Clearance depends upon factors such as pharmacokinetics.

[0265] The present compositions, preparations and formulations can be formulated into diagnostic or therapeutic compositions for enteral, parenteral, topical, aerosol, inhalation, or cutaneous administration. Topical or cutaneous delivery of the compositions, preparations and formulations may also include aerosol formulation, creams, gels, solutions, etc. The present compositions, preparations and formulations are administered in doses effective to achieve the desired diagnostic and/or therapeutic effect. Such doses may vary widely depending upon the particular compositions employed in the composition, the organs or tissues to be examined, the equipment employed in the clinical procedure, the efficacy of the treatment achieved, and the like. These compositions, preparations and formulations contain an effective amount of the composition(s), along with conventional pharmaceutical carriers and excipients appropriate for the type of administration contemplated. These compositions, preparations and formulations may also optionally include stabilizing agents and skin penetration enhancing agents.
Methods of this invention comprise the step of administering an "effective amount" of the present diagnostic and therapeutic compositions, formulations and preparations containing the present compounds, to diagnosis, image, monitor, evaluate treat, reduce or regulate a biological condition and/or disease state in a patient. The term "effective amount," as used herein, refers to the amount of the diagnostic and therapeutic formulation, that, when administered to the individual is effective diagnosis, image, monitor, evaluate treat, reduce or regulate a biological condition and/or disease state. As is understood in the art, the effective amount of a given composition or formulation will depend at least in part upon, the mode of administration (e.g. intravenous, oral, topical administration), any carrier or vehicle employed, and the specific individual to whom the formulation is to be administered (age, weight, condition, sex, etc.). The dosage requirements need to achieve the "effective amount" vary with the particular formulations employed, the route of administration, and clinical objectives. Based on the results obtained in standard pharmacological test procedures, projected daily dosages of active compound can be determined as is understood in the art.

Any suitable form of administration can be employed in connection with the diagnostic and therapeutic formulations of the present invention. The diagnostic and therapeutic formulations of this invention can be administered intravenously, in oral dosage forms, intraperitoneally, subcutaneously, or intramuscularly, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

The diagnostic and therapeutic formulations of this invention can be administered alone, but may be administered with a pharmaceutical carrier selected upon the basis of the chosen route of administration and standard pharmaceutical practice.

The diagnostic and therapeutic formulations of this invention and medicaments of this invention may further comprise one or more pharmaceutically acceptable carrier, excipient, buffer, emulsifier, surfactant, electrolyte or diluent. Such compositions and medicaments are prepared in accordance with acceptable pharmaceutical procedures, such as, for example, those described in Remingtons Pharmaceutical Sciences, 17th edition, ed. Alfonoso R. Gennaro, Mack Publishing Company, Easton, Pa. (1985).

Whenever a range is given in the specification, for example, a range of integers, a temperature range, a time range, a composition range, or concentration range, all intermediate ranges and subranges, as well as all individual values included in the ranges given are intended to be included in the disclosure. As used herein, ranges specifically include the values provided as endpoint values of the range. For example, a range of 1 to 100 specifically includes the end point values of 1 and 100. It will be understood that any subranges or individual values in a range or subrange that are included in the description herein can be excluded from the claims herein.

As used herein, "comprising" is synonymous with "including," "containing," or "characterized by," and is inclusive or open-ended and does not exclude additional, unrecited
elements or method steps. As used herein, "consisting of excludes any element, step, or ingredient not specified in the claim element. As used herein, "consisting essentially of" does not exclude materials or steps that do not materially affect the basic and novel characteristics of the claim. In each instance herein any of the terms "comprising", "consisting essentially of and "consisting of" may be replaced with either of the other two terms. The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein.

[0272] One of ordinary skill in the art will appreciate that starting materials, biological materials, reagents, synthetic methods, purification methods, analytical methods, assay methods, and biological methods other than those specifically exemplified can be employed in the practice of the invention without resort to undue experimentation. All art-known functional equivalents, of any such materials and methods are intended to be included in this invention. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.
What is claimed is:

1. A compound being of the formula (FX1) or (FX2):

   ![Diagram](image)

   (FX1) or (FX2), wherein:

   G\textsuperscript{4} is -N-, -C(B)-, or -C(R\textsuperscript{4})-;
   G\textsuperscript{5} is -N-, -C(B)-, or -C(R\textsuperscript{5})-;
   G\textsuperscript{6} is -N-, -C(B)-, or -C(R\textsuperscript{6})-;
   G\textsuperscript{7} is -N-, -C(B)-, or -C(R\textsuperscript{7})-;
   G\textsuperscript{8} is -N-, -C(B)-, or -C(R\textsuperscript{8})-;
   G\textsuperscript{9} is -N-, -C(B)-, or -C(R\textsuperscript{9})-;
   G\textsuperscript{10} is -N-, -C(B)-, or -C(R\textsuperscript{10})-;
   G\textsuperscript{11} is -N-, -C(B)-, or -C(R\textsuperscript{11})-;

   wherein at most one of G\textsuperscript{4} to G\textsuperscript{11} is -N-; and wherein at least one of G\textsuperscript{4} to G\textsuperscript{11} is -C(B)-;

   each B is independently

   $$Z - Y \text{- PEPTID E}$$

   each Z is independently -CO- or -NR\textsuperscript{20}-;

   each of R\textsuperscript{1} to R\textsuperscript{11} is independently hydrogen, C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{2}-C\textsubscript{6} cycloalkyl, C\textsubscript{6}-C\textsubscript{10} aryl, C\textsubscript{5}-C\textsubscript{10} heteroaryl, C\textsubscript{2}-C\textsubscript{6} alkenyl, C\textsubscript{2}-C\textsubscript{6} alkynyl, C\textsubscript{5}-C\textsubscript{10} alkylaryl, -OR\textsuperscript{21}, -SR\textsuperscript{22}, -NR\textsuperscript{23}R\textsuperscript{24}, -CONR\textsuperscript{25}R\textsuperscript{26}, -C\textsubscript{0}R\textsuperscript{27}, -SOR\textsuperscript{28}, -CN, -N0\textsuperscript{29}, -COR\textsuperscript{29}, -S0\textsuperscript{30}R\textsuperscript{31}, -S0\textsuperscript{30}NR\textsuperscript{31}R\textsuperscript{32}, -NR\textsuperscript{46}COR\textsuperscript{47}, -CONR\textsuperscript{48}CH\textsubscript{2}OR\textsuperscript{49}, halo, trihalomethyl, or -PS\textsuperscript{1};

   each PS\textsuperscript{1} is independently a photosensitizer corresponding to a cyanine, an indocyanine, a phthalocyanine, a rhodamine, a phenoxazine, a phenothiazine, a phenoselenazine, a fluorescein, a porphyrin, a benzoporphyrin, a squaraine, a corrin, a croconium, an azo dye, a methine dye, an indolenium dye, a halogen, an anthracylene, an azide, a C\textsubscript{1}-C\textsubscript{20} peroxalkyl, a C\textsubscript{5}-C\textsubscript{20} peroxaryl, a C\textsubscript{1}-C\textsubscript{20} sulfenatoalkyl, a C\textsubscript{5}-C\textsubscript{20} sulfenatoaryl, a naphthalocyanine, a methylene blue, a chalcogenopyrylium analogue, an azo, a diazo, an oxaza, a diaza, a dithia, a thioxa, or a dioxia group;

   each Y is independently -NR\textsuperscript{33}CH\textsubscript{2}aCO\textsubscript{2}-, -NR\textsuperscript{34}CH\textsubscript{2}a, -O(CH\textsubscript{2})\textsubscript{a}CO-, -O(CH\textsubscript{2})\textsubscript{a}, -NR\textsuperscript{35}(C\textsubscript{6}H\textsubscript{4})CO-, -NR\textsuperscript{36}(C\textsubscript{6}H\textsubscript{4})CO-, -NR\textsuperscript{37}CH\textsubscript{2}aNR\textsuperscript{38}, -O(CH\textsubscript{2})\textsubscript{a}O-, -
NR\(^3\)(C\(_6\)H\(_4\))NR\(^{40}\), -NR\(^{41}\)(cyc/o-C\(_6\)H\(_{10}\))NR\(^{42}\), -NR\(^{43}\), -NR\(^{44}\)(CH\(_2\))\(_a\)CONR\(^{45}\), 1,4-diazacyclohexyl, 4-carbonylpiperidinyl, 2-carbonylpyrrolidinyl, or 3-carbonylpyrrolidinyl;

each \(a\) is independently an integer selected from the range of 0 to 10;

each of \(R^{20}\) to \(R^{49}\) is independently hydrogen, C\(_i\)-C\(_6\) alkyl, C\(_3\)-C\(_6\) cycloalkyl, C\(_5\)-Cl\(_0\) aryl, or C\(_5\)-C\(_{10}\) heteroaryl;

each PEPTIDE is independently an amino acid sequence corresponding to (-S)FFXaal_RS (SEQ ID NO:1); S(-F)XaaLRS (SEQ ID NO:1); SF(-F)XaaLRS (SEQ ID NO:1); SFF(-Xaa)LRS (SEQ ID NO:1); SFFXaa(-L)RS (SEQ ID NO:1); SFFXaa(-R)S (SEQ ID NO:1); or SFFXaaLR(-S) (SEQ ID NO:1);

each S is an amino acid corresponding to Serine;

each F is an amino acid corresponding to Phenylalanine;

each Xaa is an amino acid corresponding to Tryptophan, Asparagine, or Tyrosine;

each L is an amino acid corresponding to Leucine;

each R is an amino acid corresponding to Arginine;

wherein each Y is attached to the amino acid sequence at the C- or N- terminal end of the amino acid sequence; or each Y is attached to a side chain of any amino acid of the amino acid sequence; or wherein the side chain of any amino acid of the amino acid sequence is replaced by an optical agent corresponding to a pyrazine, azulene, or azaazulene; or wherein the side chain of any amino acid of the amino acid sequence is replaced by Y; and

wherein a dash (-) in the amino acid sequence denotes the position in the amino acid sequence at which Y attaches.

2. The compound of claim 1, wherein the side chain of any amino acid of the amino acid sequence is replaced by Y.

3. The compound of claim 1, wherein the side chain of any amino acid of the amino acid sequence is replaced by an optical agent corresponding to an azulene or azaazulene.

4. The compound of claim 1, wherein Xaa is Tryptophan.

5. The compound of claim 1, wherein each Y is attached to the amino acid sequence at the C- or N- terminal end of the amino acid sequence.

6. The compound of claim 1, wherein the side chain of any Serine, Phenylalanine, Leucine, or Arginine of the amino acid sequence is replaced by Y.
7. The compound of claim 1, wherein the side chain of any Serine, Phenylalanine, Leucine, or Arginine of the amino acid sequence is replaced by an optical agent corresponding to an azulene or azaazulene.

8. The compound of claim 1 wherein only one of G^4 to G^{11} is -C(B)-.

9. The compound of claim 1 wherein more than one of G^4 to G^{11} is -C(B)-.

10. The compound of claim 1 being any of formula (FX3), (FX4), (FX5), (FX6), (FX7), (FX8), (FX9), (FX10), or (FX11):

![Diagram of chemical structures](attachment:image.png)
(FX7),

(FX8),

(FX9),

(FX10), or
11. The compound of claim 1, wherein Y is attached to the amino acid sequence at the N- or C-terminus of the amino acid sequence.

12. The compound of claim 1 being any of formula (FX12), (FX13), (FX14), (FX15), (FX16) or (FX17):
The compound of claim 1 being any of formula (FX18), (FX19), or (FX20):

(FX15),

(FX16), or

(FX17).

13. The compound of claim 1 being any of formula (FX18), (FX19), or (FX20):

(FX18),
14. The compound of claim 1, wherein \( Y \) is attached to the side chain of any amino acid in the amino acid sequence.

15. The compound of any of claims 1-14, wherein \( PS^1 \) is a Type 1 photosensitizing agent.

16. The compound of claim 15, wherein \( PS^1 \) is a group corresponding to a phenoxazine, a phenothiazine, an indolenium dye, an azide, a \( C_{1-20} \) peroxalkyl, a \( C_{5-20} \) peroxyaryl, a \( C_1-C_20 \) sulfoalkyl, a \( C_5-C_{20} \) sulfoaryl, or a diazo, oxaza, diaza, dithia, thioxa, dioxa, or azo dye.

17. The compound of claim 1 being of formula (FX1), wherein:

   each \( Z \) is \( -CO- \);

   each of \( R^1 \) and \( R^2 \) is independently \( \text{Ci-C}_6 \) alkyl, \( \text{Cs-C}_{10} \) aryl, \( \text{C}_2\text{-C}_6 \) cycloalkyl, \( \text{C}_5\text{-C}_{10} \) heteroaryl, \( \text{C}_2\text{-C}_6 \) alkenyl, \( \text{C}_2\text{-C}_6 \) alkynyl, \( \text{C}_5\text{-C}_{10} \) alkyaryl, \( -OR \), \( -SR \), \( -NR^2 R^4 \), or \( -PS^1 \); and

   each \( R^3 \) is independently \( -CONR^2 R^6 \), \( -C0_{2R^7} \), \( -SOR^8 \), \( -CN \), \( -NO_{2R^9} \), \( -COR \), \( -SO_{2R^{10}} \), \( -S0_{2N R^1 R^2} \), or \( -PS^1 \).

18. The compound of claim 1 being of formula (FX1), wherein:

   each \( Z \) is \( -NR_{20} \);

   each of \( R^1 \) and \( R^2 \) is independently \( -CON \), \( -R_{2C_6} \), \( -C0_{2R^7} \), \( -SOR^8 \), \( -CN \), \( -NO_{2R^9} \), \( -COR \), \( -SO_{2R^{10}} \), \( -S0_{2N R^1 R^2} \), or \( -PS^1 \); and
each R³ is independently C₁-C₆ alkyl, C₅-C₁₀ aryl, C₃-C₆ cycloalkyl, C₅-C₁₀ heteroaryl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₅-C₁₀ alkylaryl, -OR ²¹, -SR ²², -NR ²³R₂⁴, or -PS ¹.

19. The compound of claim 1, wherein at least one of R¹ to R³ or at least one of R⁴ to R¹¹ is an electron donating group.

20. The compound of claim 1, wherein at least one of R¹ to R³ or at least one of R⁴ to R¹¹ is -OR ²¹, -SR ²², -NR ²³R₂⁴, -CONR ²⁵R₂⁶, or -NR ⁴⁶COR ⁴⁷.

21. The compound of claim 1, wherein at least one of R¹ to R³ or at least one of R⁴ to R¹¹ is an electron withdrawing group.

22. The compound of claim 1, wherein at least one of R¹ to R³ or at least one of R⁴ to R¹¹ is -CN, -C₀₂R²⁷, -COR ²⁹, -S₀₂R³⁰, -N₀₂, or -S₀₂NR ³¹R³².

23. The compound of claim 1, wherein:

   at least one of R¹ to R³ or at least one of R⁴ to R¹¹ is -OR ²¹, -SR ²², -NR ²³R₂⁴, -CONR ²⁵R₂⁶, or -NR ⁴⁶COR ⁴⁷; and

   at least one of R¹ to R³ or at least one of R⁴ to R¹¹ is -CN, -C₀₂R²⁷, -COR ²⁹, -S₀₂R³⁰, -N₀₂, or -S₀₂NR ³¹R³².

24. The compound of claim 1 being of formula (FX1) and having R group substituent pairings (R¹ and R²), (R² and R³), or (R¹ and R³), wherein one of the identified R groups in the R group substituent pairings is C₁-C₆ alkyl, C₃-C₆ cycloalkyl, -OR ²¹, -SR ²², -NR ²³R₂⁴, or -NR ⁴⁶COR ⁴⁷ and the other of the identified R groups in the R group substituent pairings is halo, trihalomethyl, -CN, -C₀₂R²⁷, -CONR ²⁵R₂⁶, -COR ²⁹, -N₀₂, -SOR ²⁸, -S₀₂R³⁰, or -S₀₂NR ³¹R³².

25. The compound of any of claims 1-24, wherein the compound binds to a leukemia cell.

26. The compound of claim 25, wherein the leukemia cell is a lymphocytic leukemia cell or a myelogenous leukemia cell.

27. The compound of claim 26, wherein the leukemia cell is an acute lymphocytic leukemia cell, a chronic lymphocytic leukemia cell, an acute myelogenous leukemia cell, or a chronic myelogenous leukemia cell.

28. The compound of claim 27, wherein the acute myelogenous leukemia cell is an MO, M₁, M₂, M₃, M₄, M₄eo, M₅, M₆, or M₇ acute myelogenous leukemia cell.

29. The compound of claim 27, wherein the acute lymphocytic leukemia cell is an early pre-B, common, pre-B, mature B-cell, pre-T, or mature T-cell acute lymphocytic leukemia cell.

30. The compound of any of claims 1-29 for use in an optical imaging, diagnostic, monitoring or therapeutic biomedical procedure.
31. The compound of claim 30, wherein the biomedical procedure comprises:
   administering to a subject a therapeutically or diagnostically effective amount of the
   compound under conditions sufficient for contacting a target tissue or cell of the subject
   with the compound;
   exposing the administered compound to a therapeutically or diagnostically effective
   amount of electromagnetic radiation; and
   detecting electromagnetic radiation emitted from the compound in the subject.

32. The compound of claim 31, wherein the procedure comprises exposing the administered
   compound to electromagnetic radiation having wavelengths selected over the range of 350
   nanometers to 900 nanometers.

33. The compound of any of claims 31-32, wherein the procedure comprises collecting
   electromagnetic radiation emitted from the compound in the subject.

34. The compound of claim 33, wherein the electromagnetic radiation is collected proximate to
   an ear, hand, head, forehead, or finger of the subject.

35. The compound of any of claims 31-34, wherein exposing the compound administered to
   the subject to the electromagnetic radiation generates a diagnostically effective amount of
   fluorescence from the compound.

36. The compound of claim 35, wherein the fluorescence from the compound has wavelengths
   selected over the range of 500 nanometers to 1300 nanometers.

37. The compound of any of claims 35-36, comprising generating an image of the fluorescence
   from the compound.

38. The compound of any of claims 31-37, wherein the target cell is a leukemia cell.

39. The compound of claim 38, wherein the leukemia cell is a lymphocytic leukemia cell or a
   myelogenous leukemia cell.

40. The compound of claim 39, wherein the leukemia cell is an acute lymphocytic leukemia
   cell, a chronic lymphocytic leukemia cell, an acute myelogenous leukemia cell, or a chronic
   myelogenous leukemia cell.

41. The compound of claim 40, wherein the acute myelogenous leukemia cell is an M0, M1,
   M2, M3, M4, M4eo, M5, M6, or M7 acute myelogenous leukemia cell.

42. The compound of claim 40, wherein the acute lymphocytic leukemia cell is an early pre-B,
   common, pre-B, mature B-cell, pre-T, or mature T-cell acute lymphocytic leukemia cell.

43. The compound of any of claims 31-37, wherein the target tissue is a colon, prostate,
   gastric, esophageal, uterine, endometrial, pancreatic, breast, cervical, brain, skin,
   gallbladder, lung, or ovary tissue.
44. A device for monitoring leukemia in a subject, the device comprising:
an electromagnetic radiation source for exciting an optical agent administered to a subject, 
wherein the optical agent selectively binds to leukemia cells in the subject; and
a detector for detecting electromagnetic radiation from the optical agent bound to the 
leukemia cells in the subject, wherein the detector monitors the electromagnetic radiation 
from the optical agent bound to the leukemia cells in the subject as a function of time.

45. The device of claim 44, further comprising:
an electromagnetic radiation delivery system in optical communication with the 
electromagnetic radiation source;
an electromagnetic radiation collection system in optical communication with the detector; and
a data processing system in optical or electronic communication with the detector.

46. The device of claim 45, further comprising a catheter, endoscope, ear clip, hand band, 
head band, forehead sensor, surface coil, or finger probe.

47. The device of any of claims 44-46, wherein the leukemia cells are lymphocytic leukemia 
cells or myelogenous leukemia cells.

48. The device of claim 47, wherein the leukemia cells are acute lymphocytic leukemia cells, 
chronic lymphocytic leukemia cells, acute myelogenous leukemia cells, or chronic 
myelogenous leukemia cells.

49. The device of claim 48, wherein the acute myelogenous leukemia cells are MO, M1, M2, 
M3, M4, M4eo, M5, M6, or M7 acute myelogenous leukemia cells.

50. The device of claim 48, wherein the acute lymphocytic leukemia cells are early pre-B, 
common, pre-B, mature B-cell, pre-T, or mature T-cell acute lymphocytic leukemia cells.

51. The device of any of claims 44-50, wherein the detector detects electromagnetic radiation 
from the optical agent in the subject.

52. The device of any of claims 44-51, wherein the device monitors progression or a disease 
stage of leukemia.

53. The device of any of claims 44-52, wherein the optical agent is a compound being of the 
formula $(FX_1)$ or $(FX_2)$:

![Chemical structures](image)

$(FX_1)$ or $(FX_2)$, wherein:
G^4 \text{ is } -N-, \text{ -C(B)-, or -C(R^4)-;}

G^5 \text{ is } -N-, \text{ -C(B)-, or -C(R^5)-;}

G^6 \text{ is } -N-, \text{ -C(B)-, or -C(R^6)-;}

G^7 \text{ is } -N-, \text{ -C(B)-, or -C(R^7)-;}

G^8 \text{ is } -N-, \text{ -C(B)-, or -C(R^8)-;}

G^9 \text{ is } -N-, \text{ -C(B)-, or -C(R^9)-;}

G^{10} \text{ is } -N-, \text{ -C(B)-, or -C(R^{10})-;}

G^{11} \text{ is } -N-, \text{ -C(B)-, or -C(R^{11})-;}

\text{wherein at most one of } G^4 \text{ to } G^{11} \text{ is } -N--; \text{ and wherein at least one of } G^4 \text{ to } G^{11} \text{ is } -C(B)-;

\text{each } B \text{ is independently } -CO- \text{ or } -NR^{20} -;

\text{each } Z \text{ is independently } -CO- \text{ or } -NR^{20} -;

\text{each of } R^1 \text{ to } R^{11} \text{ is independently hydrogen, } C_1-C_6 \text{ alkyl, } C_2-C_6 \text{ cycloalkyl, } C_2-C_10 \text{ aryl, } C_5-C_{10} \text{ heteroaryl, } C_2-C_6 \text{ alkenyl, } C_2-C_6 \text{ alkynyl, } C_5-C_{10} \text{ alkylaryl, } -OR^{21}, -SR^{22}, -NR^{23}R^{24}, -CONR^{25}R^{26}, -C0_2R^{27}, -SOR^{28}, -CN, -NO_2, -COR^{29}, -S0_2R^{30}, -S0_2NR^{31}R^{32}, -NR^{46}COR^{47}, -CONR^{48}(CH_2)_aOR^{49}, \text{ halo, trihalomethyl, or } -PS^1 -;

\text{each } PS^1 \text{ is independently a photosensitizer corresponding to a cyanine, an indocyanine, a phthalocyanine, a rhodamine, a phenoxazine, a phenothiazine, a phenoalizarin, a fluorescein, a porphyrin, a benzoporphyrin, a squaraine, a corrin, a croconium, an azo dye, a methine dye, an indolenium dye, a halogen, an anthracylene, an azide, a } C_1-C_{20} \text{ peroxalkyl, a } C_5-C_{20} \text{ peroxaryl, a } C_1-C_{20} \text{ sulfenaalkyl, a } C_5-C_{20} \text{ sulfenaaryl, a naphthalocyanine, a methylene blue, a chalcogenopyrall analogue, an azo, a diazo, an oxaza, a diaza, a thia, a thiaza, or a dioxa group;}

\text{each } Y \text{ is independently } -NR^{33}(CH_2)_aCO_2-, -NR^{34}(CH_2)_aCO_2-, -0(CH_2)_aCO_2-, -NR^{35}(C_6H_5)CO-, -NR^{36}(cyc/o-C_6H_10)CO-, -NR^{37}(CH_2)_aNR^{38}R^{39}, -0(CH_2)_aCO_2-, -NR^{39}(C_6H_5)NR^{40}, -NR^{41}(cyc/o-C_6H_10)NR^{42}, -NR^{43}, -NR^{44}(CH_2)_aCONR^{45}, 1,4-diazacyclohexyl, 4-carbonylpiperidinyl, 2-carbonylpiperidinyl, or 3-carbonylpiperidinyl;

\text{each a is independently an integer selected from the range of 0 to 10;}

\text{each of } R^{20} \text{ to } R^{49} \text{ is independently hydrogen, } C_1-C_6 \text{ alkyl, } C_2-C_6 \text{ cycloalkyl, } C_5-C_{10} \text{ aryl, or } C_5-C_{10} \text{ heteroaryl;}

\text{each PEPTIDE is independently an amino acid sequence corresponding to } (-S)FFXaal_RS \text{ (SEQ ID NO:1)}; \text{ S(-F)FXaalRS } \text{ (SEQ ID NO:1)}; \text{ SF(-F)XaalRS } \text{ (SEQ ID NO:1)};
The compound of claim 1 being of the formula (FX23):

A device for monitoring leukemia in a subject, the device comprising:

an electromagnetic radiation source for exciting an optical agent of any of claims 1-43 administered to a subject, wherein the optical agent selectively binds to leukemia cells in the subject; and

a detector for detecting electromagnetic radiation from the optical agent bound to the leukemia cells in the subject, wherein the detector monitors the electromagnetic radiation from the optical agent bound to the leukemia cells in the subject as a function of time.
Figure 3
Figure 4