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(71) **Demandeur/Applicant:**
LAMBDA PHARMACEUTICALS, INC., US

(72) **Inventeurs/Inventors:**
WANG, RUIZHENG, US;
MENES, MICHAEL E., US;
MORGAN, ALAN R., US

(74) **Agent:** FURMAN & KALLIO

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(57) **Abrégé/Abstract:**

A family of benzochlorin derivatives of formulas of Figs. 1A and 1B of the attached drawing are suitable for use as photosensitizers in photodynamic therapy. Solutions of the benzochlorin derivatives are physiologically accepted for selective destruction of cells and tissues. A method of destroying cells and tissues through a photodynamic process wherein a pharmaceutical composition including the benzochlorin derivates of formulas of Figs, 1A and 1B are administered to a human or animal patient and light sufficient to generate a cytotoxic effect is supplied.

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(71) Applicant *(for all designated States except US)*: LAMBDA PHARMACEUTICALS, INC. [US/US]; Suite 203, 1500 San Juan Hills Drive, Las Vegas, NV 89134 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MORGAN, Alan, R. [GB/US]; 1500 San Juan Hills Drive #203, Las Vegas, NV 89134 (US). MENES, Michael, E. [US/US]; 207 South Sherrin Avenue, Louisville, KY 40207 (US). WANG, Ruizheng [CN/US]; 2065 Tahiti Place, Louisville, KY 40218 (US).

(74) Agents: STELTER, Daniel, C. et al.; Middleton & Reutlinger, 2500 Brown & Williamson Tower, Louisville, KY 40202-3410 (US).

(54) Title: PHOTOSENSITIZERS FOR PHOTODYNAMIC APPLICATIONS

(57) Abstract

A family of benzochlorin derivatives of formulas of Figs. IA and IB of the attached drawing are suitable for use as photosensitizers in photodynamic therapy. Solutions of the benzochlorin derivatives are physiologically accepted for selective destruction of cells and tissues. A method of destroying cells and tissues through a photodynamic process wherein a pharmaceutical composition including the benzochlorin derivates of formulas of Figs. IA and IB are administered to a human or animal patient and light sufficient to generate a cytotoxic effect is supplied.

PHOTOSENSITIZERS FOR PHOTODYNAMIC APPLICATIONS

BACKGROUND OF THE INVENTION

The present invention relates to benzochlorin derivatives that can be used as photosensitizers in photodynamic therapy ("PDT"). More particularly, the present invention relates to pharmaceutically acceptable formulations of benzochlorin and benzochlorin imine derivatives and to the use of these new benzochlorin and benzochlorin imine compositions for the selective destruction of cells and tissues in PDT.

PDT is an emerging technology for the selective destruction of cells and/or tissues. The process requires the presence of a photosensitizing agent which is capable of being taken up by target cells and tissues and which, on irradiation by light of a particular wavelength, generates species which are toxic to those cells and tissues.

It has been discovered that a porphyrin-derived preparation known as Photofrin®, a photosensitizing agent, when applied to a human or animal body is taken up by certain cells and tissues. The cells and tissues containing the photosensitizing agent can then be exposed to light of a certain wavelength. The light is generated and directed to the target cells and/or tissue by the use of lasers, photodiode arrays or lamps. If the target cells and tissues are located deeper into the body, light is delivered by the use of fiber-optic systems, endoscopic devices and catheters.

It has also been shown that Photofrin®, a certain amount of time after it is administered, is retained in greater concentrations in certain types of cells. The time period for such "selective" accumulation is 24-48 hours. Cells that show such selectivity have been characterized as hyperproliferating cells, i.e., cells which are growing at a faster rate than normal. Such cells are representative of many diseased tissues and states, including but not limited to cancer, dermatological disease such as psoriasis, cardiovascular disease such as atherosclerosis and restenosis and diseases which are characterized by a rapid growth of blood vessels, for example, as is the case in ophthalmologic conditions such as age-related macular degeneration. Additionally, certain cells associated with immunological functions have been shown to selectively retain photosensitizing agents. Thus, photodynamic therapy to reduce the potential for graft rejection and for autoimmune disease such as rheumatoid arthritis has been reported. And, it can be seen that, following the deliverance of light, its absorption by the photosensitizer and the subsequent generation of species toxic to cells and tissues, cells and tissues such as those associated with cancer, dermatological disease, cardiovascular disease, ophthalmologic diseases and immune disorders can be effectively treated.

Photodynamic therapy has advantages over many other conventional therapies due to the selectivity of the photodynamic process. For example, in the case of cancer, therapies such as chemotherapy and radiation therapy are known to have significant side-effects and are toxic to normal as well as abnormal cells. Consequently these treatments are associated with the destruction of a significant amount of normal cells and tissues. In the case of photodynamic therapy, the increased affinity of the photosensitizing agent for hyperproliferating cells such as those found in tumors reduces the potential for destruction of normal cells and tissues while increasing the potential for destruction of the lesion. In addition, the ability to direct the light specifically onto the target cells and tissues by the use of fiber-optic technology or the ability to protect adjacent normal cells or tissues by the use of filters further increases the selectivity of the photodynamic process. Furthermore, the use of photosensitizing agents which elicit no response until irradiated with light reduces significantly the potential for side-effects which may complicate the process. Thus, for example, it has been shown that the only significant side-effect associated with the use of Photofrin® as a photodynamic agent is a general skin response which has been characterized as a sunburn and which is associated with activation of Photofrin® retained in the patient's skin following exposure to sunlight. This side-effect however, is only significant for the first 4 to 12 weeks following treatment during which time the patient is asked to avoid exposure of skin to strong sunlight.

It has also been shown that cells that are not characterized as hyperproliferating can also be destroyed using photodynamic therapy. In such a case, light activation of the photosensitizing agent is effected shortly after administration of the photosensitizer. At this time, the photosensitizing agent is present in many cell and tissue types and the selective retention of the photosensitizer in hyperproliferating cells has not occurred. Selectivity of treatment in this case is controlled by the delivery of light to the target tissues. For example, the photodynamic response can be controlled by the wavelength of light used. Since, as is known, light of longer wavelengths penetrate deeper into tissues, then the use of longer wavelengths of light will result in a greater depth of treatment. The biological response can also be controlled by the amount of light given, thus, the greater the amount of light, the greater the biological response. More light can be given by increasing the time of irradiation, by increasing the intensity of the light or by both. Such a regimen is useful for the treatment of diseases including but not limited to benign prostatic hypertrophy and endometriosis.

Consequently, photodynamic therapy has received approval for certain indications in certain countries. Thus, in the USA, the FDA has approved the use of Photofrin® as a photosensitizer in photodynamic therapy for the treatment of certain esophageal tumors and lung cancer. In Japan, the use of Photofrin has been approved for photodynamic treatment of a variety of cancers including lung, stomach and cervical; in Canada the same procedure has been approved for use in treatment of bladder cancer and in the Netherlands, France, Italy and Germany, approval has been granted for use in esophageal cancer.

The mechanisms by which photosensitizers generate cytotoxic species following irradiation with light have not yet been fully identified in the human or animal patient. However, it is thought that the initial mechanism involves photoactivation of the photosensitizer. The next step of the reaction is dependent on the photosensitizer used. In most cases, including when Photofrin is the sensitizer used, it is thought that the photoactivated photosensitizer transfers energy to molecular oxygen, which is present in cells and tissues. This process generates singlet oxygen, a species that is known to be toxic to cells and tissues, leading eventually to cell death. The process of cell death is not well understood but is thought to involve interaction of the singlet oxygen with cellular components such as lipids and proteins, particularly those found in cell membranes. Loss of membrane integrity can eventually result in loss of cell viability. It has also recently been reported that photodynamic therapy may also result in activation of a process known as apoptosis, which is defined as programmed cell death and is the mechanism by which cells die naturally. Thus, photodynamic therapy may also be advantageous in that the mechanism of cell death may involve processes that biological systems use in their natural state to remove cells that are no longer useful.

A second mechanism by which the photodynamic effect may be generated involves not the generation of singlet oxygen, but the generation of radical species. Such species can be generated by the interaction of the photoactivated photosensitizer with oxygen to produce radical species such as superoxide and/or hydroxyl radical that are known to be toxic to cells. Alternatively, the photoactivated photosensitizer can itself react directly with cellular components to generate a free-radical type reaction which again results in loss of cell integrity and thus, of cell viability.

Although the exact mechanisms by which photodynamic therapy exerts its effects are not yet well understood and depend to some extent on the specific photosensitizer used, it is clear that photodynamic therapy has advantages over many current day procedures. The process appears to have minimum side-effects and a greater degree of selectivity for target cells and tissues. In addition, photodynamic therapy can be used in conjunction with other treatment modalities as well as in a stand-alone treatment.

Photofrin® is the only photosensitizer to have gained approval anywhere in the world to date, however a number of photosensitizers have been proposed for use in photodynamic therapy and are in pre-clinical or clinical trials for the treatment of various indications including cancer, dermatology, cardiovascular, immunology, ophthalmology and urology. Examples of photosensitizers which have received attention include Purpurins, Benzoporphyrin Derivatives, Porphycenes, Texaphyrins Pheophorbides and Phthalocyanines Application of the use of photodynamic therapy in the treatment of cancer, cardiovascular disease, blood components, viral lesions, ophthalmologic disease, urological conditions, dermatological disease and in the treatment of immunological related disease have all been demonstrated in pre-clinical and/or clinical studies.

Notwithstanding the above, the use of these potential photodynamic agents is associated with various disadvantages which limit their usefulness in photodynamic therapy. Such disadvantages range from inefficient or costly synthetic procedures, the necessity of complex delivery vehicles in order to effect administration to patients, absorbance of light in regions of the visible spectrum which limit light production to costly and complex light devices and clinical symptoms, more specifically the presence of an unwanted skin reaction due to poor photosensitizer clearance from skin, or as has been reported with some experimental photosensitizers, pain at the treatment site during light activation.

In Morgan *et al*, Photochem. Photobiol. 1992, 55, 133; SPIE vol. 1065, 1989, 146, Morgan et al teaches benzochlorins having the formulas as set forth in Figs. IA and IB, when applied to an animal body are taken up by certain cancer cells and tissues over a period of typically 24 hours. The cells and tissues containing the photosensitizing agent can then be exposed to light of a wavelength which activates the sensitizer, the light being generated and directed to the target cells and/or tissue by the use of lasers or lamps.

The specific benzochlorins disclosed by Morgan et al. are those where R_1 through R_8 is ethyl, R_{9},$_{10}$ and $_{14}$ are H, R_{12} is SO_3Na or H and M is Sn. Compounds having the general formula of Figs. IA and IB are also disclosed in US Patents 4,988,808, 5,438,051 and 5,552,134 in which R_{12} is either H, SO_3Na or CR'R"R". A further series of patents, US Patents 5,512,559 and 5,744,598 disclose benzochlorins of general Figs. IA and IB where R_{14} is $-CH=N^+RR'A^-$ and R_{12} have the meanings set forth above. Finally, US Patent 5,789,586 discloses benzochlorins of general Figs. IA and IB where R_{12} is SO_2R, SO_2NHR or SO_3X, where R is a compound containing a reactive carboxyl or amine group and X is halide.

BRIEF DESCRIPTION OF THE PRESENT INVENTION

The present invention is directed to a family of photoreactive benzochlorin derivatives and their metallo-analogs having the structures set forth in Figs. IA and IB and identified by legend thereafter. The present invention is also directed to photoreactive benzochlorin derivatives and their metallo-analogs which are used in photodynamic therapy.

Wherein:

R_1 to R_{10} can be the same or different and each is:

H, Br, Cl, CHO,

an alkyl, an alkenyl group having from 1 to 6 carbon atoms,

-$R_1N(R_2)_2$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms and where R_2 is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different,

-$R_1N(R_2)_3^+ A^-$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms and where R_2 is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different, A is a physiologically acceptable anion,

-R_1OR_2 where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, and R_2 is H or an amino acid residue, a carbohydrate residue or an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms,

-R_1COR_2 where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, R_2 is NH_2, an amino acid group or a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups, OR_3 where R_3 is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, an amino acid group or a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue, or

-COR_1 where R_1 is an amino acid residue, polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue,

R_{11} and R_{13} are H.

R_{12} is:

NO_2, Br,

-$N(R_2)_2$ where R_2 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different,

-$N(R_2)_3^+ A^-$ where R_2 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different and A^- is a physiologically acceptable anion, or

$-OR_2$ where R_2 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, an amino acid residue or a carbohydrate residue

R_{14} is as defined for R_1 to R_{10} and also may be:

$-C{=}N^+(R_1)_2\ A^-$ where R_1 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_1 can be the same or different and A is a physiologically acceptable anion, or,

-C=N-NR where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue or $-C_6H_4SO_2R_1$ where R_1 is OH, an amino acid group, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue.

M is any metal which results in a photodynamically active molecule but is preferentially selected from the group, Al, Zn, Sn, Ge, Cu.

The present invention is further directed to a pharmaceutical composition wherein the active ingredient is a composition having the structure of one of Figs. IA or IB above.

The present invention is even further directed to methods for destroying cells and tissues through a photodynamic process comprising the steps of administering to a human or animal patient, or to fluids such as blood, plasma, bone marrow, from a human or animal patient one of the compositions of Figs. IA or IB and supplying sufficient light to generate a cytotoxic effect.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. IA is a structural formula for a family of benzochlorins, including the present invention.

Fig. IB is a structural formula for metal complexes of a family of benzochlorins including the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples constitute the best methods currently contemplated for carrying out the present invention, but are presented solely to illustrate and disclose the invention, and are not intended to be unduly limitative thereof.

Example 1 describes the synthesis of bromooctaethylbenzochlorin (Fig. IA where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, and R_{12} is Br), a key compound for the subsequent generation of many of the other compounds disclosed in this invention.

EXAMPLE 1

(Production of Bromobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} R_{14} are H, and R_{12} is Br)

The synthesis of Fig. IA where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, and R_{12} is Br was accomplished by the dropwise addition of phosphorous oxychloride to a stirred solution of Nickel octaethylporphyrin and 2-bromo-N,N-dimethylaminoacrolein in dichloromethane at -5° C. The mixture was allowed to react for 12 hours and then quenched with $NaHCO_3$ (aq). After extraction the (dried) dichloromethane fractions were collected and taken up in concentrated sulfuric acid at room temperature. Aliquots were taken, neutralized with sodium bicarbonate, extracted with dichloromethane and analyzed spectrophotometrically to monitor the course of the reaction.

Initial formation of nickel bromobenzochlorin (Fig. IB) where R_1 to R_8 is ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, R_{12} is Br, and, M is Ni was shown by the presence of a visible absorption band at 665nm. Further treatment resulted in a decrease in the intensity of this band and an increase in intensity of a visible absorption band at 656nm, indicative of the removal of the metal from the benzochlorin nucleus. The mixture was then neutralized and extracted as described above and the organic fraction concentrated and chromatographed using a mixture of hexanes/dichloromethane as eluant. The product, bromobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, and, R_{12} is Br was recrystallized from dichloromethane - methanol and the structure of the product was confirmed by the characteristic 656 nm peak in the visible spectrum and the distinguishing 0.03 ppm resonance in the ^1H NMR spectra.

The procedure of Example 1 can be used to produce a wide variety of bromo-benzochlorins. By exchanging the octaethylporphyrin reactant in Example 1 with a wide variety of porphyrins, bromobenzochlorins in which R_1 to R_8 can be varied according to the invention, are produced. The requisite porphyrins are generated using standard procedures, which involve production of the necessary intermediate pyrroles followed by condensations and other known reactions, to produce the porphyrin products. A comprehensive overview of this technology has been described in "*The Porphyrins*" Volume 1, Structure and Synthesis, Part A, Academic Press, New York, San Francisco and London 1978.

Example 2a illustrates the method for introduction of a halogen at R_{10} and at R_{14} of the bromobenzochlorin prepared in Example 1. Example 2b illustrates a method for the production of a bromobenzochlorin halogenated at R_{10} and Example 2c illustrates a method for the production of a bromobenzochlorin halogenated at R_{14}.

EXAMPLE 2a

(Production of Dichlorobromobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{11}, R_{13} are H, R_{10} and R_{14} are Cl, and, R_{12} is Br)

Excess thionyl chloride was added to a solution of bromobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, and, R_{12} is Br in dichloromethane. The reaction was refluxed while stirring for 2 hrs, neutralized with aqueous sodium bicarbonate and the combined organic fractions were chromatographed (Hexanes/CH_2Cl_2). The isolated dichlorinated product (Fig.

IA) where R_1 to R_8 are ethyl, R_9, R_{11}, R_{13} are H, R_{10} and R_{14} is Cl, and, R_{12} is Br) was recrystallized from methanol:dichloromethane. The structure was confirmed by visible spectroscopy which gave a characteristic 689nm absorption maximum and by ^{1}H NMR where a distinguishing 0.1ppm resonance was also observed.

EXAMPLE 2b

(Production of bromochlorobenzochlin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{11}, R_{13}, R_{14} are H, R_{10} is Cl and R_{12} is Br)

The above dichlorinated bromobenzochlorin prepared in Example 2a was treated with $SnCl_2$ in dimethyl formamide at reflux temperature for 45 minutes. The resulting solution was poured into water, washed with aqueous hydrochloric acid and then extracted into dichloromethane. The solvent was removed and the residue chromatographed on silica using dichloromethane-hexanes as eluant. The major fraction was collected and was found to be the monochloro-monobromobenzochlorin (Fig. IA), where R_1 to R_8 are ethyl, R_9, R_{11}, R_{13}, R_{14} are H, R10 is Cl, and, R_{12} is Br. Visible spectroscopy gave a maximum absorption at 663nm while NMR showed a characteristic resonance at 0.02 ppm.

EXAMPLE 2c

(Production of bromochloro-benzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{11}, R_{13}, R_{10} are H, R_{14} is Cl, and, R_{12} is Br)

The second fraction of dichlorobromobenzochlorin was treated with $SnCl_2$ in acetic acid at reflux and the reaction progress monitored by visible spectroscopy. Once the absorption at 675nm had reached maximum intensity, the reaction was stopped, the solvent removed and the residue taken up in dichloromethane and washed with aqueous hydrochloric acid. The organic fraction was collected and purified by silica gel chromatography using dichloromethane-hexanes as eluant. The major product was collected and shown to be bromochlorobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{11}, R_{13}, R_{10} are H, R_{14} is Cl, and, R_{12} is Br. Visible spectroscopy gave a maximum absorption at 675nm while NMR gave a characteristic resonance at 0.30 ppm.

Example 3 illustrates the method by which metals can be inserted into the benzochlorin cavity.

Example 3

(Preparation of zinc derivative of bromobenzochlorin (Fig. IB) where R_1 to R_8 are ethyl, R_9, R_{11}, R_{13}, R_{10} are H, and R_{12} is Br, and, M is Zn)

Zinc was inserted into bromobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, and, R_{12} is Br by addition of zinc acetate to the bromobenzochlorin in dimethylformamide. The mixture was then heated to reflux for 1 hr. The reaction mixture was added to water, extracted with dichloromethane and chromatographed with a combination of hexanes/dichloromethane. After recrystalization in methanol/dichloromethane the structure, according to Fig. IB, where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, R_{12} is Br, and M is Zn was obtained and confirmed by visible spectroscopic analysis (characteristic 672 nm peak) and ^1H NMR (characteristic 0.1 ppm peak).

Examples 4a and 4b illustrate the preparation of aminobenzochlorins from bromo-benzochlorins such as that prepared in Example 1.

Example 4a

(Preparation of aminobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, R_{12} is Phthalimido)

Nickel bromobenzochlorin (Fig. IB) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, R_{12} are Br, and, M is Ni was taken up in dimethyl acetamide and copper (I) iodide and potassium phthalimide added. The resulting mixture was refluxed for 20 hours. The solvent was then removed and the residue chromatographed on silica using hexanes-dichloromethane. The major band was collected and shown to be the nickel phthalimidobenzochlorin (Fig. IB) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, R_{12} is

Phthalimido, and, M is Ni. Demetallation was achieved by adding concentrated sulfuric aid to the nickel phthalimidobenzochlorin at room temperature. After 1 hour, the solution was neutralized with aq. sodium bicarbonate and extracted with dichloromethane. The organic layer was collected and recrystalized from hexanes-dichloromethane to give the product (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, R_{12} is Phthalimido, characterized by a visible absorption band at 660nm.

Example 4b

(Preparation of aminobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, and, R_{12} is NH_2)

Phthalimidobenzochlorin (Fig. IA) prepared in Example 4a was treated with excess hydrazine hydrate in ethanol, at reflux, for 3 hours. The mixture was then acidified with conc. Hydrochloric acid and refluxed a further 30 minutes. After cooling, the mixture was filtered and the filtrate concentrated. The concentrate was neutralized with sodium bicarbonate and extracted with dichloromethane. The organic layer was collected and the solvent removed. The residue was recrystallized from dichloromethane-hexanes to give aminobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, and, R_{12} is NH_2. NMR gave a characteristic resonance at 0.14ppm while visible spectroscopy gave an absorption at 657nm.

Example 5 illustrates the preparation of a quarternized aminobenzochlorin.

Example 5

(Preparation of aminobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, and, R_{12} are $NMe_3^+ I)^-$

Aminobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, and, R_{12} is NH_2 was treated with nickel acetate using the method of Example 3. The product of this reaction was treated with excess methyl iodide at 50°C for 2 hours and then the solvent removed. The product was taken up in concentrated sulfuric acid for

1 hour. The resulting solution was then neutralized with sodium bicarbonate and extracted with dichloromethane. The organic layer was collected, the solvent removed and the residue purified by chromatography on silica gel using dichloromethane-methanol. The product (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, and, R_{12} is $NMe_3^+ I^-$ was collected and characterized by visible spectroscopy (absorption band at 654nm).

Example 6 illustrates the preparation of a formyl bromobenzochlorin.

Example 6

(Preparation of a formylbromobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} are H, R_{12} is Br, and, R_{14} is CHO)

Nickel bromobenzochlorin (Fig. IB) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, R_{12} is Br, and, M is Ni was taken up in dichloromethane and an excess of Vilsmeier reagent (prepared from $POCl_3$ and DMF) added. The resulting solution was refluxed for 1 hour. After cooling, aq. sodium acetate was added and the mixture refluxed a further 1 hour. The organic layer was collected and concentrated. Sulfuric acid was added to the residue at room temperature. After 2 hours, the resulting mixture was neutralized with aq. sodium bicarbonate and extracted into dichloromethane. The organic layer was collected and concentrated. The residue was then purified by silica gel chromatography using dichloromethane as eluant. The product (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} are H, R_{12} is Br, and, R_{14} is CHO was collected and characterized by visible spectroscopy (absorption band at 693nm).

Examples 7a and 7b illustrates the preparation of a hydrazone derivative of formylbromobenzochlorin.

Example 7a

(Preparation of a bromobenzochlorin hydrazone (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} are H, R_{12} is Br, and, R_{14} is $CH{=}N{-}NH_2$)

To a solution of formylbromobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} are H, R_{12} is Br, and, R_{14} is CHO in ethanol was added excess hydrazine hydrate and a drop of acetic acid. The resulting solution was refluxed for 2 hours. The solvent was removed and the residue taken up in dichloromethane and washed with aq. sodium bicarbonate. Chromatography using dichloromethane-hexane as eluant gave a major band which was collected and shown to be the expected product (Fig. IA) where R_1 to R_8 is ethyl, R_9, R_{10}, R_{11}, R_{13} are H, R_{12} is Br, and, R_{14} is $CH{=}N{-}NH_2$. The product was characterized by a visible absorption band at 668nm and a resonance at 5.9ppm in the NMR spectrum.

Example 7b

(Preparation of a bromobenzochlorin hydrazone (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} are H, R_{12} is Br, and, R_{14} is $CH{=}N{-}NH{-}C_6H_4SO_3H$)

To a solution of formylbromobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} are H, R_{12} is Br, and, R_{14} is CHO in ethanol was added excess phenyhydrazine-4-sulfonic acid and a drop of acetic acid. The resulting solution was refluxed for 2 hours. The solvent was removed and the residue taken up in dichloromethane and washed with aq. sodium bicarbonate. Chromatography using dichloromethane-hexane as eluant gave a major band which was collected and shown to be the expected product (Fig. IA) where R_1 to R_8 is ethyl, R_9, R_{10}, R_{11}, R_{13} is H, R_{12} is Br, and, R_{14} are $CH{=}N{-}NH{-}C_6H_4SO_3H$. The product was characterized by a visible absorption band at 668nm and a resonance at 0.03ppm in the NMR spectrum.

Example 8a-c illustrates the method by which iminium derivatives of benzochlorins can be generated.

Example 8a

(Preparation of a copper bromobenzochlorin iminium salt (Fig. IA) where R_{12} is Br, R_{14} is $CH{=}NMe_2{}^{+}Cl^{-}$, and, M is Cu)

Bromobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13}, R_{14} are H, and, R_{12} is Br was treated with copper acetate according to the method described in Example 2 to produce copper bromobenzochlorin (Fig. IB) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13}, $R_{14}$are H, R_{12} is Br, and M is

Cu. To a solution of this copper bromobenzochlorin was added excess Vilsmeier reagent prepared from $POCl_3$ and DMF. The resulting solution was refluxed for 1 hour, cooled and washed with water. The organic layer was collected and the solvent removed. The residue was purified using silica gel chromatography using methanol-dichloromethane. The resulting product was recrystallized using hexane-dichloromethane. A characteristic visible absorption band at 750nm was observed.

EXAMPLE 8b

(Preparation of a bromobenzochlorin iminium salt (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} are H, R_{12} is Br, and, R_{14} is $CH{=}NMe_2^+ Cl^-$)

The copper iminium salt prepared in Example 8a was treated with concentrated sulfuric acid at room temperature for 24 hours. The mixture was neutralized with aq. sodium bicarbonate and extracted with dichloromethane. The organic layer was collected and the solvent removed. The residue was purified using silica gel chromatography using methanol-dichloromethane. The resulting product was recrystallized using hexane-dichloromethane. A characteristic visible absorption band at 784nm was observed.

EXAMPLE 8c

(Preparation of a zinc bromobenzochlorin iminium salt (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} are H, R_{12} is Br, R_{14} is $CH{=}NMe_2^+ Cl^-$, and, M is Zn)

The iminium salt prepared in Example 8b was treated with zinc acetate according to the procedure described in Example 2. The product (Fig. IB) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} are H, R_{12} is Br, R_{14} is $CH{=}NMe_2^+ Cl^-$, and, M is Zn was characterized by a visible absorption band at 738nm.

Example 9 illustrates the synthesis of nitrobenzochlorins.

Example 9

(Preparation of a nitrobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13}, R_{14} are H, and, R_{12} is Br)

Nickel benzochlorin, prepared as described in Morgan et al, (Photochem. Photobiol. 1992, 55, 133) was treated with a mixture of concentrated nitric and sulfuric acid for 2 hours at room temperature. The mixture was neutralized with aq. sodium bicarbonate and extracted with dichloromethane. The organic layer was collected and the solvent removed. The residue was purified using silica gel chromatography using methanol-dichloromethane. The resulting product was recrystallized using hexane-dichloromethane. The nitrobenzochlorin (Fig. IA) where R_1 to R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13}, R_{14} are H, and, R_{12} is Br was characterized by a resonance at 0.03ppm in the NMR spectrum and an absorption at 661nm in the visible spectrum.

The procedure of Example 1 can be used to produce a wide variety of bromo-benzochlorins. By exchanging the octaethylporphyrin reactant in Example 1 with a wide variety of porphyrins, bromobenzochlorins in which R_1 to R_8 can be varied according to the invention, are produced. The requisite porphyrins are generated using standard procedures, which involve production of the necessary intermediate pyrroles followed by condensations and other known reactions, to produce the porphyrin products. A comprehensive overview of this technology has been described in "*The Porphyrins*" Volume 1, Structure and Synthesis, Part A, Academic Press, New York, San Francisco and London 1978. The procedure of Example 2 introduces halogens into the benzochlorin nucleus, specifically chloro- by use of thionyl chloride but also bromo- when thionyl bromide is used. Example 3 demonstrates the process for metal insertion into the benzochlorin cavity with the replacement of zinc acetate for other metal salts, such as copper acetate, tin chloride, and the like. This generates the corresponding metallo-derivative. Example 4a illustrates introduction of a phthalimido group. Use of substituted phthalimido groups such as 4-nitrophthalimide in this reaction will generate benzochlorins bearing the nitrophthalimido- moiety. Reaction of the nitro group, for example, by reduction to the amine can generate further benzochlorin derivatives which may also be further derivatized using standard methods for organic group transformations to produce compounds of this invention. The generation of an aminobenzochlorin is also described in Example 4b. It will be appreciated that condensation of the amino- functionality with a large number of carboxylates or acyl chlorides can readily be effected to generate additional compounds of this invention. Preferred reactants in such transformations are amino acids such as lysine, glutamic acid, aspartic acid, serine, cystine and arginine. Other preferred reactants include carbohydrates such as ribose that can be condensed at the carbohydrate anomeric center or carbohydrates bearing a carboxylate function, such as sialic acid, gluconic acid, galactaric acid and mannonic acid. Example 5 demonstrates a standard procedure for generation of quaternary ammonium salts at the amino functionality of the aminobenzochlorin. While methyl iodide is the preferred reagent in this process, nevertheless, other reagents may be substituted to generate additional salt derivatives. In addition, quaternization of the amino functionality of other amino groups attached to the benzochlorin nucleus arising, for example, through condensation of an aminobenzochlorin with the carboxylate function of an amino acid can be effected through a similar procedure, leading to other quaternary ammonium salt analogs. The introduction of a formyl group into the benzochlorin nucleus is illustrated in Example 6. This general process can be used to formylate a large number of benzochlorins and the formyl group so introduced can then be reacted using standard organic chemistry procedures. For example, the formyl group can be treated with Grignard or alkyl lithium reagents to generate alcohols that may condense to form alkenes. Addition of cyanohydrin in a similar fashion will generate the cyanohydrin which may undergo further transformation. Particularly useful reactions are those illustrated in Example 7 in which a hydrazone is generated or that illustrated in Example 8 where an iminium functionality is generated. Hydrazones that are favored for reaction as described in Example 7 include hydrazine hydrate itself since the $-NH_2$ terminus generated can undergo additional reactions as described above for aminobenzochlorins. A second hydrazine which is useful for further derivatization is phenylhydrazine-4-sulfonic acid as outlined in Example 7b. In this case, the terminus SO_3H group can be converted to SO_2Cl by reaction with a number of chlorinating agents including PCl_5, SO_2Cl and $POCl_3$/DMF and the sulfonyl chloride so formed reacted with an amine to produce a sulfonamide. Preferred amines include amino acids or aminoalcohols. The iminium salt of Example 8 is formed by use of $POCl_3$/DMF and the iminium group is thus substituted with two methyl groups. By replacing the DMF with other substituted formamides, a wide variety of analogs can be prepared, for example, methylphenylformamide would produce the iminium salt in which the iminium group contains one methyl and one phenyl group. Finally, Example 9 illustrates how the nitro group can be added to form nitrobenzochlorins. Other nitrating agents can also be used to produce nitrobenzochlorins, for example, $NaNO_2$/TFA, $NO_2^+ BF_4^-$, $NO_2^+ CF_3SO_3^-$. Since the nitro group is inert to many reagents, the above chemistry to insert and alter functionality at R_{14} of the benzochlorin nucleus is also applicable to nitrobenzochlorins. Alternatively, the nitro group can be reduced, thus forming an alternative route to aminobenzochlorins.

By suitable substitution of starting materials, reactants and reagents as discussed above, the procedures of Examples 1-8 can be used to produce benzochlorins according to the invention having the structures set forth in (Figs IA and IB where:

R_1 to R_{10} can be the same or different and each is H, Br, Cl, or CHO,

an alkyl or alkenyl group having from 1 to 6 carbon atoms,

-$R_1N(R_2)_2$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms and where R_2 is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different,

-$R_1N(R_2)_3^+ A^-$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms and where R_2 is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different, A is a physiologically acceptable anion,

-R_1OR_2 where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, and R_2 is H or an amino acid residue, a carbohydrate residue or an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms,

-R_1COR_2 where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, R_2 is NH_2, an amino acid group or a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups, OR_3 where R_3 is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, an amino acid group or a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue,

-COR_1 where R_1 is an amino acid residue, polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue.

R_{11} and R_{13} are H,

R_{12} is:

NO_2, Br,

-$N(R_2)_2$ where R_2 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different,

-$N(R_2)_3^+ A^-$ where R_2 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different and A^- is a physiologically acceptable anion,

$-OR_2$ where R_2 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, an amino acid residue or a carbohydrate residue

R_{14} is: as defined for R_1 to R_{10} and also

$-C=N^+(R_1)_2\ A^-$ where R_1 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_1 can be the same or different and A is a physiologically acceptable anion,

-C=N-NR where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue or

$-C_6H_4SO_2R_1$ where R_1 is OH, an amino acid group, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue.

M is any metal which results in a photodynamically active molecule but is preferentially selected from the group, Al, Zn, Sn, Ge, Cu.

The compounds of the invention are useful as photosensitizers and can be used to destroy cells and tissues following activation by light. In general, the benzochlorin derivatives are administered in a therapeutic amount to a human or animal patient in whom it is desired to destroy certain cells or tissues. The administration may be intravenous, intramuscular or topical. Following accumulation of the photosensitizer in the target cells and tissues, the target cells and tissues are exposed to light of a wavelength that causes the photosensitizer to become cytotoxic. Thus, the target cells and tissues are destroyed. The process may also be applied to an *in vitro* situation where, for example, blood or blood products collected from a human or animal patient can be treated photodynamically and then readministered to the same or to another human or animal patient.

The compositions are formulated into pharmaceutical compositions for administration using techniques which are well known to those skilled in the art and which are described in general in texts such as *Remington's Pharmaceutical Sciences*. More specifically, the preferred formulations are those prepared in conventional forms in which suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol and the like or emulsions based on medium chain triglycerides, non-ionic solubilizers such as Cremophor or Tween 80 or phospholipids such as EYP. For applications such as in the treatment of dermatological diseases such as psoriasis, the compositions may be topically administered using standard topical compositions involving penetrating solvents, or in the form of lotions, creams, gels or ointments. It is necessary only for the solution or emulsion to be one which is physiologically acceptable and of a suitable concentration or dilutable to a suitable concentration for administration. An indefinitely large number of such solutions and emulsions will be apparent to those skilled in the relevant art from the foregoing disclosures.

Typical indications for which these compositions have utility include, but are not limited to, cancer, dermatological applications, cardiovascular applications, urology applications, ophthalmologic applications, immunology applications, treatment of viral and fungal conditions and treatment of blood or blood products.

The following example is illustrative of a method used to assess the photodynamic potential of the compositions of this invention.

EXAMPLE 10
(In Vivo Biological Response - Tumor Treatment)

The benzochlorin derivative (identified below) is dissolved in saline containing 1% ethanol to give a solution with a final photosensitizer concentration of approximately 0.5mg/ml. The solution is filtered through a 0.22 micron Millipore filter. Ten C3H/HeJ mice with 0.5mm diameter subcutaneous RIF tumors in the flank are injected IV with 2.5 mg/kg body weight of the above solution. After

24 hours, the tumor area is exposed to light at for 30 min at a power density of 100mW/cm^2. The light source is a Xenon arc lamp filtered to remove IR radiation and all wavelengths below 620nm.

In all cases, twenty-four hours following light treatment, the treatment site appears cyanotic in nature and tumors are seen to become flat and non-palpable. An eschar forms over the treatment site. At 7 days post treatment, 100% of animals are shown to have responded to the photodynamic therapy. At thirty days post treatment, some of the animals remain tumor free. Normal tissue surrounding the tumor and included in the treatment site is shown to be minimally affected by the photodynamic treatment, indicating a selectivity for response in the tumorous tissue.

The following table illustrate examples from this invention which when tested in the above system give the responses indicated and compares the data to Photofrin® and to three previously reported benzochlorin derivatives.

Drug Tested	7 Day Response	30 Day Response
IA (R_1-R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, and R_{12} is Br)	100%	10%
IB (R_1-R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, R_{12} is Br, and, M is Zn)	100%	15%
IB (R_1-R_8 is ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, R_{12} is NO_2 , and, M is Zn)	100%	20%
IA (R_1-R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, and, R_{12} is NH_2)	100%	20%
IA (R_1-R_8 is ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, and R_{12} is NMe_3^+)	100%	15%
IB (R_1-R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are $-C=NMe_2^+$, R_{12} is Br, and, M is Zn)	100%	15%
IA (R_1-R_8 is ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are $-C=NMe_2^+$, R_{12} is NMe_2^+ , and, M is Zn)	100%	15%
IB (R_1-R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, R_{12} is N(Aspartate)$_2$, and, M is Zn)	100%	30%
Photofrin®	40%	0%

*IA (R_1-R_8 are ethyl, R_9, R_{10}, R_{11}, R_{13} and R_{14} are H, and, R_{12} is SO_3H)	40%	0%
**IB (R_1-R_8 is ethyl, R_9, R_{10} R_{11}, R_{13} and R_{14} are H, R_{12} is $-C=NMe_2^{+}$, M is Cu)	20%	0%
***IA (R_1-R_8 is ethyl, R_9,R_{10},R_{11}, R_{13} and R_{14} are H, R_{12} is $SO_2NHCH_2CH_2OH$)	50%	0%

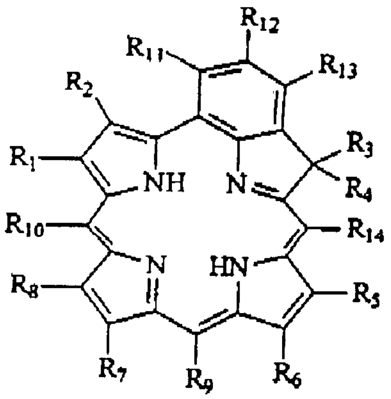
* Morgan et al, Photochem. Photobiol. 1992, 55, 133; ** US Patents 5,744,498, *** US Patent 5,789,586

The data clearly demonstrate the ability of the compounds of the present invention to effectively cause a more significant cytotoxic response, at low doses when compared to Photofrin® and other reported benzochlorins, which is significant in the target tissues and minimal in surrounding healthy tissue. These are desirable features since lowering the amount of photosensitizer needed to generate the desired effect reduces further the possibility of unwanted side-effects while the reduced response to normal tissue indicates that patients are not subjected to the prolonged skin sensitivity reported with Photofrin.®

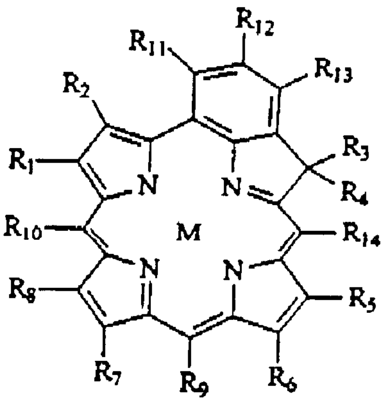
It is to be understood that this invention is not limited to the particular compounds, compositions, methods of use or synthesis as described herein. It is also understood that the terminology used is for the purpose of describing particular embodiments only and is not intended to be limiting. It is also to be understood that various changes may be made and equivalents substituted without departure from the scope and spirit of the invention. The scope of the present invention will be limited only by the appended claims.

What is Claimed is:

1. A photoreactive benzochlorin derivative composition selected from the group of Fig. IA and Fig. IB



IA



IB

wherein:

R_1 to R_{10} can be the same or different and each is H, Br, Cl, CHO,

an alkyl or alkenyl group having from 1 to 6 carbon atoms,

$-R_1N(R_2)_2$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms and where R_2 is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different,

$-R_1N(R_2)_3^+ A^-$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms and where R_2 is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different, A is a physiologically acceptable anion,

$-R_1OR_2$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, and R_2 is H or an amino acid residue, a carbohydrate residue or an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms,

$-R_1COR_2$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, R_2 is NH_2, an amino acid group or a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups, OR_3 where R_3 is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, an amino acid group or a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue, or

-COR_1 where R_1 is an amino acid residue, polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue.

R_{11} and R_{13} is H,

R_{12} is NO_2, Br,

-$N(R_2)_2$ where R_2 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different,

-$N(R_2)_3^+ A^-$ where R_2 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different and A^- is a physiologically acceptable anion,

-OR_2 where R_2 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, an amino acid residue or a carbohydrate residue,

R_{14} is the same as R_1 to R_{10} and also

-$C{=}N^+(R_1)_2\ A^-$ where R_1 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_1 can be the same or different and A is a physiologically acceptable anion,

-C=N-NR where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue or

-$C_6H_4SO_2R_1$ where R_1 is OH, an amino acid group, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue, and

M is any metal which results in a photodynamically active molecule selected from the group, Al, Zn, Sn, Ge, Cu.

2. The composition of claim 1 wherein R_{12} is NO_2.

3. The composition of claim 1 wherein R_{12} is Br.

4. The composition of claim 1 wherein R_{12} is $N(R)_2$ where R is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different.

5. The composition of claim 1 wherein R_{12} is $N(R_2)_3^+ A^-$ where R_2 can be H, an alkyl, or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different and A^- is a physiologically acceptable anion.

6. The composition of claim 1 wherein R_{12} is specifically OR where R is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, an amino acid residue or a carbohydrate residue.

7. The composition of claim 2 wherein each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, R_{14} is $C{=}NMe_2^+ A^-$ where A is a physiologically acceptable anion.

8. The composition of claim 3 wherein each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and R_{14} is $C{=}NMe_2^+ A^-$ where A is a physiologically acceptable anion.

9. The composition of claim 4 wherein each of R_1 to R_8 is ethyl, R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $C{=}NMe_2^+ A^-$ where A is a physiologically acceptable anion.

10. The composition of claim 5 wherein each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $C{=}NMe_2^+ A^-$ where A is a physiologically acceptable anion.

11. The composition of claim 6 wherein each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $C{=}NMe_2^+ A^-$ where A is a physiologically acceptable anion.

12. The composition of claim 2 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $-C{=}N{-}NR_2$ where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or the amino acid residues aspartate, glutamate, lysine, arginine.

13. The composition of claim 2 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and R_{14} is $-C{=}N{-}NH{-}C_6H_4{-}SO_2R$ where R can be OH, a polyhydroxyamino moiety

having from 1 to 6 hydroxyl groups or a carbohydrate residue or the amino acid residues aspartate, glutamate, lysine, arginine.

14. The composition of claim 3 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and R_{14} is -C=N-NR_2 where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or the amino acid residues aspartate, glutamate, lysine, arginine.

15. The composition of claim 3 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is -C=N-NH-C_6H_4-SO_2R where R can be OH, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue or the amino acid residues aspartate, glutamate, lysine, arginine

16. The composition of claim 4 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is -C=N-NR_2 where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or the amino acid residues aspartate, glutamate, lysine, arginine.

17. The composition of claim 4 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is -C=N-NH-C_6H_4-SO_2R where R can be OH, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue or the amino acid residues aspartate, glutamate, lysine, arginine.

18. The composition of claim 5 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is -C=N- where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or the amino acid residues aspartate, glutamate, lysine, arginine.

19. The composition of claim 5 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is -C=N-NH-C_6H_4-SO_2R where R can be OH, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue or the amino acid residues aspartate, glutamate, lysine, arginine.

20. The composition of claim 6 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and R_{14} is -C=N-NR_2

where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or the amino acid residues aspartate, glutamate, lysine, arginine.

21. The composition of claim 6 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and R_{14} is -C=N-NH-C_6H_4-SO_2R where R can be OH, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue or the amino acid residues aspartate, glutamate, lysine, arginine.

22. The composition of claim 1, having the structure of Fig. IA where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, and, R_{12} is Br.

23. The composition of claim 1, having the structure of Fig. IB where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, R_{12} is Br, and, M is Sn or Zn.

24. The composition of claim 1, having the structure of Fig. IA where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, and, R_{12} is NO_2.

25. The composition of claim 1, having the structure of Fig. IB where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, R_{12} is NO_2, and M is Zn or Sn.

26. The composition of claim 1, having the structure of Fig. IA where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, and, R_{12} is NH_2.

27. The composition of claim 1, having the structure of Fig. IB where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, R_{12} is NH_2, and, M is Zn or Sn.

28. The composition of claim 1, having the structure of Fig. IA where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, and, R_{12} is NMe_3^+

29. The composition of claim 1, having the structure of Fig. IB where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, R_{12} is NMe_3^+, and, M is Zn or Sn.

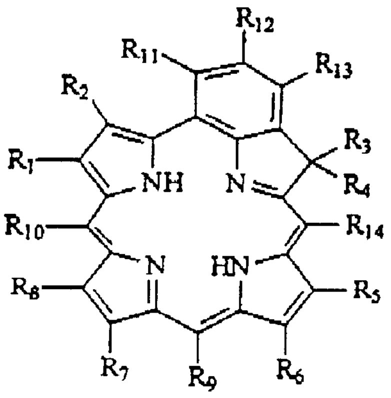
30. The composition of claim 1, having the structure of Fig. IA where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is -C=NMe_2^+, and, R_{12} is NMe_2^+.

31. The composition of claim 1, having the structure of Fig. IB where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is $-C{=}NMe_2^+$, R_{12} is NMe_2^+, and, M is Zn or Cu.

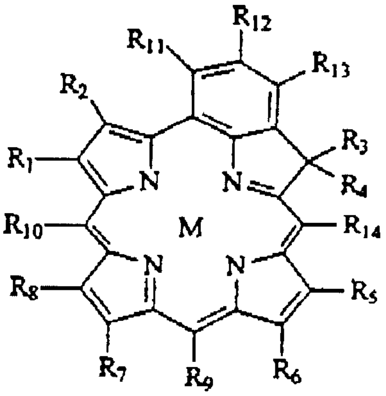
32. The composition of claim 1, having the structure of Fig. IA where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, and, R_{12} is $N(Aspartate)_2$ or $N(Glutamate)_2$.

33. The composition of claim 1, having the structure of Fig. IB where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, R_{12} is $N(Aspartate)_2$ or $N(Glutamate)_2$, and, M is Zn or Sn.

34. A pharmaceutical composition wherein the active ingredient is a composition having the structure of a composition selected from the group of Fig. IA and Fig. IB.



IA



IB

wherein:

each of R_1 to R_{10} is H, Br, Cl, CHO, an alkyl or alkenyl group having from 1 to 6 carbon atoms, $-R_1N(R_2)_2$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms and where R_2 is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different,

$-R_1N(R_2)_3^+ A^-$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms and where R_2 is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different, A is a physiologically acceptable anion,

$-R_1OR_2$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, and R_2 is H or an amino acid residue, a carbohydrate residue or an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms,

$-R_1COR_2$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, R_2 is NH_2, an amino acid group or a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups, OR_3 where R_3 is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, an amino acid group or a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue,

$-COR_1$ where R_1 is an amino acid residue, polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue,

R_{11} and R_{13} is H,

R_{12} is NO_2, Br

$-N(R_2)_2$ where R_2 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different,

$-N(R_2)_3^+ A^-$ where R_2 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different and A^- is a physiologically acceptable anion,

$-OR_2$ where R_2 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, an amino acid residue or a carbohydrate residue,

R_{14} is the same as R_1 to R_{10} and also

$-C=N^+(R_1)_2\ A^-$ where R_1 can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_1 can be the same or different and A is a physiologically acceptable anion,

-C=N-NR where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue or $-C_6H_4SO_2R_1$ where R_1 is OH, an amino acid group, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue, and

M is any metal which results in a photodynamically active molecule selected from the group, Al, Zn, Sn, Ge, Cu, and,

compounds selected from the group consisting of water, saline, dextrose, glycerol, ethanol, emulsions of triglycerides, non-ionic solubilizers, phospholipids and mixtures thereof.

35. The composition of claim 34 wherein R_{12} is NO_2.

36. The composition of claim 34 wherein R_{12} is Br.

37. The composition of claim 34 wherein R_{12} is $N(R)_2$ where R is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different.

38. The composition of claim 34 wherein R_{12} is $N(R_2)_3^+$ A^- where R_2 can be H, an alkyl, or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different and A^- is a physiologically acceptable anion.

39. The composition of claim 34 wherein each of R_{12} is specifically OR where R is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, an amino acid residue or a carbohydrate residue.

40. The composition of claim 35 wherein each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, R_{14} is $C=NMe_2^+$ A^- where A is a physiologically acceptable anion.

41. The composition of claim 36 wherein each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and R_{14} is $C=NMe_2^+$ A^- where A is a physiologically acceptable anion.

42. The composition of claim 37 wherein each of R_1 to R_8 is ethyl, R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $C{=}NMe_2^+ A^-$ where A is a physiologically acceptable anion.

43. The composition of claim 38 wherein each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $C{=}NMe_2^+ A^-$ where A is a physiologically acceptable anion.

44. The composition of claim 39 wherein each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $C{=}NMe_2^+ A^-$ where A is a physiologically acceptable anion.

45. The composition of claim 35 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $-C{=}N{-}NR_2$ where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or the amino acid residues aspartate, glutamate, lysine, arginine.

46. The composition of claim 35 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and R_{14} is $-C{=}N{-}NH{-}C_6H_4{-}SO_2R$ where R can be OH, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue or the amino acid residues aspartate, glutamate, lysine, arginine.

47. The composition of claim 36 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and R_{14} is $-C{=}N{-}NR_2$ where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or the amino acid residues aspartate, glutamate, lysine, arginine.

48. The composition of claim 36 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $-C{=}N{-}NH{-}C_6H_4{-}SO_2R$ where R can be OH, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue or the amino acid residues aspartate, glutamate, lysine, arginine.

49. The composition of claim 37 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $-C{=}N{-}NR_2$ where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or the amino acid residues aspartate, glutamate, lysine, arginine.

50. The composition of claim 37 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $-C{=}N{-}NH{-}$

C_6H_4-SO_2R where R can be OH, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue or the amino acid residues aspartate, glutamate, lysine, arginine.

51. The composition of claim 38 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is -C=N- where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or the amino acid residues aspartate, glutamate, lysine, arginine.

52. The composition of claim 38 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is -C=N-NH-C_6H_4-SO_2R where R can be OH, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue or the amino acid residues aspartate, glutamate, lysine, arginine.

53. The composition of claim 39 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and R_{14} is -C=N-NR_2 where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or the amino acid residues aspartate, glutamate, lysine, arginine.

54. The composition of claim 39 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and R_{14} is -C=N-NH-C_6H_4-SO_2R where R can be OH, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue or the amino acid residues aspartate, glutamate, lysine, arginine.

55. The composition of claim 34, having the structure of Fig. IA where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, and, R_{12} is Br.

56. The composition of claim 34, having the structure of Fig. IB where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, R_2 is Br, and, M is Sn or Zn.

57. The composition of claim 34, having the structure of Fig. IA where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, and, R_{12} is NO_2.

58. The composition of claim 34, having the structure of Fig. IB where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, and R_{12} is NO_2, and, M is Zn or Sn.

59. The composition of claim 34, having the structure of Fig. IA where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, and, R_{12} is NH_2.

60. The composition of claim 34, having the structure of Fig. IB where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, R_{12} is NH_2, and, M is Zn or Sn.

61. The composition of claim 34, having the structure of Fig. IA where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, and, R_{12} is NMe_3^+.

62. The composition of claim 34, having the structure of Fig. IB where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, R_{12} is NMe_3^+, and, M is Zn or Sn.

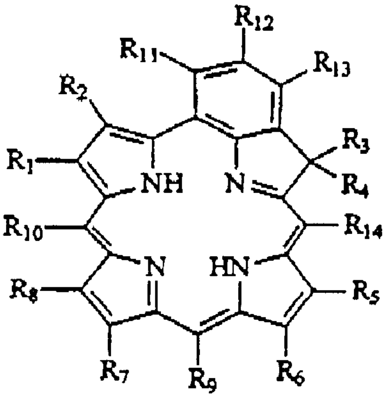
63. The composition of claim 34, having the structure of Fig. IA where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is $-C{=}NMe_2^+$ and, R_{12} is NMe_2^+.

64. The composition of claim 34, having the structure of Fig. IB where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is $-C{=}NMe_2^+$, R_{12} is NMe_2^+, and, M is Zn or Cu.

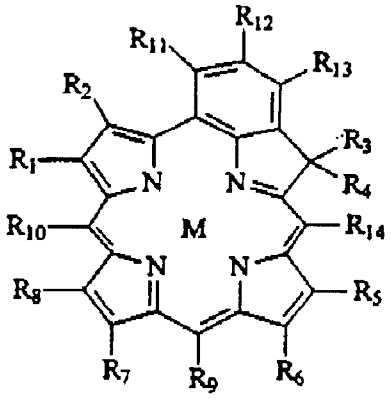
65. The composition of claim 34, having the structure of Fig. IA where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, and, R_{12} is $N(Aspartate)_2$ or $N(Glutamate)_2$.

66. The composition of claim 34, having the structure of Fig. IB where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, R_{12} is $N(Aspartate)_2$ or $N(Glutamate)_2$, and, M is Zn or Sn.

67. A method of destroying cells and tissues through a photodynamic process comprising the steps of administering to a human or animal patients, or to fluids including blood, plasma, or bone marrow from a human or animal patient, a pharmaceutical composition including one of the compositions selected from the group of Fig. IA and Fig. IB below and supplying light sufficient to generate a cytotoxic effect,



IA



IB

wherein

each of R_1 to R_{10} is H, Br, Cl, CHO, an alkyl or alkenyl group having from 1 to 6 carbon atoms,

a group having the formula

$-R_1N(R_2)_2$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms and where R_2 is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different,

$-R_1N(R_2)_3^+ A^-$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms and where R_2 is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different, A is a physiologically acceptable anion,

$-R_1OR_2$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, and R_2 is H or an amino acid residue, a carbohydrate residue or an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms,

$-R_1COR_2$ where R_1 is an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, R_2 is NH_2, an amino acid group or a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups, OR_3 where R_3 is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, an amino acid group or a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue,

-COR$_1$ where R$_1$ is an amino acid residue, polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue.

\R$_{11}$ and R$_{13}$ is H,

R$_{12}$ is NO$_2$, Br,

-N(R$_2$)$_2$ where R$_2$ can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R$_2$ can be the same or different,

-N(R$_2$)$_3^+$ A$^-$ where R$_2$ can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R$_2$ can be the same or different and A$^-$ is a physiologically acceptable anion,

-OR$_2$ where R$_2$ can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, an amino acid residue or a carbohydrate residue,

R$_{14}$ is the same as R$_1$ to R$_{10}$ and also

-C=N$^+$(R$_1$)$_2$ A$^-$ where R$_1$ can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R$_1$ can be the same or different and A is a physiologically acceptable anion,

-C=N-NR where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue or -C$_6$H$_4$SO$_2$R$_1$ where R$_1$ is OH, an amino acid group, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue, and

M is any metal which results in a photodynamically active molecule selected from the group, Al, Zn, Sn, Ge, Cu.

68. The method of claim 67 wherein R$_{12}$ is NO$_2$.

69. The method of claim 67 wherein R$_{12}$ is Br.

70. The method of claim 67 wherein R_{12} is $N(R)_2$ where R is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different.

71. The method of claim 67 wherein R_{12} is $N(R_2)_3^+ A^-$ where R_2 can be H, an alkyl, or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or an amino acid residue or an amino acid residue or a carbohydrate residue and each R_2 can be the same or different and A^- is a physiologically acceptable anion.

72. The method of claim 67 wherein R_{12} is specifically OR where R is H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms, an amino acid residue or a carbohydrate residue.

73. The method of claim 68 wherein each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, R_{14} is $C{=}NMe_2^+ A^-$ where A is a physiologically acceptable anion.

74. The method of claim 69 wherein each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and R_{14} is $C{=}NMe_2^+ A^-$ where A is a physiologically acceptable anion.

75. The method of claim 70 wherein each of R_1 to R_8 is ethyl, R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $C{=}NMe_2^+ A^-$ where A is a physiologically acceptable anion.

76. The method of claim 71 wherein each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $C{=}NMe_2^+ A^-$ where A is a physiologically acceptable anion.

77. The method of claim 72 wherein each of R_1 to $R_8$is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $C{=}NMe_2^+ A^-$ where A is a physiologically acceptable anion.

78. The method of claim 68 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $-C{=}N{-}NR_2$ where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or the amino acid residues aspartate, glutamate, lysine, arginine.

79. The method of claim 68 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and R_{14} is $-C{=}N{-}NH{-}C_6H_4{-}SO_2R$ where R can be OH, a polyhydroxyamino moiety

having from 1 to 6 hydroxyl groups or a carbohydrate residue or the amino acid residues aspartate, glutamate, lysine, arginine.

80. The method of claim 69 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and R_{14} is $-C=N-NR_2$ where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or the amino acid residues aspartate, glutamate, lysine, arginine.

81. The method of claim 69 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $-C=N-NH-C_6H_4-SO_2R$ where R can be OH, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue or the amino acid residues aspartate, glutamate, lysine, arginine.

82. The method of claim 70 where each of $R_1$to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $-C=N-NR_2$ where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or the amino acid residues aspartate, glutamate, lysine, arginine.

83. The method of claim 70 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $-C=N-NH-C_6H_4-SO_2R$ where R can be OH, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue or the amino acid residues aspartate, glutamate, lysine, arginine.

84. The method of claim 71 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $-C=N-$ where R can be H, an alkyl or alkenyl hydrocarbon radical having from 1 to 6 carbon atoms or the amino acid residues aspartate, glutamate, lysine, arginine.

85. The method of claim 71 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and, R_{14} is $-C=N-NH-C_6H_4-SO_2R$ where R can be OH, a polyhydroxyamino moiety having from 1 to 6 hydroxyl groups or a carbohydrate residue or the amino acid residues aspartate, glutamate, lysine, arginine.

86. The method of claim 72 where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} is H, and R_{14} is $-C=N-NR_2$

97. The method of claim 67, having the structure of Fig. IB where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is $-C=NMe_2^+$, R_{12} is NMe_2^+, and, M is Zn or Cu.

98. The method of claim 67, having the structure of Fig. IA where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, and, R_{12} is $N(Aspartate)_2$ or $N(Glutamate)_2$.

99. The method of claim 67, having the structure of Fig. IB where each of R_1 to R_8 is ethyl, each of R_9, R_{10}, R_{11}, R_{13} and R_{14} is H, R_{12} is $N(Aspartate)_2$ or $N(Glutamate)_2$, and, M is Zn or Sn.

100. The method of claim 67 wherein the pharmaceutical composition includes a compound selected from the group consisting of water, saline, dextrose, glycerol, ethanol, triglycerides, non-ionic solubilizers, phospholipids, and mixtures thereof.