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(54) SUBSTITUTED 11-PHENYL-DIBENZAZEPINE COMPOUNDS USEFUL FOR THE TREATMENT OR PREVENTION OF DISEASES CHARACTERIZED BY ABNORMAL CELL PROLIFERATION

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(57) **ABSTRACT**

The present invention provides substituted 11-phenyl-dibenzazepine compounds which are specific, potent and safe inhibitors of mammalian cell proliferation. The compounds can be used to inhibit mammalian cell proliferation in situ as a therapeutic approach towards the treatment or prevention of diseases characterized by abnormal cell proliferation, such as cancer.

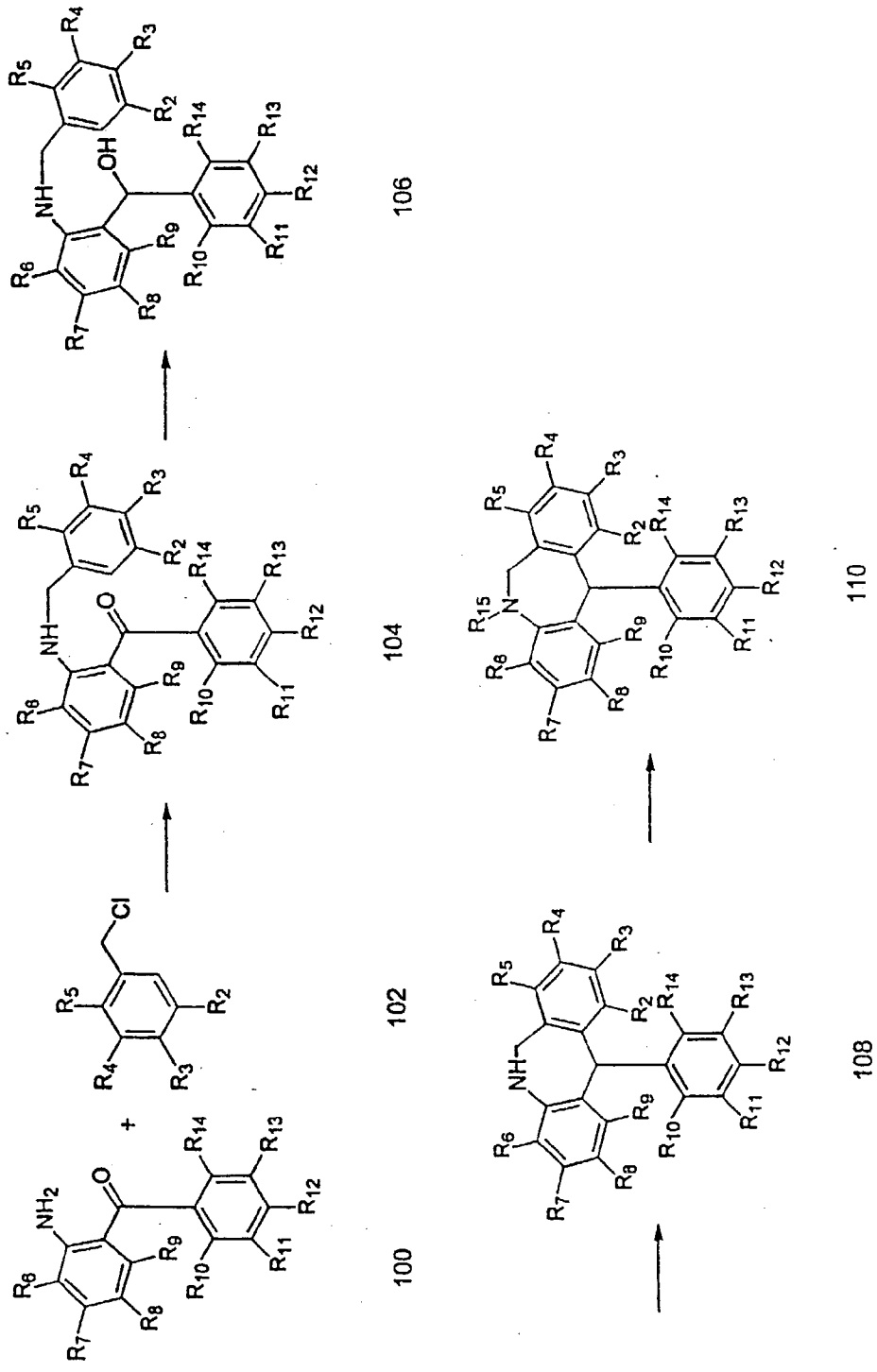


FIG. 1

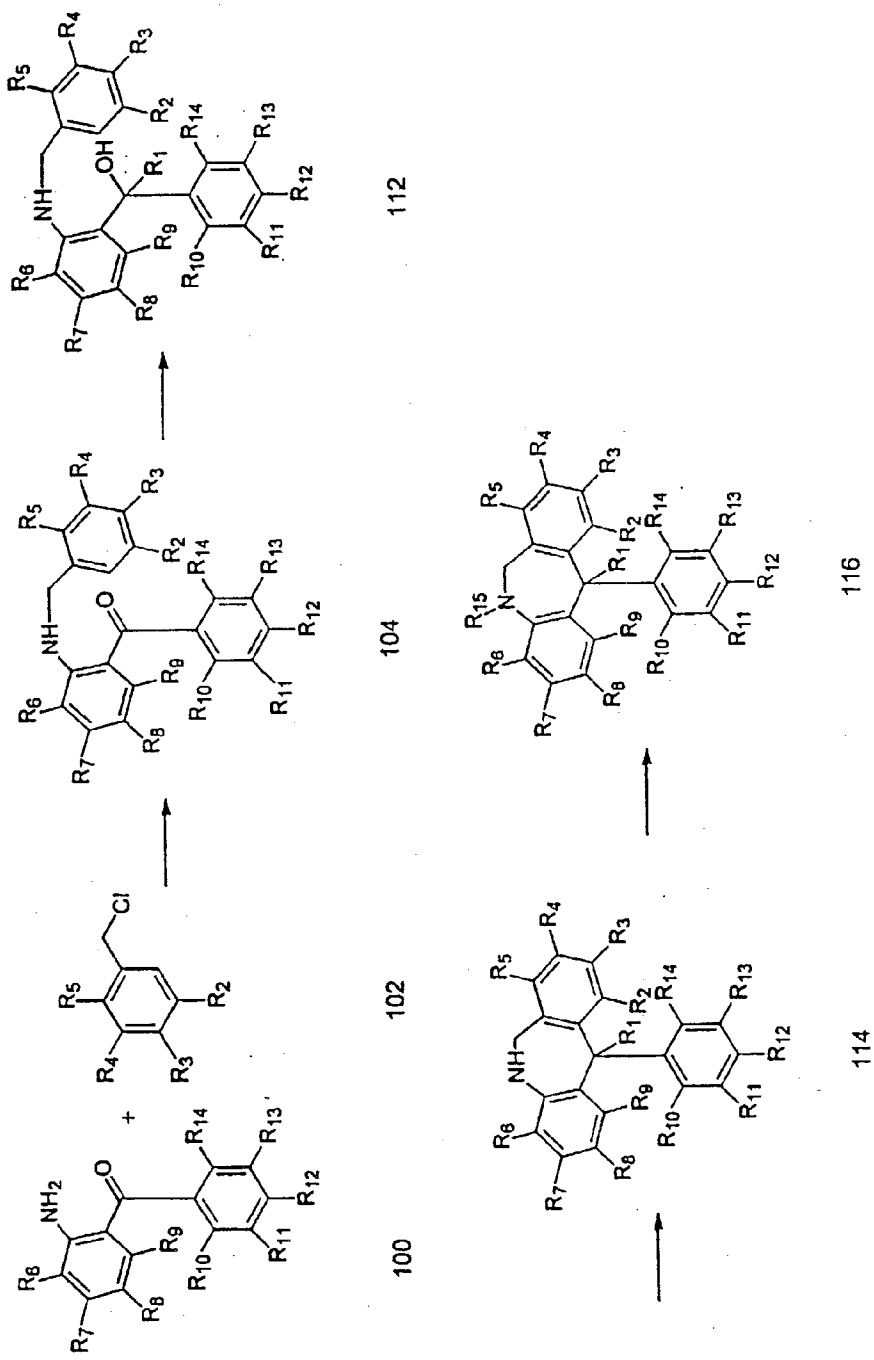


FIG. 2

SUBSTITUTED 11-PHENYL-DIBENZAZEPINE COMPOUNDS USEFUL FOR THE TREATMENT OR PREVENTION OF DISEASES CHARACTERIZED BY ABNORMAL CELL PROLIFERATION

1. FIELD OF THE INVENTION

[0001] The present invention relates to aromatic organic compounds which are specific, potent and safe inhibitors of the Ca^{2+}-activated potassium channel (Gardos channel) of erythrocytes and/or of mammalian cell proliferation. More particularly, the invention relates to substituted 11-phenyl dibenzazepine compounds capable of inhibiting the Gardos channel of sickle erythrocytes and/or mitogen-induced mammalian cell proliferation. The compounds can be used to reduce sickle erythrocyte dehydration and/or delay the occurrence of erythrocyte sickling or deformation in situ as a therapeutic approach towards the treatment or prevention of sickle cell disease. The compounds can also be used to inhibit mammalian cell proliferation in situ as a therapeutic approach towards the treatment or prevention of diseases characterized by abnormal cell proliferations.

2. BACKGROUND OF THE INVENTION

[0002] Sickle cell disease has been recognized within West Africa for several centuries. Sickle cell anemia and the existence of sickle hemoglobin (Hb S) was the first genetic disease to be understood at the molecular level. It is recognized today as the morphological and clinical result of a glycine to valine substitution at the No. 6 position of the beta globin chain (Ingram, 1956, *Nature* 178:792-794). The origin of the amino acid change and of the disease state is the consequence of-a single nucleotide substitution (Marotta et al., 1977, *J. Biol. Chem.* 252:5040-5053).

[0003] The major source of morbidity and mortality of patients suffering from sickle cell disease is vascular occlusion caused by sickled erythrocytes, which causes repeated episodes of pain in both acute and chronic form and also causes ongoing organ damage with the passage of time. It has long been recognized and accepted that the deformation and distortion of sickle cell erythrocytes upon complete deoxygenation is caused by polymerization and intracellular gelation of sickle hemoglobin, hemoglobin S (Hb S). The phenomenon is well reviewed and discussed by Eaton and Hofrichter, 1987, *Blood* 70:1245. The intracellular gelation and polymerization of Hb S can occur at any time during erythrocyte's journey through the vasculature. Thus, erythrocytes in patients with sickle cell disease containing no polymerized hemoglobin S may pass through the microcirculation and return to the lungs without sickling, may sickle in the veins or may sickle in the capillaries.

[0004] The probability of each of these events occurring is determined by the delay time for intracellular gelation relative to the appropriate capillary transit time (Eaton et al., 1976, *Blood* 47:621). In turn, the delay time is dependent upon the oxygenation state of the hemoglobin, with deoxygenation shortening the delay time. Thus, if it is thermodynamically impossible for intracellular gelation to take place, or if the delay time at venous oxygen pressures is longer than about 15 seconds, cell sickling will not occur. Alternatively, if the delay time is between about 1 and 15 seconds, the red cell will likely sickle in the veins. However, if the delay time is less than about 1 second, red cells will sickle within the capillaries.

[0005] For red cells that sickle within the capillaries, a number of possible consequent events exist, ranging from no effect on transit time, to transient occlusion of the capillary, to a more permanent blockage that may ultimately result in ischemia or infarction of the surrounding cells and in destruction of the red cell.

[0006] It has long been recognized that the cytoplasm of the normal erythrocyte comprises approximately 70% water. Water crosses a normal erythrocyte membrane in milliseconds; however, the loss of cell water causes an exponential increase in cytoplasmic viscosity as the mean cell hemoglobin concentration (MCHC) rises above about 32 g/dl. Since cytoplasmic viscosity is a major determinate of erythrocyte deformability and sickling, the dehydration of the erythrocyte has substantial Theological and pathological consequences. Thus, the physiological mechanisms that maintain the water content of normal erythrocytes and the pathological conditions that cause loss of water from erythrocytes in the blood circulation are critically important. Not surprisingly, regulation of erythrocyte dehydration has been recognized as an important therapeutic approach towards the treatment of sickle cell disease. Since cell water will follow any osmotic change in the intracellular concentration of ions, the maintenance of the red cell's potassium concentration is of particular importance (Stuart and Ellory, 1988, *Brit J. Haematol.* 69:1-4).

[0007] Many attempts and approaches to therapeutically treating dehydrated sickle cells (and thus decreasing polymerization of hemoglobin S by lowering the osmolality of plasma) have been tried with limited success, including the following approaches: intravenous infusion of distilled water (Gye et al., 1973, *Am. J. Med. Sci.* 266:267-277); administration of the antidiuretic hormone vasopressin together with a high fluid intake and salt restriction (Rosa et al., 1980, *M. Eng. J. Med.* 303:1138-1143; Charache and Walker, 1981, *Blood* 58:892-896); the use of monensin to increase the cation content of the sickle cell (Clark et al., 1982, *J. Clin. Invest.* 70:1074-1080; Fahim and Pressman, 1981, *Life Sciences* 29:1959-1966); intravenous administration of cetiedil citrate (Benjamin et al., 1986, *Blood* 67:1442-1447; Berkowitz and orringer, 1984, *Am. J. Hematol.* 17:217-223; Stuart et al., 1987, *J. Clin. Pathol.* 40:1182-1186); and the use of oxpentifylline (Stuart et al., 1987, *J. Clin. Pathol.* 40:1182-1186).

[0008] Another approach towards therapeutically treating dehydrated sickle cells involves the administration of imidazole, nitroimidazole and triazole antimycotic agents such as Clotrimazole (U.S. Pat. No. 5,273,992 to Brugnara et al.). Clotrimazole, an imidazole-containing antimycotic agent, has been shown to be a specific, potent inhibitor of the Gardos channel of normal and sickle erythrocytes, and to prevent Ca^{2+}-dependent dehydration of sickle cells both in vitro and in vivo (Brugnara et al., 1993, *J. Clin. Invest.* 92:520-526; De Franceschi et al., 1994, *J. Clin. Invest.* 93:1670-1676). When combined with a compound which stabilizes the oxyconformation of Hb S, Clotrimazole induces an additive reduction in the clogging rate of a micropore filter and may attenuate the formation of irreversibly sickled cells (Stuart et al., 1994, *J. Haematol.* 86:820-823). Other compounds that contain a heteroaryl imidazole-like moiety believed to be useful in reducing sickle erythrocyte dehydration via Gardos channel inhibition include miconazole, econazole, butoconazole, oxiconazole

and sulconazole. Each of these compounds is a known antimycotic. Other imidazole-containing compounds have been found to be incapable of inhibiting the Gardos channel and preventing loss of potassium.

[0009] As can be seen from the above discussion, reducing sickle erythrocyte dehydration via blockade of the Gardos channel is a powerful therapeutic approach towards the treatment and/or prevention of sickle cell disease. Compounds capable of inhibiting the Gardos channel as a means of reducing sickle cell dehydration are highly desirable, and are therefore an object of the present invention.

[0010] Cell proliferation is a normal part of mammalian existence, necessary for life itself. However, cell proliferation is not always desirable, and has recently been shown to be the root of many life-threatening diseases such as cancer, certain skin disorders, inflammatory diseases, fibrotic conditions and arteriosclerotic conditions.

[0011] Cell proliferation is critically dependent on the regulated movement of ions across various cellular compartments, and is associated with the synthesis of DNA. Binding of specific polypeptide growth factors to specific receptors in growth-arrested cells triggers an array of early ionic signals that are critical in the cascade of mitogenic events eventually leading to DNA synthesis (Rozengurt, 1986, *Science* 234:161-164). These include: (1) a rapid increase in cystolic Ca^{2+}, mostly due to rapid release of Ca^{2+} from intracellular stores; (2) capacitative Ca^{2+} influx in response to opening of ligand-bound and hyperpolarization-sensitive Ca^{2+} channels in the plasma membrane that contribute further to increased intracellular Ca^{2+} concentration (Tsien and Tsien, 1990, *Annu. Rev. Cell Biol.* 6:715-760; Peppelenbosch et al., 1991, *J. Biol. Chem.* 266:19938-19944); and (3) activation of Ca^{2+}-dependent K^+ channels in the plasma membrane with increased K^+ conductance and membrane hyperpolarization (Magni et al., 1991, *J. Biol. Chem.* 261:9321-9327). These mitogen-induced early ionic changes, considered critical events in the signal transduction pathways, are powerful therapeutic targets for inhibition of cell proliferation in normal and malignant cells.

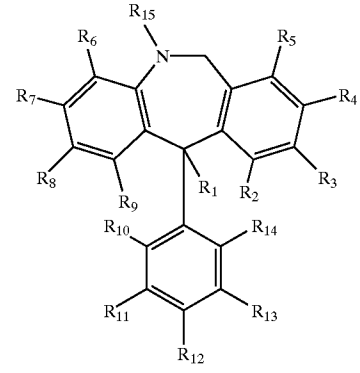
[0012] One therapeutic approach towards the treatment of diseases characterized by unwanted or abnormal cell proliferation via alteration of the ionic fluxes associated with early mitogenic signals involves the administration of Clotrimazole. As discussed above, Clotrimazole has been shown to inhibit the Ca^{2+}-activated potassium channel of erythrocytes. In addition, Clotrimazole inhibits voltage- and ligand-stimulated Ca^{2+} influx mechanisms in nucleated cells (Villalobos et al., 1992, *FASEB J.* 6:2742-2747; Montero et al., 1991, *Biochem. J.* 277:73-79) and inhibits cell proliferation both in vitro and in vivo (Benzaquen et al., 1995, *Nature Medicine* 1:534-540). Recently, Clotrimazole and other imidazole-containing antimycotic agents capable of inhibiting Ca^{2+}-activated potassium channels have been shown to be useful in the treatment of arteriosclerosis (U.S. Pat. No. 5,358,959 to Halperin et al.), as well as other disorders characterized by unwanted or abnormal cell proliferation.

[0013] As can be seen from the above discussion, inhibiting mammalian cell proliferation via alteration of ionic fluxes associated with early mitogenic signals is a powerful therapeutic approach towards the treatment and/or prevention of diseases characterized by unwanted or abnormal cell proliferation. Compounds capable of inhibiting mammalian cell proliferation are highly desirable, and are therefore also an object of the present invention.

3. SUMMARY OF THE INVENTION

[0014] These and other objects are provided by the present invention, which in one aspect provides a novel class of organic compounds which are potent, selective and safe inhibitors of the Ca^{2+}-activated potassium channel (Gardos channel) of erythrocytes, particularly sickle erythrocytes, and/or of mammalian cell proliferation. The compounds are generally substituted 11-phenyl-dibenzazepine compounds. In one illustrative embodiment, the compounds capable of inhibiting the Gardos channel and/or mammalian cell proliferation according to the invention are compounds having the structural formula:

(I)



[0015] or pharmaceutically acceptable salts of hydrates thereof, wherein:

[0016] R_1 is —R', (C_6-C_{20}) aryl or substituted (C_6-C_{20}) aryl;

[0017] R_2 is —R', —OR', —SR', halogen or trihalomethyl;

[0018] R_3 is —R', —OR', —SR', halogen or trihalomethyl or, when taken together with R_4, is (C_6-C_{20}) aryleno;

[0019] R_4 is —R', —OR', —SR', halogen or trihalomethyl or, when taken together with R_3, is (C_6-C_{20}) aryleno;

[0020] each of R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} is independently selected from the group consisting of —R', halogen and trihalomethyl;

[0021] R_{15} is —R", —C(O)R", —C(S)R", —C(O)OR", —C(S)OR", —C(O)SR", —C(S)SR", —C(O)N(R")$_2$, —C(S)N(R")$_2$, —C(O)C(O)R", —C(S)C(O)R", —C(O)C(S)R", —C(S)C(S)R", —C(O)C(O)OR", —C(S)C(O)OR", —C(O)C(S)OR", —C(O)C(O)SR", —C(S)C(S)OR", —C(S)C(O)SR", —C(O)C(S)SR", —C(S)C(S)SR", —C(O)C(O)N(R")$_2$, —C(S)C(O)N(R")$_2$, —C(O)C(S)N(R")$_2$ or —C(S)C(S)N(R")$_2$;

[0022] each R' is independently selected from the group consisting of —H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl and (C_1-C_6) alkynyl;

[0023] each R" is independently selected from the group consisting of —H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_6-C_{20}) aryl, substituted (C_6-C_{20}) aryl, (C_6-C_{26}) alkaryl and substituted (C_6-C_{26}) alkaryl; and

[0024] the aryl and alkaryl substituents are each independently selected from the group consisting of —CN, —OR', —SR', —NO_2, —NR'R', halogen, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl and trihalomethyl.

[0025] In another aspect, the present invention provides pharmaceutical compositions comprising one or more compounds according to the invention in admixture with a pharmaceutically acceptable carrier, excipient or diluent. Such a preparation can be administered in the methods of the invention.

[0026] In still another aspect, the invention provides a method for reducing sickle erythrocyte dehydration and/or delaying the occurrence of erythrocyte sickling or deformation in situ. The method involves contacting a sickle erythrocyte in situ with an amount of at least one compound according to the invention, or a pharmaceutical composition thereof, effective to reduce sickle erythrocyte dehydration and/or delay the occurrence of erythrocyte sickling or deformation. In a preferred embodiment, the sickle cell dehydration is reduced and erythrocyte deformation is delayed in a sickle erythrocyte that is within the microcirculation vasculature of a subject, thereby preventing or reducing the vaso-occlusion and consequent adverse effects that are commonly caused by sickled cells.

[0027] In still another aspect, the invention provides a method for the treatment and/or prevention of sickle cell disease in a subject, such as a human. The method involves administering a prophylactically or therapeutically effective amount of at least one compound according to the invention, or a pharmaceutical composition thereof, to a patient suffering from sickle cell disease. The patient may be suffering from either acute sickle crisis or chronic sickle cell episodes.

[0028] In yet another aspect, the invention provides a method for inhibiting mammalian cell proliferation in situ. The method involves contacting a mammalian cell in situ with an amount of at least one compound according to the invention, or a pharmaceutical composition thereof, effective to inhibit cell proliferation. The compound or composition may act either cytostatically, cytotoxically or a by a combination of both mechanisms to inhibit proliferation. Mammalian cells that can be treated in this manner include vascular smooth muscle cells, fibroblasts, endothelial cells, various types of pre-cancer cells and various types of cancer cells.

[0029] In still another aspect, the invention provides a method for treating and/or preventing unwanted or abnormal cell proliferation in a subject, such as a human. In the method, at least one compound according to the invention, or a pharmaceutical composition thereof, is administered to a subject in need of such treatment in an amount effective to inhibit the unwanted or abnormal mammalian cell proliferation. The compound and/or composition may be applied locally to the proliferating cells, or may be administered to the subject systemically. Preferably, the compound and/or composition is administered to a subject that has a disorder characterized by unwanted or abnormal cell proliferation. Such disorders include, but are not limited to, cancer, epithelial precancerous lesions, non-cancerous angiogenic conditions or arteriosclerosis.

[0030] In a final aspect, the invention provides a method for the treatment and/or prevention of diseases that are characterized by unwanted and/or abnormal mammalian cell proliferation. The method involves administering a prophylactically or therapeutically effective amount of at least one compound according to the invention, or a pharmaceutical composition thereof, to a subject in need of such treatment. Diseases that are characterized by abnormal mammalian cell proliferation which can be treated or prevented by way of the methods of the invention include, but are not limited to, cancer, blood vessel proliferative disorders, fibrotic disorders and arteriosclerotic conditions.

[0031] 3.1 Definitions

[0032] As used herein, the following terms shall have the following meanings:

[0033] "Alkyl:" refers to a saturated branched, straight chain or cyclic hydrocarbon radical. Typical alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl, and the like. In preferred embodiments, the alkyl groups are (C_1-C_6) alkyl, with (C_1-C_3) being particularly preferred.

[0034] "Substituted Alkyl:" refers to an alkyl radical wherein one or more hydrogen atoms are each independently replaced with other substituents. Typical substituents include, but are not limited to, —OR, —SR, —NRR, —CN, —NO_2, -halogen and -trihalomethyl, where each R is independently —H, alkyl, alkenyl, alkynyl, aryl or alkaryl as defined herein.

[0035] "Alkenyl:" refers to an unsaturated branched, straight chain or cyclic hydrocarbon radical having at least one carbon-carbon double bond. The radical may be in either the cis or trans conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, tert-butenyl, pentenyl, hexenyl and the like. In preferred embodiments, the alkenyl group is (C_1-C_6) alkenyl, with (C_1-C_3) being particularly preferred.

[0036] "Substituted Alkenyl:" refers to an alkenyl radical wherein one or more hydrogen atoms are each independently replaced with other substituents. Typical substituents include, but are not limited to, —OR, —SR, —NRR, —CN, —NO_2, -halogen and -trihalomethyl, where each R is independently —H, alkyl, alkenyl, alkynyl, aryl or alkaryl as defined herein.

[0037] "Alkynyl:" refers to an unsaturated branched, straight chain or cyclic hydrocarbon radical having at least one carbon-carbon triple bond. Typical alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, isobutynyl, pentynyl, hexynyl and the like. In preferred embodiments, the alkynyl group is (C_1-C_6) alkynyl, with (C_1-C_3) being particularly preferred.

[0038] "Substituted Alkynyl:" refers to an alkynyl radical wherein one or more hydrogen atoms are each independently replaced with other substituents. Typical substituents include, but are not limited to, —OR, —SR, —NRR, —CN, —NO_2, -halogen and -trihalomethyl, where each R is independently —H, alkyl, alkenyl, alkynyl, aryl or alkaryl as defined herein.

[0039] "Aryl:" refers to an unsaturated cyclic hydrocarbon radical having a conjugated η electron system. Typical aryl groups include, but are not limited to, penta-2,4-diene, phenyl, naphthyl, anthracyl, azulenyl, indacenyl, and the like. In preferred embodiments, the aryl group is (C_5-C_{20}) aryl, with (C_5-C_{10}) being particularly preferred.

[0040] "Substituted Aryl:" refers to an aryl radical wherein one or more hydrogen atoms are each independently replaced with other substituents. Typical substituents include, but are not limited to, —OR, —SR, —NRR, —CN, —NO_2, -halogen and -trihalomethyl where each R is independently —H, alkyl, alkenyl, alkynyl, aryl or alkaryl as defined herein.

[0041] "Aryleno:" refers to an aryl radical that is capable of fusing to another aryl group. Typical aryleno groups include, but are not limited to, benzeno, naphthaleno, anthracaleno and the like. In preferred embodiments, the aryleno group is (C_6-C_{20}) aryleno.

[0042] "Substituted Aryleno:" refers to an aryleno group wherein one or more hydrogen atoms are each independently replaced with other substituents. Typical substituents include, but are not limited to, —OR, —SR, —NRR, —CN, —NO_2, -halogen and -trihalomethyl, where each R is independently —H, alkyl, alkenyl, alkynyl, aryl or alkaryl as defined herein.

[0043] "Alkaryl:" refers to a straight-chain alkyl, alkenyl or alkynyl group wherein one of the hydrogen atoms bonded to a terminal carbon is replaced with an aryl moiety. Typical alkaryl groups include, but are not limited to, benzyl, benzylidene, benzylidyne, benzenobenzyl, naphthalenobenzyl and the like. In preferred embodiments, the alkaryl group is (C_6-C_{26}) alkaryl, i.e., the alkyl, alkenyl or alkynyl moiety of the alkaryl group is (C_1-C_6) and the aryl moiety is (C_5-C_{20}). In particularly preferred embodiments the alkaryl group is (C_6-C_{13}), i.e., the alkyl, alkenyl or alkynyl moiety of the alkaryl group is (C_1-C_3) and the aryl moiety is (C_5-C_{10}).

[0044] "Substituted Alkaryl:" refers to an alkaryl radical wherein one or more hydrogen atoms on the aryl moiety of the alkaryl group are each independently replaced with other substituents. Typical substituents include, but are not limited to, —OR, —SR, —NRR, —CN, —NO_2, -halogen and -trihalomethyl, where each R is independently —H, alkyl, alkenyl, alkynyl, aryl or alkaryl as defined herein.

[0045] "In Situ:" refers to and includes the terms"in vivo,""ex vivo," and"in vitro" as these terms are commonly recognized and understood by persons ordinarily skilled in the art. Moreover, the phrase"in situ" is employed herein in its broadest connotative and denotative contexts to identify an entity, cell or tissue as found or in place, without regard to its source or origin, its condition or status or its duration or longevity at that location or position.

4. BRIEF DESCRIPTION OF THE DRAWINGS

[0046] **FIG. 1** provides a reaction scheme for synthesizing 11-aryl-5,6-dihydro-11H-dibenz[b,e]azepine compounds according to the invention; and

[0047] **FIG. 2** provides a reaction scheme for synthesizing 11-aryl-11-substituted-5,6-dihydro-dibenz[b,e]azepine compounds according to the invention.

5. DETAILED DESCRIPTION OF THE INVENTION

[0048] As discussed in the Background section, blockade of sickle dehydration via inhibition of the Gardos channel is a powerful therapeutic approach towards the treatment and/or prevention of sickle cell disease. Studies have shown that antimycotic agents such as Clotrimazole block Ca^{2+}-activated K^+ transport and reduce cell dehydration in sickle erythrocytes in vitro (Brugnara et al., 1993, *J. Clin. Invest.* 92:520-526), and also inhibit the Gardos channel of erythrocytes, increase red cell K^+ content, decrease the mean cell hemoglobin concentration (MCHC) and decrease red cell density in vivo in a transgenic mouse model for sickle cell disease (SAD mouse, Trudel et al., 1991, *EMBO J.* 11:3157-3165; De Franceschi et al., 1994, *J. Clin. Invest.* 93:1670-1676). Moreover, therapy with oral Clotrimazole induces inhibition of the Gardos channel and reduces erythrocyte dehydration in human patients with sickle cell disease (Brugnara et al., 1996, *J. Clin. Invest.* 97:1227-1234). Other antimycotic agents which inhibit the Gardos channel in vitro include miconazole, econazole, butoconazole, oxiconazole and sulconazole (U.S. Pat. No. 5,273,992 to Brugnara et al.). All of these compounds contain an imidazole-like ring, i.e., a heteroaryl ring containing two or more nitrogens.

[0049] Also as discussed in the Background section, the modulation of early ionic mitogenic signals and inhibition of cell proliferation are powerful therapeutic approaches towards the treatment and/or prevention of disorders characterized by abnormal cell proliferation. It has been shown that Clotrimazole, in addition to inhibiting the Gardos channel of erythrocytes, also modulates ionic mitogenic signals and inhibits cell proliferation both in vitro and in vivo.

[0050] For example, Clotrimazole inhibits the rate of cell proliferation of normal and cancer cell lines in a reversible and dose-dependent manner in vitro (Benzaquen et al., 1995 *Nature Medicine* 1:534-540). Clotrimazole also depletes the intracellular Ca^{2+} stores and prevents the rise in cystolic Ca^{2+} that normally follows mitogenic stimulation. Moreover, in mice with severe combined immunodeficiency disease (SCID) and inoculated with MM-RU human melanoma cells, daily administration of Clotrimazole resulted in a significant reduction in the number of lung metastases observed (Benzaquen et al., supra).

[0051] It has now been discovered that substituted 11-phenyl dibenzazepine compounds also inhibit the Gardos channel of erythrocytes and/or mammalian cell proliferation. Thus, in one aspect, the present invention provides a new class of organic compounds that are capable of inhibiting the

Ca^{2+}-activated potassium channel (Gardos channel) of erythrocytes, particularly sickle erythrocytes and/or of inhibiting mammalian cell proliferation, particularly mitogen-induced cell proliferation.

[0052] The discovery that 11-phenyl dibenzazepine compounds inhibit the Gardos channel and/or mammalian cell proliferation was quite surprising. Significantly, the compounds of the invention do not contain an imidazole or imidazole-like moiety. The imidazole or imidazole-like moiety is well-recognized as the essential functionality underlying the antimycotic and other biological activities of Clotrimazole and the other above-mentioned anti-mycotic agents. Thus, the 11-phenyl dibenzazepine compounds of the invention provide an entirely new class of compounds that are capable of effecting inhibition of the Gardos channel and/or mammalian cell proliferation and that are therefore Useful for the treatment of sickle cell disease and/or diseases related to abnormal or unwanted cell proliferation.

[0053] In another aspect, the invention provides a method of reducing sickle cell dehydration and/or delaying the occurrence of erythrocyte sickling in situ as a therapeutic approach towards the treatment of sickle cell disease. In its broadest sense, the method involves only a single step—the administration of at least one pharmacologically active compound of the invention, or a composition thereof, to a sickle erythrocyte in situ in an amount effective to reduce dehydration and/or delay the occurrence of cell sickling or deformation.

[0054] While not intending to be bound by any particular theory, it is believed that administration of the active compounds described herein in appropriate amounts to sickle erythrocytes in situ causes nearly complete inhibition of the Gardos channel of sickle cells, thereby reducing the dehydration of sickle cells and/or delaying the occurrence of cell sickling or deformation. In a preferred embodiment, the dehydration of a sickle cell is reduced and/or the occurrence of sickling is delayed in a sickle cell that is within the microcirculation vasculature of the subject, thereby reducing or eliminating the vaso-occlusion that is commonly caused by sickled cells.

[0055] Based in part on the surmised importance of the Gardos channel as a therapeutic target in the treatment of sickle cell disease, the invention is also directed to methods of treating or preventing sickle cell disease. In the method, an effective amount of one or more compounds according to the invention, or a pharmaceutical composition thereof, is administered to a patient suffering from sickle cell disease. The methods may be used to treat sickle cell disease prophylactically to decrease intracellular Hb S concentration and/or polymerization, and thus diminish the time and duration of red cell sickling and vaso-occlusion in the blood circulation. The methods may also be used therapeutically in patients with acute sickle cell crisis, and in patients suffering chronic sickle cell episodes to control both the frequency and duration of the crises.

[0056] The compounds of the invention are also potent, specific inhibitors of mammalian cell proliferation. Thus, in another aspect, the invention provides methods of inhibiting mammalian cell proliferation as a therapeutic approach towards the treatment or prevention of diseases characterized by unwanted or abnormal cell proliferation. In its broadest sense, the method involves only a single step—the administration of an effective amount of at least one pharmacologically active compound according to the invention to a mammalian cell in situ. The compound may act cytostatically, cytotoxically, or by a combination of both mechanisms to inhibit cell proliferation. Mammalian cells treatable in this manner include vascular smooth muscle cells, fibroblasts, endothelial cells, various pre-cancer cells and various cancer cells. In a preferred embodiment, cell proliferation is inhibited in a subject suffering from a disorder that is characterized by unwanted or abnormal cell proliferation. Such diseases are described more fully below.

[0057] Based in part on the surmised role of mammalian cell proliferation in certain diseases, the invention is also directed to methods of treating or preventing diseases characterized by abnormal cell proliferation. In the method, an effective amount of at least one compound according to the invention, or a pharmaceutical composition thereof, is administered to a patient suffering from a disorder that is characterized by abnormal cell proliferation. While not intending to be bound. by any particular theory, it is believed that administration of an appropriate amount of a compound according to the invention to a subject inhibits cell proliferation by altering the ionic fluxes associated with early mitogenic signals. Such alteration of ionic fluxes is thought to be due to the ability of the compounds of the invention to inhibit potassium channels of cells, particularly Ca^{2+}-activated potassium channels. The method can be used prophylactically to prevent unwanted or abnormal cell proliferation, or may be used therapeutically to reduce or arrest proliferation of abnormally proliferating cells. The compound, or a pharmaceutical formulation thereof, can be applied locally to proliferating cells to arrest or inhibit proliferation at a desired time, or may be administered to a subject systemically to arrest or inhibit cell proliferation.

[0058] Diseases which are characterized by abnormal cell proliferation that can be treated or prevented by means of the present invention include blood vessel proliferative disorders, fibrotic disorders, arteriosclerotic disorders and various cancers.

[0059] Blood vessel proliferation disorders refer to angiogenic and vasculogenic disorders generally resulting in abnormal proliferation of blood vessels. The formation and spreading of blood vessels, or vasculogenesis and angiogenesis, respectively, play important roles in a variety of physiological processes such as embryonic development, corpus luteum formation, wound healing and organ regeneration. They also play a pivotal role in cancer development. Other examples of blood vessel proliferative disorders include arthritis, where new capillary blood vessels invade the joint and destroy cartilage and ocular diseases such as diabetic retinopathy, where new capillaries in the retina invade the vitreous, bleed and cause blindness and neovascular glaucoma.

[0060] Another example of abnormal neovascularization is that associated with solid tumors. It is now established that unrestricted growth of tumors is dependent upon angiogenesis and that induction of angiogenesis by liberation of angiogenic factors can be an important step in carcinogenesis. For example, basic fibroblast growth factor (bFGF) is liberated by several cancer cells and plays a crucial role in cancer angiogenesis. The demonstration that certain animal tumors regress when angiogenesis is inhibited has provided

the most compelling evidence for the role of angiogenesis in tumor growth. Other cancers that are associated with neovascularization include hemangioendotheliomas, hemangiomas and Kaposi's sarcoma.

[0061] Proliferation of endothelial and vascular smooth muscle cells is the main feature of neovascularization. The invention is useful in inhibiting such proliferation, and therefore in inhibiting or arresting altogether the progression of the angiogenic condition which depends in whole or in part upon such neovascularization. The invention is particularly useful when the condition has an additional element of endothelial or vascular smooth muscle cell proliferation that is not necessarily associated with neovascularization. For example, psoriasis may additionally involve endothelial cell proliferation that is independent of the endothelial cell proliferation associated with neovascularization. Likewise, a solid tumor which requires neovascularization for continued growth may also be a tumor of endothelial or vascular smooth muscle cells. In this case, growth of the tumor cells themselves, as well as the neovascularization, is inhibited by the compounds described herein.

[0062] The invention is also useful for the treatment of fibrotic disorders such as fibrosis and other medical complications of fibrosis which result in whole or in part from the proliferation of fibroblasts. Medical conditions involving fibrosis (other than atherosclerosis, discussed below) include undesirable tissue adhesion resulting from surgery or injury.

[0063] Other cell proliferative disorders which can be treated by means of the invention include arteriosclerotic conditions. Arteriosclerosis is a term used to describe a thickening and hardening of the arterial wall. An arteriosclerotic condition as used herein means classical atherosclerosis, accelerated atherosclerosis, atherosclerotic lesions and any other arteriosclerotic conditions characterized by undesirable endothelial and/or vascular smooth muscle cell proliferation, including vascular complications of diabetes.

[0064] Proliferation of vascular smooth muscle cells is a main pathological feature in classical atherosclerosis. It is believed that liberation of growth factors from endothelial cells stimulates the proliferation of subintimal smooth muscle which, in turn, reduces the caliber and finally obstructs the artery. The invention is useful in inhibiting such proliferation, and therefore in delaying the onset of, inhibiting the progression of, or even halting the progression of such proliferation and the associated atherosclerotic condition.

[0065] Proliferation of vascular smooth muscle cells produces accelerated atherosclerosis, which is the main reason for failure of heart transplants that are not rejected. This proliferation is also believed to be mediated by growth factors, and can ultimately result in obstruction of the coronary arteries. The invention is useful in inhibiting such obstruction and reducing the risk of, or even preventing, such failures.

[0066] Vascular injury can also result in endothelial and vascular smooth muscle cell proliferation. The injury can be caused by any number of traumatic events or interventions, including vascular surgery and balloon angioplasty. Restenosis is the main complication of successful balloon angioplasty of the coronary arteries. It is believed to be caused by the release of growth factors as a result of mechanical injury to the endothelial cells lining the coronary arteries. Thus, by inhibiting unwanted endothelial and smooth muscle cell proliferation, the compounds described herein can be used to delay, or even avoid, the onset of restenosis.

[0067] Other atherosclerotic conditions which can be treated or prevented by means of the present invention include diseases of the arterial walls that involve proliferation of endothelial and/or vascular smooth muscle cells, such as complications of diabetes, diabetic glomerulosclerosis and diabetic retinopathy.

[0068] The compounds described herein are also potent antineoplastic agents and are therefore useful in treating or preventing various types of neoplastic diseases. Neoplastic diseases which can be treated by means of the present invention include, but are not limited to, biliary tract cancer; brain cancer, including glioblastomas and medulloblastomas; breast cancer; cervical cancer; choriocarcinoma; colon cancer; endometrial cancer; esophageal cancer; gastric cancer; hematological neoplasms, including acute and chronic lymphocytic and myelogenous leukemia, multiple myeloma, AIDS associated leukemias and adult T-cell leukemia lymphoma; intraepithelial neoplasms, including Bowen's disease and Paget's disease; liver cancer; lung cancer; lymphomas, including Hodgkin's disease and lymphocytic lymphomas; neuroblastomas; oral cancer, including squamous cell carcinoma; ovarian cancer, including those arising from epithelial cells, stromal cells, germ cells and mesenchymal cells; pancreas cancer; prostate cancer; rectal cancer; sarcomas, including leiomyosarcoma, rhabdomyosarcoma, liposarcoma, fibrosarcoma and osteosarcoma; skin cancer, including melanoma, Kaposi's sarcoma, basocellular cancer and squamous cell cancer; testicular cancer, including germinal tumors (seminoma, non-seminoma (teratomas, choriocarcinomas)), stromal tumors and germ cell tumors; thyroid cancer, including thyroid adenocarcinoma and medullar carcinoma; and renal cancer including adenocarcinoma and Wilms tumor.

[0069] The compounds of the invention are useful with hormone dependent and also with nonhormone dependent cancers. They also are useful with prostate and breast cancers. They further are useful with multidrug resistant strains of cancer.

[0070] In addition to the particular disorders enumerated above, the invention is also useful in treating or preventing dermatological diseases including keloids, hypertrophic scars, seborrheic dermatosis, papilloma virus infection (e.g., producing verruca vulgaris, verruca plantaris, verruca plan, condylomata, etc.), eczema and epithelial precancerous lesions such as actinic keratosis; other inflammatory diseases including proliferative glomerulonephritis; lupus erythematosus; scleroderma; temporal arthritis; thromboangiitis obliterans; mucocutaneous lymph node syndrome; and other pathologies mediated by growth factors including uterine leiomyomas.

[0071] The compounds and methods of the invention provide myriad advantages over agents and methods commonly used to treat sickle cell disease and/or cell proliferative disorders. The compounds and methods of the invention also provide myriad advantages over the treatment of sickle cell disease and/or cell proliferative disorders with Clotrimazole or other antimycotic agents. For example, many of the compounds of the invention are more potent than Clo-

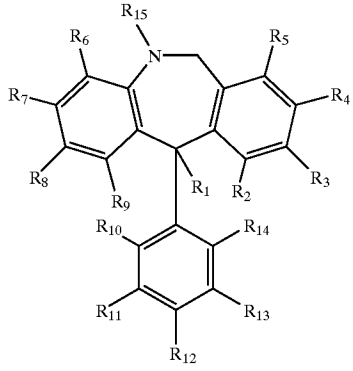
trimazole in in vitro tests, and therefore may provide consequential therapeutic advantages in clinical settings.

[0072] Most significantly, the compounds of the invention have reduced toxicity as compared with Clotrimazole and other antimycotic agents. For Clotrimazole, it is well-known that the imidazole moiety is responsible for inhibiting a wide range of cytochrome P-450 isozyme catalyzed reactions, which constitutes their main toxicological effects (Pappas and Franklin, 1993, *Toxicology* 80:27-35; Matsuura et al., 1991, *Biochemical Pharmacology* 41:1949-1956). Analogues and metabolites of Clotrimazole do not induce cytochrome P-450 (Matsuura et al., 1991, *Biochemical Pharmacology* 41:1949-1956), and therefore do not share Clotrimazole's toxicity.

[0073] 5.1 The Compounds

[0074] The compounds which are capable of inhibiting the Gardos channel and/or mammalian cell proliferation according to the invention are generally substituted 11-phenyl dibenzazepine compounds. In one illustrative embodiment, the compounds capable of inhibiting the Gardos channel and/or mammalian cell proliferation according to the invention are compounds having the structural formula:

(I)



[0075] wherein:

[0076] R_1 is —R', (C_6-C_{20}) aryl or substituted (C_6-C_{20}) aryl;

[0077] R_2 is —R', —OR', —SR', halogen or trihalomethyl;

[0078] R_3 is —R', —OR', —SR', halogen or trihalomethyl or, when taken together with R_4, is (C_6-C_{20}) aryleno;

[0079] R_4 is —R', —OR', —SR', halogen or trihalomethyl or, when taken together with R_3, is (C_6-C_{20}) aryleno;

[0080] each of R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} is independently selected from the group consisting of —R', halogen and trihalomethyl;

[0081] R_{15} is —R", —C(O)R", —C(S)R", —C(O)OR", —C(S)OR", —C(O)SR", —C(S)SR", —C(O)N(R")$_2$, —C(S)N(R")$_2$, —C(O)C(O)R", —C(S)C(O)R", —C(O)C(S)R", —C(S)C(S)R", —C(O)C(O)OR", —C(S)C(O)OR", —C(O)C(S)OR", —C(O)C(O)SR", —C(S)C(S)OR", —C(S)C(O)SR", —C(O)C(S)SR", —C(S)C(S)SR", —C(O)C(O)N(R")$_2$, —C(S)C(O)N(R")$_2$, —C(O)C(S)N(R")$_2$ or —C(S)C(S)N(R")$_2$,

[0082] each R' is independently selected from the group consisting of —H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl and (C_1-C_6) alkynyl;

[0083] each R" is independently selected from the group consisting of —H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_6-C_{20}) aryl, (C_6-C_{20}) substituted aryl, (C_6-C_{26}) alkaryl and substituted (C_6-C_{26}) alkaryl; and

[0084] the aryl and alkaryl substituents are each independently selected from the group consisting of —CN, —OR', —SR', —NO_2, —NR'R', halogen, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl and trihalomethyl.

[0085] In a preferred embodiment of the invention, the compounds are those of structure (I) wherein the chalcogens are each oxygen.

[0086] In another preferred embodiment, the compounds are those of structure (I) wherein the halogens are each independently —F, —Cl, —Br or —I.

[0087] In another preferred embodiment, the alkyl, alkenyl and alkynyl groups are each independently (C_1-C_3) and/or the aryl groups are phenyl and/or the aryleno groups are benzeno.

[0088] In another preferred embodiment, R_5, R_6, R_7, R_9, R_{10},R_{11} and R_{13} are each independently —R'.

[0089] In another preferred embodiment, the substituted aryl and alkaryl are mono-substituted.

[0090] In another preferred embodiment, R_{15} is —R", —C(O)R", —C(O)OR", —C(O)N(R")$_2$, —C(O)C(O)R", —C(O)C(O)OR" or —C(O)C(O)N(R")$_2$.

[0091] In another preferred embodiment of the invention, the compounds are those of structural formula (I) wherein:

[0092] R_1 is —R' or (C_6-C_{20}) aryl;

[0093] R_2 is —R' or —OR';

[0094] R_3 is —R' or —OR' or, when taken together with R_4, is (C_6-C_{20}) aryleno;

[0095] R_4 is —R' or —OR' or, when taken together with R_3, is (C_6-C_{20}) aryleno;

[0096] each of R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} is independently selected from the group consisting of —R' and halogen;

[0097] R_{15} is —R", —C(O)R", —C(O)OR", —C(O)N(R")$_2$, —C(O)C(O)R", —C(O)C(O)OR" or —C(O)C(O)N(R")$_2$;

[0098] each R' is independently selected from the group consisting of —H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl and (C_1-C_6) alkynyl;

[0099] each R" is independently selected from the group consisting of —H, (C_1-C_6) alkyl, (C_1-C_6)

alkenyl, (C_1-C_6) alkynyl, (C_6-C_{20}) aryl, substituted (C_6-C_{20}) aryl, (C_6-C_{26}) alkaryl and substituted (C_6-C_{26}) alkaryl; and

[0100] the aryl and alkaryl substituents are each independently selected from the group consisting of —CN, —OR', —NO_2, —NR'R', halogen, (C_1-C_6) alkyl, (C_1-C_6) alkenyl and (C_1-C_6) alkynyl.

[0101] In another preferred embodiment, the compounds are those of formula (I) wherein:

[0102] R_1 is —R' or (C_6-C_{10}) aryl;

[0103] R_2 is —R' or —OR';

[0104] R_3 is —R' or —OR' or, when taken together with R_{14} is (C_6-C_{10}) aryleno;

[0105] R_4 is —R' or —OR' or, when taken together with R_3, is (C_6-C_{10}) aryleno;

[0106] each of R_5, R_6 and R_7 is —H;

[0107] R_8 is —R', —F, —Cl, —Br or —I;

[0108] each of R_9, R_{10} and R_{11} is —H;

[0109] R_{12} is —R', —F, —Cl, —Br or —I;

[0110] R_{13} is —H;

[0111] R_{14} is —R', —F, —Cl, —Br or —I;

[0112] R_{15} is —R", —C(O)R", —C(O)OR", —C(O)N(R")$_2$, —C(O)C(O)R", —C(O)C(O)OR" or —C(O)C(O)N(R")$_2$;

[0113] each R' is independently selected from the group consisting of —H, (C_1-C_3) alkyl, (C_1-C_3) alkenyl and (C_1-C_3) alkynyl;

[0114] each R" is independently selected from the group consisting of —H, (C_1-C_3) alkyl, (C_1-C_3) alkenyl, (C_1-C_3) alkynyl, (C_6-C_{10}) aryl, substituted (C_6-C_{10}) aryl, (C_6-C_{13}) alkaryl or substituted (C_6-C_{13}) alkaryl; and

[0115] the aryl and alkaryl substituents are each independently selected from the group consisting of —OR',—NO_2, —NR'R', —F, —Cl, —Br, —I, (C_1-C_3) alkyl, (C_1-C_3) alkenyl and (C_1-C_3) alkynyl.

[0116] In still another preferred embodiment, the compounds are those of structural formula (I) wherein:

[0117] R_1 is —R' or phenyl;

[0118] R_2 is —R' or —OR';

[0119] R_3 is —R' or —OR' or, when taken together with R_4, is benzeno;

[0120] R_4 is —R' or —OR' or, when taken together with R_3, is benzeno;

[0121] each of R_5, R_6 and R_7 is —H;

[0122] R_9 is —R', —Cl or —Br;

[0123] each of R_9, R_{10} and R_{11} is —H;

[0124] R_{12} is —R', —F or —Cl;

[0125] R_{13} is —H;

[0126] R_{14} is —R' or —Cl;

[0127] R_{15} is —R", —C(O)R", —C(O)OR", —C(O)NHR", —C(O)C(**0**)R" or —C(O)C(O)OR";

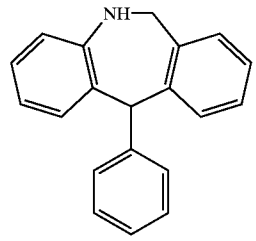
[0128] each R' is independently selected from the group consisting of —H, (C_1-C_3) alkyl, (C_1-C_3) alkenyl and (C_1-C_3) alkynyl;

[0129] each R" is independently selected from the group consisting of —H, (C_1-C_3) alkyl, (C_1-C_3) alkenyl, (C_1-C_3) alkynyl, (C_6-C_{10}) aryl, mono-substituted (C_6-C_{10}) aryl, (C_6-C_{13}) alkaryl or mono-substituted (C_6-C_{13}) alkaryl; and

[0130] the aryl and alkaryl substituents are each independently selected from the group consisting of —OR', —NO_2, —NR'R', —Cl, (C_1-C_3) alkyl, (C_1-C_3) alkenyl and (C_1-C_3)alkynyl.

[0131] In still another preferred embodiment, the compounds of the invention are as follows:

(1)



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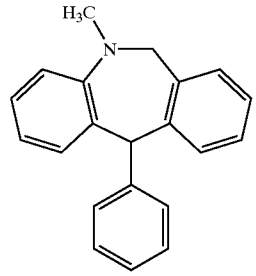

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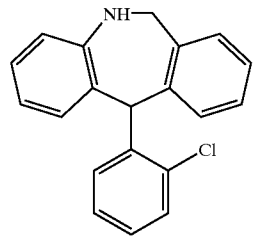

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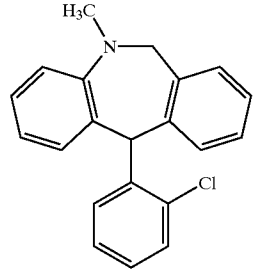

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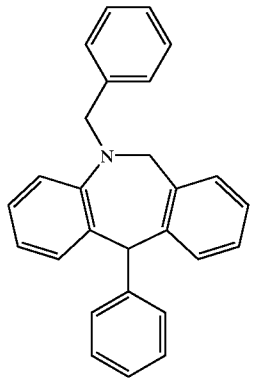

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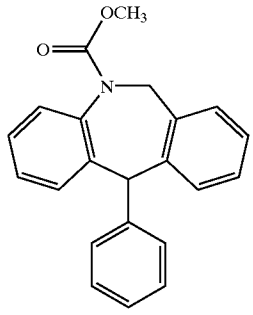

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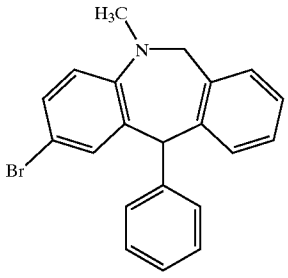

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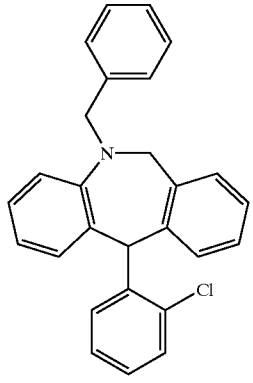

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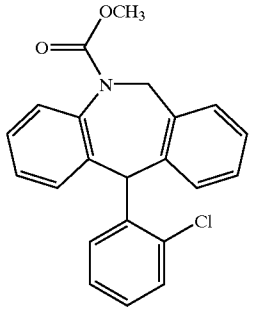

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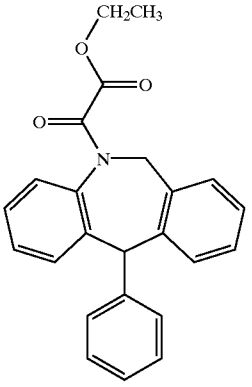

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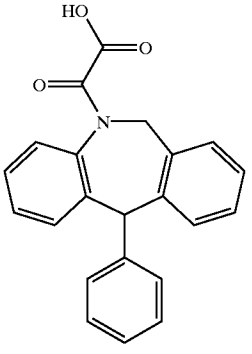

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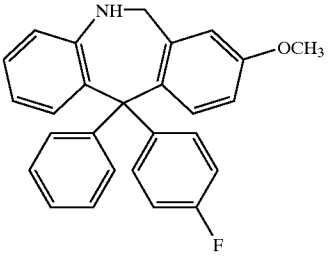

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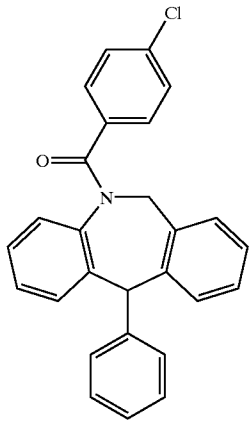

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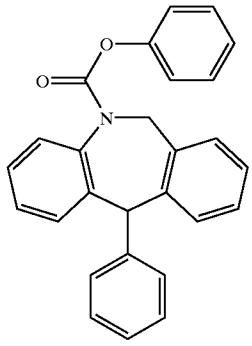

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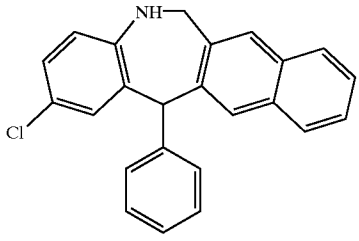

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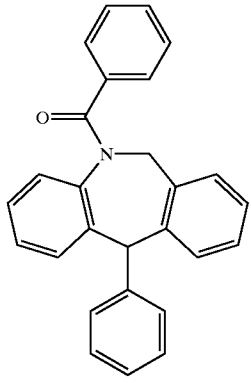

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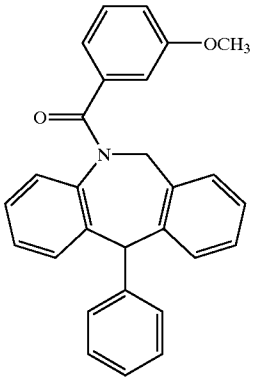

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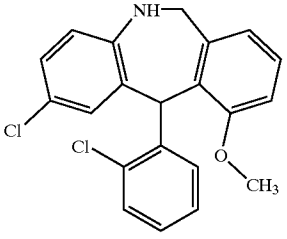

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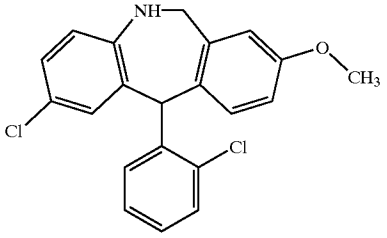

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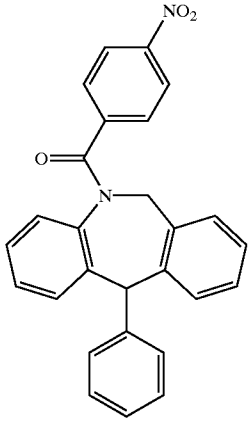

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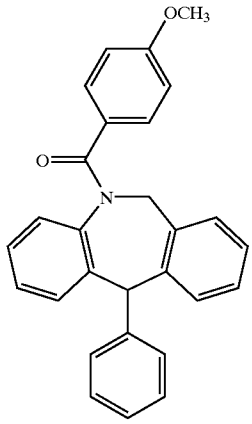

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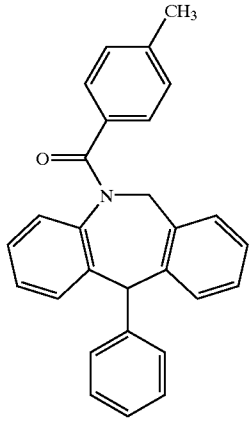

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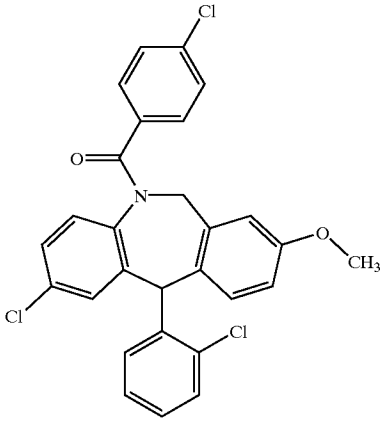

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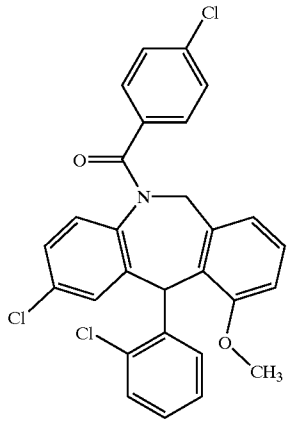

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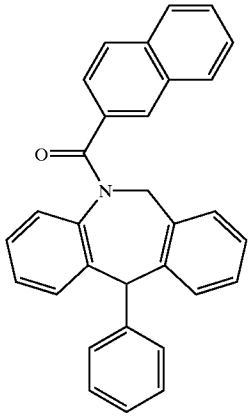

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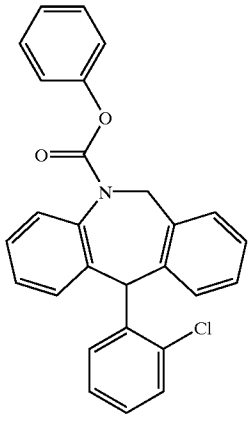

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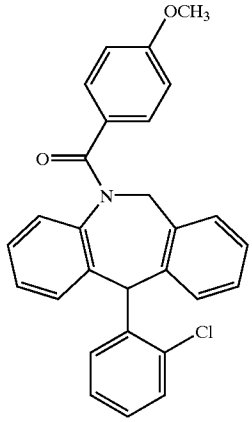

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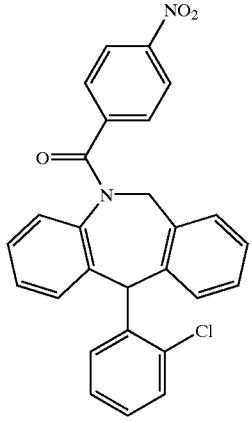

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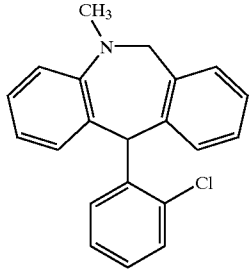

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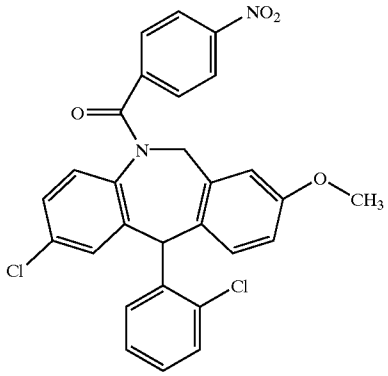

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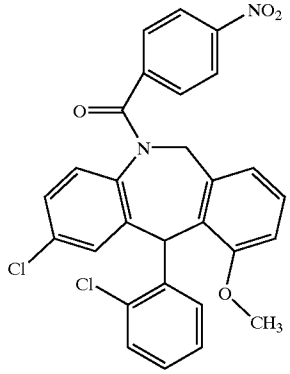

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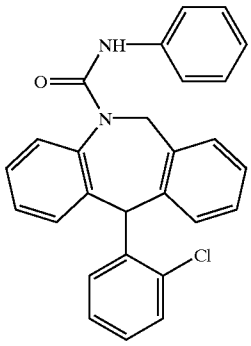

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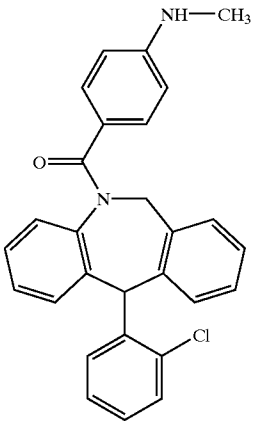

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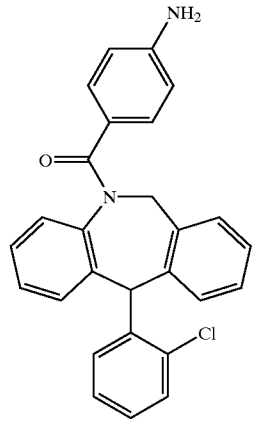

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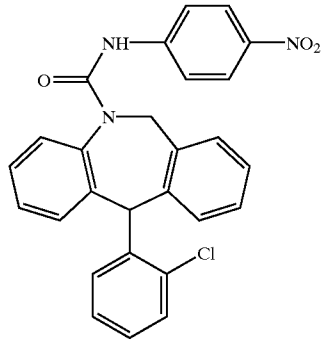


[0132] In yet another preferred embodiment, the compounds are those of structural formula (I), with the proviso that when R_1 and R_{15} are each —R', at least one of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_9, R_{10},R_{11}, R_{12}, R_{13} or R_{14} is other than —R', R_8 is other than —R' or halogen and at least three of R_2, R_3, R_4 and R_5 are other than —OR'.

[0133] In yet another preferred embodiment, the compounds are those of structural formula (I), with the proviso that when R_1 and R_{15} are each —H, at least one of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_9, R_{10}, R_{11}, R_{12}, R_{13} or R_{14} is other than —H, R_8 is other than —H or —Cl and at least three of R_2, R_3, R_4, and R_5 are other than —OCH_3.

[0134] In a final preferred embodiment, the compounds of the invention are not 11-phenyl-5,6-dihydro-11H-dibenz[b,e]azepine, 11-phenyl-9-halo-5,6-dihydro-11H-dibenz[b,e]azepine, 11-phenyl-9-chloro-5,6-dihydro-11H-dibenz[b,e]azepine, 11-phenyl-5,6-dihydro-1,2,3-trialkoxy-11H-dibenz[b,e]azepine, 11-phenyl-5,6-dihydro-1,2,3-trimethoxy-11H-dibenz[b,e]azepine, 11-phenyl-5,6-dihydro-2,3,4-trialkoxy-11H-dibenz[b,e]azepine and/or 11-phenyl-5,6-dihydro-2,3,4-trimethoxy-11H-dibenz[b,e]azepine.

[0135] The chemical formulae referred to herein may exhibit the phenomena of tautomerism, conformational isomerism, stereo isomerism or geometric isomerism. As the formulae drawings within this specification can represent only one of the possible tautomeric, conformational isomeric, enantiomeric or geometric isomeric forms, it should be understood that the invention encompasses any tautomeric, conformational isomeric, enantiomeric or geometric isomeric forms which exhibit biological or pharmacological activity as described herein.

[0136] The compounds of the invention may be in the form of free acids, free bases or pharmaceutically effective salts thereof. Such salts can be readily prepared by treating a compound with an appropriate acid. Such acids include, by way of example and not limitation, inorganic acids such as hydrohalic acids (hydrochloric, hydrobromic, etc.), sulfuric acid, nitric acid, phosphoric acid, etc.; and organic acids such as acetic acid, propanoic acid, 2-hydroxyacetic acid, 2-hydroxypropanoic acid, 2-oxopropanoic acid, propandioic acid, butandioic acid, etc. Conversely, the salt can be converted into the free base form by treatment with alkali.

[0137] In addition to the above-described compounds and their pharmaceutically acceptable salts, the invention may employ, where applicable, solvated as well as unsolvated forms of the compounds (e.g. hydrated forms).

[0138] The compounds described herein may be prepared by any processes known to be applicable to the preparation of chemical compounds. Suitable processes are well known in the art. Preferred processes are illustrated by the representative examples. Additional methods are described in copending application Ser. No. _____, entitled "SYNTHESIS OF 11-ARYL-5,6-DIHYDRO-11H[b,e]AZEPINES, filed concurrently herewith (Attorney Docket No. PEL97-06), which is incorporated herein by reference in its entirety. Necessary starting materials may be obtained commercially or by standard procedures of organic chemistry. Moreover, many of the compounds are commercially available.

[0139] An individual compound's relevant activity and potency as an agent to affect sickle cell dehydration or deformation and/or mammalian cell proliferation may be determined using standard techniques. Preferentially, a compound is subject to a series of screens to determine its pharmacological activity.

[0140] In most cases, the active compounds of the invention exhibit two pharmacological activities: inhibition of the Gardos channel of erythrocytes and inhibition of mammalian cell proliferation. However, in some cases, the compounds of the invention may exhibit only one of these pharmacological activities. Any compound encompassed by formula (I) which exhibits at least one of these pharmacological activities is considered to be within the scope of the present invention.

[0141] In general, the active compounds of the invention are those which induce at least about 25% inhibition of the Gardos channel of erythrocytes (measured at about 10 μM) and/or about 25% inhibition of mammalian cell proliferation (measured at about 10 μM), as measured using in vitro assays that are commonly known in the art (see, e.g., Brugnara et al., 1993, *J. Biol. Chem.* 268(12):8760-8768; Benzaquen et al., 1995, *Nature Medicine* 1:534-540). Alternatively, or in addition, the active compounds of the invention generally will have an IC_{50} (concentration of compound that yields 50% inhibition) for inhibition of the Gardos channel of less than about 10 μM and/or an IC_{50} for inhibition of cell proliferation of less than about 10 μM, as measured using in vitro assays that are commonly known in the art (see, e.g., Brugnara et al., 1993, *J. Biol. Chem.* 268(12):8760-8768; Benzaquen et al., 1995, *Nature Medicine* 1:534-540).

[0142] Representative active compounds according to the invention include Compounds 1 through 35, as illustrated above.

[0143] In certain embodiments of the invention, compounds which exhibit only one pharmacological activity, or a higher degree of one activity, may be preferred. Thus, when the compound is to be used in methods to treat or prevent sickle cell disease, or in methods to reduce sickle cell dehydration and/or delay the occurrence of erythrocyte sickling or deformation in situ, it is preferred that the compound exhibit at least about 75% Gardos channel inhibition (measured at about 10 μM) and/or have an IC_{50} for Gardos channel inhibition of less than about 1 μM, with at least about 90% inhibition and/or an IC_{50} of less than about 0.1 μM being particularly preferred. Even more preferred are compounds which meet both the % inhibition and IC_{50} criteria.

[0144] Exemplary preferred compounds for use in methods related to Gardos channel inhibition and sickle cell disease include Compounds 1, 2, 3, 4, 6, 9, 18, 29 and 35, with Compounds 2, 3, 4, 6, 9, 29 and 35 being particularly preferred.

[0145] When the compound is to be used in methods to treat or prevent disorders characterized by abnormal cell proliferation or in methods to inhibit cell proliferation in situ, it is preferable that the compound exhibit at least about 75% inhibition of mitogen-induced cell proliferation (measured at about 10 μM) and/or have an IC_{50} of cell proliferation of less than about 3.5 μM, with at least about 90% inhibition and/or an IC_{50} of less than about 1 μM being particularly preferred. Even more preferred are compounds which meet both the % inhibition and IC_{50} criteria.

[0146] Exemplary preferred compounds for use in methods of inhibiting mammalian cell proliferation or for the treatment or prevention of diseases characterized by abnormal cell proliferation include Compounds 2, 3, 4, 7, 8, 9, 13, 14, 16, 17, 18, 19, 20, 21, 22, 26, 27, 28, 29, 30, 31, 32, 33 and 34, with Compounds 14, 26, 28, 29, 30 and 31 being particularly preferred.

[0147] 5.2 Formulation and Routes of Administration

[0148] The compounds described herein, or pharmaceutically acceptable addition salts or hydrates thereof, can be delivered to a patient using a wide variety of routes or modes of administration. Suitable routes of administration include, but are not limited to, inhalation, transdermal, oral, rectal, transmucosal, intestinal and parenteral administration, including intramuscular, subcutaneous and intravenous injections.

[0149] The compounds described herein, or pharmaceutically acceptable salts and/or hydrates thereof, may be administered singly, in combination with other compounds of the invention, and/or in cocktails combined with other therapeutic agents. of course, the choice of therapeutic agents that can be co-administered with the compounds of the invention will depend, in part, on the condition being treated.

[0150] For example, when administered to patients suffering from sickle cell disease, the compounds of the invention can be administered in cocktails containing agents used to treat the pain, infection and other symptoms and side effects commonly associated with sickle cell disease. Such agents include, e.g., analgesics, antibiotics, etc. The compounds can also be administered in cocktails containing other agents that are commonly used to treat sickle cell disease, including butyrate and butyrate derivatives (Perrine et al., 1993, *N. Enql. J. Med.* 328(2):81-86); hydroxyurea (Charache et al., 1995, *N. Enql. J. Med.* 323(20):1317-1322); erythropoietin (Goldberg et al, 1990, *N. Enql. J. Med.* 323(6): 366-372); and dietary salts such as magnesium (De Franceschi et al., 1996, *Blood* 88(648a):2580).

[0151] When administered to a patient undergoing cancer treatment, the compounds may be administered in cocktails containing other anti-cancer agents and/or supplementary potentiating agents. The compounds may also be administered in cocktails containing agents that treat the side-effects of radiation therapy, such as anti-emetics, radiation protectants, etc.

[0152] Anti-cancer drugs that can be co-administered with the compounds of the invention include, e.g., Aminoglutethimide; Asparaginase; Bleomycin; Busulfan; Carboplatin; Carmustine (BCNU); Chlorambucil; Cisplatin (cis-DDP); Cyclophosphamide; Cytarabine HCl; Dacarbazine; Dactinomycin; Daunorubicin HCl; Doxorubicin HCl; Estramustine phosphate sodium; Etoposide (VP-16); Floxuridine; Fluorouracil (5-FU); Flutamide; Hydroxyurea (hydroxycarbamide); Ifosfamide; Interferon Alfa-2a, Alfa 2b, Lueprolide acetate (LHRH-releasing factor analogue); Lomustine (CCNU); Mechlorethamine HCI (nitrogen mustard); Melphalan; Mercaptopurine; Mesna; Methotrexate (MTX); Mitomycin; Mitotane (o.p'-DDD); Mitoxantrone HCl; Octreotide; Plicamycin; Procarbazine HCl; Streptozocin; Tamoxifen citrate; Thioguanine; Thiotepa; Vinblastine sulfate; Vincristine sulfate; Amsacrine (m-AMSA); Azacitidine; Hexamethylmelamine (HMM); Interleukin 2; Mitoguazone (methyl-GAG; methyl glyoxal bis-guanylhydrazone; MGBG); Pentostatin; Semustine (methyl-CCNU); Teniposide (VM-26); paclitaxel and other taxanes; and Vindesine sulfate.

[0153] Supplementary potentiating agents that can be co-administered with the compounds of the invention include, e.g., Tricyclic anti-depressant drugs (e.g., imipramine, desipramine, amitriptyline, clomipramine, trimipramine, doxepin, nortriptyline, protriptyline, amoxapine and maprotiline); non-tricyclic and anti-depressant drugs (e.g., sertraline, trazodone and citalopram); Ca^{+} antagonists (e.g., verapamil, nifedipine, nitrendipine and caroverine); Amphotericin (e.g., Tween 80 and perhexiline maleate); Triparanol analogues (e.g., tamoxifen); antiarrhythmic drugs (e.g., quinidine); antihypertensive drugs (e.g., reserpine); Thiol depleters (e.g., buthionine and sulfoximine); and calcium leucovorin.

[0154] The active compound(s) may be administered per se or in the form of a pharmaceutical composition wherein the active compound(s) is in admixture with one or more pharmaceutically acceptable carriers, excipients or diluents. Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

[0155] For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0156] For oral administration, the compounds can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0157] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0158] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

[0159] For buccal administration,the compositions may take the form of tablets or lozenges formulated in conventional manner.

[0160] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0161] The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multidose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[0162] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0163] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0164] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

[0165] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or transcutaneous delivery (for example subcutaneously or intramuscularly), intramuscular injection or a transdermal patch. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0166] The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[0167] 5.3 Effective Dosages

[0168] Pharmaceutical compositions suitable for use with the present invention include compositions wherein the active ingredient is contained in a therapeutically effective amount, i.e., in an amount effective to achieve its intended purpose. Of course, the actual amount effective for a particular application will depend, inter alia, on the condition being treated. For example, when administered in methods to reduce sickle cell dehydration and/or delay the occurrence of erythrocyte sickling or distortion in situ, such compositions will contain an amount of active ingredient effective to achieve this result. When administered in methods to inhibit cell proliferation, such compositions will contain an amount of active ingredient effective to achieve this result. When administered to patients suffering from sickle cell disease or

disorders characterized by abnormal cell proliferation, such compositions will contain an amount of active ingredient effective to, inter alia, prevent the development of or alleviate the existing symptoms of, or prolong the survival of, the patient being treated. For use in the treatment of cancer, a therapeutically effective amount further includes that amount of compound which arrests or regresses the growth of a tumor. Determination of an effective amount is well within the capabilities of those skilled in the art, especially in light of the detailed disclosure herein.

[0169] For any compound described herein the therapeutically effective amount can be initially determined from cell culture arrays. Target plasma concentrations will be those concentrations of active compound(s) that are capable of inducing at least about 25% inhibition of the Gardos channel and/or at least about 25% inhibition of cell proliferation in cell culture assays, depending, of course, on the particular desired application. Target plasma concentrations of active compound(s) that are capable of inducing at least about 50%, 75%, or even 90% or higher inhibition of the Gardos channel and/or cell proliferation in cell culture assays are preferred. The percentage of inhibition of the Gardos channel and/or cell proliferation in the patient can be monitored to assess the appropriateness of the plasma drug concentration achieved, and the dosage can be adjusted upwards or downwards to achieve the desired percentage of inhibition.

[0170] Therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a circulating concentration that has been found to be effective in animals. A particularly useful animal model for sickle cell disease is the SAD mouse model (Trudel et al., 1991, *EMBO J.* 11:3157-3165). Useful animal models for diseases characterized by abnormal cell proliferation are well-known in the art. In particular, the following references provide suitable animal models for cancer xenografts (Corbett et al., 1996, *J. Exp. Ther. Oncol.* 1:95-108; Dykes et al., 1992, *Contrib. Oncol. Basel. Karqer* 42:1-22), restenosis (Carter et al., 1994, *J. Am. Coll. Cardiol.* 24(5):1398-1405), atherosclerosis (Zhu et al., 1994, *Cardiology* 85(6):370-377) and neovascularization (Epstein et al., 1987, *cornea* 6(4):250-257). The dosage in humans can be adjusted by monitoring Gardos channel inhibition and/or inhibition of cell proliferation and adjusting the dosage upwards or downwards, as described above.

[0171] A therapeutically effective dose can also be determined from human data for compounds which are known to exhibit similar pharmacological activities, such as Clotrimazole and other antimycotic agents (see, e.g., Brugnara et al., 1995, *JPET* 273:266-272; Benzaquen et al., 1995, *Nature Medicine* 1:534-540; Brugnara et al., 1996, *J. Clin. Invest.* 97(5):1227-1234). The applied dose can be adjusted based on the relative bioavailability and potency of the administered compound as compared with Clotrimazole.

[0172] Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods as are well-known in the art is well within the capabilities of the ordinarily skilled artisan.

[0173] Of course, in the case of local administration, the systemic circulating concentration of administered compound will not be of particular importance. In such instances, the compound is administered so as to achieve a concentration at the local area effective to achieve the intended result.

[0174] For use in the prophylaxis and/or treatment of sickle cell disease, including both chronic sickle cell episodes and acute sickle cell crisis, a circulating concentration of administered compound of about 0.001 μM to 20 μM is considered to be effective, with about 0.1 μM to 5 μM being preferred.

[0175] Patient doses for oral administration of the compounds described herein, which is the preferred mode of administration for prophylaxis and for treatment of chronic sickle cell episodes, typically range from about 80 mg/day to 16,000 mg/day, more typically from about 800 mg/day to 8000 mg/day, and most typically from about 800 mg/day to 4000 mg/day. Stated in terms of patient body weight, typical dosages range from about 1 to 200 mg/kg/day, more typically from about 10 to 100 mg/kg/day, and most typically from about 10 to 50 mg/kg/day. Stated in terms of patient body surface areas, typical dosages range from about 40 to 8000 mg/m^2/day, more typically from about 400 to 4000 mg/m^2/day, and most typically from about 400 to 2000 mg/m^2/day.

[0176] For use in the treatment of disorders characterized by abnormal cell proliferation, including cancer, arteriosclerosis and angiogenic conditions such as restenosis, a circulating concentration of administered compound of about 0.001 μM to 20 μM is considered to be effective, with about 0.1 μM to 5 μM being preferred.

[0177] Patient doses for oral administration of the compounds described herein for the treatment or prevention of cell proliferative disorders typically range from about 80 mg/day to 16,000 mg/day, more typically from about 800 mg/day to 8000 mg/day, and most typically from about 800 mg/day to 4000 mg/day. Stated in terms of patient body weight, typical dosages range from about 1 to 200 mg/kg/day, more typically from about 10 to 100 mg/kg/day, and most typically from about 10 to 50 mg/kg/day. Stated in terms of patient body surface areas, typical dosages range from about 40 to 8000 mg/m^2/day, more typically from about 400 to 4000 mg/m^2/day, and most typically from about 400 to 2000 mg/m^2/day.

[0178] For other modes of administration, dosage amount and interval can be adjusted individually to provide plasma levels of the administered compound effective for the particular clinical indication being treated. For example, if acute sickle crises are-the most dominant clinical manifestation, a compound according to the invention can be administered in relatively high concentrations multiple times per day. Alternatively, if the patient exhibits only periodic sickle cell crises on an infrequent or periodic or irregular basis, it may be more desirable to administer a compound of the invention at minimal effective concentrations and to use a less frequent regimen of administration. This will provide a therapeutic regimen that is commensurate with the severity of the sickle cell disease state.

[0179] For use in the treatment of tumorigenic cancers, the compounds can be administered before, during or after surgical removal of the tumor. For example, the compounds can be administered to the tumor via injection into the tumor mass prior to surgery in a single or several doses. The tumor,

or as much as possible of the tumor, may then be removed surgically. Further dosages of the drug at the tumor site can be applied post removal. Alternatively, surgical removal of as much as possible of the tumor can precede administration of the compounds at the tumor site.

[0180] Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and preferred mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial toxicity and yet is entirely effective to treat the clinical symptoms demonstrated by the particular patient. Of course, many factors are important in determining a therapeutic regimen suitable for a particular indication or patient. Severe indications such as cancer may warrant administration of higher dosages as compared with less severe indications such as sickle cell disease.

[0181] 5.4 Toxicity

[0182] The ratio between toxicity and therapeutic effect for a particular compound is its therapeutic index and can be expressed as the ratio between LD_{50} (the amount of compound lethal in 50% of the population) and ED_{50} (the amount of compound effective in 50% of the population). Compounds which exhibit high therapeutic indices are preferred. Therapeutic index data obtained from cell culture assays and/or animal studies can be used in formulating a range of dosages for use in humans. The dosage of such compounds preferably lies within a range of plasma concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g. Fingl et al., 1975, In: *The Pharmacological Basis of Therapeutics*, **8**Ch. 1 p1).

[0183] The invention having been described, the following examples are intended to illustrate, not limit, the invention.

6. EXAMPLE

[0184] Compound Syntheses

[0185] This Example demonstrates general methods for synthesizing the compounds of the invention, as well as preferred methods for synthesizing certain exemplary compounds of the invention. In all the reaction schemes described herein, suitable starting materials are either commercially available or readily obtainable using standard techniques of organic synthesis. Where necessary, suitable groups and schemes for protecting the various functionalities are well-known in the art, and can be found, for example, in Kocienski, *Protecting Groups*, Georg Thieme Verlag, New York, 1994 and Greene & Wuts, *Protective Groups in Organic Chemistry*, John Wiley & Sons, New York, 1991.

[0186] In **FIGS. 1 and 2**, the various substituents are as defined for structure (I).

[0187] 6.1 Synthesis of 11-Aryl-5,6-dihydro-11H-dibenz [b,e] azepines

[0188] This example provides a general method for synthesizing substituted 11-aryl-5,6-dihydro-11H-dibenz[b,e] azepine compounds according to the invention. A general reaction scheme is provided in **FIG. 1**. In **FIG. 1**, R_2-R_{15} are as previously defined for structural formula (I).

[0189] Referring to **FIG. 1, a** mixture of an appropriately substituted 2-aminobenzophenone 100 (1 equivalent), an appropriately substituted benzyl chloride 102 (1 equivalent), potassium carbonate (2 equivalents) and sodium iodide (1 equivalent) in acetonitrile is refluxed for 12 hours. The reaction mixture is cooled to room temperature and water added. The mixture is extracted with ethyl acetate. The combined ethyl acetate extracts are washed with water then dried over sodium sulfate. Evaporation of the solvent followed by column chromatography gives the substituted N-alkyl-2-aminobenzophenone derivative 104 in about 55-80% yield.

[0190] The substituted N-alkyl-2-aminobenzophenone derivative 104 (1 equivalent) is dissolved in a 3:1 mixture of tetrahydrofuran:methanol. Sodium borohydride (10 equivalents) is slowly added and the reaction mixture is stirred at room temperature for 12 hours. The reaction is quenched by adding 2 N aqueous hydrochloric acid solution. The reaction mixture is neutralized by adding 4 N aqueous sodium hydroxide solution and extracted with ethyl acetate. The combined ethyl acetate extracts are dried over sodium sulfate. Evaporation of the solvent followed by column chromatography gives the substituted N-alkyl-2-amino-benzyl alcohol derivative 106 in about 40-60% yield.

[0191] A mixture of the substituted N-alkyl-2-amino-benzylalcohol derivative 106 (1 equivalent), phosphorous pentoxide (5 equivalents) and methanesulfonic acid (5 equivalents) in dichloromethane is stirred at room temperature for 12 hours. The mixture is neutralized by adding aqueous sodium carbonate and then extracted with dichloromethane. The organic solution is dried over sodium sulfate. Evaporation of the solvent followed by column chromatography gives the substituted 11-aryl-5,6-dihydro-11H-dibenz[b,e] azepine derivative 108 in about 45-70% yield.

[0192] The substituted 11-aryl-5,6-dihydro-11H-dibenz[b, e]azepine derivative 108 (1 equivalent) is combined with potassium carbonate (3.5 equivalents) and alkyl or acyl halide (3 equivalents) in acetonitrile and stirred at room temperature for two days. Water is added and the mixture is stirred for 15 min. at room temperature and extracted with ethyl acetate. Evaporation of the solvent gives the crude product as an oil. Tituration of the product from ethanol followed by washing with hexane gives the pure N-substituted 11-aryl-5,6-dihydro-11H-dibenz[b,e]azepine product 110 as a white solid in 30-80% yield.

[0193] Alternatively, the substituted 11-aryl-5,6-dihydro-11H-dibenz[b,e]azepines can be synthesized from appropriate starting materials according to the methods described in Sasakura and Sugasawa, 1981, *Heterocycles* 15:421-425.

[0194] 6.2 Synthesis of 11-Aryl-11-substituted-5,6-dihydro-dibenz[b,e]azepines

[0195] This example provides a general method for synthesizing 11-aryl-11-substituted-5,6-dihydro-dibenz[b,e] azepine compounds according to the invention. A general reaction scheme is provided in **FIG. 2**. In **FIG. 2**, R_1-R_{15} are as previously defined for structural formula (I).

[0196] Referring to **FIG. 2**, the substituted N-alkyl-2-aminobenzophenone derivative 104 is prepared as described

in Section 6.1, supra. To a solution (0.25 M) of an approriate grignard reagent in diethyl ether at −40° C. is added a solution (0.1 M) of the substituted N-alkyl-2-aminobenzophenone derivative 104 in diethyl ether. The mixture is stirred at −40° C. for 30 min., warmed to room temperature and quenched with water. Extraction with ethyl acetate and evaporation of the solvent gives the crude alcohol product 112 as an oil. The alcohol product 112 is purified by column chromatography to give the pure alcohol product 112 as a white solid in 85-90% yield.

[0197] Compound 112 (1 equivalent) is dissolved in dichloromethane to 0.5-1.0 M. Phosphorous pentoxide (4 equivalents) and methane sulfonic acid (4 equivalents) are added and the mixture is stirred at room temperature for 2 hours. The reaction is quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. Evaporation of the solvent followed by column chromatography gives the 11-aryl-11-substituted-5,6-dihydro-dibenz[b,e] azepine 114 in about 90% yield.

[0198] The 11-aryl-11-substituted-5,6-dihydro-dibenz[b,e]azepine 114 can be converted to the corresponding N-substituted-11-aryl-11-substituted-5,6-dihydro-dibenz[b,e] azepine 116 as described in Section 6.1, supra.

[0199] 6.3 Synthesis of N-Methoxycarbonyl -11-(2'-chlorophenyl)-5,6-dihydro-11H-dibenz[b,e]azepine (Compound 9)

[0200] A preferred method of synthesis of N-methoxycarbonyl -11-(2'-chlorophenyl)-5,6-dihydro-11H-dibenz[b,e] azepine (Compound 9) is as follows: A mixture of 0.3 g (0.00098 mole) of **11**-(2'-chlorophenyl)-5,6-dihydro-11H-dibenz[b,e]azepine, 1.08 g (0.0078 mole) of potassium carbonate and 1.54 g (0.016 mole) of methyl chloroformate in 10 mL of acetonitrile, was refluxed for 12 hours. The mixture was then allowed to cool to room temperature and stirred with 15 mL of water for 10 minutes. The reaction mixture was extracted with ethyl acetate (2×15 mL). The organic layer was dried over magnesium sulfate. Evaporation gave the crude product as a brown solid. Trituration of the crude product with ethanol and washing the obtained solid with hexane gave 0.172 g (48% yield) of a white solid having a melting point of 159-161° C.

[0201] The product. gave the following analytical data: NMR ($CDCl_3$): δ3.10 ppm (3H, s, OCH_3); δ 4.45 ppm (1H, d, J=10 Hz, CH_2N); δ5.48 ppm (1H, s, CH); δ5.82 ppm (1H, d, J=10 Hz, CH_2N); δ6.94 ppm (1H, m, aryl); δ7.10 ppm (4H, m, aryl); δ7.28 ppm (6H, m, aryl); δ7.69 ppm (1H, m, aryl).

[0202] 6.4 Synthesis of N-Phenoxycarbonyl-11-phenyl-5,6-dihydro-11H-dibenz[b,e]azepine (Compound 14)

[0203] A preferred method of synthesis of N-phenoxycarbonyl-11-phenyl-5,6-dihydro-11H-dibenz[b,e]azepine (Compound 14) is as follows: A mixture of 0.25 g (0.00092 mole) of 11-phenyl-5,6-dihydro-11H-dibenz[b,e]azepine, 0.318 g (0.0023 mole) of potassium carbonate and 0.318 g (0.002 mole) of phenyl chloroformate in 10 mL of acetonitrile, was stirred at room temperature for 2 days. The mixture was stirred with 15 mL of water for 15 minutes and then extracted with ethyl acetate (2×35 mL). The organic layer was dried over magnesium sulfate. Evaporation gave the crude product as an oily material. Trituration of the obtained oil with ethanol then washing it with hexane gave 0.285 g (80% yield) of a white solid having a melting point of 155-165° C.

[0204] The product gave the following analytical data: NMR ($CDCl_3$): δ4.46 ppm (1H, d, J=7 Hz, CH_2N); δ5.28 ppm (1H, s, CH); δ5.69 ppm (1H, d, J=7 Hz, CH_2N); δ6.52 ppm (2H, m, aryl); δ6.98 ppm (2H, m, aryl); δ7.14-7.42 ppm (13H, m, aryl); δ7.58 (1H, m, aryl).

[0205] 6.5 Synthesis of N-Phenoxycarbonyl-11-(2'-chlorophenyl)-5,6-dihydro-11H-dibenz[b,e]azepine (Compound 26)

[0206] A preferred method of synthesis of N-phenoxycarbonyl **-11**-(2'-chlorophenyl)-5,6-dihydro-11H-dibenz[b,e] azepine (Compound 26) is as follows: A mixture of 0.2 g (0.00065 mole) of 11-(2'-chlorophenyl)-5,6-dihydro-11H-dibenz[b,e]azepine, 0.18 g (0.0013 mole) of potassium carbonate and 0.204 g (0.0013 mole) of phenyl chloroformate in 10 mL of acetonitrile, was stirred at room temperature for 2 days. The mixture was stirred with 15 mL of water for 10 minutes and then extracted with ethyl acetate (2×35 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent was evaporated. Trituration of the obtained residue with ethanol then washing it with hexane gave 0.082 g (30% yield) of a white solid having a melting point of 95-99° C.

[0207] The product gave the following analytical data: NMR ($CDCl_3$): δ4.50 ppm (1H, d, J=7 Hz, CH_2N); δ5.58 ppm (1H, s, CH); δ5.80 ppm (1H, d, J=7 Hz, CH_2N); δ6.52 ppm (2H, m, aryl); δ7.06-7.38 ppm (14H, m, aryl); δ7.79 ppm (1H, m, aryl).

[0208] 6.6 Synthesis of N-(4'-Nitrobenzoyl)-11-(2'-chlorophenyl)-5,6-dihydro-11H-dibenz[b,e]azepine (Compound 28)

[0209] A preferred method of synthesis of N-(4'-nitrobenzoyl)-11-(2'-chlorophenyl)-5,6-dihydro-11H-dibenz[b,e] azepine (Compound 28) is as follows: A mixture of 0.2 g (0.00065 mole) of 11-(2'-chlorophenyl)-5,6-dihydro-11H-dibenz[b,e]azepine, 0.179 g (0.0013 mole) of potassium carbonate and 0.133 g (0.00072 mole) of 4-nitrobenzoyl chloride in 10 mL of acetonitrile, was stirred at room temperature for 12 hours. The mixture was stirred with 15 mL of water for 10 minutes. The reaction mixture was extracted with ethyl acetate (2×15 mL). The organic layer was dried over magnesium sulfate. Evaporation gave the crude product as a sticky solid. Trituration of the crude product with ethanol and washing the obtained solid with hexane gave 0.148 g (50% yield) of a white solid having a melting point of 178-181° C.

[0210] The product gave the following analytical data: NMR ($CDCl_3$): δ4.42 ppm (1H, d, J=7 Hz, CH_2N); δ5.68 ppm (1H, s, CH); δ6.36 ppm (1H, d, J=7 Hz, CH_2N); δ6.52 ppm (3H, m, aryl); δ7.06 ppm (3H, m, aryl); δ7.12 ppm (1H, m, aryl); δ7.26 ppm (6H, m, aryl); δ7.79 ppm (3H, m, aryl).

[0211] 6.7 Other Compounds

[0212] Other compounds of the invention can be synthesized by routine modification of the above-described syntheses, or by other methods that are well known in the art. Appropriate starting materials are commercially available or can be synthesized using routine methods.

7. EXAMPLE

[0213] In Vitro Activity

[0214] This Example demonstrates the ability of several exemplary compounds of formula (I) to inhibit the Gardos channel of erythrocytes (Gardos channel assay) and/or mitogen-induced cell proliferation (mitogenic assay) in vitro. The assays are generally applicable for demonstrating the in vitro activity of other compounds of formula (I).

[0215] 7.1 Experimental Protocol

[0216] The percent inhibition of the Gardos channel (10 μM compound) and the IC_{50} were determined as described in Brugnara et al., 1993, *J. Biol. Chem.* 268(12):8760-8768. The percent inhibition of mitogen-induced cell proliferation (10 μM compound) and the IC_{50} were determined as described in Benzaquen et al. (1995, *Nature Medicine* 1:534-540) with NIH 3T3 mouse fibroblast cells (ATCC No. CRL 1658). Other cell lines, e.g., cancer cells, endothelial cells and fibroblasts, as well as many others, may be used in the cell proliferation assay. Selection of a particular cell line will depend in part on the desired application, and is well within the capabilities of an ordinarily skilled artisan.

[0217] 7.2 Results

[0218] The results of the experiment are provided in TABLE 1, below. Clotrimazole is reported for purposes of comparison.

TABLE 1

IN VITRO DATA FOR EXEMPLARY COMPOUNDS

	Mitogenic Assay		Gardos Channel Assay	
Compound	IC_{50} (μM)	Inhibition (%)	IC_{50} (μM)	Inhibition (%)
Clotrimazole	0.626	93.0	0.046	99.3
(1)		56.0	0.775	75.2
(2)	5.20	99.0	1.30	99.0
(3)	2.40	99.0	0.886	97.4
(4)	1.5	89.0	0.384	98.1
(5)		91.0	>10.0	14.4
(6)		87.0	0.236	97.5
(7)	1.60	99.0	>10.0	35.8
(8)	2.20	84.0		0
(9)	2.10	99.0	0.0850–0.093	97.3
(10)		53.0	2.533–1.940	63.0
(11)		32.0	>10.0	9.5
(12)		13.0	>10.0	54.8
(13)	1.7	97.0		0
(14)	0.04	98.0	>10.0	14.8
(15)		40.0	>10.0	9.50
(16)	1.7	99.0	>10.0	0.45
(17)	1.6	99.0	>10.0	20.6
(18)	2.6	99.0	0.502–0.692	81.5
(19)	1.6	99.0	>10.0	52.0
(20)	1.7	95.0	>10.0	13.6
(21)	2.7	93.0	>10.0	2.1
(22)	3.6	99.0	>10.0	14.9
(23)		55.0	>10.0	18.2
(24)		89.0	>10.0	32–55
(25)		75.0	>10.0	8.5
(26)	0.04–0.90	99.0	>10.0	0.8
(27)	2.20	99.0	>10.0	3.0
(28)	0.04–0.50	99.0		0
(29)	0.800	99.0	0.414–0.433	95.1
(30)	0.600	99.0	>10	14.6
(31)	0.400	99.0	>10	12.3
(32)	1.100	99.0		0
(33)	2.400	99.0	>10	67.5
(34)	4.00	99.0	>10	12.0
(35)		0	0.071–0.099	98.3

8. EXAMPLE

[0219] Activity in Cancer Cell Lines

[0220] This Example demonstrates the antiproliferative effect of several exemplary compounds of formula (I) against a variety of cancer cell lines. The assays are generally applicable for demonstrating the antiproliferative activity of other compounds of formula (I).

[0221] 8.1 Growth of Cells

[0222] The antiproliferative assays described herein were performed using standard aseptic procedures and universal precautions for the use of tissues. Cells were propagated using RPMI 1640 media (Gibco) containing 2% or 5% fetal calf serum (FCS) (Biowhittaker) at 37° C., 5% CO_2 and 95% humidity. The cells were passaged using Trypsin (Gibco). Prior to addition of test compound, the cells were harvested, the cell number counted and seeded at 10,000 cells/well in 100 μl 5% fetal calf serum (FCS) containing RPMI medium in 96-well plates and incubated overnight at 37° C., 5% CO_2 and 95% humidity.

[0223] On the day of the treatment, stock solutions of the test compounds (10 mM compound/DMSO) were added in 100 μl FCS containing medium to a final concentration of 10-0.125 μM and the cells were incubated for 2, 3 or 5 days at 37° C., 5% CO_2 and 95% humidity.

[0224] Following incubation, the cellular protein was determined with the Sulforhodamine B (SRB) assay (Skehan et al., 1990, *J. Natl. Cancer Inst.* 82:1107-1112). Growth inhibition, reported as the concentration of test compound which inhibited 50% of cell proliferation (IC_{50}) was determined by curve fitting.

[0225] Values for VP-16, a standard anti-cancer agent, are provided for comparison.

[0226] Except for MMRU cells, all cancer cell lines tested were obtained from the American Type Culture Collection (ATCC, Rockville, Md.). The ATCC assession numbers were as follows: HeLa (CCL-2); CaSki (CRL-1550); MDA-MB-231 (HTB-26); MCF-7 (HTB-22); A549 (CCL-185); HTB-174 (HTB-174); HEPG2 (HB-8065); DU-145 (HTB-81); SK-MEL-28 (HTB-72); HT-29 (HTB-38); HCT-15 (CCL-225); ACHN (CRL-1611); U-118MG (HTB-15); SK-OV-3 (HTB-77).

[0227] MMRU cells (Stender et al., 1993, *J. Dermatology* 20:611-617) were a gift of one of the authors.

[0228] 8.2 Results

[0229] The results of the cell culture assays are presented in TABLES 2 and 3, below.

TABLE 2

RESULTS OF SRB ASSAY 5% FCS/5 DAY INCUBATION

Cancer	Cell	Test Compound IC_{50} (μM)														
Type	Line	VP-16	13	16	17	20	21	22	23	27	28	30	31	33	34	35
Cervical	HeLa	<1.25				0.6				0.2	0.3	0.5	0.2			
	CaSki	1.8				0.9				0.9	0.5	0.7	0.5			
Breast	MDA-MB-23	<1.25				>1				>1	0.5	0.9	0.4			
	MCF7	<1.25	2.7	4.2	4.5	>1	3.5	1.8	3.1	0.5	0.6	1.3	0.7	2.1	2	2.4
Lung	A549	<1.25	3.1	>5	>5	>1	4.2	1.9	3.4	1.1	0.8	1.5	0.6	3.1	>5	>5
	HTB174	<1.25	1.4	2.6	3.6	0.7	1.9	1.4	1.8	0.3	0.1	0.5	0.2	1.4	0.9	4
Hepatocel	HEPG2	<1.25	1.8	3.4	2.6	0.9	1.9	1.4	2.3	0.4	0.3	0.9	0.4	1.4	1.5	4.5
Prostate	DU-145	<1.25				>1				>1	0.9	>1	0.9			
Melanoma	SK-MEL-28	<1.25				0.9				0.7	0.4	0.6	0.3			
	MMRU	<1.25	1.5	2.7	2.5	0.5	1.5	0.9	2.2	0.2	0.2	0.5	0.2	1.3	1.2	3.1
Colon	HT29	<1.25	1.5	2.6	1.7	0.7	1.8	0.7	2.1	0.4	0.3	0.6	0.2	1.2	1.6	4.8
	HCT-15	1.3				0.9				0.4	0.4	0.5	0.3			
Renal	ACHN	<1.25				>1				>1	0.7	>1	0.8			
CNS	U118MG	2.2				0.9				0.4	0.5	0.8	0.4			
Ovary	SK-OV-3					>1				>1	>1	>1	0.6			
Normal	HUVEC	<1.25				>1				>1	0.7	>1	0.8			
human	GM	1.4				>1				>1	0.9	>1	>1			
	3T3					>1				>1	>1	>1	>1			
mouse	L929	<1.25				0.9				>1	0.6	>1	0.9			

[0230]

TABLE 3

RESULTS OF SRB ASSAY

	Conditions	Test Compound IC_{50} (μM) Value in Cell Lines					
Compound	% FCS/days	A549	HT29	MMRU	MCF7	HEPG2	U118MG
VP-16	2%/3 days	2.3	20	<2.5	<2.5		
4	2%/3 days	11.4	9.7	4.6	1.7		
5	5%/2 days	1.4	1	>10			
6	5%/2 days	>10	>10	10			
7	5%/2	days	>10	>10	>10		
14	5%/2 days	>10	10	>10			
26	5%/3 days	7	7.2	4.9	5.9	5.4	5.7
27	5%/3 days	<1.25	<1.25	<1.25	<1.25	<1.25	1.9
28	5%/3 days	1.8	<1.25	<1.25	2.1	<1.25	1.3
29	5%/2 days	>10	>10	>10			
30	5%/3 days	1.7	<1.25	<1.25	1.6	<1.25	<1.25
31	5%/3 days	<1.25	<1.25	<1.25	<1.25	<1.25	<1.25
32	5%/3 days	6.9	6.3	4.9	5.4	6.2	6.8
33	5%/3 days	6.9	6.3	4.9	5.4	6.2	6.8
34	5%/2 days	>10	6.8	>10			
35	5%/2 days	>10	10	>10			

[0231] As can be seen in Tables 2 and 3, compounds which exhibited significant activity in the mitogenic assay described in Section 7, supra, exhibit significant antiproliferative activity against a variety of cancer cell lines and cancer types (IC_{50} of less than about 10 μM).

[0232] Many of the compounds exhibit comparable or even greater antiproliferative activity against a variety of cancer cell types than VP-16, a known anti-cancer agent.

9. EXAMPLE

[0233] Formulations

[0234] The following examples provide exemplary, not limiting, formulations for administering the compounds of the invention to mammalian, especially human, patients. Any of the compounds described herein, or pharmaceutical salts or hydrates thereof, may be formulated as provided in the following examples.

[0235] 9.1 Tablet Formulation

[0236] Tablets each containing 60 mg of active ingredient are made up as follows:

Active Compound	60 mg
Starch	45 mg
Microcrystalline Cellulose	45 mg
Sodium carboxymethyl starch	4.5 mg
Talc	1 mg
Polyvinylpyrrolidone (10% in water)	4 mg
Magnesium Stearate	0.5 mg
	150 mg

[0237] The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules are dried at 50°-60° C. and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules, which, after mixing are compressed by a tablet machine to yield tablets each weighing 150 mg.

[0238] Tablets can be prepared from the ingredients listed by wet granulation followed by compression.

[0239] 9.2 Gelatin Capsules

[0240] Hard gelatin capsules are prepared using the following ingredients:

Active Compound	250 mg/capsule
Starch dried	200 mg/capsule
Magnesium Stearate	10 mg/capsule

[0241] The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

[0242] 9.3 Aerosol Solution

[0243] An aerosol solution is prepared containing the following components:

Active Compound	0.25% (w/w)
Ethanol	29.75% (w/w)
Propellant 22 (Chlorodifluoromethane)	77.00% (w/w)

[0244] The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to −30° C. and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

[0245] 9.4 Suppositories

[0246] Suppositories each containing 225 mg of active ingredient are made as follows:

Active Compound	225 mg
Saturated fatty acid glycerides	2,000 mg

[0247] 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 g capacity and allowed to cool.

[0248] 9.5 Suspensions

[0249] Suspensions each containing 50 mg of medicament per 5 mL dose are made as follows:

Active Compound	50 mg
Sodium carboxymethylcellulose	50 mg
Syrup	1.25 mL
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

[0250] The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and some color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

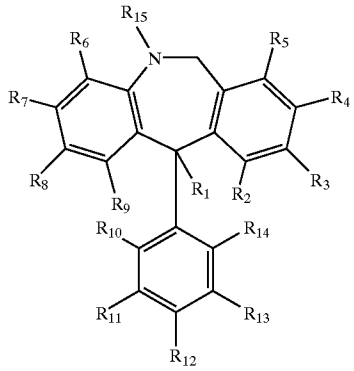
[0251] The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. Various modifications of the above-described modes for carrying out the invention which are obvious to those skilled in the pharmaceutical arts or related fields are intended to be within the scope of the following claims.

[0252] All cited references are hereby incorporated in their entireties by reference herein.

What is claimed is:

1. A process for preparing a compound having the formula:

(I)



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

R_1 is —R', (C_6-C_{20}) aryl or substituted (C_6-C_{20}) aryl;

R_2 is —R', —OR', —SR', halogen or trihalomethyl;

R_3 is —R', —OR', —SR', halogen or trihalomethyl or, when taken together with R_4, is (C_6-C_{20}) aryleno;

R_4 is —R', —OR', —SR', halogen or trihalomethyl or, when taken together with R_3, is (C_6-C_{20}) aryleno;

each of R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} is independently selected from the group consisting of —R', halogen and trihalomethyl;

R_{15} is —R", —C(O)R", —C(S)R", —C(O)OR", —C(S)OR", —C(O)SR", —C(S)SR", —C(O)N(R")$_2$, —C(S)N(R")$_2$, —C(O)C(O)R"—C(S)C(O)R", —C(O)C(S)R", —C(S)C(S)R", —C(O)C(O)OR", —C(S)C(O)OR", —C(O)C(S)OR", —C(O)C(O)SR", —C(S)C(S)OR", —C(S)C(O)SR", —C(O)C(S)SR", —C(S)C(S)SR", —C(O)C(O)N(R")$_2$, —C(S)C(O)N(R")$_2$, —C(O)C(S)N(R")$_2$ or —C(S)C(S)N(R")$_2$;

each R' is independently selected from the group consisting of —H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl and (C_2-C_6) alkynyl;

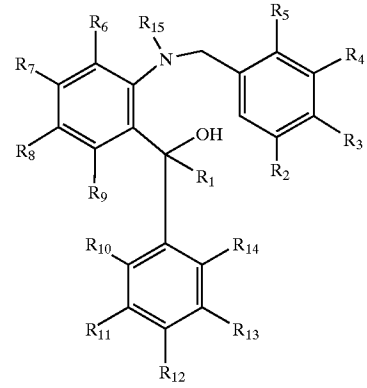
each R" is independently selected from the group consisting of —H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_6-C_{20}) aryl, (C_6-C_{20}) substituted aryl, (C_6-C_{26}) alkaryl and substituted (C_6-C_{26}) alkaryl; and

the aryl and alkaryl substituents are each independently selected from the group consisting of —CN, —OR', —SR', —NO_2, —NR'R', halogen, (C_1-C_6)alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl and trihalomethyl,

with the provisos that when R_1 and R_{15} are each —H, at least one of R_2, R_3, R_4, R_5, R_6, R_7, R_9, R_{10}, R_{11}, R_{12}, R_{13} or R_{14} is other than —H, R_8 is other than —H or —Cl and at least three of R_2, R_3, R_4 and R_5 are other than —OCH_3; when R_1-R_7 and R_9-R_{14} are —H, and R_8 is —H or —Cl, then R_{15} is other than —H or —CH_3; when R_1-R_7 and R_9-R_{14} are —H and R_8 is —F or —I or —Br, then R_{15} is other than —H; when R_1 and R_6-R_{15} are —H, then three of R_2, R_3, R_4, and R_5 are not —OCH_3 at the same time; when R_1-R_5, R_8 and R_{10}-R_{15} are —H, then at least one of R_6, R_7 or R_9 is other than —Cl; when R_1 and R_5-R_{14} are —H, and R_{15} is —CH_3, then R_2, R_3 and R_4 are not —OCH_3 at the same time; said method comprising:

a) cyclizing a diphenyl methanol compound according to Formula II:

(II)

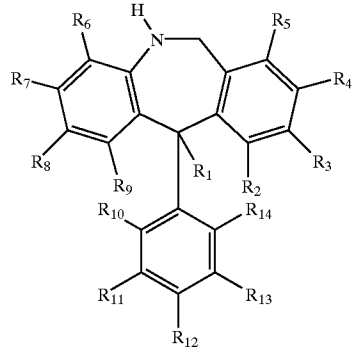


under acidic conditions; and optionally

b) if R_{15} is hydrogen, said method further comprising a step for derivatizing the nitrogen of the azepine ring.

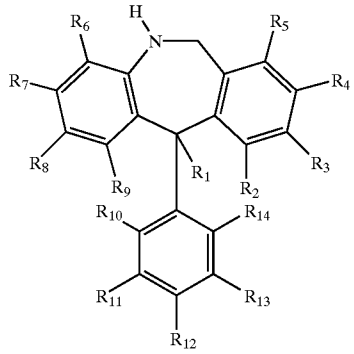
2. The method of claim 1 wherein said acidic conditions comprise one or more compounds selected from the group of sulfuric acid, acetic acid, methanesulfonic acid and phosphorus pentoxide.

3. The method of claim 1 wherein the derivatizing step comprises reacting a compound of the formula:



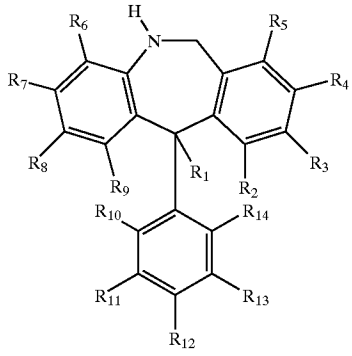
wherein R_1-R_{14} are defined as above, with an acylating agent having the formula R"C(O)X, wherein X is Br, Cl or I and R" is defined as above.

4. The method of claim 1 wherein the derivatizing step comprises reacting a compound of the formula:

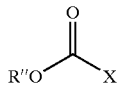


wherein R_1-R_4 are defined as above, with an alkylating agent having the formula R"X, wherein X is Br, Cl or I and R" is defined as above.

5. The method of claim 1 wherein the derivatizing step comprises reacting a compound of the formula:



wherein R_1-R_4 are defined as above, with a chloroformate reagent of the formula:



wherein X is Br or Cl and R" is defined as above.

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