USE OF 17-KETOSTEROID COMPOUNDS AND DERIVATIVES, METABOLITES AND PRECURSORS THEREOF IN THE TREATMENT OF MALARIA AND THE TREATMENT OF AFRICAN AND AMERICAN TRYPANOSOMIASIS

BACKGROUND OF THE INVENTION

The present invention is directed to the use of 17-ketosteroid compounds, as well as derivatives, metabolites and precursors of such compounds, and pharmaceutically acceptable salts of any of these compounds, collectively defined herein as the "compounds of the present invention", optionally together with one or more additional administration and/or treatment (as described below) in the treatment of malaria, African Trypanosomiasis and American Trypanosomiasis. The present invention is further directed to the use of such compounds (and combinations) in the treatment of one or more kind of parasites and/or one or more diseases caused by such parasites, against one or more kind of Mycoplasma and/or one or more diseases caused by such Mycoplasmas and/or against one or more of the following indications or infections: (a) hairy Leukoplakia, (b) oral candidosis, (c) mouth ulcerations-aphthous/herpetic/bacterial, (d) fungal candida, (e) human papilloma virus, (f) molluscum contagiosum, (g) squamous oral carcinoma, (h) Kaposi's sarcoma oral lesions, (i) periodontitis, (j) necrotizing gingivitis, (k) orafacial herpes zoster, and (1) rotaviruses, as well as all other indications and infections disclosed in U.S. Patent No. 5,292,725, the entire disclosure of which is hereby incorporated by reference, (in particular, the disclosure from column 1, line 13 through column 4, line 25).

In the case of malaria, infection of man occurs by mosquito bites, during which "sporozoites" are introduced into the human bloodstream. Sporozoites travel through the bloodstream, and eventually reach and penetrate parenchymal cells of the liver (sporozoites can remain in the blood for up to 1 hour).

The preerythrocytic cycle, the first cycle of growth and reproduction, lasts about one week and takes place in the liver. The preerythrocytic cycle liberates several thousand merozoites, which then pass into the blood.

The merozoites parasitize erythrocytes. Growth and reproduction take place in red blood cells, bringing about rhythmic fever attacks and other symptoms as the number of parasites in the blood increases. In the course of the erythrocytic growth cycle, upon entering a red cell, the parasite assumes a ring form with a central vacuole. After about 6 hours, the vacuole gradually disappears as the parasite increases in size until it nearly fills the red cell. During the last 12 hours of the growth cycle, nuclear fission occurs from which, on average, about sixteen merozoites are formed. The growing parasite is termed a trophozoite and, after nuclear fission has started, it is called a schizont.

The malaria parasite feeds on hemoglobin, utilizing the protein portion of the molecule and leaving the heme portion, which accumulates to form malarial pigment. It has been shown by EM that the parasite feeds by phagocytosis, engulfing red cell cytoplasm; digestion takes place in food vacuoles, where the pigment accumulates until it is released into the plasma when the host cell ruptures and the merozoites escape. Shortly after the parasite has started reproducing in the blood, the sexual forms or gametocytes begin to appear in the red cells. Gametocytes may survive for several days in the mammalian host, but they cannot develop further unless they are ingested by a suitable mosquito host. The single nucleus of the gametocyte distinguishes it from the fully-grown asexual forms.

Sleeping sickness is caused by *T. gambiense* and *T. rhodesiense* and is transmitted from man to man or from animals to man by tsetse flies *(Glossina)*. In the mammalian host, the organisms inhabit the blood but may penetrate other organs where they occur in intercellular spaces. In a drop of blood, the trypanosomes appear as minute, wriggling objects.

When a tsetse fly feeds, its toothed proboscis tears the skin, causing a small hemorrhage to form. If trypanosomes are present, they are sucked into the gut of the fly with the blood drawn up from this pool. For the first few days after an infective feed, the trypanosomes are found in the midgut. Then some travel forwards to the proventriculus. For development to be successful, some must pass right forward to near the tip of the proboscis where the opening of the salivary duct is located. They must then pass up the duct to the salivary glands where forms develop which are infective to the mammal. These are called metacyclic trypanosomes because they appear at the end of the developmental cycle. Reproduction takes place at all sites in the fly. The time required for this cycle is 2-3 weeks or even longer. Not only do the trypanosomes alter in morphology in the insect host, but they also differ physiologically from the blood stream forms.

If a tsetse fly harboring a mature infection bites man, metacyclic trypanosomes may be injected along with saliva. In the early stages of an infection, the parasites may be found in the blood. A characteristic feature is that the number of trypanosomes builds up to a peak and then declines, and these cycles are repeated. The trypanosomes stimulate the host to produce antibody, which agglutinates and lyses the organisms. Some of the trypanosomes become resistant to antibody and so a new population develops of different antigenic type; these flourish until specific antibody is again formed to destroy them. At later stages of the infection, the trypanosomes become scarce or absent from the blood but invade the central nervous system to cause sleeping sickness.

Trypanosomes can establish and develop in a wide range of mammalian species, and have been isolated from many species of African game animals. In these hosts, the association seems to be a benign one and the mammal remains in good health. But the same trypanosomes in man or in

man's domestic animals are highly pathogenic. Trypanosomiasis of domestic animals is an urgent problem in large areas of Africa where stock cannot be reared because of the presence of tsetse flies and game animals.

Chagas disease (American Trypanosomiasis) is caused by *T. cruzi*. It is transmitted by blood-feeding insects of the family *Triatomidae*.

After infection in man, the parasite soon leaves the blood and settles in tissues, most frequently in cardiac, striated or smooth muscle. Here they lose their flagella and round up. Next, they multiply and clusters of several hundred cells may be formed, displacing muscle fibers. After a time, the colony starts to disperse; the cells elongate, each develops a flagellum and the new trypanosomes enter the circulation. The trypanosomes remain in the circulation for several days and then again disappear into the tissues to undergo another reproductive cycle. In chronic infections, the tissue phase predominates, since the blood forms can rarely be detected.

If an insect feeds on blood containing trypanosomes, these trypanosomes become established first in the midgut. In the midgut, the trypanosomes multiply rapidly and within a few days some pass into the hindgut and infective forms begin to appear in the feces. In contrast to the African trypanosomes, where the infective forms are situated anteriorly in the vector and are introduced into man by inoculation, the infective forms of *T. cruzi* are located at the posterior end of the vector's gut and infection is by contamination. Triatomid insects ingest a large amount of blood relative to their body weight and the ingested blood is concentrated by fluid excretion while the insect feeds. In this way, infective trypanosomes are deposited on the skin of the host. The trypanosomes cannot penetrate unbroken skin but may gain entry through the puncture wound. Since the insects are nocturnal and feed in the facial areas, the trypanosomes are commonly smeared into eyes, mouth or nose where they penetrate mucous membranes.

T. cruzi develops in several species of insects, all of which function as hosts. If ten insects were allowed to feed on an infected person, all ten would probably become infected. Laboratory reared or "clean" insects are often used in diagnosis.

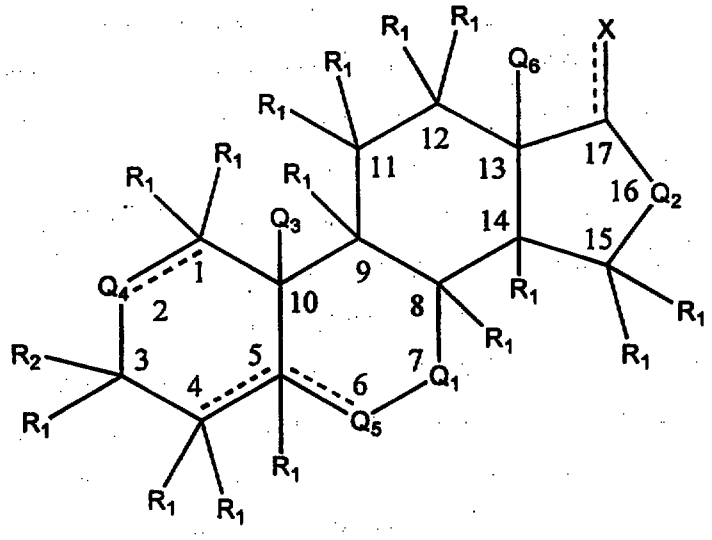
T. cruzi has been found in many species of wild animals and in reduviid insects in Central and South America and in some of the Southern states of the USA. Human infection in the USA is rare, but in parts of Central and South America, the incidence of infection in man may be as high as 20 per cent. It has been established that some 35 million people are at risk to the infection. The infection may be spread from man to man or from animals to man. Domestic dogs and cats are reservoirs in urban areas. Drugs that are effective against the African trypanosomes have no action on human infections with *T. cruzi*; no curative drugs have yet been discovered that combat this parasite.

A number of steroid compounds and their uses have been described. See, e.g., U.S. patent numbers 4956355, 5859000, 4268441, 4666898, 5837269, 5827841, 5811418, 5824313, 5686438, 5635496, 5587369, 5583126, 5562910, 5532230, 5518725, 5736537, 5843932, 5837700, 5824671, 5807849, 5798347, 5780460, 5776923, 5728688, 5610150, 5593981, 5372996, 5110810, 5807848, 5707983, 5641766, 5585371, 5506223, 5424463, 5296481, 5292730, 5776921, 5641768, 5559107, 5478566, 5461042, 5407684, 5387583, 5277907, 5206008, 5077284, 5162198, 5660835, 5527789, 5756482, 5709878, 5804576, 5744462, 5714481, 5700793, 5696106, 5656621, 5175154, 5157031, 5028631, 5001119, 4898694, 5824668, 5710143, 5795880, 5527788, 5591736, 5861390 and PCT publication numbers WO 98/05338, WO 95/21617, WO 98/50040, WO 98/50041 and WO 97/48367, all of which are incorporated herein by reference.

A number of flavonoids, methods to obtain them and their uses have been described. See, e.g., J.A. Manthey and B.S. Buslig, editors, *Flavonoids in the living system, Advances in experimental medicine and biology*, volume 439, Plenum Press, New York, 1998, chapter 15 (pages 191-225), chapter 16 (pages 227-235) and chapter 17 (pages 237-247), which are incorporated herein by reference.

SUMMARY OF THE INVENTION

In accordance with one aspect of the present invention, it now has been discovered that surprisingly, Trypanosome parasites, e.g., the malaria parasites, may be treated with compounds (or pharmaceutically acceptable salts thereof) of the following formula 1



1

wherein

Q_1 is $-C(R_1)_2-$ or $-C(O)-$;

Q_2 is $-C(R_1)_2-$, $-C(R_1)(Y)-$, $-C(Y)-$ or $-CH_2-CH_2-$;

Q_3 is $-H$ or $-C(R_1)_3-$;

Q_4 is $-C(R_1)_2-$, $-C(O)-$, hydroxyvinylidine ($-CH(CH=CHOH)-$) or methyl methylene ($-CH(CH)_3-$);

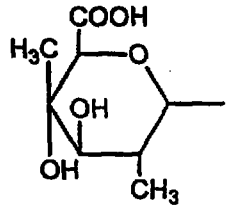
Q_5 is $-C(R_1)_2-$ or -C(O)-;

X and Y independently are -OH, -H, lower alkyl (e.g., C_{1-6} alkyl), -O-C(O)-R_5, -C(O)-OR_5, halogen (i.e., -F, -Cl, -Br or -I) or =O;

each R_1 independently is -H, -F, -Cl, -Br, -I, -OH, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_2 is -H, -OH, -F, -Cl, -Br, -I, C_{1-6} alkyl, C_{1-6} alkoxy, -OR_3, an ester (e.g., -O-C(O)-R_4 or -C(O)-O-R_4), a thioester (e.g., -O-C(S)-R_4 or -C(S)-O-R_4), a thioacetal (e.g., -S-C(O)-R_4, or -C(O)-S-R_4), a sulfate ester (e.g., -O-S(O)(O)-O-R_4), a sulfonate ester (e.g., -O-S(O)-O-R_4) or a carbamate (e.g., -O-C(O)-NH-R_4 or -NH-C(O)-O-R_4) or R_2, together with the R_1 that is bonded to the same carbon atom is =O;

R_3 is -S(O)(O)-OM, -S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6, -P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7, a glucuronide group of structure (A)



(A),

or R_3 is C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, a C_{1-18} ester or a C_{1-18} thioester, where any of the foregoing C_{1-18} or C_{2-18} moieties are optionally substituted at one or more hydrogen atoms with one or more independently selected -OR^{PR}, (including -OH), -NHR^{PR}, (including -NH_2) or -SR^{PR}, (including -SH) groups, or R_3 is a C_{1-18} fatty acid, C_{2-10} alkynyl, $(J)_n$-phenyl-C_{1-5}-alkyl, $(J)_n$-phenyl-C_{2-5}-alkenyl;

R_4 is -H, a protecting group, optionally substituted C_{1-18} alkyl, optionally substituted C_{1-18} alkenyl, optionally substituted C_{1-18} alkynyl, optionally substituted aryl, optionally substituted aryl-C_{1-6} alkyl, optionally substituted aryl-C_{2-6} alkenyl, optionally substituted aryl-C_{2-6} alkynyl, optionally substituted heterocycle-C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl-heterocycle, optionally substituted C_{2-6} alkynyl-heterocycle or an optionally substituted heterocycle, where any of the foregoing moieties are optionally substituted at one, two, three, four, five or more carbon or hydrogen atoms with one or more independently selected -O-, -S-, -NR^{PR}- (including -NH-), -NH-C(O)-, -OR^{PR} (including -OH), -NHR^{PR} (including -NH_2), -SR^{PR} (including -SH), =O, =S, =N-OH, -CN, -NO_2, -F, -Cl, -Br or -I groups or atoms;

each R_5 independently is straight or branched C_{1-14} alkyl;

each R_6 independently is straight or branched C_{1-14} alkyl;

each R_7 independently is straight or branched C_{1-14} alkyl or a glucuronide group of structure (A);

each R^{PR} independently is -H or an independently selected protecting group;

n is 0, 1, 2 or 3;

each J independently is -F, -Cl, -Br, -I, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, carboxy, nitro, sulfate, sulfonyl, a C_{1-6} carboxyl ester or a C_{1-6} sulfate ester;

M is hydrogen, sodium, -S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6, -P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7 or a glucuronide group of structure (A);

the dotted lines in formula 1 represent an optional double bond, provided that there are not double bonds at both the 4-5 and 5-6 positions and provided that when a double bond is present, zero or 1 R_1 group is bonded to carbon atoms at the 1-, 2-, 4-, 5-, 6- or 17 positions so that these carbon atoms are tetravalent; and

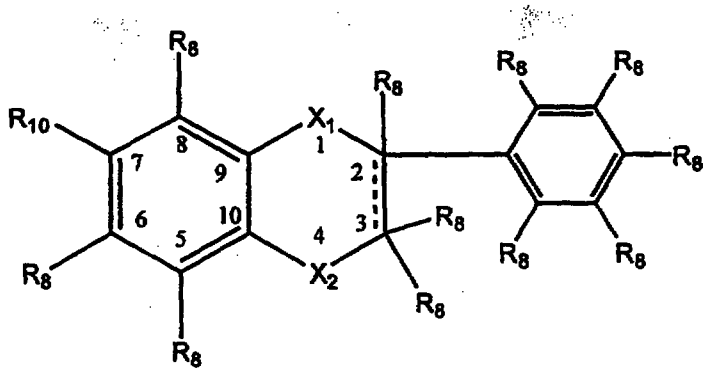
the salts, stereoisomers, positional isomers, metabolites, analogs, precursors, hydrates, tautomers, ionized forms and solvates thereof. The formula 1 compounds are collectively referred herein to as the "compounds of the invention" or the "compounds of the present invention".

In addition, as discussed above, the present invention is directed to the treatment of sleeping sickness and the treatment of Chagas disease by administering one or more of the compounds of the present invention. Also, the present invention relates to the use of the compounds of the present invention in the treatment of one or more kind of parasites and/or one or more diseases caused by such parasites, against one or more kind of Mycoplasma and/or one or more diseases caused by such Mycoplasmas and/or against one or more of the following indications or infections: (a) hairy Leukoplakia, (b) oral candidosis, (c) mouth ulcerations (aphthous/herpetic/bacterial), (d) fungal candida, (e) human papilloma virus, (f) molluscum contagiosum, (g) squamous oral carcinoma, (h) Kaposi's sarcoma oral lesions, (i) periodontitis, (j) necrotizing gingivitis, (k) orafacial herpes zoster, and (l) rotaviruses, as well as all other indications and infections disclosed in U.S. Patent No. 5,292,725, which is incorporated herein by reference.

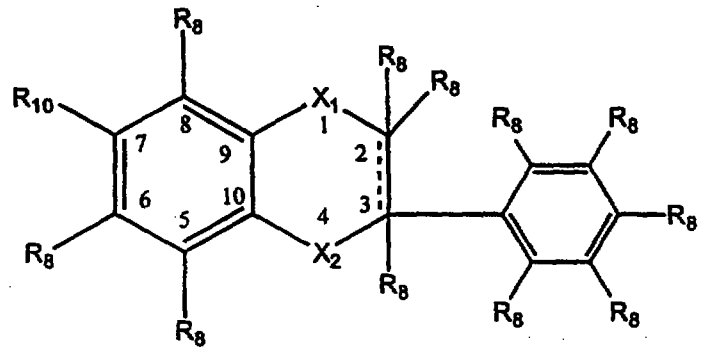
Accordingly, the present invention provides a method for treating these parasitic infections which comprises administering to an afflicted host a therapeutically effective amount of a compound (or a pharmaceutically acceptable salt thereof) having the structure of Formula 1 (defined above), as well as derivatives, metabolites, and precursors thereof, as defined herein.

The present invention is further directed to a method for treating any of the conditions described herein by administering a compound that inhibits glucose-6phosphate dehydrogenase.

Another invention embodiment comprises a method to treat or prevent a *Trypanosome* or *Plasmodium* infection comprising administering to a subject a compound of the invention simultaneously or sequentially with a compound of formula 2A or 2B



2A



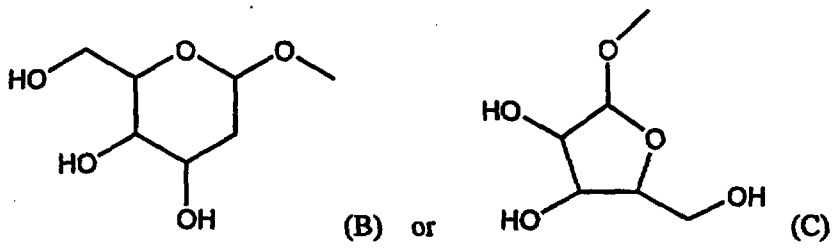
2B

wherein a double or a single bond is present at the dotted line and, when a double bond is present, (i) the optionally substituted phenyl ring at the 2- or 3-position is present and the R_8 that is bonded to the carbon is absent, and (ii) one R_8 at the adjacent 2- or 3-position is absent;

X_1 is -O- or $-C(R_8)_2-$;

X_2 is -C(O)- or $-C(R_{11})_2-$;

each R_8 independently is -H, -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide, a C_{1-25} fatty acid, the residue of a formula 2A or 2B compound where a hydrogen atom is removed to form the formula 2A or 2B compound radical, $-CH_2CH=C(CH_3)_2$, glucoside, a group having structure (B) or (C),



(B) or (C)

R_{10} is C_{1-6} alkyl, C_{1-6} alkoxy, neohesperidoside, apioglucoside, rutinoside, glucoside, galactoside, rhamnoside, arabinoside, or a stereoisomer, hydrate, analog, derivative or metabolite of any of these moieties, any of which are optionally independently substituted at one or more hydrogen atoms with -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide or a C_{1-25} fatty acid or R_{10} is -H, -OH or halogen;

each R_{11} independently is -H, -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide, a C_{1-25} fatty acid, or both R_{11} together are =O; and

the salts, stereoisomers, positional isomers, metabolites, analogs, precursors, hydrates, tautomers, ionized forms and solvates thereof.

DETAILED DESCRIPTION OF THE INVENTION

As used herein and unless otherwise stated or implied by context, the following terms have the meanings defined here.

A "patient" or "subject" means a human or animal. Usually the animal is a vertebrate such as a primate, rodent, domestic animal or game animal. Primates include chimpanzees, cynomologous monkeys, spider monkeys, and macaques, e.g., *Rhesus*. Rodents include mice, rats, woodchucks, ferrets, rabbits and hamsters. Domestic and game animals include cows, horses, pigs, deer, bison, buffalo, felines, e.g., domestic cat, canines, e.g., dog, avians, e.g., chicken, emu, ostrich, and fish, e.g., trout, catfish and salmon. Patient or subject includes any subset of the foregoing, e.g., all of the above, but excluding one or more groups or species such as humans, primates or rodents.

"Alkyl" as used herein, unless stated to the contrary, is a C_1-C_{18} hydrocarbon containing 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18 carbon atoms in the form of normal, secondary, tertiary, cyclic or mixed structures. Examples are $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH(CH_3)CH_2CH_3$, $-C(CH_3)_3$, $-CH_2CH_2CH_2CH_2CH_3$, $-CH(CH_3)CH_2CH_2CH_3$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_2CH_2CH_3$, $-CH(CH_3)CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)CH_2CH_3$, $-CH_2C(CH_3)_3$, $-CH_2CH_2CH_2CH_2CH_2CH_3$, $-CH(CH_3)CH_2CH_2CH_2CH_3$, $-CH(CH_2CH_3)(CH_2CH_2CH_3)$, $-C(CH_3)_2CH_2CH_2CH_3$, $-CH(CH_3)CH(CH_3)CH_2CH_3$, $-CH(CH_3)CH_2CH(CH_3)_2$, $-C(CH_3)(CH_2CH_3)_2$, $-CH(CH_2CH_3)CH(CH_3)_2$, $-C(CH_3)_2CH(CH_3)_2$, $-CH(CH_3)C(CH_3)_3$, cyclopropyl, cyclobutyl, cyclopropylmethyl, cyclopentyl, cyclobutylmethyl, 1-cyclopropyl-1-ethyl, 2-cyclopropyl-1-ethyl, cyclohexyl, cyclopentylmethyl, 1-cyclobutyl-1-ethyl, 2-cyclobutyl-1-ethyl, 1-cyclopropyl-1-propyl, 2-cyclopropyl-1-propyl, 3-cyclopropyl-1-propyl, 2-cyclopropyl-2-propyl, and 1-cyclopropyl-2-propyl.

"Alkenyl" as used herein, unless stated to the contrary, is C_2-C_{18} hydrocarbon comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18 carbon atoms in the form of normal, secondary, tertiary, cyclic or mixed structures and comprising 1, 2, 3 or more double bonds between adjacent carbon atoms. Examples are $-CH=CH_2$, $-CH=CHCH_3$, $-CH_2CH=CH_2$, $-C(=CH_2)(CH_3)$, $-CH=CHCH_2CH_3$, $-CH_2CH=CHCH_3$, $-CH_2CH_2CH=CH_2$, $-CH=C(CH_3)_2$, $-CH_2C(=CH_2)(CH_3)$, $-C(=CH_2)CH_2CH_3$, $-C(CH_3)=CHCH_3$, $-CH(CH_3)CH=CH_2$, -

C=CHCH$_2$CH$_2$CH$_3$, -CHCH=CHCH$_2$CH$_3$, -CHCH$_2$CH=CHCH$_3$, -CHCH$_2$CH$_2$CH=CH$_2$, -C(=CH$_2$)CH$_2$CH$_2$CH$_3$, -C(CH$_3$)=CH$_2$CH$_2$CH$_3$, -CH(CH$_3$)CH=CHCH$_3$, -CH(CH$_3$)CH$_2$CH=CH$_2$, -CH$_2$CH=C(CH$_3$)$_2$, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, and 1-cyclohex-3-enyl.

"Alkynyl" as used herein, unless stated to the contrary, is C_2-C_{18} hydrocarbon comprising 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18 carbon atoms in the form of normal, secondary, tertiary, cyclic or mixed structures and comprising 1, 2, 3 or more triple bonds between adjacent carbon atoms. Examples are -CCH, -CCCH$_3$, -CH$_2$CCH, -CCCH$_2$CH$_3$, -CH$_2$CCCH$_3$, -CH$_2$CH$_2$CCH, -CH(CH$_3$)CCH, -CCCH$_2$CH$_2$CH$_3$, -CH$_2$CCCH$_2$CH$_3$, -CH$_2$CH$_2$CCCH$_3$ and -CH$_2$CH$_2$CH$_2$CCH.

"Halogen" or "halo" means fluorine (-F), chlorine (-Cl), bromine (-Br) or iodine (-I) and if more than one halogen is referred to (e.g., two or more variable groups may be a halogen), each halogen is independently selected.

"Steroid nucleus" means 4 fused rings having the formula 1 structure.

"PEG" means an ethylene glycol polymer that contains about 20 to about 2000000 linked monomers, typically about 50-1000 linked monomers, usually about 100-300. Polyethylene glycols include PEGs containing various numbers of linked monomers, e.g., PEG20, PEG30, PEG40, PEG60, PEG80, PEG100, PEG115, PEG 200, PEG 300, PEG400, PEG500, PEG600, PEG 1000, PEG1500, PEG2000, PEG 3350, PEG4000, PEG4600, PEG5000, PEG6000, PEG8000, PEG11000, PEG12000, PEG2000000 and any mixtures thereof.

An "excipient" or a "carrier" means a component or an ingredient that is acceptable in the sense of being compatible with the other ingredients of compositions or formulations as disclosed herein and not overly deleterious to the patient or animal to which the formulation is to be administered. As used here, excipients and carriers include liquids, including benzyl benzoate, cottonseed oil, N,N-dimethylacetamide, a C_{2-12} alcohol (e.g., ethanol), glycerol, peanut oil, a PEG, vitamin E, poppyseed oil, propylene glycol, safflower oil, sesame oil, soybean oil and vegetable oil. Excipients, as used herein may exclude solvents such as chloroform, dioxane or DMSO. Excipients comprise one or more components typically used in the pharmaceutical formulation arts, e.g., fillers, binders, disintegrants and lubricants.

Unless otherwise specified, expressions that refer to "a formula 1 compound(s)", a "compound of the invention", a "formula 2A or 2B compound", a "plasma concentration-enhanching compound" and the like mean compositions or methods, e.g., methods to treat a *Trypanosome* infection as disclosed herein, where one or more than one formula 1 or formula 2A or 2B compound is present, typically 1, 2, 3 or 4, usually 1.

"Alcohol" as used herein, includes excipients, means an alcohol that comprises a C_{1-12} alkyl moiety substituted at one or more hydrogen atoms with one or more hydroxyl groups, usually one, two or three. Alcohols include, e.g., ethanol, *n*-propanol, *i*-propanol, *n*-butanol, *i*-butanol, *s*-butanol, *t*-butanol, *n*-pentanol, *i*-pentanol, *n*-hexanol, cyclohexanol, *n*-heptanol, *n*-octanol, *n*-nonanol, *n*-decanol and benzyl alcohol. The carbon atoms in alcohols can be straight, branched or cyclic. Alcohol includes any subset of the foregoing, e.g., C_{2-4} alcohols (alcohols having 2, 3 or 4 carbon atoms).

"Ester" means a moiety that comprises a -C(O)-O- structure. Typically, esters as used here comprise an organic moiety containing about 1-50 carbon atoms (e.g., about 2-12 carbon atoms) and 0 to about 10 independently selected heteroatoms (e.g., O, S, N, P, Si), where the organic moiety is bonded to a formula 1 steroid nucleus at R^2 through the -C(O)-O- structure, e.g., organic moiety-C(O)-O-steroid or organic moiety-O-C(O)-steroid. The organic moiety usually comprises one or more of any of the organic groups described above, e.g., C_{1-20} alkyl moieties, C_{2-20} alkenyl moieties, C_{2-20} alkynyl moieties, aryl moieties, C_{2-9} heterocycles or substituted derivatives of any of these, e.g., comprising 1, 2, 3, 4 or more substituents, where each substituent is independently chosen. Typical substitutions for hydrogen or carbon atoms in these organic groups include 1, 2, 3, 4 or more, usually 1, 2, or 3 -O-, -S-, $-NR^{PR}-$ (including -NH-), -C(O)-, =O, =S, $-N(R^{PR})_2$ (including $-NH_2$), $-C(O)OR^{PR}$ (including -C(O)OH), $-OC(O)R^{PR}$ (including -O-C(O)-H), $-OR^{PR}$ (including -OH), $-SR^{PR}$ (including -SH), $-NO_2$, -CN, -NHC(O)-, -C(O)NH-, -OC(O)-, -C(O)O-, -O-A8, -S-A8, -C(O)-A8, -OC(O)-A8, -C(O)O-A8, =N-, -N=, =N-OH, $-OPO_3(R^{PR})_2$, $-OSO_3H_2$ or halogen moieties or atoms, where each R^{PR} is -H, an independently selected protecting group or both R^{PR} together comprise a protecting group, and A8 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-4} alkyl-aryl (e.g., benzyl), aryl (e.g. phenyl) or C_{0-4} alkyl-C_{2-9} heterocycle. Substitutions are independently chosen. The organic moiety includes compounds defined by the R_4 variable. The organic moieties exclude obviously unstable moieties, e.g., -O-O-, except where such unstable moieties are transient species that one can use to make a compound with sufficient chemical stability for the one or more of the uses described herein. The substitutions listed above are typically substituents that one can use to replace one or more carbon atoms, e.g., -O- or -C(O)-, or one or more hydrogen atom, e.g., halogen, $-NH_2$ or -OH.

"Thioester" means a moiety that comprises a -C(S)-O- structure. Typically, thioesters as used here comprise an organic moiety containing about 1-50 carbon atoms (e.g., about 2-12 carbon atoms) and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si), where the organic moiety is bonded to a formula 1 steroid nucleus at R^2 through the -C(S)-O- structure, e.g., organic moiety-C(S)-O-steroid or organic moiety-O-C(S)-steroid. The organic moiety usually comprises one or more of any of the organic groups described above, e.g., C_{1-20} alkyl moieties, C_{2-20} alkenyl moieties, C_{2-20} alkynyl moieties, aryl moieties, C_{2-9} heterocycles or substituted derivatives of any of these, e.g., comprising 1, 2, 3, 4 or more substituents, where each substituent is independently chosen. Typical substitutions for hydrogen or carbon atoms in these organic groups include 1, 2, 3, 4 or

more, usually 1, 2, or 3 -O-, -S-, -NR^{PR}- (including -NH-), -C(O)-, =O, =S, -$N(R^{PR})_2$ (including -NH_2), -$C(O)OR^{PR}$ (including -C(O)OH), -$OC(O)R^{PR}$ (including -O-C(O)-H), -OR^{PR} (including -OH), -SR^{PR} (including -SH), -NO_2, -CN, -NHC(O)-, -C(O)NH-, -OC(O)-, -C(O)O-, -O-A8, -S-A8, -C(O)-A8, -OC(O)-A8, -C(O)O-A8, =N-, -N=, =N-OH, -$OPO_3(R^{PR})_2$, -OSO_3H_2 or halogen moieties or atoms, where each R^{PR} is -H, an independently selected protecting group or both R^{PR} together comprise a protecting group, and A8 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-4} alkyl-aryl (e.g., benzyl), aryl (e.g. phenyl) or C_{0-4} alkyl-C_{2-9} heterocycle. Substitutions are independently chosen. The organic moiety includes compounds defined by the R_4 variable. The organic moieties exclude obviously unstable moieties, e.g., -O-O-, except where such unstable moieties are transient species that one can use to make a compound with sufficient chemical stability for the one or more of the uses described herein. The substitutions listed above are typically substituents that one can use to replace one or more carbon atoms, e.g., -O- or -C(O)-, or one or more hydrogen atom, e.g., halogen, -NH_2 or -OH.

"Thioacetal" means a moiety that comprises a -C(O)-S- structure. Typically, thioacetals as used here comprise an organic moiety containing about 1-50 carbon atoms (e.g., about 2-12 carbon atoms) and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si), where the organic moiety is bonded to a formula 1 steroid nucleus at R^2 through the -C(O)-S- structure, e.g., organic moiety-C(O)-S-steroid or organic moiety-S-C(O)-steroid. The organic moiety is as described above for thioesters.

"Carbamate" means an organic moiety as described for ester that comprises 1, 2, 3, 4 or more -O-C(O)NR^{PR}- structures where R^{PR} is -H, a protecting group or an organic moiety as described for ester. Typically, carbamate groups as used here comprise an organic moiety containing about 1-50 carbon atoms (e.g., about 2-12 carbon atoms) and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si), where the organic moiety is bonded to a formula 1 steroid nucleus at R^2 through the -O-C(O)-NR^{PR}- structure, e.g., organic moiety-NR^{PR}-C(O)-O-steroid or organic moiety-O-C(O)-NR^{PR}-steroid. The organic moiety is as described above for thioesters.

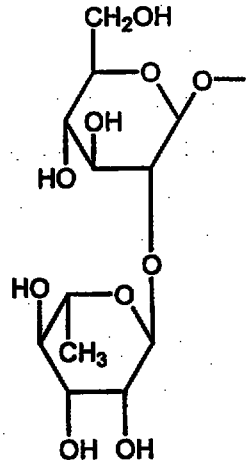
"Sulfate ester" means a moiety that comprises a -O-S(O)(O)-O- structure. Typically, sulfate esters as used here comprise an organic moiety containing about 1-50 carbon atoms (e.g., about 2-12 carbon atoms) and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si), where the organic moiety is bonded to a formula 1 steroid nucleus at R^2 through the -O-S(O)(O)-O- structure, e.g., organic moiety-O-S(O)(O)-O-steroid. The organic moiety is as described above for thioesters.

"Sulfite ester" means a moiety that comprises a -O-S(O)-O- structure. Typically, sulfite esters as used here comprise an organic moiety containing about 1-50 carbon atoms (e.g., about 2-12 carbon atoms) and 0 to about 10 heteroatoms (e.g., O, S, N, P, Si), where the organic moiety is bonded to a formula 1 steroid nucleus at R^2 through the -O-S(O)-O- structure, e.g., organic moiety-O-S(O)-O-steroid. The organic moiety is as described above for thioesters.

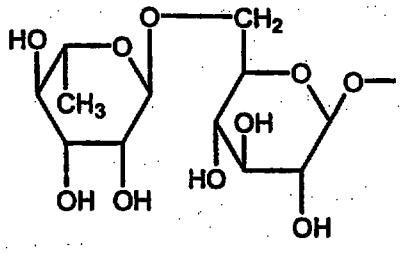
The compositions disclosed herein optionally comprise salts of the formula 1 and 2 compounds that comprise an ionizable moiety or a polar moiety. As used herein, "salts" include complexes that comprise moieties of opposite charge. Ionizable moieties include -O-S(O)(O)-OH or a -NH_2 group at R_2 and polar moieties include -OH. Salts include pharmaceutically acceptable

salts that comprise, for example, an uncharged moiety or a monovalent anion moiety or a monovalent cation moiety. Salts include compounds derived by combination of appropriate anions such as inorganic acids. Suitable acids include those having sufficient acidity to form a stable salt, preferably acids of low toxicity. For example, one may form invention salts from acid addition of certain inorganic acids, e.g., HF, HCl, HBr, HI, H_2SO_4, H_3PO_4, to basic centers, typically amines that may be present in formula 1, 2A or 2B compounds. Or one may use certain organic acids, e.g., organic sulfonic acids, organic carboxylic acids in the same manner. Exemplary organic sulfonic acids include C_{6-16} aryl sulfonic acids, C_{6-16} heteroaryl sulfonic acids and C_{1-16} alkyl sulfonic acids such as phenyl, α-naphthyl, β-naphthyl, (*S*)-camphor, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *s*-butyl, *i*-butyl, *t*-butyl, pentyl and hexyl sulfonic acids. Exemplary organic carboxylic acids include C_{1-16} alkyl, C_{6-16} aryl carboxylic acids and C_{4-16} heteroaryl carboxylic acids such as acetic, glycolic, lactic, pyruvic, malonic, glutaric, tartaric, citric, fumaric, succinic, malic, maleic, hydroxymaleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, salicylic and 2-phenoxybenzoic. Salts also include the invention compound salts with one or more amino acids. Many amino acids are suitable, especially the naturally occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine. Salts are usually biologically compatible or pharmaceutically acceptable or non-toxic, particularly for mammalian cells. Salts that are biologically toxic are generally used as synthetic intermediates for making other invention compounds.

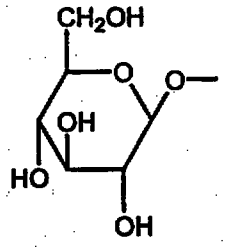
The neohesperidoside, rutinoside and glucoside groups have the structures



,



and



, respectively

wherein one or more of the hydrogen atoms are optionally independently substituted with hydroxy, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide or a C_{1-25} fatty acid.

Heterocycle. "Heterocycle" or "heterocyclic" includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The

Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* 1960, 82:5566; and U.S. patent 5763483, all of which are incorporated herein by reference.

Examples of heterocycles include by way of example and not limitation pyridyl, thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl.

By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Heteroaryl" means an aromatic ring or two or more fused rings that contain one or more aromatic rings where the ring or fused rings comprise 1, 2, 3 or more heteroatoms, usually oxygen

(-O-), nitrogen (-NX-) or sulfur (-S-) where X is -H, a protecting group or C_{1-6} alkyl, usually -H. Examples are as described for heterocycle.

Protecting groups. Various groups that the formula 1, 2A or 2B compounds may comprise include, e.g., substituted alkyl groups, substituted alkenyl groups, esters or substituted heterocycles, which can contain one or more reactive moieties such as hydroxyl, or thiol. Intermediates used to make formula 1 or formula 2A or 2B compounds may be protected as is apparent in the art. Noncyclic and cyclic protecting groups and corresponding cleavage reactions are described in "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) (hereafter "Greene"). In the context of the present invention, these protecting groups are groups that can be removed from the molecule of the invention without irreversibly changing the covalent bond structure or oxidation/reduction state of the remainder of the molecule. For example, the protecting group, -X, that is bonded to a -OX or -NHX group can be removed to form -OH or $-NH_2$, respectively, without affecting other covalent bonds in the molecule. At times, when desired, more than one protecting group can be removed at a time, or they can be removed sequentially. In compounds of the invention containing more than one protecting group, the protecting groups are the same or different.

Protecting groups are intended to be removed by known procedures, although it will be understood that the protected intermediates fall within the scope of this invention. The removal of the protecting group may be arduous or straightforward, depending upon the economics and nature of the conversions involved. In general, one will use a protecting group with exocyclic amines or with carboxyl groups during synthesis of a formula 1 compound. For most therapeutic applications amine groups should be deprotected. Protecting groups commonly are employed to protect against covalent modification of a sensitive group in reactions such as alkylation or acylation. Ordinarily, protecting groups are removed by, e.g. hydrolysis, elimination or aminolysis. Thus, simple functional considerations will suffice to guide the selection of a reversible or an irreversible protecting group at a given locus on the invention compounds. Suitable protecting groups and criteria for their selection are described in T.W. Greene and P.G.M. Wuts, Eds. "Protective Groups in Organic Synthesis" 2nd edition, Wiley Press, at pps. 10-142, 143-174, 175-223, 224-276, 277-308, 309-405 and 406-454, which is incorporated herein by reference.

Determination of whether a group is a protecting group is made in the conventional manner, e.g., as illustrated by Kocienski, Philip J.; "*Protecting Groups*" (Georg Thieme Verlag Stuttgart, New York, 1994) (hereafter "Kocienski"), Section 1.1, page 2, and Greene Chapter 1, pages 1-9; and U.S. patent 5763483, all of which are incorporated herein by reference. In particular, a group is a protecting group if when, based on mole ratio, 90% of that protecting group has been removed by a deprotection reaction, no more than 50%, preferably 25%, more preferably

10%, of the deprotected product molecules of the invention have undergone changes to their covalent bond structure or oxidation/reduction state other than those occasioned by the removal of the protecting group. When multiple protecting groups of the same type are present in the molecule, the mole ratios are determined when all of the groups of that type are removed. When multiple protecting groups of different types are present in the molecule, each type of protecting group is treated (and the mole ratios are determined) independently or together with others depending on whether the deprotection reaction conditions pertinent to one type are also pertinent to the other types present. In one embodiment of the invention, a group is a protecting group if when, based on mole ratio determined by conventional techniques, 90% of that protecting group has been removed by a conventional deprotection reaction, no more than 50%, preferably 25%, more preferably 10%, of the deprotected product molecules of the invention have undergone irreversible changes to their covalent bond structure or oxidation/reduction state other than those occasioned by the removal of the protecting group. Irreversible changes require chemical reactions (beyond those resulting from aqueous hydrolysis, acid/base neutralization or conventional separation, isolation or purification) to restore the covalent bond structure or oxidation/reduction state of the deprotected molecule of the invention.

Protecting groups are also described in detail together with general concepts and specific strategies for their use in Kocienski, Philip J.; "Protecting Groups" (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184, Chapter 6, Amino Protecting Groups, pages 185-243, Chapter 7, Epilog, pages 244-252, and Index, pages 253-260, are incorporated with specificity in the context of their contents. More particularly, Sections 2.3 Silyl Ethers, 2.4 Alkyl Ethers, 2.5 Alkoxyalkyl Ethers (Acetals), 2.6 Reviews (hydroxy and thiol protecting groups), 3.2 Acetals, 3.3 Silylene Derivatives, 3.4 1,1,3,3-Tetraisopropyldisiloxanylidene Derivatives, 3.5 Reviews (diol protecting groups), 4.2 Esters, 4.3 2,6,7-Trioxabicyclo[2.2.2]octanes [OBO] and Other Ortho Esters, 4.4 Oxazolines, 4.5 Reviews (carboxyl protecting groups), 5.2 O,O-Acetals, 5.3 S,S-Acetals, 5.4 O,S-Acetals, 5.5 Reviews (carbonyl protecting groups), 6.2 N-Acyl Derivatives, 6.3 N-Sulfonyl Derivatives, 6.4 N-Sulfenyl Derivatives, 6.5 N-Alkyl Derivatives, 6.6 N-Silyl Derivatives, 6.7 Imine Derivatives, and 6.8 Reviews (amino protecting groups), are each incorporated with specificity where protection/deprotection of the requisite functionalities is discussed. Further still, the tables "Index to the Principal Protecting Groups" appearing on the inside front cover and facing page,

"Abbreviations" at page xiv, and "reagents and Solvents" at page xv are each incorporated in their entirety herein at this location.

Typical hydroxy protecting groups are described in Greene at pages 14-118 and include Ethers (Methyl); Substituted Methyl Ethers (Methoxymethyl, Methylthiomethyl, t-Butylthiomethyl, (Phenyldimethylsilyl)methoxymethyl, Benzyloxymethyl, p-Methoxybenzyloxymethyl, (4-Methoxyphenoxy)methyl, Guaiacolmethyl, t-Butoxymethyl, 4-Pentenyloxymethyl, Siloxymethyl, 2-Methoxyethoxymethyl, 2,2,2-Trichloroethoxymethyl, Bis(2-chloroethoxy)methyl, 2-(Trimethylsilyl)ethoxymethyl, Tetrahydropyranyl, 3-Bromotetrahydropyranyl, Tetrahydropthiopyranyl, 1-Methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-Methoxytetrahydrothiopyranyl, 4-Methoxytetrahydropthiopyranyl S,S-Dioxido, 1-[(2-Chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-Dioxan-2-yl, Tetrahydrofuranyl, Tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl); Substituted Ethyl Ethers (1-Ethoxyethyl, 1-(2-Chloroethoxy)ethyl, 1-Methyl-1-methoxyethyl, 1-Methyl-1-benzyloxyethyl, 1-Methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-Trichloroethyl, 2-Trimethylsilylethyl, 2-(Phenylselenyl)ethyl, t-Butyl, Allyl, p-Chlorophenyl, p-Methoxyphenyl, 2,4-Dinitrophenyl, Benzyl); Substituted Benzyl Ethers (p-Methoxybenzyl, 3,4-Dimethoxybenzyl, o-Nitrobenzyl, p-Nitrobenzyl, p-Halobenzyl, 2,6-Dichlorobenzyl, p-Cyanobenzyl, p-Phenylbenzyl, 2- and 4-Picolyl, 3-Methyl-2-picolyl N-Oxido, Diphenylmethyl, p, p'-Dinitrobenzhydryl, 5-Dibenzosuberyl, Triphenylmethyl, alpha-Naphthyldiphenylmethyl, p-methoxyphenyldiphenylmethyl, Di(p-methoxyphenyl)phenylmethyl, Tri(p-methoxyphenyl)methyl, 4-(4'-Bromophenacyloxy)phenyldiphenylmethyl, 4,4', 4"-Tris(4,5-dichlorophthalimidophenyl)methyl, 4,4', 4"-Tris(levulinoyloxyphenyl)methyl, 4,4', 4"-Tris(benzoyloxyphenyl)methyl, 3-(Imidazol-1-ylmethyl)bis(4', 4"-dimethoxyphenyl)methyl, 1,1-Bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-Anthryl, 9-(9-Phenyl)xanthenyl, 9-(9-Phenyl-10-oxo)anthryl, 1,3-Benzodithiolan-2-yl, Benzisothiazolyl, S,S-Dioxido); Silyl Ethers (Trimethylsilyl, Triethylsilyl, Triisopropylsilyl, Dimethylisopropylsilyl, Diethylisopropylsily, Dimethylthexylsilyl, t-Butyldimethylsilyl, t-Butyldiphenylsilyl, Tribenzylsilyl, Tri-p-xylylsilyl, Triphenylsilyl, Diphenylmethylsilyl, t-Butylmethoxyphenylsilyl); Esters (Formate, Benzoylformate, Acetate, Choroacetate, Dichloroacetate, Trichloroacetate, Trifluoroacetate, Methoxyacetate, Triphenylmethoxyacetate, Phenoxyacetate, p-Chlorophenoxyacetate, p-poly-Phenylacetate, 3-Phenylpropionate, 4-Oxopentanoate (Levulinate), 4,4-(Ethylenedithio)pentanoate, Pivaloate, Adamantoate, Crotonate, 4-Methoxycrotonate, Benzoate, p-Phenylbenzoate, 2,4,6-Trimethylbenzoate (Mesitoate); Carbonates (Methyl, 9-Fluorenylmethyl, Ethyl, 2,2,2-Trichloroethyl, 2-(Trimethylsilyl)ethyl, 2-(Phenylsulfonyl)ethyl, 2-(Triphenylphosphonio)ethyl, Isobutyl, Vinyl, Allyl, p-Nitrophenyl, Benzyl, p-Methoxybenzyl, 3,4-Dimethoxybenzyl, o-

Nitrobenzyl, p-Nitrobenzyl, S-Benzyl Thiocarbonate, 4-Ethoxy-1-naphthyl, Methyl Dithiocarbonate); Groups With Assisted Cleavage (2-Iodobenzoate, 4-Azidobutyrate, 4-Nitro-4-methylpentanoate, o-(Dibromomethyl)benzoate, 2-Formylbenzenesulfonate, 2-(Methylthiomethoxy)ethyl Carbonate, 4-(Methylthiomethoxy)butyrate, 2-(Methylthiomethoxymethyl)benzoate); Miscellaneous Esters (2,6-Dichloro-4-methylphenoxyacetate, 2,6-Dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-Bis(1,1-dimethylpropyl)phenoxyacetate, Chorodiphenylacetate, Isobutyrate, Monosuccinoate, (E)-2-Methyl-2-butenoate (Tigloate), o-(Methoxycarbonyl)benzoate, p-poly-Benzoate, α-Naphthoate, Nitrate, Alkyl N,N,N', N'-Tetramethylphosphorodiamidate, N-Phenylcarbamate, Borate, Dimethylphosphinothioyl, 2,4-Dinitrophenylsulfenate); and Sulfonates (Sulfate, Methanesulfonate (Mesylate), Benzylsulfonate, Tosylate).

More typically hydroxy protecting groups include subtituted methyl ethers, substituted benzyl ethers, silyl ethers, and esters including sulfonic acid esters, still more typically, trialkylsilyl ethers, tosylates and acetates.

Typical 1,2- and 1,3-diol protecting groups are described in Greene at pages 118-142 and include Cyclic Acetals and Ketals (Methylene, Ethylidene, 1-t-Butylethylidene, 1-Phenylethylidene, (4-Methoxyphenyl)ethylidene, 2,2,2-Trichloroethylidene, Acetonide (Isopropylidene), Cyclopentylidene, Cyclohexylidene, Cycloheptylidene, Benzylidene, p-Methoxybenzylidene, 2,4-Dimethoxybenzylidene, 3,4-Dimethoxybenzylidene, 2-Nitrobenzylidene); Cyclic Ortho Esters (Methoxymethylene, Ethoxymethylene, Dimethoxymethylene, 1-Methoxyethylidene, 1-Ethoxyethylidine, 1,2-Dimethoxyethylidene, alpha-Methoxybenzylidene, 1-(N,N-Dimethylamino)ethylidene Derivative, alpha-(N,N-Dimethylamino)benzylidene Derivative, 2-Oxacyclopentylidene); and Silyl Derivatives (Di-t-butylsilylene Group, 1,3-(1,1,3,3-Tetraisopropyldisiloxanylidene) Derivative, Tetra-t-butoxydisiloxane-1,3-diylidene Derivative, Cyclic Carbonates, Cyclic Boronates, Ethyl Boronate, Phenyl Boronate).

More typically, 1,2- and 1,3-diol protecting groups include epoxides and acetonides.

Typical amino protecting groups are described in Greene at pages 315-385 and include Carbamates (Methyl and Ethyl, 9-Fluorenylmethyl, 9(2-Sulfo)fluoroenylmethyl, 9-(2,7-Dibromo)fluorenylmethyl, 2,7-Di-t-buthyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]-methyl, 4-Methoxyphenacyl); Substituted Ethyl (2,2,2-Trichoroethyl, 2-Trimethylsilylethyl, 2-Phenylethyl, 1-(1-Adamantyl)-1-methylethyl, 1,1-Dimethyl-2-haloethyl, 1,1-Dimethyl-2,2-dibromoethyl, 1,1-Dimethyl-2,2,2-trichloroethyl, 1-Methyl-1-(4-biphenylyl)ethyl, 1-(3,5-Di-t-butylphenyl)-1-methylethyl, 2-(2'- and 4'-Pyridyl)ethyl, 2-(N,N-Dicyclohexylcarboxamido)ethyl, t-Butyl, 1-Adamantyl, Vinyl, Allyl, 1-Isopropylallyl, Cinnamyl, 4-Nitrocinnamyl, 8-Quinolyl, N-

Hydroxypiperidinyl, Alkyldithio, Benzyl, p-Methoxybenzyl, p-Nitrobenzyl, p-Bromobenzyl, p-Chorobenzyl, 2,4-Dichlorobenzyl, 4-Methylsulfinylbenzyl, 9-Anthrylmethyl, Diphenylmethyl); Groups With Assisted Cleavage (2-Methylthioethyl, 2-Methylsulfonylethyl, 2-(p-Toluenesulfonyl)ethyl, [2-(1,3-Dithianyl)]methyl, 4-Methylthiophenyl, 2,4-Dimethylthiophenyl, 2-Phosphonioethyl, 2-Triphenylphosphonioisopropyl, 1,1-Dimethyl-2-cyanoethyl, m-Choro-p-acyloxybenzyl, p-(Dihydroxyboryl)benzyl, 5-Benzisoxazolylmethyl, 2-(Trifluoromethyl)-6-chromonylmethyl); Groups Capable of Photolytic Cleavage (m-Nitrophenyl, 3,5-Dimethoxybenzyl, o-Nitrobenzyl, 3,4-Dimethoxy-6-nitrobenzyl, Phenyl(o-nitrophenyl)methyl); Urea-Type Derivatives (Phenothiazinyl-(10)-carbonyl Derivative, N'-p-Toluenesulfonylaminocarbonyl, N'-Phenylaminothiocarbonyl); Miscellaneous Carbamates (t-Amyl, S-Benzyl Thiocarbamate, p-Cyanobenzyl, Cyclobutyl, Cyclohexyl, Cyclopentyl, Cyclopropylmethyl, p-Decyloxybenzyl, Diisopropylmethyl, 2,2-Dimethoxycarbonylvinyl, o-(N,N-Dimethylcarboxamido)benzyl, 1,1-Dimethyl-3-(N,N-dimethylcarboxamido)propyl, 1,1-Dimethylpropynyl, Di(2-pyridyl)methyl, 2-Furanylmethyl, 2-Iodoethyl, Isobornyl, Isobutyl, Isonicotinyl, p-(p'-Methoxyphenylazo)benzyl, 1-Methylcyclobutyl, 1-Methylcyclohexyl, 1-Methyl-1-cyclopropylmethyl, 1-Methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-Methyl-1-(p-phenylazophenyl)ethyl, 1-Methyl-1-phenylethyl, 1-Methyl-1-(4-pyridyl)ethyl, Phenyl, p-(Phenylazo)benzyl, 2,4,6-Tri-t-butylphenyl, 4-(Trimethylammonium)benzyl, 2,4,6-Trimethylbenzyl); Amides (N-Formyl, N-Acetyl, N-Choroacetyl, N-Trichoroacetyl, N-Trifluoroacetyl, N-Phenylacetyl, N-3-Phenylpropionyl, N-Picolinoyl, N-3-Pyridylcarboxamide, N-Benzoylphenylalanyl Derivative, N-Benzoyl, N-p-Phenylbenzoyl); Amides With Assisted Cleavage (N-o-Nitrophenylacetyl, N-o-Nitrophenoxyacetyl, N-Acetoacetyl, (N'-Dithiobenzyloxycarbonylamino)acetyl, N-3-(p-Hydroxyphenyl)propionyl, N-3-(o-Nitrophenyl)propionyl, N-2-Methyl-2-(o-nitrophenoxy)propionyl, N-2-Methyl-2-(o-phenylazophenoxy)propionyl, N-4-Chlorobutyryl, N-3-Methyl-3-nitrobutyryl, N-o-Nitrocinnamoyl, N-Acetylmethionine Derivative, N-o-Nitrobenzoyl, N-o-(Benzoyloxymethyl)benzoyl, 4,5-Diphenyl-3-oxazolin-2-one); Cyclic Imide Derivatives (N-Phthalimide, N-Dithiasuccinoyl, N-2,3-Diphenylmaleoyl, N-2,5-Dimethylpyrrolyl, N-1,1,4,4-Tetramethyldisilylazacyclopentane Adduct, 5-Substituted 1,3-Dimethyl-1,3,5-triazacyclohexan-2-one, 5-Substituted 1,3-Dibenzyl-1,3,5-triazacyclohexan-2-one, 1-Substituted 3,5-Dinitro-4-pyridonyl); N-Alkyl and N-Aryl Amines (N-Methyl, N-Allyl, N-[2-(Trimethylsilyl)ethoxy]methyl, N-3-Acetoxypropyl, N-(1-Isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), Quaternary Ammonium Salts, N-Benzyl, N-Di(4-methoxyphenyl)methyl, N-5-Dibenzosuberyl, N-Triphenylmethyl, N-(4-Methoxyphenyl)diphenylmethyl, N-9-Phenylfluorenyl, N-2,7-Dichloro-9-fluorenylmethylene, N-Ferrocenylmethyl, N-2-Picolylamine N'-Oxide); Imine Derivatives (N-1,1-Dimethylthiomethylene,

N-Benzylidene, N-p-methoxybenylidene, N-Diphenylmethylene, N-[(2-Pyridyl)mesityl]methylene, N,(N',N'-Dimethylaminomethylene, N,N'-Isopropylidene, N-p-Nitrobenzylidene, N-Salicylidene, N-5-Chlorosalicylidene, N-(5-Chloro-2-hydroxyphenyl)phenylmethylene, N-Cyclohexylidene); Enamine Derivative (N-(5,5-Dimethyl-3-oxo-1-cyclohexenyl)); N-Metal Derivatives (N-Borane Derivatives, N-Diphenylborinic Acid Derivative, N-[Phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, N-Copper or N-Zinc Chelate); N-N Derivatives (N-Nitro, N-Nitroso, N-Oxide); N-P Derivatives (N-Diphenylphosphinyl, N-Dimethylthiophosphinyl, N-Diphenylthiophosphinyl, N-Dialkyl Phosphoryl, N-Dibenzyl Phosphoryl, N-Diphenyl Phosphoryl); N-Si Derivatives; N-S Derivatives; N-Sulfenyl Derivatives (N-Benzenesulfenyl, N-o-Nitrobenzenesulfenyl, N-2,4-Dinitrobenzenesulfenyl, N-Pentachlorobenzenesulfenyl, N-2-nitro-4-methoxybenzenesulfenyl, N-Triphenylmethylsulfenyl, N-3-Nitropyridinesulfenyl); andN-Sulfonyl Derivatives (N-p-Toluenesulfonyl, N-Benzenesulfonyl, N-2,3,6-Trimethyl-4-methoxybenzenesulfonyl, N-2,4,6-Trimethoxybenzenesulfonyl, N-2,6-Dimethyl-4-methoxybenzenesulfonyl, N-Pentamethylbenzenesulfonyl, N-2,3,5,6,-Tetramethyl-4-methoxybenzenesulfonyl, N-4-methoxybenzenesulfonyl, N-2,4,6- Trimethylbenzenesulfonyl, N-2,6-Dimethoxy-4-methylbenzenesulfonyl, N-2,2,5,7,8-Pentamethylchroman-6-sulfonyl, N-Methanesulfonyl, N-.beta.-Trimethylsilyethanesulfonyl, N-9-Anthracenesulfonyl, N-4-(4', 8'-Dimethoxynaphthylmethyl)benzenesulfonyl, N-Benzylsulfonyl, N-Trifluoromethylsulfonyl, N-Phenacylsulfonyl).

More typically, amino protecting groups include carbamates and amides, still more typically, N-acetyl groups.

Stereoisomers. The formula 1 and formula 2A or 2B compounds include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions. Both racemic and diasteromeric mixtures, as well as the individual optical isomers can be isolated or synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these are all within the scope of the invention. Chiral centers may be found in invention compounds at, for example, R^1, R^2 or R^4.

One or more of the following methods are used to prepare the enantiomerically enriched or pure isomers herein. The methods are listed in approximately their order of preference, i.e.; one ordinarily should employ stereospecific synthesis from chiral precursors before chromatographic resolution before spontaneous crystallization.

Stereospecific synthesis is described in the examples. Methods of this type conveniently are used when the appropriate chiral starting material is available and reaction steps are chosen that do not result in undesired racemization at chiral sites. One advantage of stereospecific synthesis is that it does not produce undesired enantiomers that must be removed from the final product,

thereby lowering overall synthetic yield. In general, those skilled in the art would understand what starting materials and reaction conditions should be used to obtain the desired enantiomerically enriched or pure isomers by stereospecific synthesis.

If a suitable stereospecific synthesis cannot be empirically designed or determined with routine experimentation then those skilled in the art would turn to other methods. One method of general utility is chromatographic resolution of enantiomers on chiral chromatography resins. These resins are packed in columns, commonly called Pirkle columns, and are commercially available. The columns contain a chiral stationary phase. The racemate is placed in solution and loaded onto the column, and thereafter separated by HPLC. See for example, Proceedings Chromatographic Society - International Symposium on Chiral Separations, Sept. 3-4, 1987, which is incorporated herein by reference. Examples of chiral columns that could be used to screen for the optimal separation technique would include Diacel Chriacel OD, Regis Pirkle Covalent D-phenylglycine, Regis Pirkle Type 1A, Astec Cyclobond II, Astec Cyclobond III, Serva Chiral D-DL=Daltosil 100, Bakerbond DNBLeu, Sumipax OA-1000, Merck Cellulose Triacetate column, Astec Cyclobond I-Beta, or Regis Pirkle Covalent D-Naphthylalanine. Not all of these columns are likely to be effective with every racemic mixture. However, those skilled in the art understand that a certain amount of routine screening may be required to identify the most effective stationary phase. When using such columns it is desirable to employ embodiments of the compounds of this invention in which the charges are not neutralized, e.g., where acidic functionalities such as carboxyl are not esterified or amidated.

Another method entails converting the enantiomers in the mixture to diasteriomers with chiral auxiliaries and then separating the conjugates by ordinary column chromatography. This is a very suitable method, particularly when the embodiment contains a free hydroxyl that will form a salt or covalent bond to a chiral auxiliary. Chirally pure amino acids, organic acids or organosulfonic acids are all worthwhile exploring as chiral auxiliaries, all of which are well known in the art. Salts with such auxiliaries can be formed, or they can be covalently (but reversibly) bonded to the functional group.

Enzymatic resolution is another method of potential value. In such methods one prepares covalent derivatives of the enantiomers in the racemic mixture, generally lower alkyl esters, and then exposes the derivative to enzymatic cleavage, generally hydrolysis. For this method to be successful an enzyme must be chosen that is capable of stereospecific cleavage, so it is frequently necessary to routinely screen several enzymes. If esters are to be cleaved, then one selects a group of esterases, phosphatases, and lipases and determines their activity on the derivative. Typical esterases are from liver, pancreas or other animal organs, and include porcine liver esterase.

If the enatiomeric mixture separates from solution or a melt as a conglomerate, i.e., a mixture of enantiomerically pure crystals, then the crystals can be mechanically separated, thereby producing the enantiomerically enriched preparation. This method, however, is not practical for large-scale preparations and is of limited value for true racemic compounds.

Asymmetric synthesis is another technique for achieving enantiomeric enrichment. For example, a chiral protecting group is reacted with the group to be protected and the reaction mixture allowed to equilibrate. If the reaction is enantiomerically specific then the product will be enriched in that enantiomer.

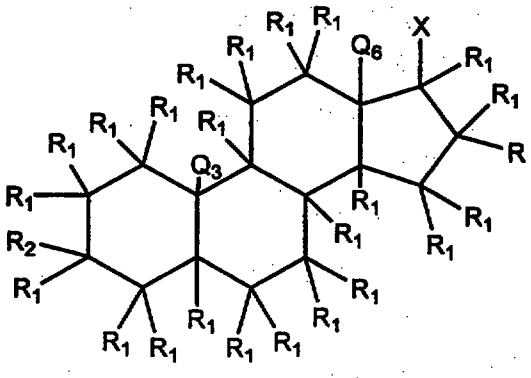
Further guidance in the separation of enantiomeric mixtures can be found, by way of example and not limitation, in "Enantiomers, Racemates, and resolutions", Jean Jacques, Andre Collet, and Samuel H. Wilen (Krieger Publishing Company, Malabar, FL, 1991, ISBN 0-89464-618-4): Part 2, Resolution of Enantiomer Mixture, pages 217-435; more particularly, section 4, Resolution by Direct Crystallization, pages 217-251, section 5, Formation and Separation of Diastereomers, pages 251-369, section 6, Crystallization-Induced Asymmetric Transformations, pages 369-378, and section 7, Experimental Aspects and Art of Resolutions, pages 378-435; still more particularly, section 5.1.4, Resolution of Alcohols, Transformation of Alcohols into Salt-Forming Derivatives, pages 263-266, section 5.2.3, Covalent Derivatives of Alcohols, Thiols, and Phenols, pages 332-335, section 5.1.1, Resolution of Acids, pages 257-259, section 5.1.2, Resolution of Bases, pages 259-260, section 5.1.3, Resolution of Amino Acids, page 261-263, section 5.2.1, Covalent Derivatives of Acids, page 329, section 5.2.2, Covalent derivatives of Amines, pages 330-331, section 5.2.4, Covalent Derivatives of Aldehydes, Ketones, and Sulfoxides, pages 335-339, and section 5.2.7, Chromatographic Behavior of Covalent Diastereomers, pages 348-354, all of which are incorporated herein by reference.

Embodiments include compositions that transiently occur when a method step or operation is performed. For example, when a formula 1 compound is contacted with an excipient, e.g., water, a cyclodextrin, a PEG, an alcohol, propylene glycol, benzyl alcohol or benzyl benzoate, the composition before addition of one ingredient with another is a non-homogenous mixture. As the ingredients are contacted, the mixture's homogeneity increases and the proportion of ingredients relative to each other approaches a desired value. Thus, some compositions as disclosed herein, optionally contain less than about 3% w/w water, e.g., less than 0.5% w/w water, can comprise about 0.0001-99% w/w of a formula 1 compound such as 16α-bromoepiandrosterone and one or more excipients. These transient compositions are intermediates that necessarily arise when one makes an invention composition or formulation and they are included in invention embodiments to the extent that they are patentable.

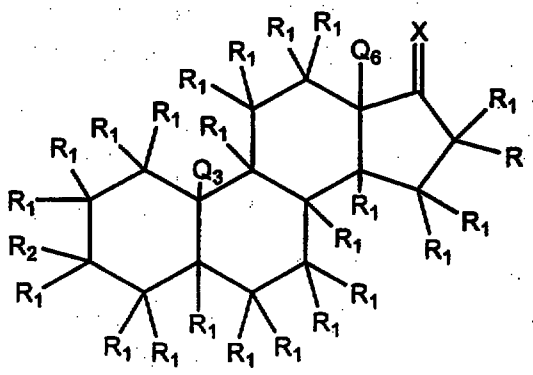
Formula 1 compounds. The formula 1 compounds, or the "compounds of the invention", are useful to treat a subject having, or prevent infection of a subject with, one or more *Trypanosome* parasites.

For preferred formula 1 compounds, the R_2 moiety bonded to the steroid ring is generally in the β-configuration, two R_1 are bonded to Q_2 and X is a double bonded oxygen moiety (=O). Typically, one of the R_1 bonded to Q_2 is hydrogen in the β-configuration, the other R_1 bonded to Q_2 is hydrogen or a halogen, usually bromine, in the α-configuration and a double bond is present at the 5-6 positions. Such preferred compounds include dehydroepiandrosterone ("DHEA") and 16α-bromodehydroepiandrosterone ("Br-DHEA").

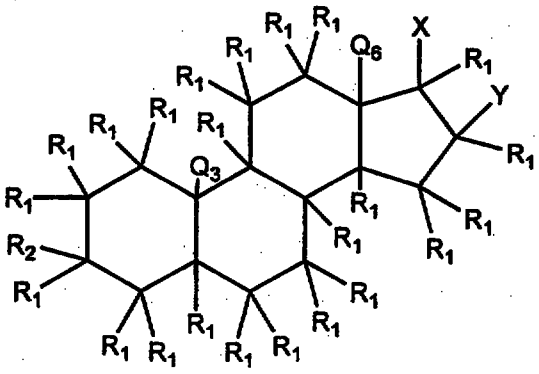
Other preferred formula 1 compounds include 17-ketosteriods of formula 1 where a double bond is present at the 5-6 positions, X is =O, Q_2 is $-CH_2-$ or -CHBr-, R_2 is -H, -S(O)(O)-OH, -S(O)(O)-ONa, $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6$ (where R6 independently is C_{1-14} straight or branched alkyl), $-P(O)(O)-O-CH_2-CH(O-C(O)R_7)-CH_2-O-C(O)-R_7$ (where R_7 independently is a glucuronide group or C_{1-14} straight or branched alkyl) or R_2 is a glucuronide group. Other preferred compounds include compound having the structures 20-43



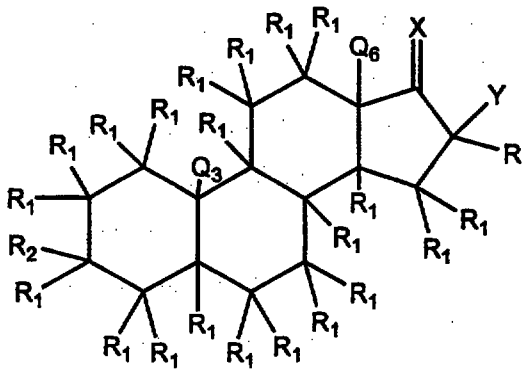
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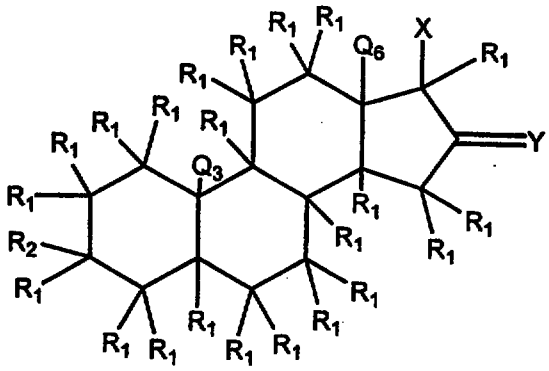
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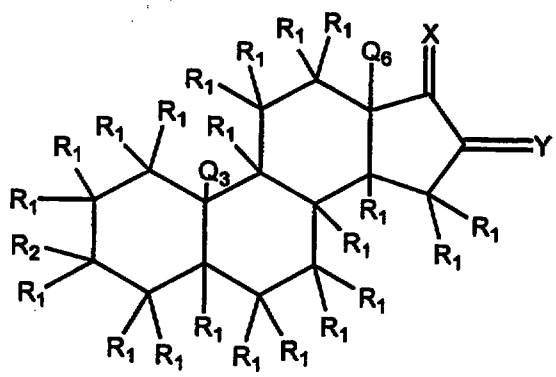
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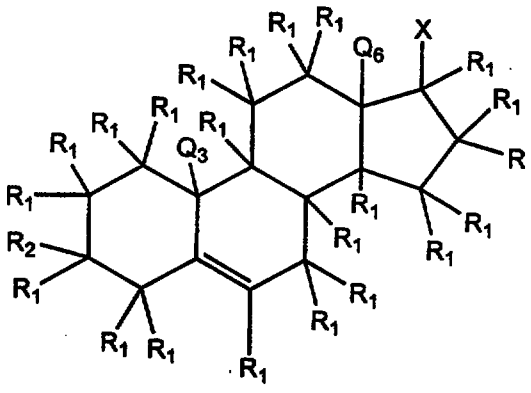
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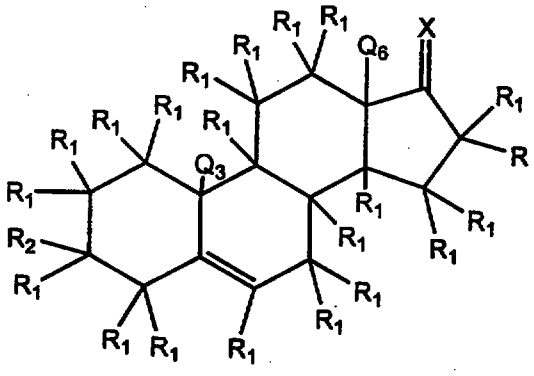
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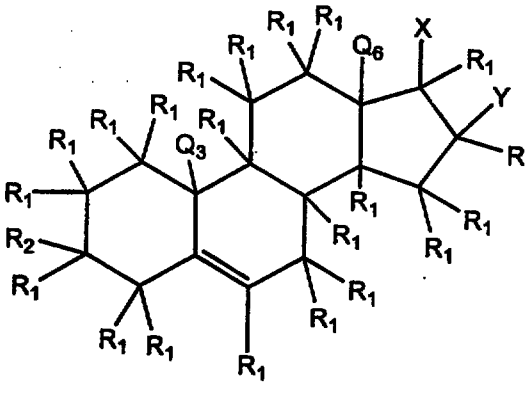
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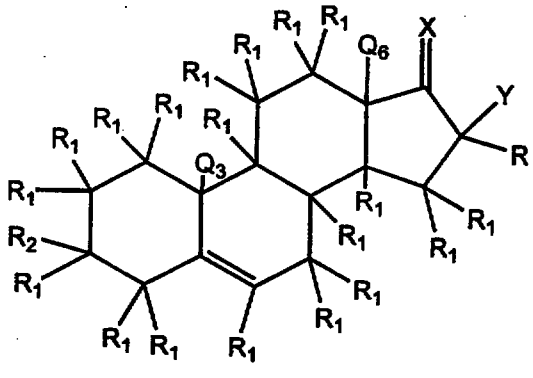
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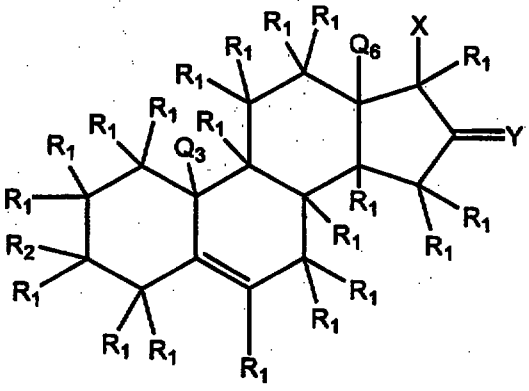
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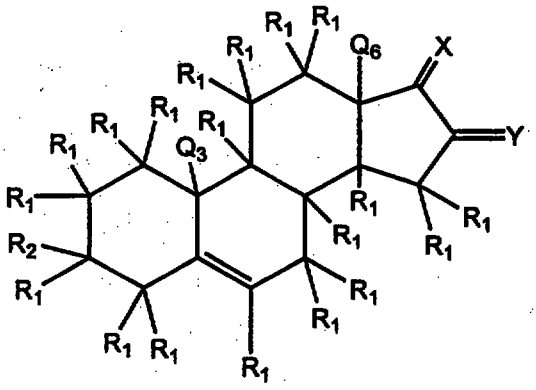
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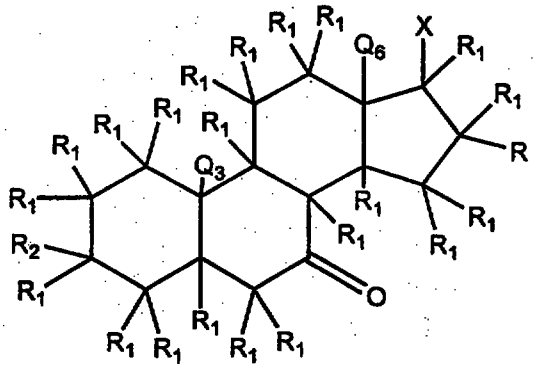
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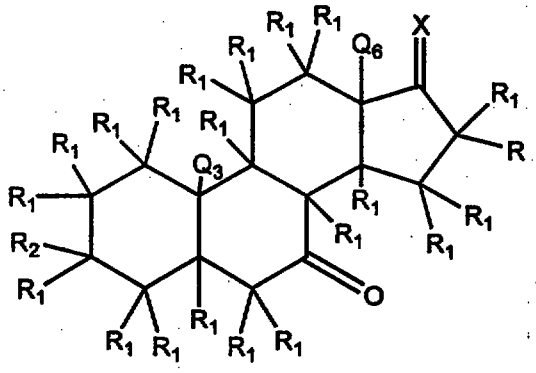
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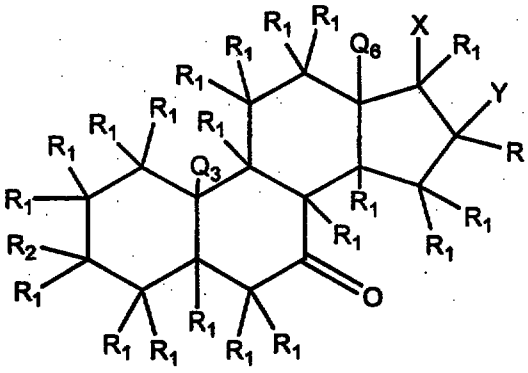
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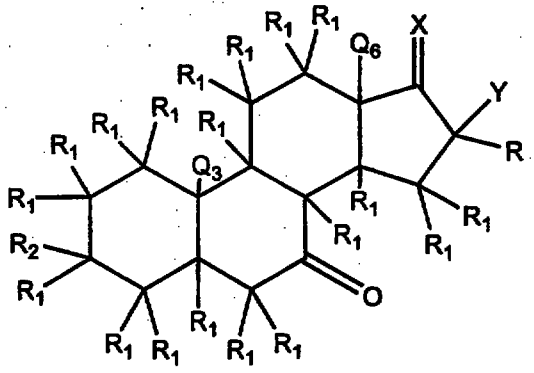
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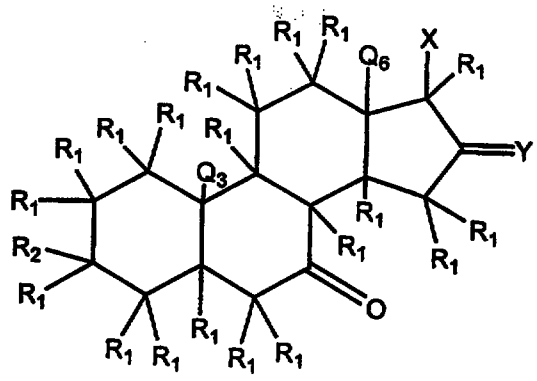
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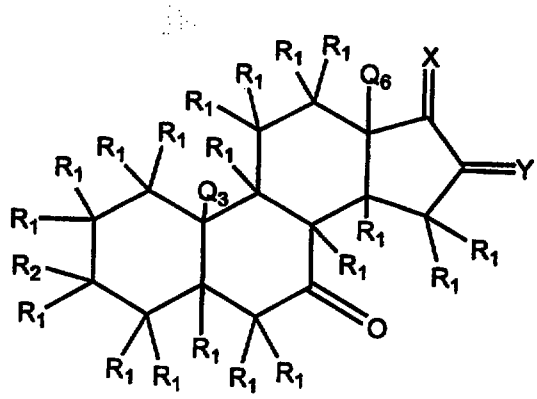
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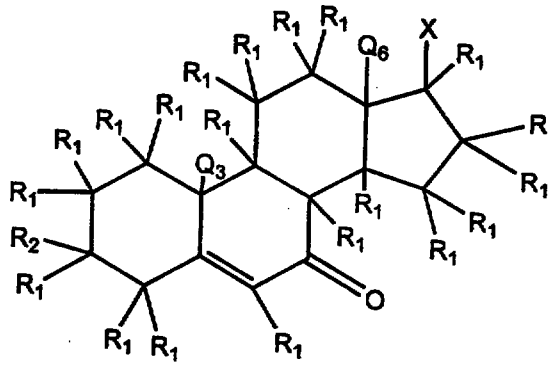
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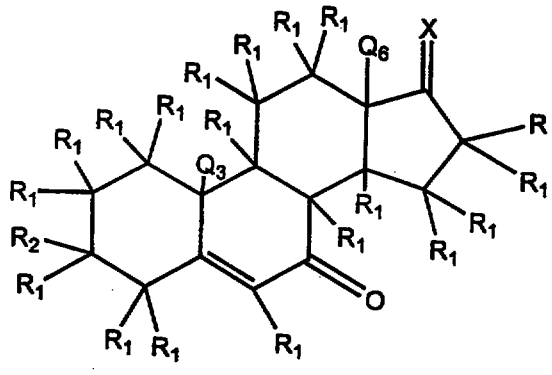
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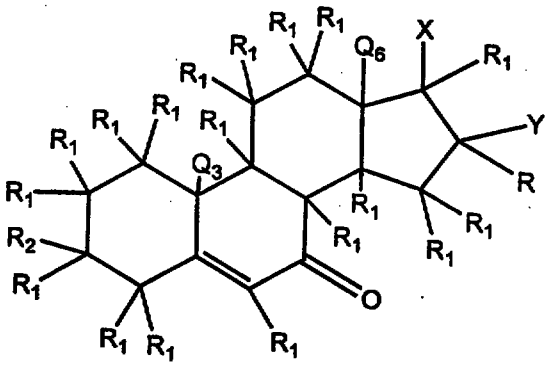
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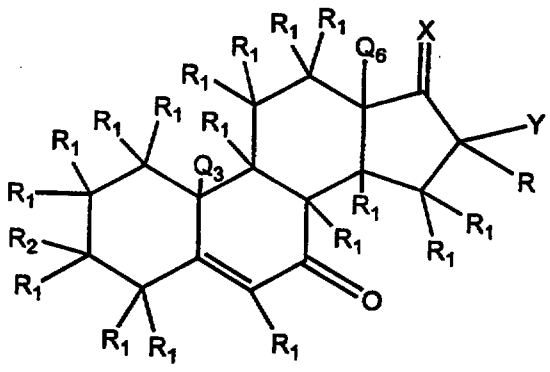
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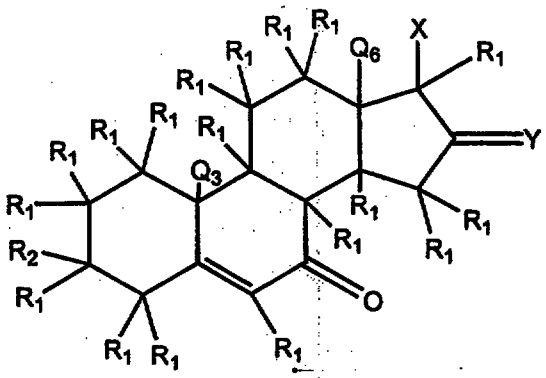
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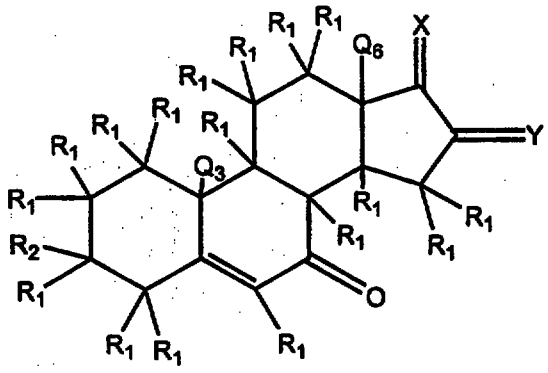
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wherein for each of structures 20-43

Q_3 and Q_6 are each $-C(R_1)_3$ wherein each R_1 is independently selected;

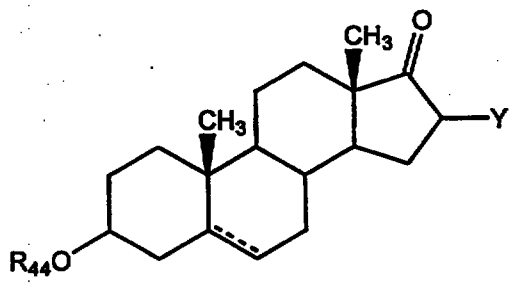
X and Y independently are -OH, -H, lower alkyl (e.g., C_{1-6} alkyl), $-C(O)-O-R_5$, $-O-C(O)-R_5$, halogen or, X and Y together with the R_1 at the same position independently are a ketone (=O);

each R_1 is independently selected and has the definition given above; and

R_2 and R_5 have the definitions given above.

In some embodiments, the formula 1 compound has the structure 20-43 and 2, 3, 4, 5 or 6 R_1 groups independently are -OH, halogen or alkoxy, and the remaining R_1 are all hydrogen; R_2 is -OH, an ester a thioester or a carbamate, or R_2, together with the R_1 at the 3-position comprises =O; Y is -H, -OH, a halogen or $-O-C(O)-R_5$, or Y, together with the R_1 at the 16-position comprises =O; X is -OH or $-O-C(O)-R_5$, or X, together with the R_1 at the 17-position comprises =O; and Q_3 and Q_6 independently are $-CH_3$ or $-CH_2OH$. Such embodiments include structure 20-43 compounds where two -OH are present at the 3-position, the 16-position or at the 17-position.

Preferred invention embodiments include compounds having the formula 44



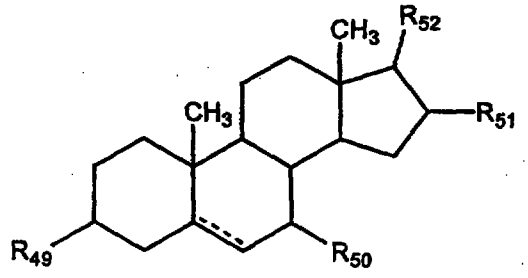
44

wherein Y is hydrogen or bromine, R_{44} is -H, -S(O)(O)-OH, -S(O)(O)-ONa, $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6$, $-P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7$ or a glucuronide group of structure (A). In other preferred embodiments, Y and R_{44} in formula 44 are both hydrogen. An especially preferred compound is dehydroepiandrosterone (Y and R_{44} in formula 44 are both hydrogen and the double bond at the 5-6 position is present). In other embodiments, the compound is epiandrosterone (Y and R_{44} in formula 44 are both hydrogen and

the double bond at the 5-6 position is absent). A 16-haloepiandrosterone with a F, Cl, Br or I at the 16 position can also be used as an antiviral agent, e.g., 16α-bromoepiandrosterone. Other preferred compounds are (i) 16α-bromodehydroepiandrosterone, (ii) dehydroepiandrosterone-3-sulfate (Y is -H and R_{44} is -S(O)(O)-OM in formula 44 are both hydrogen and the double bond at the 5-6 position is present) and (iii) 5β-androstan-3β-ol-17-one. Related embodiments comprise compounds related to formula 44 compounds comprise the formula 44 compounds wherein 1, 2, 3, 4, 5 or 6 hydrogen atoms that are bonded to the steroid nucleus are substituted with independently selected -OH, -Br, -Cl, -F, -I, $-OCH_3$ or $-OC_2H_5$ atoms or groups.

In other embodiments, the 17-ketosteroids of formula 1 are dehydro-epiandrosterone where R_{44} in formula 44 is a $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_5$, $-P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7$ or a glucuronide group of structure (A), Y is hydrogen and the 5-6 double bond is present. Other formula 44 compounds include conjugates of dehydroepiandrosterone wherein Y is hydrogen, a double bond is present at the 5-6 position and R_{44} is hexyl sulfate, dodecyl sulfate, octadecyl sulfate, octadecanoyl sulfate, O-dihexadecylglycerol sulfate, hexadecane sulfonate, dioctadecanoylglycerol phosphate or O-hexadecylglycerol phosphate.

In another preferred aspect of the invention, the steroid of formula 1 is a compound of formula 45

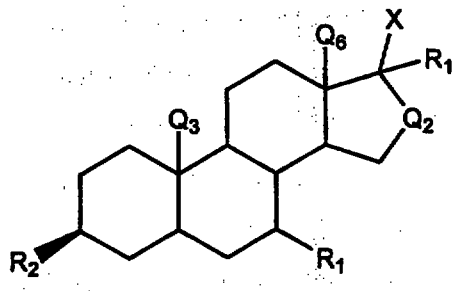


45

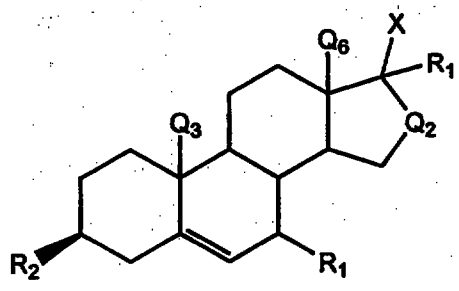
wherein R_{50} is -H, -OH or =O; R_{51} is -Br, -Cl, -F or -I; R_{52} is -OH or =O; R_{49} is -H, -OH, or $-OR_{53}$; and R_{53} is C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, a C_{1-18} ester, a C_{1-18} thioester, wherein any of the foregoing C_{1-18} or C_{2-18} groups is substituted at one or more hydrogen atoms with one or more independently selected -O-, -S-, -OH, $-NH_2$, -SH or =O groups or R_{53} is thioacetal, a sulfate ester, a sulfonate ester, a carbamate or a thioester. In one preferred aspect, R_{49} is $-O-C(O)-CH_2-CH_2-CH(R_{54})-CH(R_{55})-CH_2R_{56}$ wherein R_{54} is $-NH_2$, -OH, -SH, $-O-PO_3$, $-SO_3$ or $-OSO_3$; R_{55} is -H, $-NH_2$, -OH, -SH, $-O-PO_3$, $-SO_3$ or $-OSO_3$; and R_{56} is C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, a C_{1-18} ester, a C_{1-18} thioester, wherein any of the foregoing C_{1-18} or C_{2-18} groups is substituted at one or more hydrogen atoms with one or more independently selected -OH, $-NH_2$ or -SH groups, and the precursors, metabolites and analogs thereof. Related embodiments comprise compounds related to formula 44 compounds comprise the formula 45

compounds wherein 1, 2, 3, 4, 5 or 6 hydrogen atoms that are bonded to the steroid nucleus are substituted with independently selected -OH, -Br, -Cl, -F, -I, $-OCH_3$ or $-OC_2H_5$ atoms or groups.

In other preferred embodiments, the formula 1 compounds have the formula 1B or 1C



1B or



1C

wherein each R_1 independently is -H, -OH, a halogen, $-CHCH_2$, $-CHCHCH_3$, -CCH, $-CCCH_3$, or, or, the other moiety that is bonded to the same carbon atom is absent and R_1 is =O; R_2 is -H, -OH, a halogen, C_{1-8} alkoxy, $-S-C(O)-(CH_2)_m-R_4$, $-C(O)-S-(CH_2)_m-R_4$, $-O-S(O)(O)-(CH_2)_m-R_4$, $-O-S(O)(O)-O-(CH_2)_m-R_4$, $-O-C(O)-NH-(CH_2)_m-R_4$, $-NH-C(O)-O-(CH_2)_m-R_4$, $-O-C(S)-(CH_2)_m-R_4$, $-C(S)-O-(CH_2)_m-R_4$, $-O-C(O)-(CH_2)_m-R_4$ or $-C(O)-O-(CH_2)_m-R_4$; R_4 is -H, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-C_2H_4OH$, $-C_3H_6OH$, $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-O-CH_2-CH_3$, $-CH_2-CH_2-O-CH_2-CH_2OH$, a C_{3-6} alkenyl group, a C_{3-6} alkynyl group, benzyl or phenyl, wherein the phenyl or benzyl groups are optionally substituted with 1, 2, or 3 independently selected halogen, C_{1-4} alkoxy, -OH, -SH, -O- or -NH- moieties; and Q_3 and Q_6 independently are -H, $-CH_3$ or $-CH_2OH$; and Q_2 is $-C(R_1)_2-$ or $-CH_2-CH_2-$. In these embodiments, Q_3 and Q_6 are usually both in the β-configuration, typically they are $-CH_3$, Q_2 usually comprises $-CH_2-$, -C(O)-, -CH(Br)-, -CH(I)-, or -CH(OH)- with the Br, I or OH moieties in the α-configuration, or Q_2 comprises =O, and R_1 at the 7-position is -H, -OH or =O. Related embodiments comprise compounds related to formula 44 compounds comprise the formula 1A or 1B compounds wherein 1, 2, 3, 4, 5 or 6 hydrogen atoms that are bonded to the steroid nucleus are substituted with independently selected -OH, -Br, -Cl, -F, -I, $-OCH_3$ or $-OC_2H_5$ atoms or groups.

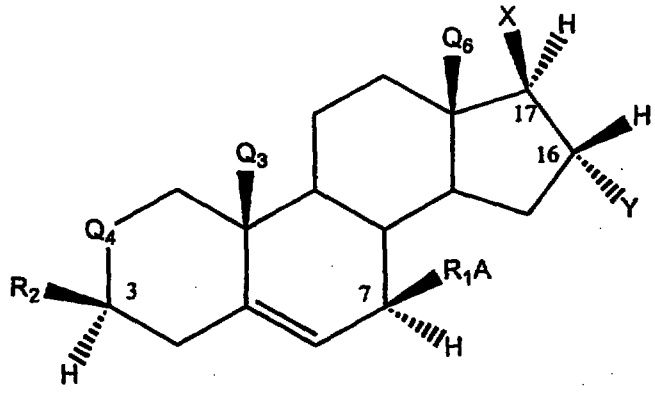
The formula 1 compounds can exist in a crystalline or polymorphic form.

Metabolites. Also falling within the scope of this invention are the *in vivo* metabolites of the compounds of the invention, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered formula 1 compound, due to enzymatic or chemical processes. Accordingly, the invention includes novel and unobvious compounds produced by a process comprising contacting a compound of this invention with a subject, e.g., a human, rodent or a primate, for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. C^{14} or H^3) compound of the invention, administering it parenterally or orally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, primate, or to a human, allowing sufficient time for

metabolism to occur (typically about 30 seconds to about 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by HPLC, MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no therapeutic activity of their own.

The following description exemplifies embodiments of the formula 1 compounds.

Group 1. Exemplary embodiments include the formula 1 compounds named in table B based on the compound structure designations defined in table A. Each compound named in Table B is depicted as a compound of formula 4

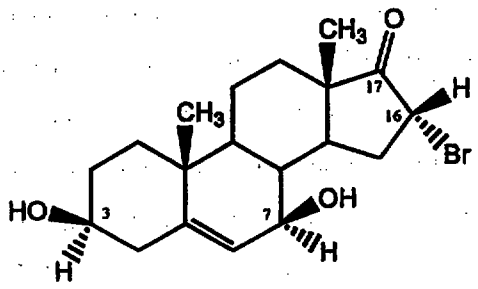


4

where Q_3 and Q_6 are both $-CH_3$, Q_4 is $-CH_2-$ and R_2, R_1A, and Y and X have the structures designated in Table A. The compounds named according to Tables A and B are referred to as "group 1" compounds.

Compounds named in Table B are designated by numbers assigned to R_2, R_1A, Y and X according to the following compound naming convention, $R_2.R_1A.Y.X$, using the numbered chemical structures depicted in Table A. As shown in formula 4, R_2 is in the 3β-position and hydrogen fills the remaining valence or R_2 is double bonded to the 3 carbon, R_1A is an R_1 group at the 7β-position or R_1A is an R_1 group double bonded to the 7 carbon, Y is in the 16α-position and hydrogen fills the remaining valence or R_2 is double bonded to the 16 carbon and X is in the 17β-position and hydrogen fills the remaining valence or X is double bonded to the 17 carbon. When R_2, R_1A, Y or X is a divalent moiety, e.g., =O, the hydrogen at the corresponding position is absent. Thus, the group 1 compound named 1.2.1.1 specifies a formula 4 structure with a β-hydroxyl bonded to carbons at the 3- and 7-positions (the variable groups R_2 and R_1A

respectively), an α-bromine bonded to carbon 16 (the variable group Y) and double bonded oxygen (=O) at carbon 17 (the variable group X), i.e., having the structure shown below.



1.2.1.1

TABLE A

	R2	R1A
1	-OH	-H
2	=O	-OH
3	-O-P(O)(O)-OH	=O
4	-O-P(O)(O)-O-CH_2-CH(O-C(O)-CH_3)-CH_2-O-C(O)CH_3	-CH_3
5	-O-S(O)(O)-OH	-OCH_3
6	-O-S(O)(O)-O^-Na^+	-OC_2H_5
7	-O-S(O)(O)-OC_2H_5	-$OCH_2CH_2CH_3$
8	-O-S(O)(O)-O-CH_2-CH(O-C(O)-CH_3)-CH_2-O-C(O)CH_3	-$OCH(CH_3)CH_3$
9	-O-S(O)(O)-$OCH_2CH_2CH_2CH_3$	-$OCH_2CH_2CH_2CH_3$
10	-O-S(O)(O)-$OC(CH_3)_3$	-$OC(CH_3)_3$

	Y	X
1	-Br	=O
2	-Cl	-OH
3	-I	-H
4	-F	-F
5	-H	-Cl
6	-OH	-Br
7	=O	-I
8	-O-C(O)-CH_3	-O-C(O)-CH_3
9	-O-C(O)-CH_2CH_3	-O-C(O)-CH_2CH_3
10	-O-C(O)-$CH_2CH_2CH_3$	-O-C(O)-$CH_2CH_2CH_3$

TABLE B

1.1.1.1, 1.1.1.2, 1.1.1.3, 1.1.1.4, 1.1.1.5, 1.1.1.6, 1.1.1.7, 1.1.1.8, 1.1.1.9, 1.1.1.10, 1.1.2.1, 1.1.2.2, 1.1.2.3, 1.1.2.4, 1.1.2.5, 1.1.2.6, 1.1.2.7, 1.1.2.8, 1.1.2.9, 1.1.2.10, 1.1.3.1, 1.1.3.2, 1.1.3.3, 1.1.3.4, 1.1.3.5, 1.1.3.6, 1.1.3.7, 1.1.3.8, 1.1.3.9, 1.1.3.10, 1.1.4.1, 1.1.4.2, 1.1.4.3, 1.1.4.4, 1.1.4.5, 1.1.4.6, 1.1.4.7, 1.1.4.8, 1.1.4.9, 1.1.4.10, 1.1.5.1, 1.1.5.2, 1.1.5.3, 1.1.5.4, 1.1.5.5, 1.1.5.6, 1.1.5.7, 1.1.5.8, 1.1.5.9, 1.1.5.10, 1.1.6.1, 1.1.6.2, 1.1.6.3, 1.1.6.4, 1.1.6.5, 1.1.6.6, 1.1.6.7, 1.1.6.8, 1.1.6.9, 1.1.6.10, 1.1.7.1, 1.1.7.2, 1.1.7.3, 1.1.7.4, 1.1.7.5, 1.1.7.6, 1.1.7.7, 1.1.7.8, 1.1.7.9, 1.1.7.10, 1.1.8.1, 1.1.8.2, 1.1.8.3, 1.1.8.4, 1.1.8.5, 1.1.8.6, 1.1.8.7, 1.1.8.8, 1.1.8.9, 1.1.8.10, 1.1.9.1, 1.1.9.2, 1.1.9.3, 1.1.9.4, 1.1.9.5, 1.1.9.6, 1.1.9.7, 1.1.9.8, 1.1.9.9, 1.1.9.10, 1.1.10.1, 1.1.10.2, 1.1.10.3, 1.1.10.4, 1.1.10.5, 1.1.10.6, 1.1.10.7, 1.1.10.8, 1.1.10.9, 1.1.10.10, 1.2.1.1, 1.2.1.2, 1.2.1.3, 1.2.1.4, 1.2.1.5, 1.2.1.6, 1.2.1.7, 1.2.1.8, 1.2.1.9, 1.2.1.10, 1.2.2.1, 1.2.2.2, 1.2.2.3, 1.2.2.4, 1.2.2.5, 1.2.2.6, 1.2.2.7, 1.2.2.8, 1.2.2.9, 1.2.2.10, 1.2.3.1, 1.2.3.2, 1.2.3.3, 1.2.3.4, 1.2.3.5, 1.2.3.6, 1.2.3.7, 1.2.3.8, 1.2.3.9, 1.2.3.10, 1.2.4.1, 1.2.4.2, 1.2.4.3, 1.2.4.4, 1.2.4.5, 1.2.4.6, 1.2.4.7, 1.2.4.8, 1.2.4.9, 1.2.4.10, 1.2.5.1, 1.2.5.2, 1.2.5.3, 1.2.5.4, 1.2.5.5, 1.2.5.6, 1.2.5.7, 1.2.5.8, 1.2.5.9, 1.2.5.10, 1.2.6.1, 1.2.6.2, 1.2.6.3, 1.2.6.4, 1.2.6.5, 1.2.6.6, 1.2.6.7, 1.2.6.8, 1.2.6.9, 1.2.6.10, 1.2.7.1, 1.2.7.2, 1.2.7.3, 1.2.7.4, 1.2.7.5, 1.2.7.6, 1.2.7.7, 1.2.7.8, 1.2.7.9, 1.2.7.10, 1.2.8.1, 1.2.8.2, 1.2.8.3, 1.2.8.4, 1.2.8.5, 1.2.8.6, 1.2.8.7, 1.2.8.8, 1.2.8.9, 1.2.8.10, 1.2.9.1, 1.2.9.2, 1.2.9.3, 1.2.9.4, 1.2.9.5, 1.2.9.6, 1.2.9.7, 1.2.9.8, 1.2.9.9, 1.2.9.10, 1.2.10.1, 1.2.10.2, 1.2.10.3, 1.2.10.4, 1.2.10.5, 1.2.10.6, 1.2.10.7, 1.2.10.8, 1.2.10.9, 1.2.10.10, 1.3.1.1, 1.3.1.2, 1.3.1.3, 1.3.1.4, 1.3.1.5, 1.3.1.6, 1.3.1.7, 1.3.1.8, 1.3.1.9, 1.3.1.10, 1.3.2.1, 1.3.2.2, 1.3.2.3, 1.3.2.4, 1.3.2.5, 1.3.2.6, 1.3.2.7, 1.3.2.8, 1.3.2.9, 1.3.2.10, 1.3.3.1, 1.3.3.2, 1.3.3.3, 1.3.3.4, 1.3.3.5, 1.3.3.6, 1.3.3.7, 1.3.3.8, 1.3.3.9, 1.3.3.10, 1.3.4.1, 1.3.4.2, 1.3.4.3, 1.3.4.4, 1.3.4.5, 1.3.4.6, 1.3.4.7, 1.3.4.8, 1.3.4.9, 1.3.4.10, 1.3.5.1, 1.3.5.2, 1.3.5.3, 1.3.5.4, 1.3.5.5, 1.3.5.6, 1.3.5.7, 1.3.5.8, 1.3.5.9, 1.3.5.10, 1.3.6.1, 1.3.6.2, 1.3.6.3, 1.3.6.4, 1.3.6.5, 1.3.6.6, 1.3.6.7, 1.3.6.8, 1.3.6.9, 1.3.6.10, 1.3.7.1, 1.3.7.2, 1.3.7.3, 1.3.7.4, 1.3.7.5, 1.3.7.6, 1.3.7.7, 1.3.7.8, 1.3.7.9, 1.3.7.10, 1.3.8.1, 1.3.8.2, 1.3.8.3, 1.3.8.4, 1.3.8.5, 1.3.8.6, 1.3.8.7, 1.3.8.8, 1.3.8.9, 1.3.8.10, 1.3.9.1, 1.3.9.2, 1.3.9.3, 1.3.9.4, 1.3.9.5, 1.3.9.6, 1.3.9.7, 1.3.9.8, 1.3.9.9, 1.3.9.10, 1.3.10.1, 1.3.10.2, 1.3.10.3, 1.3.10.4, 1.3.10.5, 1.3.10.6, 1.3.10.7, 1.3.10.8, 1.3.10.9, 1.3.10.10, 1.4.1.1, 1.4.1.2, 1.4.1.3, 1.4.1.4, 1.4.1.5, 1.4.1.6, 1.4.1.7, 1.4.1.8, 1.4.1.9, 1.4.1.10, 1.4.2.1, 1.4.2.2, 1.4.2.3, 1.4.2.4, 1.4.2.5, 1.4.2.6, 1.4.2.7, 1.4.2.8, 1.4.2.9, 1.4.2.10, 1.4.3.1, 1.4.3.2, 1.4.3.3, 1.4.3.4, 1.4.3.5, 1.4.3.6, 1.4.3.7, 1.4.3.8, 1.4.3.9, 1.4.3.10, 1.4.4.1, 1.4.4.2, 1.4.4.3, 1.4.4.4, 1.4.4.5, 1.4.4.6, 1.4.4.7, 1.4.4.8, 1.4.4.9, 1.4.4.10, 1.4.5.1, 1.4.5.2, 1.4.5.3, 1.4.5.4, 1.4.5.5, 1.4.5.6, 1.4.5.7, 1.4.5.8, 1.4.5.9, 1.4.5.10, 1.4.6.1, 1.4.6.2, 1.4.6.3, 1.4.6.4, 1.4.6.5, 1.4.6.6, 1.4.6.7, 1.4.6.8, 1.4.6.9, 1.4.6.10, 1.4.7.1, 1.4.7.2, 1.4.7.3, 1.4.7.4, 1.4.7.5, 1.4.7.6, 1.4.7.7, 1.4.7.8, 1.4.7.9, 1.4.7.10, 1.4.8.1, 1.4.8.2, 1.4.8.3, 1.4.8.4, 1.4.8.5, 1.4.8.6, 1.4.8.7, 1.4.8.8, 1.4.8.9, 1.4.8.10, 1.4.9.1, 1.4.9.2, 1.4.9.3, 1.4.9.4, 1.4.9.5, 1.4.9.6, 1.4.9.7, 1.4.9.8, 1.4.9.9, 1.4.9.10, 1.4.10.1, 1.4.10.2, 1.4.10.3, 1.4.10.4, 1.4.10.5, 1.4.10.6, 1.4.10.7, 1.4.10.8, 1.4.10.9, 1.4.10.10, 1.5.1.1, 1.5.1.2, 1.5.1.3, 1.5.1.4, 1.5.1.5, 1.5.1.6, 1.5.1.7, 1.5.1.8, 1.5.1.9, 1.5.1.10, 1.5.2.1, 1.5.2.2,

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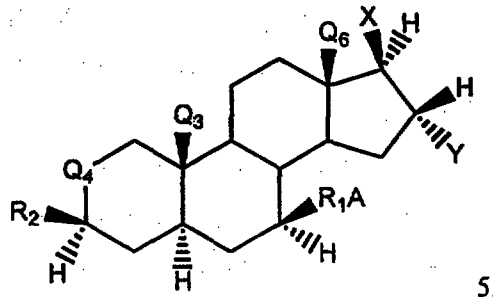
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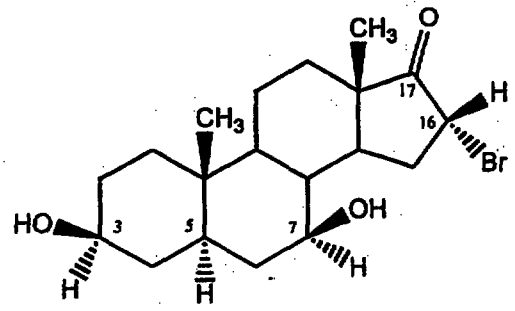
Additional exemplary formula 1 compound groups include the following groups as disclosed below.

Group 2. Group 2 compounds are as named in Table B, i.e., R_2, R_1A, Y and X substituents are as defined in Table A, but they are bonded to the steroid nucleus shown in formula 5, which is the same as the formula 4 steroid nucleus, except that the 5-6 double bond is absent and hydrogen is present at the 5-position in the α-configuration



5.

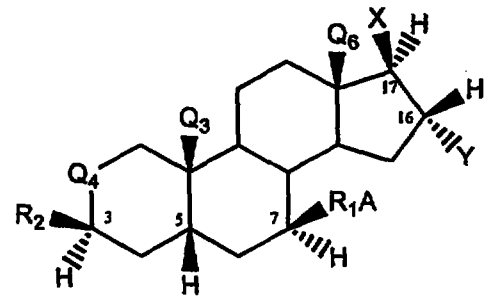
Thus, the group 2 compound named 1.2.1.1 has the structure



group 2, compound 1.2.1.1.

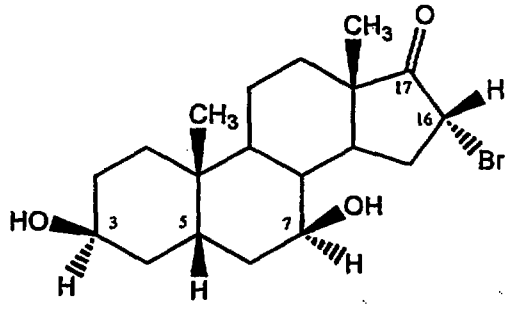
Group 3. Group 3 compounds are as named in Table B, i.e., R_2, R_1A, Y and X substituents are as defined in Table A, but they are bonded to the steroid nucleus shown in formula

6, which is the same as the formula 4 steroid nucleus, except that the 5-6 double bond is absent and hydrogen is present at the 5-position in the β-configuration



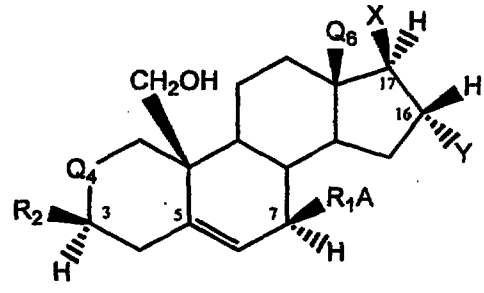
6.

Thus, the group 3 compound named 1.2.1.1 has the structure



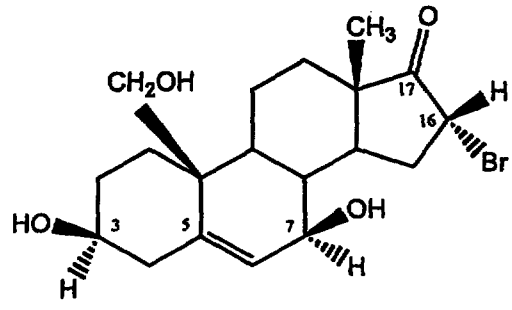
group 3, compound 1.2.1.1.

Group 4. Group 4 compounds are as named in Table B, i.e., R_2, R_1A, Y and X substituents are as defined in Table A, but they are bonded to the steroid nucleus shown in formula 7, which is the same as the formula 4 steroid nucleus, except that Q_3 is $-CH_2OH$



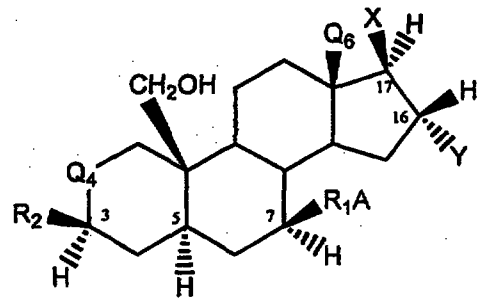
7.

Thus, the group 4 compound named 1.2.1.1 has the structure



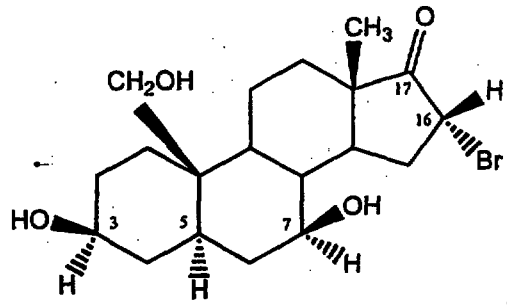
group 4, compound 1.2.1.1.

Group 5. Group 2 compounds are as named in Table B, i.e., R_2, R_1A, Y and X substituents are as defined in Table A, but they are bonded to the steroid nucleus shown in formula 8, which is the same as the formula 4 steroid nucleus, except that the 5-6 double bond is absent and hydrogen is present at the 5-position in the α-configuration and Q_3 is $-CH_2OH$

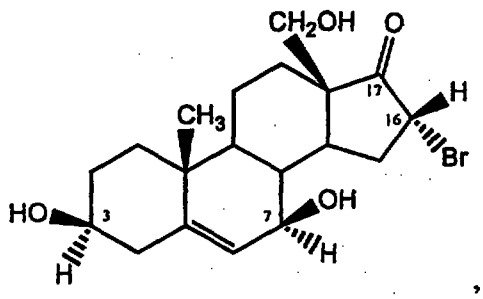


8.

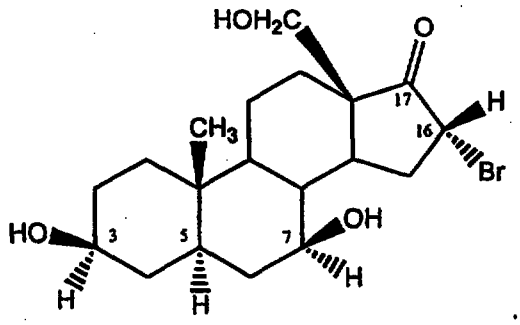
Thus, the group 5 compound named 1.2.1.1 has the structure



Group 6. Group 6 compounds are as named in groups 1-5, except that Q_6 in formulas 4-8 is $-CH_2OH$ instead of methyl. In group 6, there are 5 subgroups of group 6 compounds. The first subgroup, subgroup 6-1, has the same steroid nucleus with the substituents as defined for group 1 compounds while the second, subgroup 6-2, has the same steroid nucleus with the substituents as defined for group 2 compounds. Subgroups 6-3 through 6-5 have the same steroid nucleus with the substituents as defined for group 3 through 5 respectively. Thus, for example, the subgroup 6-1 compound named 1.2.1.1 has the structure



and the subgroup 6-2 compound named 1.2.1.1 has the structure



Group 7. Group 7 compounds are as named in groups 1-5, except that the Y moiety in formulas 4-8 is in the β-configuration instead of in the α-configuration. Group 7 comprises 5 subgroups, wherein the compounds are named essentially as described for group 6 compounds, except that the Y group is in the β-configuration.

Group 8. Group 8 compounds are as named in groups 1-5, except that the X moiety in formulas 4-8 is in the α-configuration instead of in the β-configuration. Group 8 comprises 5 subgroups, wherein the compounds are named essentially as described for group 6 compounds, except that the X group is in the α-configuration.

Group 9. Group 9 compounds are as named in groups 1-5, except that the R_2 moiety in formulas 4-8 is in the α-configuration instead of in the β-configuration. Group 9 comprises 5 subgroups, wherein the compounds are named essentially as described for group 6 compounds, except that the R_2 group is in the α-configuration.

Group 10. Group 10 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -S-C(O)-CH_3

2 -S-C(O)-CH_2-C_6H_5

3 -O-S(O)-O-CH_3

4 -O-S(O)-O-CH_2-C_6H_5

5 -O-S(O)(O)-O-CH_3

6 -O-S(O)(O)-O-CH_2-C_6H_5

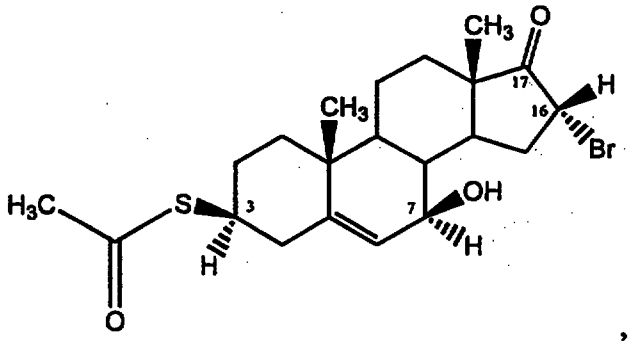
7 -O-C(O)-NH-CH_3

8 -O-C(O)-NH-C_6H_5

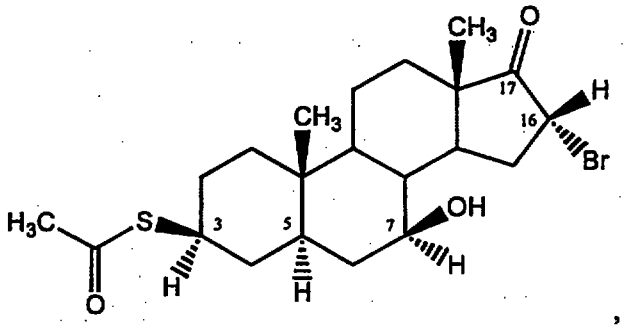
9 -O-C(S)-CH_3

10 -O-C(S)-CH_2-C_6H_5

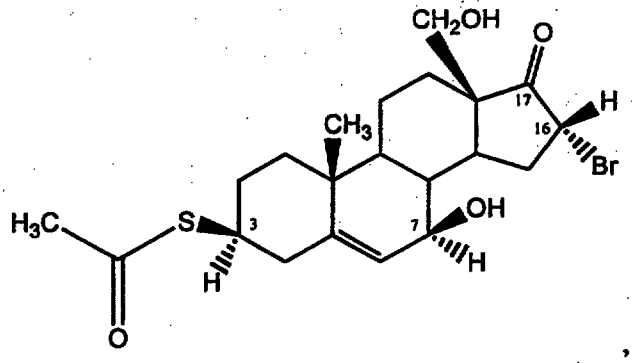
Group 10 comprises 25 subgroups of compounds. The first, subgroup 10-1, has the same steroid nucleus with substituents as defined for group 1, except that the R_2 moieties or groups listed replace those in Table A above. The subgroup 10-1 compound named 1.2.1.1 has the structure



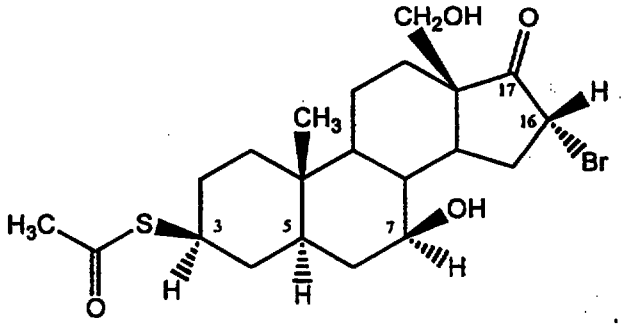
the subgroup 10-2 compound named 1.2.1.1 has the structure



the subgroup 10-6-1 compound named 1.2.1.1 has the structure



and the subgroup 10-6-2 compound named 1.2.1.1 has the structure



Group 11. Group 11 compounds are as named in groups **1-9**, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -S-C(O)-CH_2CH_2-O-CH_2CH_3

2 -S-C(O)-CH_2-$C_6H_4OCH_3$

3 -O-S(O)-O-CH_2CH_2-O-CH_2CH_3

4 -O-S(O)-O-CH_2-$C_6H_4OCH_3$

5 5 -O-S(O)(O)-O-CH_2CH_2-O-CH_2CH_3

6 -O-S(O)(O)-O-CH_2-$C_6H_4OCH_3$

7 -O-C(O)-NH-CH_2CH_2-O-CH_2CH_3

8 -O-C(O)-NH-$C_6H_4OCH_3$

9 -O-C(S)-CH_2CH_2-O-CH_2CH_3

10 10 -O-C(S)-CH_2-$C_6H_4OCH_3$

Group 12. Group 12 compounds are as named in groups **1-9**, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -S-C(O)-CH_2CH_2-O-CH_2C(O)OH

2 -S-C(O)-CH_2-C_6H_4F

15 3 -O-S(O)-O-CH_2CH_2-O-CH_2C(O)OH

4 -O-S(O)-O-CH_2-C_6H_4F

5 -O-S(O)(O)-O-CH_2CH_2-O-CH_2C(O)OH

6 -O-S(O)(O)-O-CH_2-C_6H_4F

7 -O-C(O)-NH-CH_2CH_2-O-CH_2C(O)OH

20 8 -O-C(O)-NH-C_6H_4F

9 -O-C(S)-CH_2CH_2-O-CH_2C(O)OH

10 -O-C(S)-CH_2-C_6H_4F

Group 13. Group 13 compounds are as named in groups **1-9**, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

25 1 -S-C(O)-CH_2CH_2-O-CH_2CH_2OH

2 -S-C(O)-CH_2-$C_6H_4CH_3$

3 -O-S(O)-O-CH_2CH_2-O-CH_2CH_2OH

4 -O-S(O)-O-CH_2-$C_6H_4CH_3$

5 -O-S(O)(O)-O-CH_2CH_2-O-CH_2CH_2OH

30 6 -O-S(O)(O)-O-CH_2-$C_6H_4CH_3$

7 -O-C(O)-NH-CH_2CH_2-O-CH_2CH_2OH

8 -O-C(O)-NH-$C_6H_4CH_3$

9 -O-C(S)-CH_2CH_2-O-CH_2CH_2OH

10 -O-C(S)-CH_2-$C_6H_4CH_3$

Group 14. Group 14 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -S-C(O)-CH_2CH_2-O-$CH_2CH_2OR^{PR}$

2 -S-C(O)-CH_2-$C_6H_4OR^{PR}$

3 -O-S(O)-O-CH_2CH_2-O-$CH_2CH_2OR^{PR}$

4 -O-S(O)-O-CH_2-$C_6H_4OR^{PR}$

5 -O-S(O)(O)-O-CH_2CH_2-O-$CH_2CH_2OR^{PR}$

6 -O-S(O)(O)-O-CH_2-$C_6H_4OR^{PR}$

7 -O-C(O)-NH-CH_2CH_2-O-$CH_2CH_2OR^{PR}$

8 -O-C(O)-NH-$C_6H_4OR^{PR}$

9 -O-C(S)-CH_2CH_2-O-$CH_2CH_2OR^{PR}$

10 -O-C(S)-CH_2-$C_6H_4OR^{PR}$

Group 15. Group 15 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -S-C(O)-CH_2CH_2-O-$CH_2CH_2NHR^{PR}$

2 -S-C(O)-CH_2-$C_6H_3(OR^{PR})_2$

3 -O-S(O)-O-CH_2CH_2-O-$CH_2CH_2NHR^{PR}$

4 -O-S(O)-O-CH_2-$C_6H_3(OR^{PR})_2$

5 -O-S(O)(O)-O-CH_2CH_2-O-$CH_2CH_2NHR^{PR}$

6 -O-S(O)(O)-O-CH_2-$C_6H_3(OR^{PR})_2$

7 -O-C(O)-NH-CH_2CH_2-O-$CH_2CH_2NHR^{PR}$

8 -O-C(O)-NH-$C_6H_3(OR^{PR})_2$

9 -O-C(S)-CH_2CH_2-O-$CH_2CH_2NHR^{PR}$

10 -O-C(S)-CH_2-$C_6H_3(OR^{PR})_2$

Group 16. Group 16 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -S-C(O)-$(CH_2)_{0-6}$-CH_3

2 -S-C(O)-CH_2-C_6H_5

3 -O-S(O)-O-$(CH_2)_{0-6}$-CH_3

4 -O-S(O)-O-CH_2-C_6H_5

5 -O-S(O)(O)-O-$(CH_2)_{0-6}$-CH_3

6 -O-S(O)(O)-O-CH_2-C_6H_5

7 -O-C(O)-NH-$(CH_2)_{0-6}$-CH_3

8 -O-C(O)-NH-$(CH_2)_{0-6}$-C_6H_5

9 -O-C(S)-$(CH_2)_{0-6}$-CH_3

10 -O-C(S)-CH_2-C_6H_5

Group 17. Group 17 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -S-C(O)-CH_2CH_2-(O-CH_2CH_2)$_{1-50}$-H

2 -S-C(O)-CH_2-$C_6H_4OCH_3$

3 -O-S(O)-O-CH_2CH_2-(O-CH_2CH_2)$_{1-50}$-H

4 -O-S(O)-O-CH_2-$C_6H_4OCH_3$

5 -O-S(O)(O)-O-CH_2CH_2-(O-CH_2CH_2)$_{1-50}$-H

6 -O-S(O)(O)-O-CH_2-$C_6H_4OCH_3$

7 -O-C(O)-NH-CH_2CH_2-(O-CH_2CH_2)$_{1-50}$-H

8 -O-C(O)-NH-$C_6H_4OCH_3$

9 -O-C(S)-CH_2CH_2-(O-CH_2CH_2)$_{1-50}$-H

10 -O-C(S)-CH_2-$C_6H_4OCH_3$

Group 18. Group 18 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -O-C(O)-CH_2CH_2-(O-CH_2CH_2)$_{1-50}$-H

2 -O-C(O)-CH_2-$C_6H_4OCH_3$

3 -O-C(O)-$(CH_2)_{0-6}$-CH_3

4 -O-C(O)-CH_2-$C_6H_4NO_2$

5 -O-C(O)-CH_2CH_2-(O-CH_2CH_2)$_{1-50}$-H

6 -O-C(O)-CH_2-C_6H_5

7 -O-C(O)-CH_2CH_2-O-CH_2CH_3

8 -O-C(O)-C_6H_5

9 -O-C(O)-CH_2CH_2-S-CH_2CH_3

10 -O-C(O)-CH_2-C_6H_4F

Group 19. Group 19 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -O-CH_2CH_2-(O-CH_2CH_2)$_{1-50}$-H

2 -O-CH_2-$C_6H_4OCH_3$

3 -O-$(CH_2)_{0-6}$-CH_3

4 -O-CH_2-$C_6H_4NO_2$

5 -O-CH_2CH_2-(O-CH_2CH_2)$_{1-50}$-H

6 -O-CH_2-C_6H_5

7 -O-CH_2CH_2-O-CH_2CH_3

8 -O-C_6H_5

9 -O-CH_2CH_2-S-CH_2CH_3

10 -O-CH_2-C_6H_4F

Group 20. Group 20 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -C(O)-O-CH_2CH_2-(O-CH_2CH_2)$_{1-50}$-H

2 -C(O)-O-CH_2-$C_6H_4OCH_3$

3 -C(O)-O-$(CH_2)_{0-6}$-CH_3

4 -C(O)-O-CH_2-$C_6H_4NO_2$

5 -C(O)-O-CH_2CH_2-(O-CH_2CH_2)$_{1-50}$-H

6 -C(O)-O-CH_2-C_6H_5

7 -C(O)-O-CH_2CH_2-O-CH_2CH_3

8 -C(O)-O-C_6H_5

9 -C(O)-O-CH_2CH_2-S-CH_2CH_3

10 -C(O)-O-CH_2-C_6H_4F

Group 21. Group 21 compounds are as named in groups 1-9, except that R_2 moieties 1 through 10 in Table A are replaced with the following moieties.

1 -C(O)-O-G12 (G12 is defined below)

2 -O-C(O)-G12

3 -C(O)-S-G12

4 -S-C(O)-G12

5 -C(S)-O-G12

6 -O-C(S)-G12

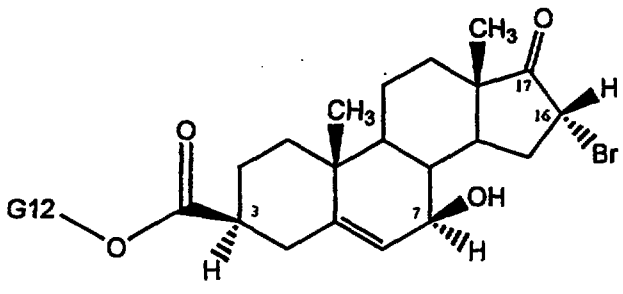
7 -O-C(O)-NH-G12

8 -NH-C(O)-O-G12

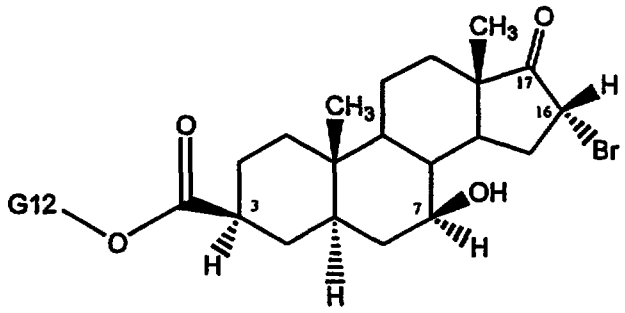
9 -C(O)-O-CH_2-G12

10 -O-C(O)-CH_2-G12

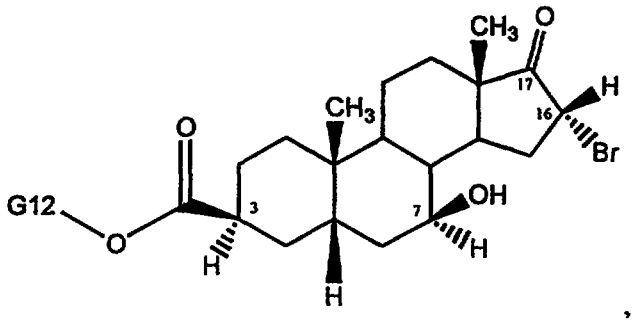
Thus, the group 21-1 compound named 1.2.1.1 has the structure



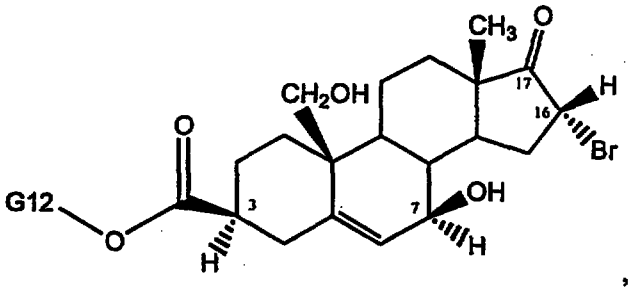
while the group 21-2 compound named 1.2.1.1 has the structure



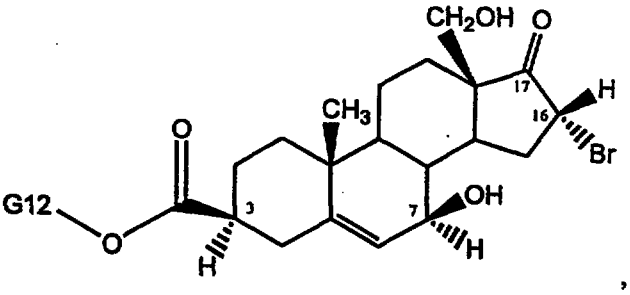
the group 21-3 compound named 1.2.1.1 has the structure



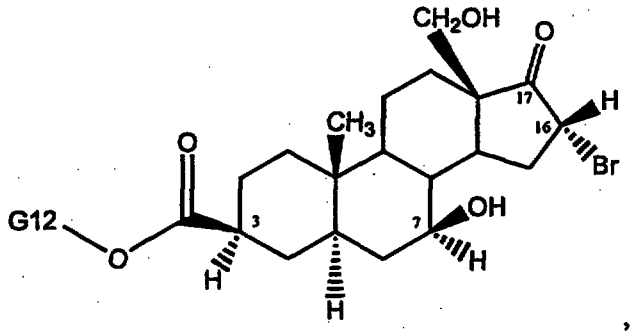
the group 21-4 compound named 1.2.1.1 has the structure



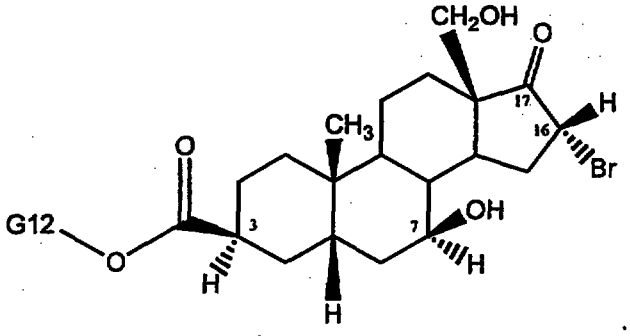
the group 21-6-1 compound named 1.2.1.1 has the structure



the group 21-6-2 compound named 1.2.1.1 has the structure



and the group 21-6-3 compound named 1.2.1.1 has the structure



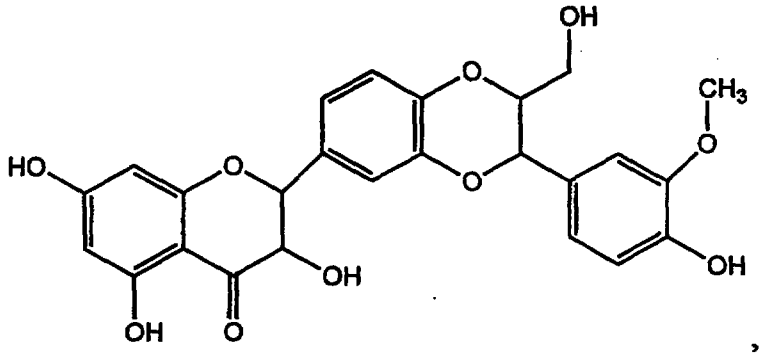
G12 in Group 21 is an organic moiety comprising 1, 2, 3, 4, 5, 6, 7, 8, 9 10, 11 or 12 carbon atoms and 0, 1, 2, 3, 4, 5, 6, 7 or 8 independently selected O, S, N, P, or Si atoms, but, if a Si or P atom is present, only one Si or P is present, wherein the organic moiety is optionally selected from C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, aryl, a C_{2-9} heterocycle or a substituted derivative of any of these comprising 1, 2, 3, 4 or more substituents, wherein each substituent is independently chosen and is selected from -O-, -S-, -NR^{PR}- (including -NH-), -C(O)-, =O, =S, -$N(R^{PR})_2$ (including -NH_2), -C(O)OR^{PR} (including -C(O)OH), -OC(O)R^{PR} (including -O-C(O)-H), -OR^{PR} (including -OH), -SR^{PR} (including -SH), -NO_2, -CN, -NHC(O)-, -C(O)NH-, -OC(O)-, -C(O)O-, -O-A8, -S-A8, -C(O)-A8, -OC(O)-A8, -C(O)O-A8, =N-, -N=, =N-OH, -$OPO_3(R^{PR})_2$, -OSO_3H_2 and halogen moieties or atoms, where each R^{PR} is -H, an independently selected protecting group or both R^{PR} together comprise a protecting group, and A8 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{1-4} alkyl-aryl (e.g., benzyl), aryl (e.g. phenyl) or C_{1-4} alkyl-C_{2-9} heterocycle. G12 moieties include -CH_3, -C_2H_5, -C_3H_7, -C_4H_9, -C_6H_{13}, -CH_2-C_6H_5, -C_2H_4-C_6H_5, -C_3H_6-C_6H_5, -C_6H_5, -CH_2-heterocycle, -CH_2-CH_2-heterocycle and a heterocycle, and of which are substituted with one, two, three or more independently selected -O-, -S-, -F, -Cl, -Br, -I, -NH-, =O, -CN, -OCH_3, -OC_2H_5, -OC_4H_9, -NO_2, -NH_2, -COOH, or -NH-C(O)- moieties.

Other embodiments include the use of any formula 4 compound or genus of formula 4 compounds that are named in any of the foregoing groups for any of the therapeutic or other applications described herein. This includes the use of any named formula 4 compound or genus for any of those applications wherein (i) R_2 is in the α-configuration, (ii) Q4 is -CH(halogen)-, (iii)

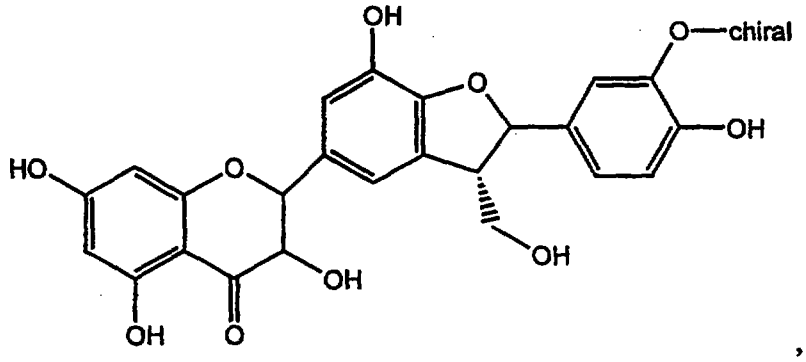
X is in the α-configuration and the -H at the 17-position is in the β-configuration, (iv) Y is in the β-configuration and the -H at the 16-position is in the α-configuration or (v) R_1A is in the α-configuration and the -H at the 7-position is in the β-configuration.

Embodiments also include formula 1 compounds (e.g., formula 4 compounds) wherein R_4 is optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{2-8} alkynyl, optionally substituted aryl, optionally substituted heterocycle, optionally substituted C_{1-8} alkyl-aryl, optionally substituted C_{1-8} alkyl-heterocycle or optionally substituted -CH_2-C_{1-8} organic moiety (where the organic moiety is as described for esters), wherein any of the foregoing are independently substitued with 1, 2, 3, 4, 5 or 6 or more -O-, -S-, -NH-, -NH-C(O)- (i.e., -NH-C(O)- or -C(O)-NH-), =O, =NOH, -NO_2, -CN, -F, -Cl, -Br, -I, -OH, -SH, or -NH_2. Such R_4 moieties include -CH_2-C_{1-6} optionally substituted alkyl, -CH_2-C_{2-6} optionally substituted alkenyl, -CH_2-C_{1-6} -optionally substituted aryl and -CH_2-C_{2-9} optionally substituted heterocycle.

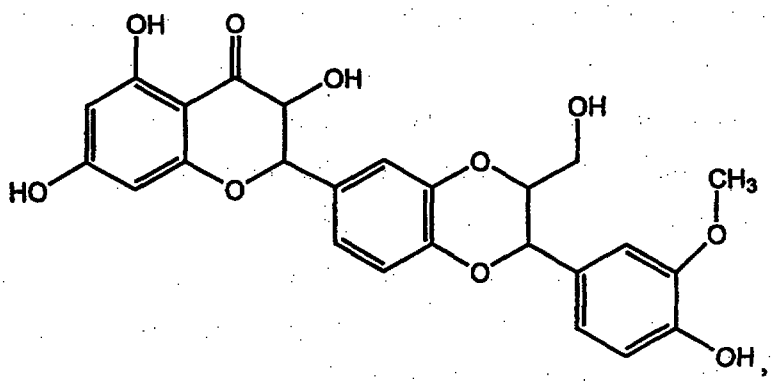
Plasma concentration-enhancing compounds. An aspect of the invention comprises administering an effective amount of a plasma concentration-enhancing compound, e.g., a compound of formula 2A or 2B compound with a formula 1 compound to facilitate preventing or treating one or more *Trypanosome* infections in a subject. In addition to the formula 2A or 2B compounds, the plasma concentration-enhancing compounds include bavachinin A, didymin (isosakuranetin-7-rutinoside or neoponcirin), flavanomarein (isookanine-7-glucoside), flavanone azine, flavanone diacetylhydrazone, flavanone hydrazone, silybin, which has the structure



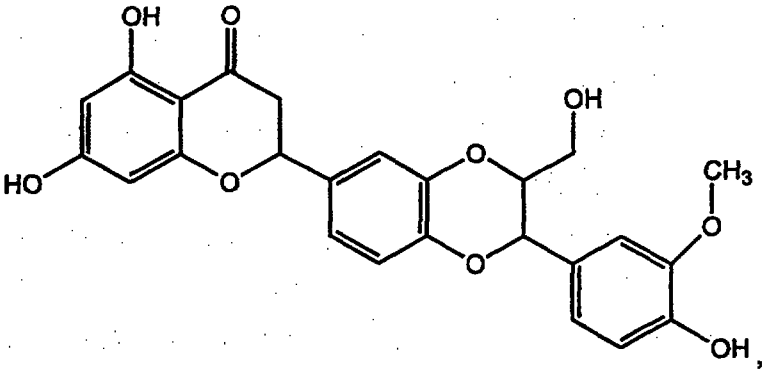
silychristin, which has the structure



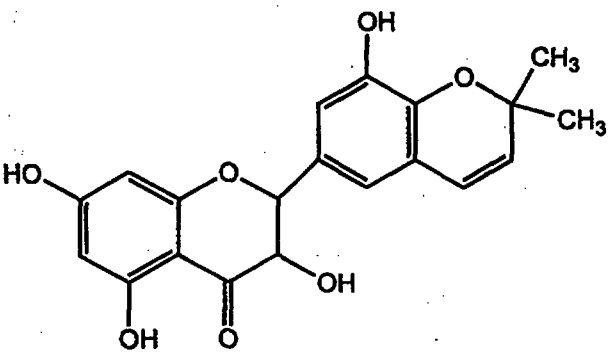
isosilybin, which has the structure



silandrin, which has the structure



and a compound having the structure (E)



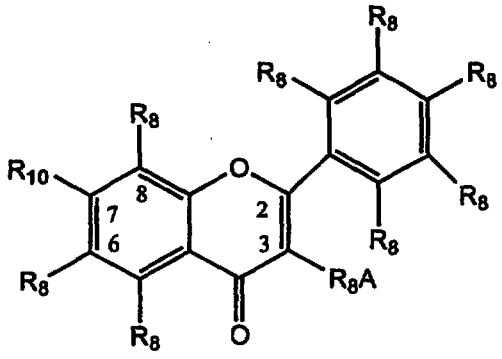
(E).

Collectively, these compounds and the formula 2A and 2B compounds are referred to as the "plasma concentration-enhancing compounds".

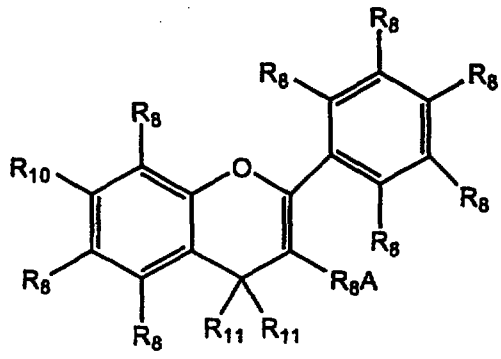
The formula 2A and 2B compounds encompass a number of natural and synthetic flavonoids, including certain flavones, flavans, and their iso analogs. The presence of a formula 2A or 2B compound in compositions comprising a formula 1 compound has been found to enhance the systemic bioavailability of formulations that comprise a formula 1 compound. The presence of a formula 2A or 2B compound, e.g., naringin or naringenin, results in enhanced plasma concentrations of the formula 1 compound. The formula 2A or 2B compound need not be present in a formulation that contains a formula 1 compound. The formula 2A or 2B can also be administered, e.g., about 1-4 hours, before or after, preferably before, the formula 1 compound is

administered. In these embodiments, one will administer an oral or parenteral formulation that contains a formula 1 compound and a formula 2A or 2B compound.

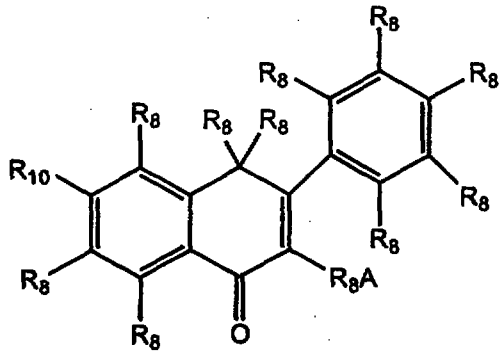
The plasma concentration-enhancing compounds include compounds of formulas 50-65



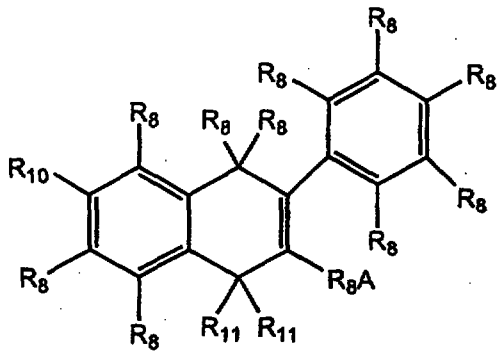
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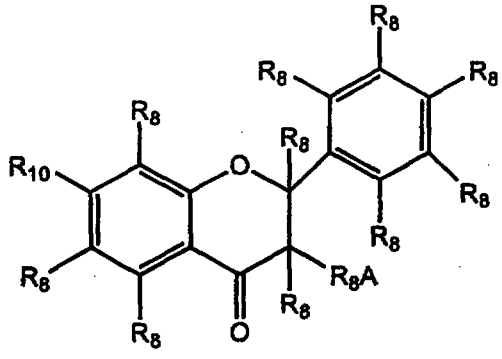
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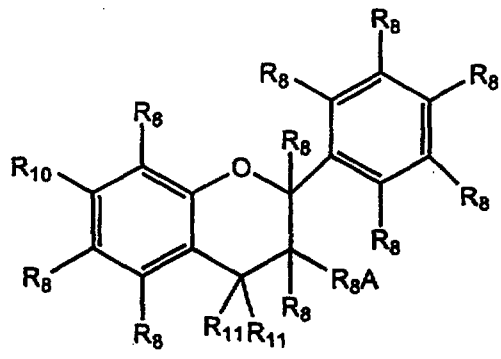
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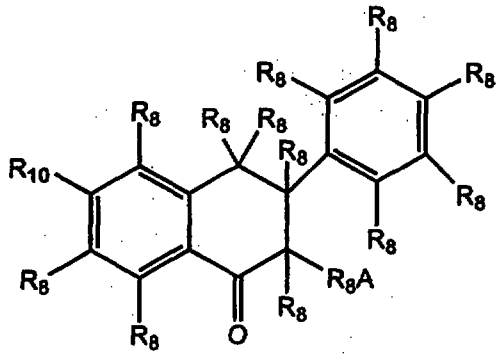
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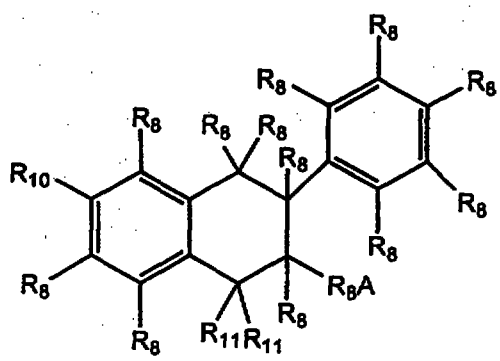
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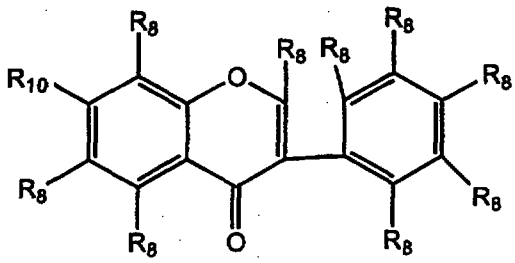
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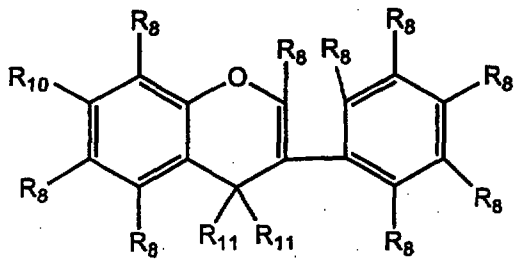
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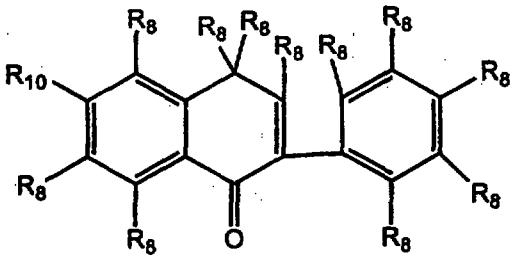
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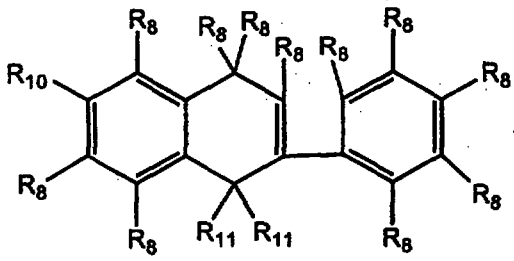
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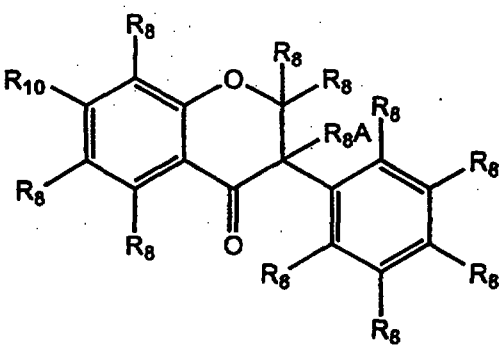
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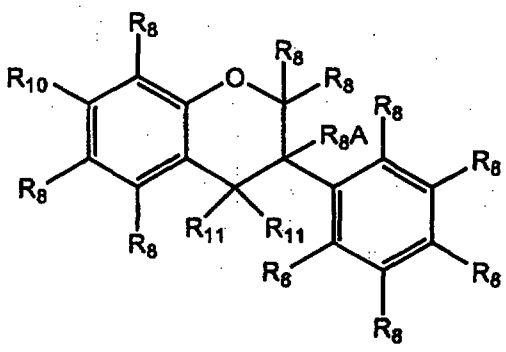
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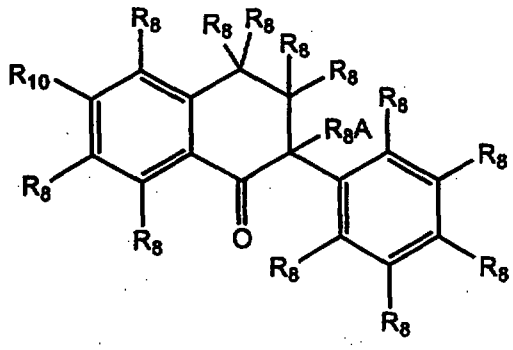
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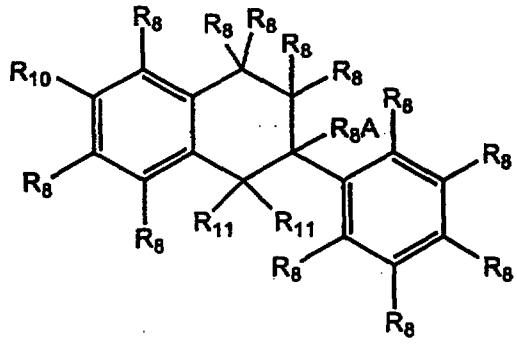
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wherein

R_8 at the 6-position independently are -H, -OH, -F, -Cl, -Br, -I, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide, a C_{1-25} fatty acid, glucoside, $-CH_2CH=C(CH_3)_2$ or a group having the structure (B);

R_8 at the 8-position independently are -H, -OH, -F, -Cl, -Br, -I, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide, a C_{1-25} fatty acid, glucoside, $-CH_2CH=C(CH_3)_2$ or the residue of a formula 50-65 compound where a hydrogen atom is removed to form the formula 50-65 radical;

R_8A independently are -H, -OH, -F, -Cl, -Br, -I, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide, a C_{1-25} fatty acid, glucoside, $-CH_2CH=C(CH_3)_2$ or a group having the structure (C);

the remaining R_8 independently are -H, -OH, -F, -Cl, -Br, -I, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide, a C_{1-25} fatty acid or $-CH_2-CH=C(CH_3)_2$; and

R_{10} (i) is -OH or -F, -Cl, -Br, -I, C_{1-6} alkyl, C_{1-6} alkoxy, neohesperidoside, apioglucoside, rutinoside, glucoside, galactoside, rhamnoside, arabinoside, or a stereoisomer, hydrate, analog, derivative or metabolite of any of these moieties, any of which are optionally independently substituted at one or more hydrogen atoms with -OH, -F, -Cl, -Br, -I, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide or a C_{1-25} fatty acid, or (ii) R_{10} is the radical of bavachinin A, didymin, flavanomarein, flavanone azine, flavanone diacetylhydrazone, flavanone hydrazone, silybin, silychristin, isosilybin, silandrin, a moiety of structure (E) or a stereoisomer, hydrate, analog, derivative or metabolite of any of these moieties.

Additional therapeutic embodiments. In accordance with another preferred aspect of the present invention, there is provided a method of treatment of one or more of the conditions described above, e.g., a *Trypanosome* infection, comprising administering a combination therapy including one or more of the compounds of the present invention administered simultaneously or sequentially with one or more macrophage stimulating factor (and optionally further co-administering one or more plasma concentration-enhancing compounds). Macrophage stimulating factors are well known to those of skill in the art, examples including GM-CSF (see, e.g., Callard et al., The Cytokine Facts Book, Academic Press, 1994, p. 139, which is incorporated herein) and Interleukin-4 (sold by Immunex as "Leukine" and by Schering Plough as "Prokine").

While not wishing to be bound by any theory, it is believed that compounds that inhibit glucose-6-phosphate dehydrogenase are surprisingly effective against malaria. Accordingly, the present invention also relates to the administration of a glucose-6-phosphate dehydrogenase inhibitor in the treatment of any of the conditions described herein, particularly in the treatment of malaria, optionally in a combination therapy with any other compounds of the present invention or any of the compounds described herein as being suitable for use in a combination therapy. Those of skill in the art are readily familiar with inhibitors of glucose-6-phosphate dehydrogenase, and can readily identify other material, which exhibits such inhibition.

In another preferred aspect of the present invention, to enhance destruction of parasite infected erythrocytes, the compounds of the present invention can be coadministered with one or more oxidation agent (optionally further together with a plasma concentration-enhancing compound and/or a macrophage stimulating factor), or the patient may be given oxygen ventilation to increase oxidative steroids in the plasma.

The components of any of the combination therapies disclosed herein can be administered simultaneously (in a combination formulation), essentially simultaneously (e.g., administration of each compound a few minutes or a few hours apart), or can be administered sequentially, e.g., several days apart, or more than a week apart. For example, a compound of the present invention and a plasma-concentration-enhancing compound (and/or a macrophage stimulating factor) can be administered together, or essentially simultaneously, e.g., administration of each compound a few minutes or a few hours apart, or can be administered sequentially, e.g., several days apart, or more than a week apart (optionally together with simultaneous or sequential administration of oxidating agent or oxygen ventilation). All such variations in administration of the combination therapy are encompassed within the scope of the invention.

The invention also includes pharmaceutical formulations containing any such combination as described herein.

The invention also includes the use of combinations of compounds as disclosed herein in the manufacture of a medicament for use in the treatment of a condition selected from malaria, African Trypanosomiasis, American Trypanosomiasis, as well as one or more kind of parasites and/or one or more diseases caused by such parasites, against one or more kind of Mycoplasma and/or one or more diseases caused by such Mycoplasmas and/or against one or more of the following indications or infections: (a) hairy Leukoplakia, (b) oral candidosis, (c) mouth ulcerations-aphthous/ herpetic/bacterial, (d) fungal candida, (e) human papilloma virus, (f) molluscum contagiosum, (g) squamous oral carcinoma, (h) Kaposi's sarcoma oral lesions, (i) periodontitis, (j) necrotizing gingivitis, (k) orafacial herpes zoster, and (l) rotaviruses, as well as all other indications and infections disclosed in U.S. Patent No. 5,292,725.

The present invention is also directed to the use of compounds of the present invention in the manufacture of a medicament for treatment as described herein.

The present invention is also directed to administering of compounds of the present invention to provide a prophylactic treatment of a patient against liver parasites, e.g., Trypanosome parasites.

Articles of manufacture. The present invention also provides articles of manufacture comprising, for example, packaging material, at least one unit-dosage of a compound of the present invention (optionally together with one or more unit-dosage of a compound which can be administered in a combination therapy) and a label or package insert indicating that the compound can be used in a method disclosed herein.

In one embodiment, an article of manufacture comprises packaging material, at least one unit dose of a 17-ketosteroid compound (a formula 1 compound) and a label or package insert indicating that the 17-ketosteroid compound (a formula 1 compound) can be used in a method as described herein. The packaging material can be made from one or more generally known materials, e.g., foam, cardboard, fiberboard, polystyrene and polypropylene, and is of a size suitable to contain the compound(s) accompanying the packaging material. A label or package insert can be a tag or label secured to the packaging material, a label printed on the packaging material or a label inserted within the packaging material. The label indicates that the 17-ketosteroid can be used in a therapy as disclosed herein, e.g., in combination with a plasma concentration-enhancing compound and/or a macrophage-stimulating factor. The label can also indicate that the compound(s) have received approval from an official agency, for example, the U.S. Food and Drug Administration, for medical or veterinary use according to the method. The label may also indicate suitable administration routes, dosage regimen, and the like. If desired, the article may contain additional components such as at least one unit dose of a plasma concentration-enhancing compound or the macrophage-stimulating factor.

Methods of administration and formulations. The dosage for a particular patient will vary depending on factors such as the overall health of the patient, the method, route and dose of administration and the severity of side effects (if any). Determination of the appropriate dose is made by the clinician using parameters known in the art. Generally, the dose begins with an amount somewhat less than the optimum dose and it is increased by small increments thereafter until the desired or optimum effect is achieved. The dosage of the compounds of the invention is suitably determined depending on the individual cases taking symptoms, age and sex of the subject and the like into consideration. With respect to the duration of treatment, it is typical for skilled clinicians to monitor patients in order to determine when inhibition is providing therapeutic

benefit, and to determine whether to increase dosage, decrease dosage, discontinue therapy, resume therapy or alter therapy.

The therapeutically effective dosage of any specific compound will vary somewhat from compound to compound and patient to patient. As a general proposition, a dosage in the range of from about 0.1 to about 500 mg/kg will have therapeutic efficacy. Typically, a dosage in the range of from about 0.5 mg/kg to about 500 mg/kg will be employed. A daily dosage of a formula 1 compound will typically comprise about 10 to about 750 mg, usually about 20 to about 400 mg, which may be administered as a single dose or as two or more subdoses. Such doses or subdoses may be administered at one or more sites or by one or more than one route of administration. The duration for the treatment is usually once per day for a sufficient length of time for the patient to become asymptomatic, or for symptoms to abate noticeably. Depending upon the severity of the infection in the individual patient, this may last several days, weeks, or longer.

With regard to the frequency and duration of treatment, it is well known that it is within the skill of the ordinary physician to monitor a patient's condition and to make appropriate decisions with regard to discontinuing, interrupting and resuming treatments.

The dosages used in accordance with the invention are suitably determined depending on the individual cases taking symptoms, age and sex of the subject and the like into consideration. In addition, it is well known that it is within the skill of ordinary artisans to determine suitable dosages based on the above and other factors.

In accordance with the present method, a compound of the present invention may be administered orally, intramuscularly (IM), intravenously (IV), or subcutaneously (SC), with intravenous administration being especially preferred. Although other routes of administration can be used, it has been, found that intravenous administration provides surprising effectiveness. For oral administration, the use of a plasma concentration-enhancing compound may be of great importance. Alternatively, the compound or salt may also be administered intravenously or intramuscularly as a liposomal suspension. The administration may also be in a cyclodextrin formulation (given orally, SC, IV or IM). Compounds of the invention and their pharmaceutically or physiologically, acceptable salts, are thus administered by any route suitable to the condition to be treated, including oral, rectal, nasal, topical (including ocular, buccal or sublingual), vaginal, parenteral (including subcutaneous, intramuscular, intravenous, intraperitoneal, intradermal, intrathecal, intradural and epidural) and pulmonary by aerosol. Generally, the compounds of the invention are administered parenterally, orally or topically. If an embodiment is not sufficiently orally bioavailable it can be administered by the other routes noted above.

Embodiments include formulations that comprise a liposome or lipid complex that comprises a formula 1 compound. Such formulations are prepared according to known methods,

e.g., U.S. patents 4427649, 5043165, 5714163, 5744158, 5783211, 5795589, 5795987, 5798348, 5811118, 5820848, 5834016 and 5882678, all of which are incorporated herein by reference. The liposomes may optionally comprise an additional therapeutic or other agent(s), e.g., a compound of formula 2A or 2B. The liposomes can be delivered to a subject by any standard route, e.g., oral, aerosol or parenteral (e.g., SC, IV, IM).

Most often, the pharmaceutical compositions useful in the present invention will comprise a compound of Formula 1, or a pharmaceutically acceptable salt thereof, in any pharmaceutically acceptable carrier. If a solution is desired, water is the carrier of choice with respect to water-soluble compounds or salts. In other embodiments, an organic vehicle, such as glycerol, ethanol, propylene glycol, polyethylene glycol, DMSO, $DMSO_2$, vegetable, mineral oils. ethanol, benzyl benzoate, or mixtures thereof, may be suitable. In general, the solutions in any instance should be sterilized in a suitable manner, preferably by filtration through a 0.22 micron filter. The compositions useful in the practice of the present invention may be provided in the form of vials, ampoules, and the like.

In some embodiments, the formula 1 compound that is present in the compositions or that is used in the methods disclosed herein is completely dissolved in non-aqueous excipients. However, in some embodiments, e.g., transient compositions or some formulations, the formula 1 compound is partially dissolved while the remaining portion is present as a solid, which can be a suspension or a colloid. In related embodiments, the formula 1 compound is incompletely dissolved and is present as a suspension or gel.

In addition to compounds of formula 1, or their salts, the pharmaceutical compositions may contain other additives, such as pH adjusting additives, in particular, agents such as acids, bases, or buffers, including sodium lactate, sodium acetate, and sodium gluconate. Further, such compositions may contain microbial preservatives, such as methylparaben, propylparaben, benzyl alcohol and benzyl benzoate. If a multiple use vial is supplied, the pharmaceutical composition should likewise include such a microbial preservative. The formulations may be, of course, lyophilized, using techniques well known in the art.

It has been found that with respect to the practice of the method of the present invention, treating malaria with a compound of formula 1, or a pharmaceutically acceptable salt thereof, certain compounds appear to possess superior efficacy to others.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques, excipients and formulations generally are found in, e.g., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA 1985, 17th edition, Nema et al., *PDA J. Pharm. Sci. Tech.* 1997 51:166-171, both of which are

incorporated herein by reference. Methods to make invention formulations include the step of bringing into association a formula 1 compound with one or more excipients or carriers. In general, the formulations are prepared by uniformly and intimately bringing into association the formula 1 compound with liquid excipients or finely divided solid excipients or both, and then, if appropriate, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the formula 1 or formula 2A or 2B compound; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The formula 1 or formula 2A or 2B compound may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more excipients. Compressed tablets may be prepared by compressing in a suitable machine the formula 1 or formula 2A or 2B compound in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the formula 1 or formula 2A or 2B compound therein.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier, which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the emulsifying wax, and the wax together with the oil and fat make up the emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulgents and emulsion stabilizers suitable for use in formulations comprising a formula 1 or a formula 2A or 2B compound include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

Formulations suitable for buccal administration include lozenges comprising a formula 1 or formula 2A or 2B compound in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the formula 1 or formula 2A or 2B compound in an inert basis such as gelatin and glycerin, or sucrose and acacia.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration will have a particle size for example in the range of 0.01 to 200 microns (including particle sizes in a range between 0.01 and 500 microns in increments of 0.1 microns such as 0.1, 0.2, 0.3, 0.4, 0.5, 1, 2, 5, 30 microns, 35 microns, etc.), which is administered by inhalation through the nasal passage or by inhalation through the mouth so as to reach the various bronchi or alveolar sacs. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of *Trypanosome* infections. Inhalation therapy is readily administered by metered dose inhalers.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the formula 1 compound such carriers or excipients as are known in the art to be appropriate.

Formulations suitable for parenteral administration are sterile and include aqueous and non-aqueous injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials with elastomeric stoppers, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. Unit dosage formulations will typically contain a daily dose or unit daily sub-dose, as recited above, or an appropriate fraction thereof, of a formula 1 or formula 2A or 2B compound.

In some embodiments, the formula 1 compounds will be administered on an intermittent basis. In these embodiments, the formula 1 compound, e.g., a dose that comprises about 5-500 mg of a formula 1 compound (typically about 50-400 mg), is administered to a subject for at least one day, followed by no dosing for at least one day (at least 24 hours), optionally followed by at least one more daily dose of, e.g., about 50-500 mg. Intermittent dosing methods may comprise dosing (1, 2, 3 or 4 doses per week) based on a weekly schedule, e.g., dosing on Monday, Wednesday and Friday, or on Tuesday, Thursday Saturday for about 1, 2, 3, 4, 6, 8 or more weeks, followed by periods of about 2, 3, 4, 5, 30, 45, 60, 90 or more days with no dosing, optionally followed by dosing again on Monday, Wednesday and Friday for about 1, 2, 3, 4, 6, 8 or more weeks. Weekly dosing methods may comprise administration of the formula 1 compound to a subject 1, 2, 3, 4 or 5

times per week for 1, 2, 3, 4, or more weeks.. In related embodiments, dosing may be administered to a subject daily for 2, 3, 4, 5, 6, 7 or more days, followed by a period of about 1, 2, 3, 4, 5, 7, 14, 30, 45 60, 90 or more days, optionally followed by another course of daily dosing. These embodiments may further comprise treatment with a formula 2A or 2B compound or another treatment as described herein.

To the extent not already indicated, it will be understood by those of ordinary skill in the art that any one of the various specific embodiments herein described and illustrated may be further modified to incorporate features shown in any of the other embodiments disclosed herein.

Therapeutic applications. For therapeutic applications, the compositions disclosed herein will typically comprise one or more compounds of formula 1, and, the methods disclosed herein will utilize such compositions, which will contain one, two or more of such compounds, usually one. While it is possible for the compounds of the invention to be administered as pure compounds it is preferable to present them as pharmaceutical formulations. The formulations of the present invention comprise at least one formula 1 compound together with one or more acceptable carriers or excipients and optionally other therapeutic agents, e.g., a formula 2A or 2B compound(s), chloroquine, a chlroquine analog, a macrophage stimulating factor(s) and/or an oxidation agent(s). The one or more carriers or excipients must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the patient.

In other embodiments, a dosing regimen for a formula 1 compound will comprise the use of a relatively high induction dose, e.g., about 150-750 mg per day or about 150-750 mg per day using an intermittent dosing schedule (such as described herein), followed by lower maintenance dosing, e.g., about 50-250 mg per day or about 50-250 mg per day on an intermittent dosing schedule. These embodiments may further comprise treatment with a formula 2A or 2B compound or another treatment as described herein.

Parenteral formulations may comprise a cyclodextrin, e.g., an α-cyclodextrin, a β-cyclodextrin (e.g., β-hydroxypropylcyclodextrin) or a γ-cyclodextrin, which are typically employed in aqueous formulations, which optionally comprise one or more of a buffer, a salt (NaCl, etc.) to, e.g., render the solution isotonic, a bacteriostat or other excipients as known in the art and a formula 1 compound at a concentration of, e.g., about 5-25 mg/mL, typically about 10-20 mg/mL. Parenteral formulations that comprise a formula 1 compound and one or more excipients may be diluted into, e.g., sterile saline and infeused into a subject. Parenteral formulations are typically administered by, e.g., intravenous, topical or oral delivery to a subject such as a human. For non-aqueous formulations, one or more solvents such as propylene glycol, a PEG, e.g., PEG 300 or PEG 400, ethanol, and benzyl benzoate may be employed. Typical aqueous and non-aqueous formulations will contain about 5 to about 400 mg/mL of a formula 1 compound, usually about 10

to about 200 mg/mL. Such parenteral formulations may be delivered orally, or by intramuscular, intravenous or subcutaneous injection.

In preparing compositions that comprise a formula 1 compound (and optionally one or more excipients), one may optionally mill or otherwise granulate the compound to obtain a desired particle size, before or after the formula 1 compound is contacted with one or more excipients. For example, one may mill a formula 1 compound such as 16α-bromoepiandrosterone, to obtain an average particle size (or diameter) of about 0.5-25 μM or about 1-10 μM (e.g., about 2, 5 or 10 μM average particle size or diameter) before contacting the milled formula 1 compound with a liquid or solid excipient. Milled formula 1 compound is useful to facilitate dissolution or suspension of the formula 1 compound in one or more liquid excipients (e.g., a PEG such as PEG 300, propylene glycol or benzyl benzoate) or to facilitate uniformly distributing drug substance when the milled compound is contacted with one or more solid excipients (e.g., a filler, a binder or a lubricant).

The compositions and formulations disclosed herein are useful in the treatment of, or ameliorate one or more symptoms associated with, the conditions or infections disclosed herein. These compositions and formulations may also be used to treat, or ameliorate one or more symptoms associated with, a retroviral infection such as a HIV1 or HIV2 infection in humans. As used herein, phrases such as "amelioration of one or more symptoms associated with" means that such compounds or formulations may be used to reduce replication of an infectious agent or to reduce the number of infectious agents that are present in a subject or to ameliorate one or more symptoms associated with, or caused by, the condition or infection (e.g., reduced fever, a shortened duration of, or reduced level of, pain, or a noticeable reduction of or elimination of diarrhea or fatigue).

In addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring or coloring agents.

The present invention further provides veterinary compositions comprising at least one formula 1 or formula 2A or 2B compound together with a veterinary carrier therefor. Also, the formula 1 compound may be present in the animal's feed or water. Excipients for veterinary applications may include compounds, e.g., small amounts of chloroform, that may not be generally suitable for human use.

Veterinary carriers are materials useful for the purpose of administering the composition to cats, dogs, horses, mice, rats, hamsters, rabbits and other animals and may be solid, liquid or gaseous materials that are otherwise inert or acceptable in the veterinary art and are compatible

with the formula 1 or formula 2A or 2B compound. These veterinary compositions may be administered orally, parenterally or by any other desired route, e.g., as described herein.

Embodiments of formula 1 compounds include or exclude any subset of compounds within the definition of formula 1, provided that at least one compound remains. For example, a subset of formula 1 compounds that are generally preferred and are usually included, for example are aqueous or nonaqueous formulations comprising 16α-bromoepiandrosterone. A subset compounds or applications for compounds that are optionally excluded from formula 1 compounds or their uses in any embodiment or claim herein comprises, e.g., the use of one or more compounds (or their use) that are disclosed in one or more prior art references or publications, to the extent that the disclosed compounds or uses renders any claim or embodiment unpatentable for novelty, obviousness and/or inventive step reasons.

In other embodiments, a formula 1 compound may be linked to an oligonucleotide or an oligonucleotide analog to facilitate delivery of the oligonucleotide or analog into cells. Typically the formula 1 compound will be linked to the steroid nucleus through a terminal hydroxyl group at a 5', 3' or 2' position of the oligonucleotide. Oligonucleotides and analogs of oligonucleotides are known and have been described, e.g., U.S. patents 4725677, 4973679, 4997927, 4415732, 4458066, 5047524, 4959463, 5212295, 5386023, 5489677, 5594121, 5614622, 5624621; and PCT publication Nos. WO 92/07864, WO 96/29337, WO 97/14706, WO 97/14709, WO 97/31009, WO 98/04585 and WO 98/04575 all of which are incorporated herein by reference.

Synthesis methods. In general, the compounds employed in the present invention in general may be synthesized in manners known and readily understood by those skilled in the art. Therefore, there is no need to explain in great detail the methodology used for the synthesis of most such compounds.

Formula 1 compounds that comprise a thioacetal moiety, sulfate ester, sulfite ester, carbamate or thioester moiety at R_2 (the 3-position) are prepared essentially according to methods known in the art. Suitably protected intermediates will be used as is apparent. See, for example, U.S. patent 5198432; European patent publications EP 576915 and EP 576914; C. Christiana et al., *J. Chem. Soc. Chem. Commun.* 1991 vol 22, C. Christiana et al., *J. Chem. Soc. Chem. Commun.* 1991 19:1403-1405, H.N. Abramson et al., *J. Pharm. Sci.* 1977 66:602-603, E.J. Corey et al., *J. Am. Chem. Soc.* 1996 118:8765-8766, A.G.M. Barrett et al., *J. Org. Chem.* 1989 54:227, D.H.R. Barton et al., *J. Chem. Soc. Perkin Trans. 1* 1976 19:2112-2116, D.H.R. Barton et al., *J. Chem. Soc. Perkin Trans. 1* 1975 16:1574-1585 and W.T. Smith et al., *Trans. Kentucky Acad. Sci.* 1984 45:76-77, all of which are incorporated herein by reference.

Enumerated embodiments. Aspects of the invention include the following enumerated embodiments, which further illustrate the invention and preferred aspects thereof or related subject matter.

1. A method of treating malaria or Trypanosomiasis in a patient in need of such treatment, comprising administering to said patient an effective amount of at least one compound selected from the group consisting of the compounds of the present invention.

2. A method as recited in embodiment 1, further comprising administering to said patient at least one plasma concentration-enhancing compound.

3. A method as recited in embodiment 2, wherein said at least one compound of the present invention and said at least one plasma concentration enhancing compound are administered simultaneously.

4. A method as recited in embodiment 2, wherein said at least one compound of the present invention and said at least one plasma concentration-enhancing compound are administered sequentially.

5. A method as recited in embodiment 2, wherein said plasma concentration-enhancing compound is naringin and/or naringenin.

6. A method as recited in any one of embodiments 1 - 5, further comprising administering to said patient at least one macrophage stimulating factor.

7. A method as recited in any one of embodiments 1 - 6, further comprising administering to said patient one or more oxidation agent and/or oxygen ventilation.

8. A method as recited in any one of embodiments 1 - 7, wherein said patient is a mammal.

9. A method as recited in embodiment 8, wherein said patient is a human.

10. A method as recited in any one of embodiments 1 - 9, wherein said administering is by injection.

11. A method as recited in any one of embodiments 1 - 9, wherein said administering is by infusion.

12. A method as recited in any one of embodiments 1 - 9, wherein said administering is by intravenous injection.

13. A method as recited in embodiment 1, wherein said at least one compound is selected from the group consisting of compounds of formula 1, wherein R_{17} is not hydroxy.

14. A method as recited in embodiment 1, wherein said at least one compound is selected from the group consisting of compounds of Formula 1, wherein Q_2 is not CH_2.

15. A method as recited in embodiment 1, wherein said double bond is not present.

16. A method as recited in embodiment 1, wherein said at least one compound is selected from the group consisting of compounds of Formula 1, wherein Q_2 is a halogen.

17. A method as recited in embodiment 1, wherein said at least one compound is not DHEA.

18. A method of treating sleeping sickness in a patient in need of such treatment, comprising administering to said patient an effective amount of a compound of the present invention.

19. A method as recited in embodiment 18, further comprising administering to said patient at least one plasma concentration-enhancing compound.

20. A method as recited in embodiment 19, wherein said at least one compound of the present invention and said at least one plasma concentration-enhancing compound are administered simultaneously.

21. A method as recited in embodiment 19, wherein said at least one compound of the 70 present invention and said at least one plasma concentration-enhancing compound are administered sequentially.

22. A method as recited in embodiment 19, wherein said plasma concentration-enhancing compound is naringin and/or naringenin.

23. A method as recited in any one of embodiments 18 - 22, further comprising administering to said patient at least one macrophage stimulating factor.

24. A method as recited in any one of embodiments 18 - 23, further comprising administering to said patient one or more oxidation agent and/or oxygen ventilation.

25. A method as recited in any one of embodiments 18 - 24, wherein said patient is a mammal.

26. A method as recited in embodiment 25, wherein said patient is a human.

27. A method as recited in any one of embodiments 18 - 26, wherein said administering is by injection.

28. A method as recited in any one of embodiments 18 - 26, wherein said administering is by infusion.

29. A method as recited in any one of embodiments 18 - 26, wherein said administering is by intravenous injection.

30. A method of treating Chagas disease in a patient in need of such treatment, comprising administering to said patient an effective amount of a compound of the present invention.

31. A method as recited in embodiment 30, further comprising administering to said patient at least one plasma concentration-enhancing compound.

32. A method as recited in embodiment 31, wherein said at least one compound of the 71 present invention and said at least one plasma concentration-enhancing compound are administered simultaneously.

33. A method as recited in embodiment 31, wherein said at least one compound of the present invention and said at least one plasma concentration-enhancing compound are administered sequentially.

34. A method as recited in embodiment 31, wherein said plasma concentration-enhancing compound is naringin and/or naringenin.

35. A method as recited in any one of embodiments 30 - 34, further comprising administering to said patient at least one macrophage stimulating factor.

36. A method as recited in any one of embodiments 30 - 35, further comprising administering to said patient one or more oxidation agent and/or oxygen ventilation.

37. A method as recited in any one of embodiments 30 - 36, wherein said patient is a mammal.

38. A method as recited in embodiment 37, wherein said patient is a human.

39. A method as recited in any one of embodiments 30 - 38, wherein said administering is by injection.

40. A method as recited in any one of embodiments 30 - 38, wherein said administering is by infusion.

41. A method as recited in any one of embodiments 30 - 38, wherein said administering is by intravenous injection.

42. A method of treating one or more kind of parasites and/or one or more diseases caused by such parasites, against one or more kind of Mycoplasma and/or one or more diseases caused by such Mycoplasmas and/or against one or more of the following indications or infections: (a) hairy Leukoplakia, (b) oral candidosis, (c) mouth ulcerations (aphthous/herpetic/bacterial), (d) fungal candida, (e) human papilloma virus, (f) molluscum contagiosum, (g) squamous oral carcinoma, (h) Kaposi's sarcoma oral lesions, (i) periodontitis, (j) necrotizing gingivitis, (k) orafacial herpes zoster, and (l) rotaviruses in a patient in need of such treatment, comprising administering to said patient an effective amount of a compound of the present invention.

43. A method as recited in embodiment 42, further comprising administering to said patient at least one plasma concentration-enhancing compound.

44. A method as recited in embodiment 43, wherein said at least one compound of the present invention and said at least one plasma concentration-enhancing compound are administered simultaneously.

45. A method as recited in embodiment 43, wherein said at least one compound of the present invention and said at least one plasma concentration-enhancing compound are administered sequentially.

46, A method as recited in embodiment 43, wherein said plasma concentration-enhancing compound is naringin and/or naringenin.

47. A method as recited in any one of embodiments 42 - 46, further comprising administering to said patient at least one macrophage stimulating factor.

48. A method as recited in any one of embodiments 42 - 47, further comprising administering to said patient one or more oxidation agent and/or oxygen ventilation.

49. A method as recited in any one of embodiments 42 - 48, wherein said patient is a mammal.

50. A method as recited in embodiment 49, wherein said patient is a human.

51. A method as recited in any one of embodiments 42 - 50, wherein said administering is by injection.

52. A method as recited in any one of embodiments 42 - 50, wherein said administering is by infusion.

53. A method as recited in any one of embodiments 42 - 50, wherein said administering is by intravenous injection.

54. A composition comprising at least one of the compounds of the present invention, and at least one plasma concentration-enhancing compound.

55. A composition as recited in embodiment 54, further comprising at least one macrophage stimulating factor.

56. A composition as recited in embodiment 54 or 55, further comprising an oxidation agent.

57. A composition comprising at least one of the compounds of the present invention, and at least one macrophage stimulating factor.

58. A composition as recited in embodiment 57, further comprising at least one oxidation agent.

59. A composition comprising at least one of the compounds of the present invention, and at least one an oxidation agent.

60. A kit comprising unit dosages of at least one of the compounds of the present invention, and unit dosages of at least one plasma concentration-enhancing compound.

61. A kit as recited in embodiment 60, further comprising unit dosages of at least one macrophage stimulating factor.

62. A kit as recited in embodiment 60 or 61, further comprising unit dosages of an oxidation agent.

63. A kit comprising unit dosages of at least one of the compounds of the present invention, and unit dosages of at least one macrophage stimulating factor.

64. A kit as recited in embodiment 63, further comprising unit dosages of at least one oxidation agent.

65. A kit comprising unit dosages of at least one of the compounds of the present invention, and unit dosages of at least one oxidation agent.

66. The method, composition or kit of any of embodiments 1-65 wherein the compound of the invention is a formula 1 compound or a metabolite thereof.

67. The method of embodiment 66 wherein the formula 1 compound is a compound named in compound groups 1-21, or in any formula 1 (e.g., any formula 4) compound or genus disclosed or named herein, or a metabolite of any of these.

68. A composition comprising 16α-bromoepiandrosterone, and 2, 3, 4 or 5 excipients selected from polyethylene glycol, dehydrated ethanol, benzyl benzoate, benzyl alcohol and propylene glycol, wherein the composition comprises less than about 3% v/v, or less than about 1% v/v, or less than about 0.5% v/v of water, or less than about 0.1% v/v of water.

69. The composition of embodiment 68 wherein the composition comprises (i) 16α-bromoepiandrosterone at a concentration of about 45-55 mg/mL, (ii) 20-30% v/v polyethylene glycol 300, polyethylene glycol 400 or a mixture of polyethylene glycol 300 and 400, (iii) 10-15% v/v dehydrated ethyl alcohol, 2.5-7.5% v/v benzyl benzoate, and (iv) 55-60% v/v propylene glycol.

70. The composition of embodiment 69 wherein the composition comprises 16α-bromoepiandrosterone at a concentration of about 50 mg/mL, about 25% v/v polyethylene glycol 300, about 12.5% v/v dehydrated ethyl alcohol, about 5% v/v benzyl benzoate, about 57.5% v/v propylene glycol and less than about 0.5% v/v water.

71. The composition of embodiment 68 wherein the composition comprises 16α-bromoepiandrosterone at a concentration of about 50-105 mg/mL, about 27-33% w/w benzyl benzoate, about 27-33% w/w polyethylene glycol 300, about 25-30% w/w propylene glycol and about 1-3% w/w benzyl alcohol.

72. The composition of embodiment 71 wherein the composition comprises 16α-bromoepiandrosterone at a concentration of about 100 mg/mL (about 10% w/w), about 30.4% w/w benzyl benzoate, about 30.7% w/w polyethylene glycol 300, about 28% w/w propylene glycol and benzyl alcohol about 1.9% w/w.

73. The use of a formula 1 compound for making a medicament for the treatment of an infection caused by one or more *Trypanosoma* or *Plasmodium* parasites or a *Mycoplasma* bacterium in a subject, including one or more of *Trypanosoma cruzi, Trypanosoma brucei, Trypanosoma gambiense, Trypanosoma rhodesiense, Trypanosoma brucei rhodesiense, Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale* or *Plasmodium berghei, Mycoplasma fermentans, Mycoplasma genitalium* or *Mycoplasma pneumoniae*.

74. The use of embodiment 73 wherein the formula 1 compound is a compound named in compound groups 1-21, or a metabolite thereof.

75. A method comprising administering an effective amount of a composition of any of embodiments 68-71 to a subject having, or susceptible to, a *Trypanosoma*, a *Plasmodium* or a *Mycoplasma* infection wherein the composition optionally comprises 16α-bromoepiandrosterone and a pharmaceutically acceptable excipient.

76. A method to ameliorate or reduce one or more symptoms associated with a *Trypanosoma*, a *Plasmodium* or a *Mycoplasma* infection in a subject, or to reduce replication of a *Trypanosoma*, a *Plasmodium* or a *Mycoplasma* in a subject infected with a *Trypanosoma*, a *Plasmodium* or a *Mycoplasma*, comprising administering to the subject an effective amount of a compound of formula 1.

77. The method of embodiment 76 wherein the formula 1 compound is a compound or within a genus of compounds as disclosed herein, e.g., a compound or genus named in compound groups 1-21 or in the claims as originally filed, or the formula 1 compound is present in a composition comprising one or more pharmaceutical excipients, e.g., any of the formulations disclosed or described herein.

78. A composition comprising a formula 1 compound wherein the formula 1 compound is a compound or within a genus of compounds as disclosed herein, e.g., a compound or genus named in compound groups 1-21 or in the claims as originally filed, and at least one excipient and a local anesthetic, wherein the local anaesthetic is optionally selected from procaine, benzocaine and lidocaine.

79. A product produced by the process of contacting a compound of formula 1, e.g., any compound named in compound groups 1-21, and a first excipient with a second excipient wherein the product optionally further comprises a local anesthetic, wherein the local anaesthetic is optionally selected from procaine, benzocaine and lidocaine.

80. A product produced by the process of contacting a compound of formula 1, e.g., any compound named in compound groups 1-21, and a first nonaqueous liquid excipient with a second nonaqueous liquid excipient wherein the product comprises less than about 3% w/w water, or less than about 0.5% w/w water, or less than about 0.1% w/w water, and wherein the first or the second nonaqueous liquid excipient optionally excludes one or more of dimethylsulfoxide, chloroform, dioxane, a vegetable oil and olive oil, and wherein the product optionally further comprises a local anesthetic, wherein the local anaesthetic is optionally selected from procaine, benzocaine and lidocaine.

81. A method comprising administering an effective amount of the composition of embodiment 78 or the product of embodiments 79 or 80 to a subject having an infection or condition described herein, e.g., Malaria, African Trypanosomiasis or Chagas disease, whereby the infection or condition, or a symptom thereof, is eliminated, reduced, treated, improved or ameliorated.

82. The method of embodiment 81 wherein the formula 1 compound is 16α-haloepiandrosterone or 16α-halodehydroepiandrosterone.

EXAMPLES

The following examples further illustrate the invention and are not to be construed as limiting the invention.

Example 1. 16α-Bromoepiandrosterone formulation 1. Two lots of a non-aqueous formulation was made at a 16α-bromoepiandrosterone ("BrEA") concentration of 50 mg/mL in 25% polyethylene glycol 300, 12.5% dehydrated ethyl alcohol, 5% benzyl benzoate, and 57.5% propylene glycol, hereafter "formulation 1", as follows. BrEA was obtained from Procyte, Inc. The remaining excipients are shown below.

Excipient	**Specifica-tion**	**Supplier Lot No.**	**Final Product Concentration**
Propylene glycol	USP	Arco Chemical HOC-61220-01104	57.5% (v:v)
Polyethylene glycol 300	NF	Union Carbide 695752	25% (v:v)
Dehydrated alcohol (ethanol)	USP	McCormick Distilling 97K10	12.5% (v:v)
Benzyl benzoate	USP	Spectrum Pharmaceuticals MG025	5% (v:v)

The formulation was prepared by suspending BrEA in polyethylene glycol 300, and sequentially adding propylene glycol, benzyl benzoate, and dehydrated ethyl alcohol to form a solution, which was diluted to the final desired volume with additional propylene glycol. The procedure is described below.

The calculated amount of polyethylene glycol 300 was added to a compounding vessel. Then, while mixing, the calculated amount of BrEA was added to the vessel, and mixed for at least 5 minutes to form a smooth, creamy liquid. Propylene glycol was added to the vessel, and mixed for a minimum of 5 minutes to form a uniform suspension. The calculated amount of benzyl benzoate is added to the vessel, and mixed for approximately 5 minutes to form a translucent liquid suspension. Dehydrated alcohol was added to the vessel, and mixed for approximately 5 minutes to form a clear, colorless solution. Propylene glycol was then added to achieve the desired final formulation, and mixed for approximately 5 minutes. The drug solution was transferred to a volume-dispensing device set to deliver 1.2 mL per vial. Under nitrogen pressure, the solution was filtered through two 0.2 μm polyvinylidene fluoride filters in series before dispensing. The vials were capped with Teflon-coated, butyl-rubber stoppers and crimp sealed.

Materials used in the product vials are listed below.

Material	Source	Product Code	Description
Vial	Wheaton	2702-B51BA	Tubing vial, 2 mL/13 mm, glass, type 1 amber
Stopper	Omniflex	V9239 FM257/2	13 mm, Teflon coated, butyl rubber stopper
Seal	West	4107	Flip seal, 13 mm, mist gray bridge

Example 2. BrEA formulation 2. A formulation containing 100 mg/mL of BrEA, 10% w/w, in benzyl benzoate (USP) 30.4% w/w, polyethylene glycol 300 (NF) 30.7% w/w, propylene glycol (USP), qs, about 28% w/w and benzyl alcohol (NF) 1.9% w/w, hereafter "formulation 2", was prepared as follows. A desired amount of BrEA (1.0 kg) was suspended in PEG 300 (about 3.0 L) in a compounding vessel and mixed for at least 5 minutes at room temperature to form a smooth creamy liquid. The needed amount of propylene glycol (about 1.5 L) was then added and mixing was continued for at least 5 minutes to form a uniform suspension. Benzyl benzoate (about 3.0 L) was then added and the vessel contents were mixed for about 5minutes to form a translucent suspension. Benzyl alcohol (about 200 mL) was then added and the mixing was continued for about 5 minutes to form a clear, colorless solution. Propylene glycol was then added to achieve the desired final formulation volume (about 1.5 L) and mixing was continued for about 5 minutes. The drug solution was transferred to a volume-dispensing device, which was set to deliver 1.2 mL per vial (2 mL, glass, type 1 amber vials). The formulation was filtered under nitrogen pressure (about 3 atm) through two 0.2 μm polyvinylidine fluoride filters in series. The vials were capped using Teflon-coated, butyl rubber stoppers and then crimp sealed essentially as described in example 1. The vials were stored in the dark at reduced temperature (about 2-8°C).

Example 3. ***In vitro* testing.** For *in vitro* antimalarial testing, micro-titer plates were used. The concentration of drugs were prepared as pMol/well according to WHO standard procedures (WHO, 1990). The test compound was dissolved in 15% DMSO in sterile RPM11640. Both chloroquine sensitive (WS/97) and resistant (MN/97) isolates were used throughout the experiments.

A. Schizont inhibition assay: The micro-titer plates were predosed with various concentrations of the test compound. 50 μL of parasitised erythrocyte suspension in RPMI-1640 (0.2 mL erythrocyte + 0.3 mL serum + 4-5 ml RPMI-1640) were dispensed in microtiter wells that contained various concentrations of drug. Triplicate readings were made for each concentration.

B. ^{3}H-Hypoxanthine incorporation assay: The testing was carried out according to the procedure of Desjardins et al.. 1979. After 30 hr culture at 37 degrees C, the same microtiter plates from schizont inhibition assays with another triplicate wells were pulsed with ^{3}H-hypoxanthine for

overnight. The cell suspensions were washed twice on millipore glass fiber filter with Millipore filter apparatus. The filter discs were counted for DPM by a Beckman LS6000 β-scintillation counter. The activity of the drug was measured by plotting DPM against concentration of drug.

Activity of compounds against Chloroquine sensitive T996/86 *P. falciparum in vitro*.

Concentration (μM)	DHEA (% Inhibition)	Bromine-Epiandrosterone (% Inhibition)	Etienic Acid Methyl Ester (% Inhibition)	Etianic Acid Methyl Ester (% Inhibition)
30	65.6	98	60	61.5
15	44	60.1	45.7	47.4
7.5	38.3	50	40.9	45.3
3.25	37.2	43.7	46	41.4
1.875	23.2	40.9	41	43.4
0.938	37.2	31.8	43.3	47.1
IC_{50}	19.0 μM	7. 5 μM	19.5 μM	17.5 μM

Concentration (nM) Chloroquine	% Inhibition Chloroquine
200	95.9
100	94.6
50	97.3
25	94.5
12.5	86.8
6.25	27.2
IC_{50}	9.0 nM

The activity of 16-chloro-epiandrosterone and DHEA-Br against chloroquine sensitive T996.86 and chloroquine resistant KI *P. falciparum in vitro* is shown below.

		T996.86	KI
16-chloroepiandrosterone	IC_{50}	~9.25 $pgmL^{-1}$	~9.25 μgmL^{-1}
DHEA-Br	IC_{50}	~25.0 $pgmL^{-1}$	~25.0 μgmL^{-1}

Example 4. Four-day *in vivo* test protocol for P. berghei. The 4-day suppressive test has been widely used since it can be performed with a 1 -week period. The test consists of the inoculation of parasitised erythrocytes on Monday, the first day of the experiment (D_0), followed by an injection of the test compound, which is repeatedly administered on D+1, D+2, D+3. On D+4 (Friday), blood films are taken and antimalarial activity is assessed either by calculating

parasitaemias, or by scoring parasite numbers on a predetermined scale (i.e., 1-5). Peters (1970) described a basic procedure using this 4-day test.

PROTOCOL

1. 5 female TO mice per test group.

2. Parasites (*P. berghei* HP15 ANKA) were collected by cardiac puncture in a heparinised syringe from a donor mouse harboring a 30+% parasitaemia.

3. Blood was diluted with diluting agent (50% HIFCS+50% sterile PBS) to a final concentration of 1% parasitaemia or $1X10^7$ infected erythrocytes per 0.2 mL infecting suspension.

4. Each mouse was inoculated intravenously, producing a more uniform infection rate than an intraperitoneal administration of parasites.

5. Test compounds were prepared at doses of 100 mg/kg in (16.7% DMSO + 83.3% Celacol).

6. Test compounds were administered intraperitoneally 2 hours after parasite inoculation.

7. The compounds were administered once a day starting on D_0, and continued on D+1, D+2 and D+3.

8. Blood films were made from tail blood on D+4, fixed with 100% methanol and stained with 10% Giemsa.

9. Parasitaemias were scored on a scale of 0-5, where a 5 would be equal to the control.

EXPERIMENTAL PROTOCOL:

5 female mice/group (strain TO) were used and an inoculum consisting of 1 % parasitaemia or $1x10^7$ parasites/mL, 0.2 mL/mouse was delivered by intravenous injection. Drug administration commenced 2 hours after inoculation on Day 1 and continued for 3 days. Blood films from all 20 mice were made on Day 5 and parasitaemias were assessed. The results are shown below.

Compound	Treatment	Parasitaemia Score (0 - 5)
Bromine-Epiandrosterone	100mg/kg x 4 days i.p.*	1
Etienic Acid	100mg/kg x 4 days i.p.	2
DHEA	100mg/kg x 4 days i.p.	1
Chloroquine	3 mg/kg x 4 days i.p.	1
control	N/A	5

* i.p. = intraperitoneal injection

Example 5. Interim in vivo malaria study.

Basic Protocol:

1. Infect mouse to 1% parasitemia using a solution containing 1 x 10^7 erythrocytes/mL by I.V. injection.
2. Two hours later give drug preferably by I.V. injection.
3. Drug Bromine-Epiandrosterone (Epi-Br) given (0.2 mL I.V. or S.C.) once a day for 4 days.
4. Tail snips to obtain blood after study.

Experimental results:

Day 0

T = 0 Mice were infected with *P. berghei*. Parasites were harvested from cardiac mouse blood, and mice were infected using 0.2 ml of blood with 14% parasitaemia per mouse I.V.

T = 2 hours First dose given: 100 mg/kg I.V. or S.C.

T=4days Daily doses of 100 mg/kg I.V. or S.C.

T = 7 days 2/5 dead in the untreated control group

3/5 dead in the S.C. group.

T = 8 days 1/3 dead in the untreated control group.

No deaths occurred in the group receiving I.V. drug at day 30, but all control animals were dead by day 10. All animals treated by S.C. delivery were dead by Day 11.

Example 6. Mouse *in vitro* and *in vivo* study. In the *in vitro* protocol the parasite (*Plasmodium falciparum*, chloroquine sensitive strain WT and chloroquine resistanr strain Dd2) level is adjusted to 1% and the hemocrit is adjusted 7% with medium. Using a 96 well plate, 50 µL of parasite and 100 µL of drug mixed with media are added to each well and the procedure is done in triplicate. The plate is placed in a chamber containing a physiological gas mixture and incubated at 37°C. The media/drug mixture is changed at 24, 48 and 72 hours. On day 5 (96 hours) slides of each well are made, stained with Gemsia and 500 red blood cells are counted for each slide. The triplicates are averaged and data are reported in percent inhibition.

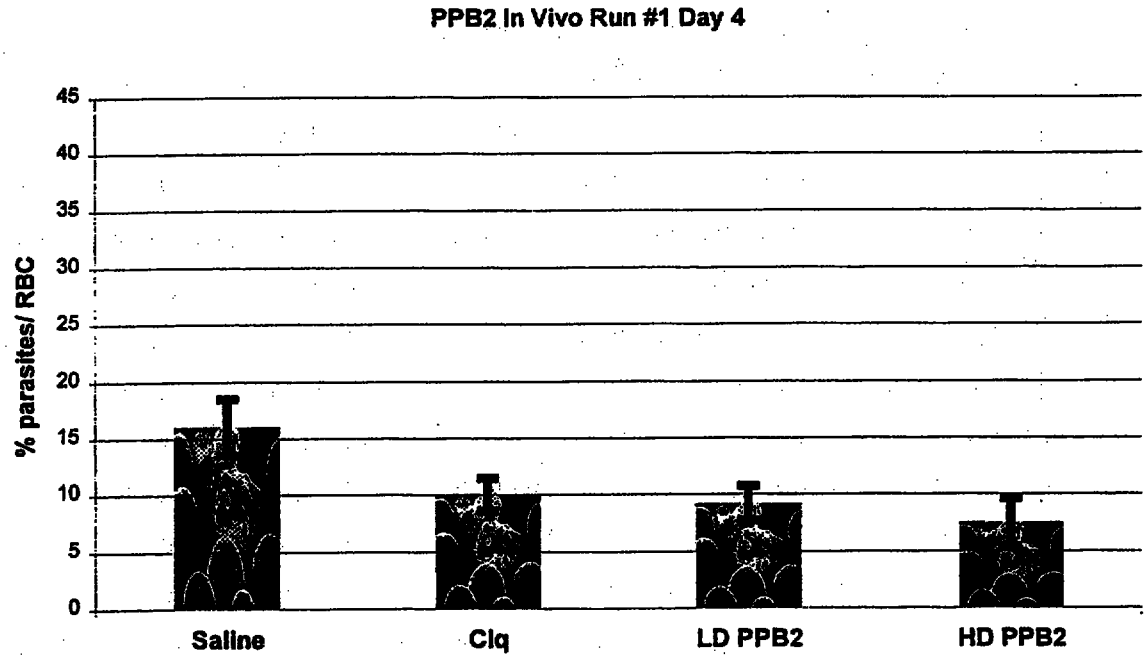
In the *in vivo* protocol, Lewis rats weighing 80-85 grams were given a standardized IP injection of parasite (*Plasmodium berghei*). Rats were then intravenously injected 2 hours later with one of the treatments described in the table below, returned to their housing, fed standard lab chow and allowed free access to water. Animals were weighed and treated again 24, 48, and 72 hours after the first treatment and again returned to their housing and they were allowed free access to food and water. The animals were weighed again and then bled using a 26-gauge needle on day 5, 11 and 28 post inoculation. Hemocrits were measured and blood smears are prepared for each

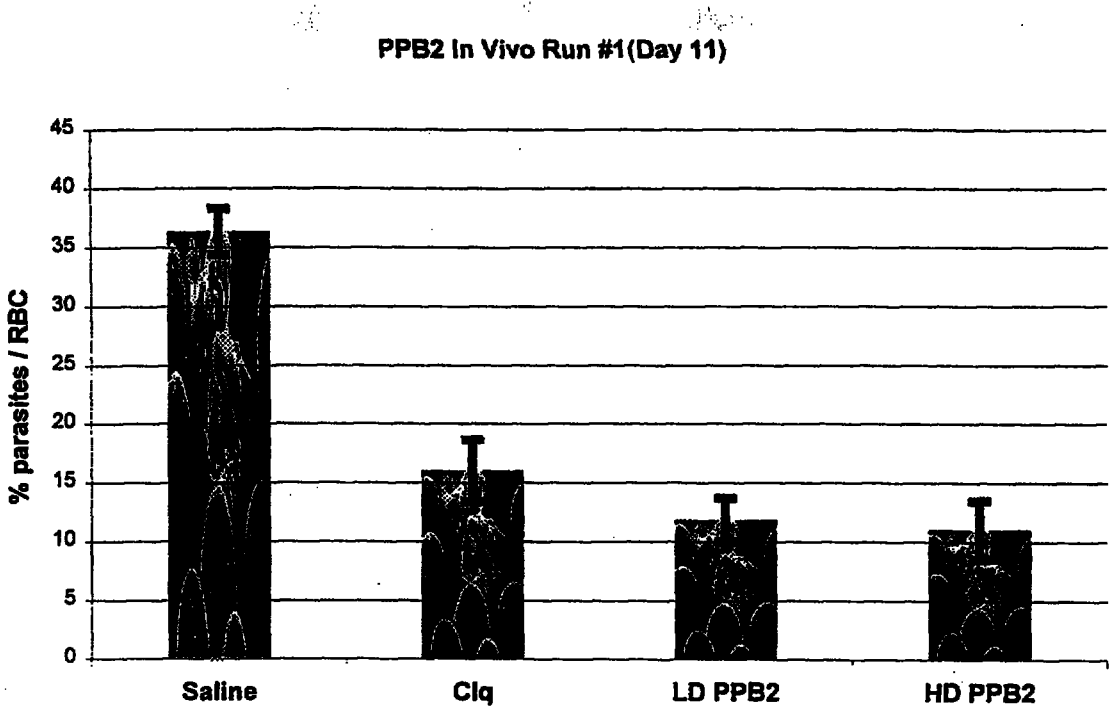
rat. The blood smears were then stained using Gemsia and the level of parasitemia (defined as the percent of red cells with parasites) were determined. Animals were again returned to their housing and observed twice daily for evidence of progressive disease, defined as listlessness and or adverse drug reaction, which is defined as a loss of 20% of original body weight, for a total of 28 days. If either progressive disease or drug reaction is noted, the animals are euthanized.

The PPB2 formulation comprised a sterile solution containing 15 mg/mL of 16α-bromoepiandrosterone in 45% β-cyclodextrin and 0.9% saline.

Group 1	Group 2	Group 3	Group 4
Control 0.9% saline	Chloroquine Control 40mg/kg	PPB2 Low Dose (LD) 30 mg/kg	PPB2 High Dose (HD) 60 mg/kg

The intravenous injections were given on days 0, 1, 2 and 3 and the results are shown below. The results showed that treatment *in vivo* with a formulation comprising 16α-bromoepiandrosterone reduced parasitemia to a level comparable to that seen with the chloroquine ("Clq") control.





Example 7. Human clinical study. Response to drug treatment was graded as per World Health Organization criteria (WHO 1973). Evaluation of therapeutic response was determined using the parasitic and fever clearance times. Parasite clearance was expressed as three indices; the time for the parasite count to fall by 50% of the pre-treatment (baseline) value (PC_{50}); to fall by 90 % of the baseline value (PC_{90}) and to fall below the level of microscopic detection (parasite clearance time PCT) (White and Krishna 1989; White et al. 1992). The fever clearance time was defined as the time from drug administration till the oral or rectal temperature fell to or below 37.2° C and remained so for at least 48 h.

Venous blood (5mL) was obtained from two patients before treatment and at 4, 6, 8, 12, 18, 20, 24, 30 and 36 h after treatment or at 4 or 6-hourly intervals after treatment until there was complete clearance of peripheral parasitemia. Blood was collected aseptically and transferred to 10 mL syringes containing 2 mL of acid citrate dextrose (ACD) for *in vitro* culture. Prior to incubation, the plasma was separated from the red blood cells and the red blood cells were washed twice. Parasites were cultured by modification of standard in vitro culture techniques (Trager and Jensen 1976; Oduola et at. 1992). Samples were dispensed into sterile centrifuge cubes within 10 min of collection and spun down. The supernatant plasma was stored while the packed cells were washed twice with culture medium (washing medium, RPMI 1640 medium, containing 25 mM HEPES buffer and 25 mmol/L NaOH). The buffy coat was removed by vacuum aspiration. A 1:10 fold dilution was done for each blood sample with complete washing medium [CMP (washing medium supplemented with 10 % human plasma)]. One milliliter each of the sample was

transferred into 2 wells of a 24 well micro culture plate. Cultures were incubated at 37 degrees C in an atmosphere of 5% CO_2, 5% 0_2 and 90% N_2 premixed gas. The culture medium was changed daily and thin blood smears were prepared for microscopy at 24 and 48 h after the culture has been set up. The culture samples were diluted with unparasitized washed type A Rh-positive red blood cells if the proportion of parasitized red blood cells was more than 2%.

Microscopy. During the *in vivo* study, thin and thick blood films were fixed with dehydrated methanol (100%) and heat, respectively, were stained with 10% Giemsa for 20 min. Parasitemia was quantified in thin films by counting 2000 red blood cells in clear contiguous fields and finding the proportion that was parasitized. In thick films, parasitemia was quantified by counting parasites against leukocytes. A film was declared negative if no parasites were found after examination of 200 microscope fields of a thick smear. During in vitro and *ex vivo* study, pretreatment thin and thick smears were, graded for ring stages by the method of Jiang as modified by Li et al. (Jiang et al, 1982; Silamut and White 1993; Li et al, 1994). Approximately 5000 erythrocytes were counted in clear contiguous fields 24 and 48 h after incubation of blood obtained at each time point and graded for maturity into tiny rings, small rings, large rings, pigmented trophozoites and schizonts. Functional viability was estimated as the percentage of asexual ring forms capable of maturing to pigmented trophozoites or schizonts after 24-48 h of *in vitro* culture (Watkins et al. 1993).

Calculations of parameters. The Patients presented with acute symptomatic severe non-cerebral pure P. Falciparum malaria, they had oral fluid intolerance and had body temperatures greater than 39 degrees C, greater than 5000 parasites per micro liter of blood and asexual parasitemia and they had a negative urine test for antimalarial drugs. They were administered 25 mL intravenously every four hours with bromine epiandrosterone (16α-bromoepiandrosterone) suspended in 45% beta-cyclodextrin in saline at a concentration of 25 mg/mL. This regimen was continued for four days. Parasitemia quantification and clinical examination were done once every 6 hours for the first 72 hours, followed by daily assessment of the parameters up to day 7 (168 hrs) and thereafter on day 14.

The blood films were Giemsa-stained and parasitemia quantification was done in thick films by counting 2000 parasites against leukocytes, and the thin films by finding the proportion of infected red blood cells. Response to drug treatment was graded according to WHO criteria. Evaluation of therapeutic response was done using the parasitic and fever clearance times. Parasite clearance was expressed as three indices: The time for the parasite count to fall by 50% of the pre-treatment (baseline) value (PC_{60}); to fall by 90% of the baseline value (PC_{90}); and to fall below the level of microscopic detection (parasite clearance time) PCT.

The fever clearance time was defined as the time from drug administration until the oral/rectal temperature fell to below 37.2 degrees C and remained so for greater than 48 hours.

I.V. Bromine Epiandrosterone Malaria Patient Trial

	Patient A	Patient B
Fever clearance time (H)	12 hrs	18 hrs
Parasite clearance times (H)		
Time to 50% clearance	18 hrs	24 hrs
Time to 90% clearance	24 hrs	48 hrs
Time to 100% clearance	48 hrs	64 hrs

Results. The response consisted of parasite clearance in both patients, i.e., the clearance rate at day 14 was 100%.

Example 8. Cellular studies *in vitro*. The effect of Bromine Epiandrosterone (EPI, 16α-bromoepiandrosterone) on pentosephosphate shunt (PPS) activity in normal human RBC was examined using whole cells. Since glucose-6-phosphate dehydrogenase ("G6PD") is the limiting enzyme of the PPS, PPS flux measurement is considered to better reflect G6PD activity in the whole cell compared to G6PD activity measurement in a cell lysate. G6PD activity measured in a cell lysate is typically about 1100-fold higher than the PPS flux in whole resting unstimulated RBC (G6PD activity in cell lysate: 165; PPS flux 0.142 micromoles/hour/ml RBC). PPS flux and G6PD activity in the whole RBC depends on a number of factors (the concentration of NADPH, NAD, and ATP, and intracellular pH), which are kept constant if the measurement is performed in the lysate and may vary in the whole RBC. Levels of G6PD activity in cells is considerably above normal basal needs and inhibition of overall G6PD activity might have no or minor consequence on PPS flux in the whole cell. For example, RBC with the Mediterranean G6PD mutant with about 1-3 percent residual activity compared with normal individuals have no impairment in basal PPS flux, but show impaired flux when flux through PPS is stimulated by methylene blue addition. A series of experiments were perfromed using varying amounts of EPI and PPS flux was measured in unstimulated basal RBC and in methylene-blue (MB)-stimulated RBC.

The data below shows PPS flux (micromoles/hour/ml RBC) in basal unstimulated, and MB-stimulated normal RBC. Different concentrations of EPI (0.3, 3.5 and 7 micromolar, final) were supplemented to suspensions of washed RBC suspended in RPMI, pH 7.4 at 10% hematocrit, whereby PPS flux was immediately measured without further incubation and without further washings. A minor inhibition of MB-stimulated PPS flux was observed with EPI at 7 μM.

	PPS flux
control, unstimulated RBC	230
DMSO control, unstimulated RBC	270
DMSO control, MB stimulated RBC	5090
0.3 μM EPI, unstimulated	250
0.3 μM EPI, MB stimulated	5000
3.5 μM EPI, unstimulated	270
3.5 μM EPI, MB stimulated	4950
7 μM EPI, unstimulated	295
7 μM EPI, MB stimulated	4660

The data below shows average values of 3 experiments, where basal, unstimulated, and MB-stimulated PPS flux (micromoles/hour/ml RBC) was measured in normal RBC. In these experiments, different concentrations of EPI ~0.8, 8 and 80 micromolar, final) were supplemented to suspensions of washed RBC suspended in RPMI, pH 7.4 at 10% hematocrit. After a 90-min incubation at 37° C with and without EPI, PPS flux was measured. The results showed a dose-dependent inhibition of MB-stimulated PPS flux. Inhibition was 10% at 8 micromolar (p=0.006 vs control+DMSO) and 25% at 80 micromolar (p=0.002 vs control+DMSO).

	PPS flux
control, unstimulated RBC	430
control, MB stimulated RBC	5410
DMSO control, unstimulated RBC	480
DMSO control, MB stimulated RBC	4890
0.8 μM EPI, unstimulated	410
0.8 μM EPI, MB stimulated	4930
8 μM EPI, unstimulated	450
8 μM EPI, MB stimulated	4430
80 μM EPI, unstimulated	450
80 μM EPI, MB stimulated	3660

Example 9. Inhibition of parasite growth. The effect of EPI (16α-bromo-epiandrosterone) on parasite (*Plasmodium falciparum*) growth was shown. EPI was active at a concentration of 1 μM.

Parasitemia after treatment

	Time 0	24hrs	48hrs	72hrs
control + DMSO	5%	5.40%	3.10%	5.20%
Epi 1 μM	5%	5.70%	5,50%	1,60%
Epi 10 μM	5%	5,60%	0.90%	0
Epi 100 μM	5%	0	0	0
Epi 500 μM	5%	0	0	0
control + DMSO	2%	8.80%	11% 8%	
Epi 50 nM	2%	9.90%	9.20%	8.30%
Epi 1 μM	2%	5.80%	6.10%	2.10%
Epi 2.5 μM	2%	7.30%	5.80%	3.20%
Epi 5 μM	2%	5.40%	6%	1.80%
Epi 10 μM	2%	4.20%	3%	0
Epi 50 μM	2%	0	0	0

Parasitemias were determined by standard methods (microscopic inspection of at least 500 cells, stained with Diff-Quick™ (Baxter). Parasites were cultured under standard conditions in RPMI-1640 supplemented with Hepes/Glucose (10 mM), glutamine (0.3 g/liter) and 10% human plasma. The hematocrit was 1%.

Example 10. Stimulation of phagocytosis. The capacity of EPI (16α-bromo-epiandrosterone) to influence phagocytosis of *Plasmodium* parasite infected RBC is examined using adherent human monocytes. The parasitemia level is about 8-10% and human monocytes are obtained from buffy coats from blood as follows. Peripheral blood mononuclear cells are separated from freshly collected platelet-poor buffy coats discarded from blood samples of heafthy adult donors of both sexes. Separated cells are washed once with luke-warm PBS supplemented with 10 mM glucose (PBS-G) and resuspended at 5 x 10^6 cells/mL in ice-cold RPMI 1640 medium supplemented with 23 mM $NaHCO_3$ and 25 mM Hepes, pH 7.4 (RMBH). Dynabeads M450 Pan B and Pan T (Dynal) are added to cells in a 4:1 ratio for 20 min at 4°C. B-lymphocytes and T-lymphocytes are removed as specified by the manufacturer. The remaining monocytes are washed 2 times in RMBH, resuspended in AIM V cell culture medium (Gibco) at 1 x 10^6 cell/mL. The monocyte layer is collected, washed with PBS-G at 37°C and resuspended in AIM V medium at 1 x 10^6 cells/mL. Purified cells are >90% monocytes as assessed by CD14 expression.

Phagocytosis of opsonized parasitized RBC (PE) is determined as follows. Phagocytosis of fresh-serum opsonized PE is initiated by mixing 10 PE/monocyte. Suspensions are briefly centrifuged (150 x g for 5 sec at room temperature) to improve contact between PE and monocytes. To avoid attachement of monocytes after centrifugation and during the whole incubation period, cells are kept in suspension at 5 x 10^6 cells/5 mL AIM V medium in 6 cm diameter teflon bottom dishes (Heraeus) in a humidified incubator (95% air, 5% CO_2) at 37°C. On average, at least 90% of the monocytes phagocytose PE, as assessed by microscopic inspection. Control cells are kept under similar conditions without phagocytosis. Quantitative assessment of phagocytosis is performed by a previously described bioluminescence method (E. Schwarzer, et al., *Br. J. Haematol.* 1994 88:740-745).

Erythrocyte treatments and parasite cultures are as follows. Fresh blood (Rh+) is used to isolate erythrocytes (RBC). Washed RBC are infected with schizont/trophozoite parasite stages (Palo Alto strain, mycoplasma-free). Stage specific parasites are isolated by the Percoll-mannitol method. Briefly, normal schizont-stage parasitized E (SPE) separated on Percoll-mannitol gradient (parasitemia > 95% SPE) are mixed with E suspended in growth medium (RPMI 1640 medium containing 25 mmol/L Hepes, 20 mmol/L glucose, 2 mmol/L glutamine, 24 mmol/L $NaHCO_3$, 32 mg/L gentamicin and 10% AB or A human serum, pH 7.30) to start synchronous cultures at selected hematocrit values. The inoculum parasitemia is adjusted to 20% normal SPE for isolation of ring parasitized RBC (RPE) and to 5% normal SPE for isolation of trophozoite-stage parasitized E (TPE). At 14-18 hours after inoculum parasites are at ring-stage in the first cycle; at 34-33 hours, parasites are at trophozoite-stage in the first cycle; and at 40-44 hours after inoculum parasites are at schizont-stage in the first cycle. RPE, TPE and SPE are separated on Percoll-mannitol gradients. The parasitemia is usually 8-10% RPE, and >95% TPE. Nonparasitized and parasitized RBC are counted electronically. To assess total parasitemia and relative contribution of RPE, TPE and SPE, slides are prepared from cultures at indicated times, stained with Diff-Quik™ parasite stain and 400-1000 cells are examined microscopically.

The effect or EPI in parasitized RBC is examined using various concentrations of EPI, e.g., 0.5 μM, 1 μM, 10 μM, 25 μM and 50 μM. Trophozoite-parasitized RBC, schizont-parasitized RBC or ring-parasitized RBC are examined as described.

Example 11. Human clinical trial. The clinical trial protocol that incorporates about 15-20 patients is established. For a phase I or I/II trial, the patients are mildly infected with one or more Plasmodium parasites and they are mildly symptomatic (less than about 8-10% parasitemia of RBC). Before treatment, the patients are optionally tested for infection with HIV, HCV, TB, and *Cryptosporidium*. Patients with one or more co-infections are given standard care for the

coinfection. The patients are hospitalized for treatment for one week. Two or more dose groups, e.g., 25, 50 or 100 mg/day of 16α-bromoepiandrosterone (BrEA), or an ester thereof, administered parenterally, e.g., by intramuscular or intravenous injection, on 3, 4 or 5 days of the week when patients are dosed. Dosing is on consecutive days or on an intermittent schedule, e.g., 2, 3 or 4 doses with one dose administrered every other day. The formulation containing BrEA is as described herein, e.g., the formulation of example 1 or 2. At day 5-7, if less than about 50% reduction in parasitemia is observed, the patients are given standard care for malaria (mefloquine). During the week of treatment and for 1, 2 3, or more weeks theerafter, blood samples are taken periodically for evaluation of parasitemia, pharmacokinetics, plasma cytokines (e.g., IL-2, IL-4, IL-10, IGF1, γIFN, GM-CSF), and intracellular cytokines (e.g., IL-2, IL-4, IL-10, IGF1, γIFN, GM-CSF). The patients are optionally treated again at about 2 to 12 weeks after the initial dosing, using the same or a similar protocol as that used in the initial dosing protocol.

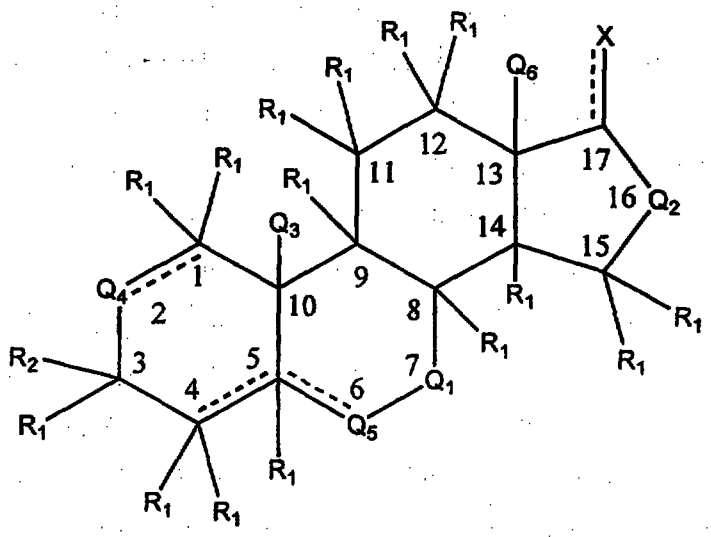
To the extent not already indicated, it will be understood by those of ordinary skill in the art that any one of the various specific embodiments herein described and illustrated may be further modified to incorporate features shown in other of the specific embodiments.

The foregoing detailed description has been provided for a better understanding of the invention only and no unnecessary limitation should be understood therefrom as some modifications will be apparent to those skilled in the art without deviating from the spirit and scope of the appended claims.

CLAIMS

What is claimed is:

1. A method to treat or prevent a *Trypanosoma* or *Plasmodium* infection, or to ameliorate one or more symptoms associated with a *Trypanosoma* or *Plasmodium* infection, in a subject suffering from or subject to a *Trypanosoma* or *Plasmodium* infection, comprising administering to the subject an effective amount of a compound having formula 1,



1

wherein

Q_1 is $-C(R_1)_2-$ or -C(O)-;

Q_2 is $-C(R_1)_2-$, $-C(R_1)(Y)-$, -C(Y)- or $-CH_2-CH_2-$;

Q_3 is -H or $-C(R_1)_3-$;

Q_4 is $-C(R_1)_2-$, -C(O)-, hydroxyvinylidine or methyl methylene;

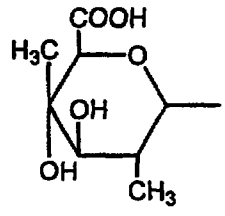
Q_5 is $-C(R_1)_2-$ or -C(O)-;

X and Y independently are -OH, -H, lower alkyl, -O-C(O)-R_5, -C(O)-OR_5, halogen or =O;

each R_1 independently is -H, halogen, -OH, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_2 is -H, -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-OR_3$, an ester, a thioester, a thioacetal, a sulfate ester, a sulfonate ester or a carbamate or R_2, together with the R_1 that is bonded to the same carbon atom is =O;

R_3 is -S(O)(O)-OM, $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6$, $-P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7$, a glucuronide group of structure (A)



(A),

or R_3 is C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, a C_{1-18} ester or a C_{1-18} thioester, where any of the foregoing C_{1-18} or C_{2-18} moieties are optionally substituted at one or more hydrogen atoms with one or more independently selected $-OR^{PR}$, $-NHR^{PR}$, or $-SR^{PR}$, groups, or R_3 is a C_{1-18} fatty acid, C_{2-10} alkynyl, $(J)_n$-phenyl-C_{1-5}-alkyl, $(J)_n$-phenyl-C_{2-5}-alkenyl;

each R_5 independently is straight or branched C_{1-14} alkyl;

each R_6 independently is C_{1-14} straight or branched alkyl; and

each R_7 independently is C_{1-14} straight or branched alkyl or a glucuronide group of structure (A);

each R^{PR} independently is -H or an independently selected protecting group;

n is 0, 1, 2 or 3;

each J independently is halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, carboxy, nitro, sulfate, sulfonyl, a C_{1-6} carboxyl ester or a C_{1-6} sulfate ester;

M is hydrogen, sodium, $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6$, $-P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7$ or a glucuronide group of structure (A); and

the dotted lines represent an optional double bond, provided that there are not double bonds at both the 4-5 and 5-6 positions and provided that when a double bond is present, zero or 1 R_1 group is bonded to carbon atoms at the 1-, 2-, 4-, 5-, 6- or 17- positions so that these carbon atoms are tetravalent; and

the salts, stereoisomers, positional isomers, metabolites, analogs, precursors, hydrates, tautomers, ionized forms and solvates thereof.

2. The method of claim 1 wherein the *Trypanosoma* or *Plasmodium* infection is a *Trypanosoma cruzi, Trypanosoma brucei, Trypanosoma gambiense, Trypanosoma rhodesiense, Trypanosoma brucei rhodesiense, Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale* or a *Plasmodium berghei* infection.

3. The method of claim 2 wherein the formula 1 compound is one or more compounds selected from compound groups **1-21**.

4. The method of claim 2 wherein the *Trypanosoma* or *Plasmodium* infection is a *Trypanosoma cruzi* infection.

5. The method of claim 4 wherein the formula 1 compound is one or more compounds selected from compound groups **1-21**.

6. The method of claim 2 wherein the *Trypanosoma* or *Plasmodium* infection is a *Plasmodium berghei* or a *Plasmodium falciparum* infection.

7. The method of claim 5 wherein the subject is a human or a primate.

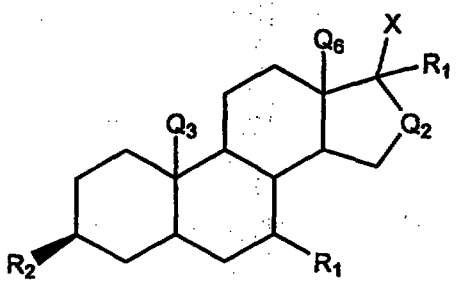
8. The method of claim 7 wherein the formula 1 compound is one or more compounds selected from compound groups **1-21**.

9. The method of claim 8 wherein the formula 1 compound is 16α-bromo-3β-hydroxy-5α-androstan-17-one or 16α-bromodehydroepiandrosterone.

10. The method of claim 1 wherein the subject is coinfected with a retrovirus.

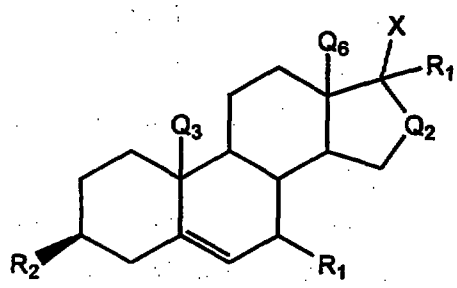
11. The method of claim 10 wherein the subject is a human and the retrovirus is HIV1 or HIV2.

12. The method of claim 1 wherein the formula 1 compound has the formula 1B or 1C



1B

or



1C

wherein,

each R_1 independently is -H, -OH, a halogen, -$CHCH_2$, -$CHCHCH_3$, -CCH, -$CCCH_3$, or, the other moiety that is bonded to the same carbon atom is absent and R_1 is =O;

R_2 is -O-C(O)-R_4, -S-C(O)-R_4, -O-S(O)(O)-R_4, -O-S(O)(O)-OR_4, -O-C(O)-NHR_4, or -O-C(S)-R_4;

R_4 is -H, a protecting group, optionally substituted C_{1-18} alkyl, optionally substituted C_{1-18} alkenyl, optionally substituted C_{1-18} alkynyl, optionally substituted aryl, optionally substituted aryl-C_{1-6} alkyl, optionally substituted aryl-C_{2-6} alkenyl, optionally substituted aryl-C_{2-6} alkynyl, optionally substituted heterocycle-C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl-heterocycle, optionally substituted C_{2-6} alkynyl-heterocycle or an optionally substituted heterocycle, where any of the foregoing moieties are optionally substituted at one, two, three, four, five or more carbon or hydrogen atoms with one or more independently selected -O-, -S-, -NR^{PR}-, -OR^{PR}, -NHR^{PR}, -SR^{PR}, =O, =S, -CN, -NO_2, -F, -Cl, -Br or -I groups or atoms; and

each R^{PR} independently is -H or an independently selected protecting group;

Q_2 is -$C(R_1)_2$-; and

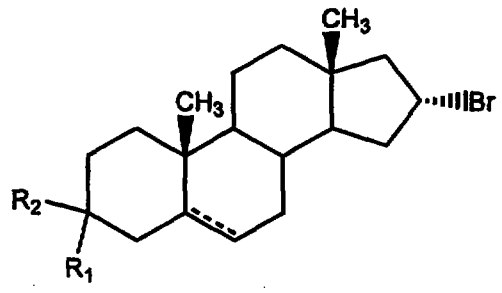
Q_3 and Q_6 independently are -H, -CH_3 or -CH_2OH.

13. The method of claim 12 wherein Q_3 and Q_6 are both -CH_3 in the β-configuration; and

Q_2 is -CH_2-, -C(O)-, -CH(Br)-, -CH(I)-, or -CH(OH)- with the Br, I or OH moieties in the α-configuration, or Q_2, together with the hydrogen atom that is bonded to the same carbon atom comprises -C(O)- or -CH_2-CH_2-; and

R_1 at the 7-position is -H, -OH or, when taken with the hydrogen atom that is bonded to the same carbon atom, R_1 is =O.

14. The method of claim 1 wherein the formula 1 compound has the formula 1A



1A

wherein,

R_2 is -OH, halogen, C_{1-6} alkoxy, $-OR_3$, a C_{1-18} fatty acid, C_{1-10} alkynyl, $(J)_n$-phenyl-C_{1-5}-alkyl, $(J)_n$-phenyl-C_{1-5}-alkenyl, an ester optionally selected from $-O-C(O)-(CH_2)_m-R_4$ and $-C(O)-O-(CH_2)_m-R_4$, or R_2 is $-S-C(O)-(CH_2)_m-R_4$, $-C(O)-S-(CH_2)_m-R_4$, $-O-S(O)(O)-(CH_2)_m-R_4$, $-O-S(O)(O)-O-(CH_2)_m-R_4$, $-O-C(O)-NH-(CH_2)_m-R_4$, $-NH-C(O)-O-(CH_2)_m-R_4$, $-O-C(S)-(CH_2)_m-R_4$, $-C(S)-O-(CH_2)_m-R_4$, $-O-C(O)-(CH_2)_m-R_4$ or $-C(O)-O-(CH_2)_m-R_4$, or R_2, together with the R_1 that is bonded to the same carbon atom is =O;

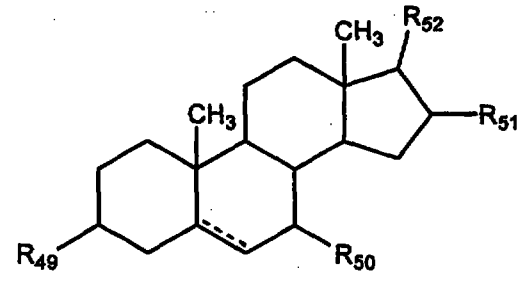
R_4 is -H, a protecting group, optionally substituted C_{1-18} alkyl, optionally substituted C_{2-18} alkenyl, optionally substituted C_{2-18} alkynyl, optionally substituted aryl, optionally substituted aryl-C_{1-6} alkyl, optionally substituted aryl-C_{2-6} alkenyl, optionally substituted aryl-C_{2-6} alkynyl, optionally substituted heterocycle-C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl-heterocycle, optionally substituted C_{2-6} alkynyl-heterocycle or an optionally substituted heterocycle, where any of the foregoing moieties are optionally substituted at one, two, three, four, five or more carbon or hydrogen atoms with one or more independently selected -O-, -S-, $-NR^{PR}-$, $-OR^{PR}$, $-NHR^{PR}$, $-SR^{PR}$, =O, =S, -CN, $-NO_2$, -F, -Cl, -Br or -I groups or atoms;

each R^{PR} independently is -H or an independently selected protecting group;

m is 0, 1, 2 or 3; and

the dotted line is an optional double bond.

15. The method of claim 1 wherein the formula 1 compound has the formula 45



45

wherein,

R_{50} is -H, -OH or =O;

R_{51} is -Br, -Cl, -F, -I or -OH;

R_{52} is -OH or, R_{52}, together with the -H bonded to the same position, is =O;

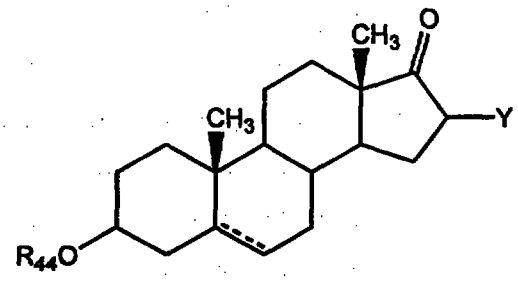
R_{49} is -H, -OH, or -OR_{53};

R_{53} is C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, a C_{1-18} ester, a C_{1-18} thioester, wherein any of the foregoing C_{1-18} or C_{2-18} groups is substituted at one or more hydrogen or carbon atoms with one or more independently selected -O-, -S-, -OH, -NH_2, -SH or =O groups or R_{53} is a thioacetal, a sulfate ester, a sulfonate ester, a carbamate or a thioester; and

the dotted line is an optional double bond.

16. The method of claim 15 wherein R_{49} is -O-C(O)-CH_2-CH_2-CH(R_{54})-CH(R_{55})-CH_2R_{56} wherein R_{54} is -NH_2, -OH, -SH, -O-PO_3, -SO_3 or -OSO_3; R_{55} is -H, -NH_2, -OH, -SH, -O-PO_3, -SO_3 or -OSO_3; and R_{56} is C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, a C_{1-18} ester or a C_{1-18} thioester, wherein any of the foregoing C_{1-18} or C_{2-18} groups is substituted at one or more hydrogen atoms with one or more independently selected -OH, -NH_2, -SH or =O groups.

17. The method of claim 1 wherein the formula 1 compound has the formula 44



44

wherein,

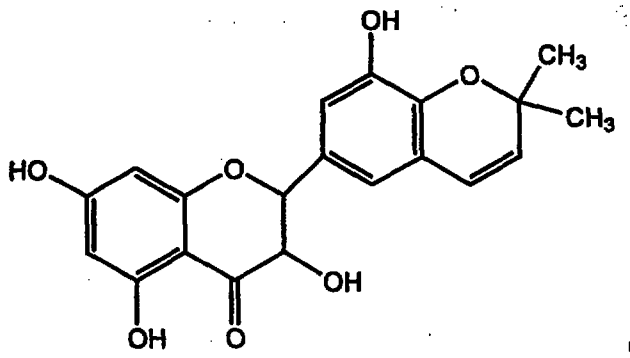
Y is hydrogen or a halogen;

R_{44} is -H, -S(O)(O)-OH, -S(O)(O)-ONa, -S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6, -P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7 or a glucuronide group of structure (A); and

the dotted line is an optional double bond.

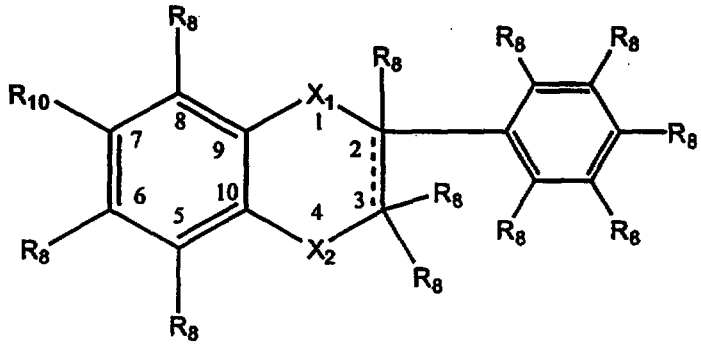
18. The method of claim 17 wherein the formula 44 compound is dehydroepiandrosterone, epiandrosterone, 16α-bromoepiandrosterone, 16α-bromodehydroepiandrosterone, dehydroepiandrosterone-3-sulfate or 5β-androstan-3β-ol-17-one.

19. The method of claim 1 wherein the method further comprises simultaneously or sequentially administering an effective amount a plasma concentration-enhancing compound selected from bavachinin A, didymin, flavanomarein, flavanone azine, flavanone diacetylhydrazone, flavanone hydrazone, silandrin, silybin, silychristin, isosilybin, a compound having the structure (E)

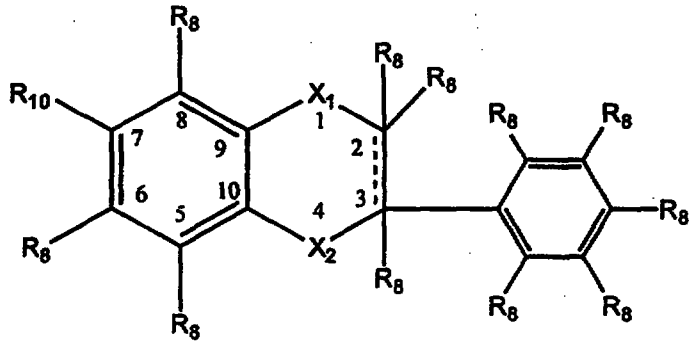


(E)

and a compound of formula 2A or 2B



2A



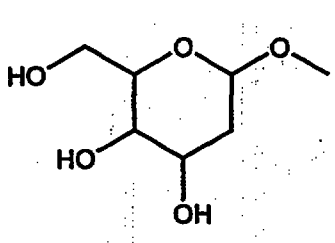
2B

wherein a double or a single bond is present at the dotted line and when a double bond is present (i) the optionally substituted phenyl ring at the 2- or 3-position is present and the R_8 that is bonded to the carbon is absent, and (ii) one R_8 at the adjacent 2- or 3-position is absent;

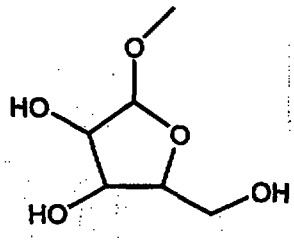
X_1 is -O- or -$C(R_8)_2$-;

X_2 is -C(O)- or -$C(R_{11})_2$-;

each R_8 independently is -H, -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide, a C_{1-25} fatty acid, the residue of a formula 2A or 2B compound where a hydrogen atom is removed to form the formula 2A or 2B compound radical, -$CH_2CH=C(CH_3)_2$, glucoside, a group having structure (B) or (C),



(B) or



(C)

R_{10} is C_{1-6} alkyl, C_{1-6} alkoxy, neohesperidoside, apioglucoside, rutinoside, glucoside, galactoside, rhamnoside, arabinoside, or a stereoisomer, hydrate, analog, derivative or metabolite of any of these moieties, any of which are optionally independently substituted at one or more hydrogen atoms with -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, glucuronide or a C_{1-25} fatty acid or R_{10} is -H, -OH or halogen;

each R_{11} independently is -H, -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, a glucuronide group of structure (A), a C_{1-25} fatty acid, or both R_{11} together are =O; and

the salts, stereoisomers, positional isomers, metabolites, analogs, precursors, hydrates, tautomers, ionized forms and solvates thereof.

20. The method of claim 19 wherein the plasma concentration-enhancing compound is naringin or naringenin.

21. The method of claim 20 wherein the subject is a human or a primate.

22. The method of claim 21 wherein the formula 1 and the plasma concentration-enhancing compound are administered simultaneously.

23. The method of claim 19 further comprising administering to the subject, or treating the subject with, one or more of ribavirin, alpha interferon, a macrophage stimulating factor, an oxidation agent and oxygen ventialtion.

24. The method of claim 23 wherein the plasma concentration-enhancing compound is naringin or naringenin.

25. The method of claim 24 wherein the subject is a human or a primate.

26. The method of claim 25 wherein the formula 1 compound and the plasma concentration-enhancing compound are administered simultaneously.

27. The method of claim 1 wherein 2, 3, 4, 5 or 6 R_1 are not hydrogen.

28. The method of claim 27 wherein the 2, 3, 4, 5 or 6 R_1 that are not hydrogen are independently selected from -OH, halogen and C_{2-4} alkoxy.

29. A method to treat or prevent a *Trypanosoma, Plasmodium* or *Mycoplasma* infection, or to ameliorate one or more symptoms associated with a *Trypanosoma, Plasmodium* or *Mycoplasma* infection, in a subject suffering from or subject to a *Trypanosoma, Plasmodium* or *Mycoplasma* infection, comprising administering to the subject an effective amount of a composition comprising 16α-bromoepiandrosterone, and 2, 3, 4 or 5 excipients selected from

polyethylene glycol, dehydrated ethanol, benzyl benzoate, benzyl alcohol and propylene glycol, wherein the composition optionally comprises less than about 3% v/v, or less than about 1% v/v, or less than about 0.5% v/v of water, or less than about 0.1% v/v of water.

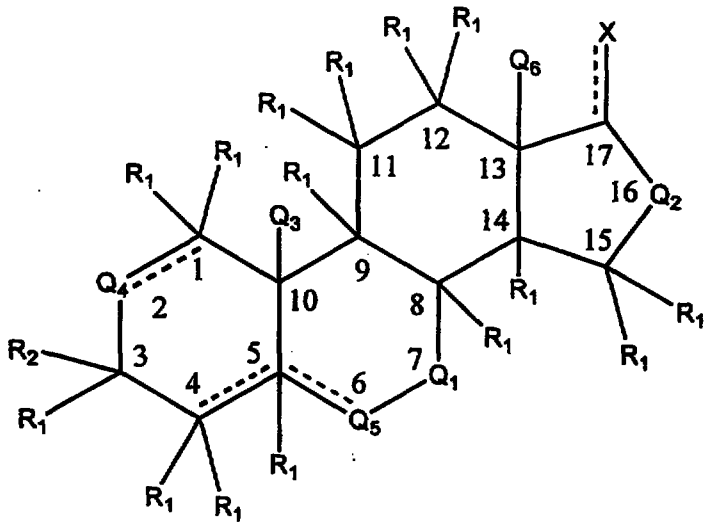
30. The method of claim 29 wherein the composition comprises 16α-bromoepiandrosterone at a concentration of about 45-55 mg/mL, 20-30% v/v polyethylene glycol 300, polyethylene glycol 400 or a mixture of polyethylene glycol 300 and 400, 10-15% v/v dehydrated ethyl alcohol, 2.5-7.5% v/v benzyl benzoate, and 55-60% v/v propylene glycol.

31. The method of claim 30 wherein the composition comprises 16α-bromoepiandrosterone at a concentration of about 50 mg/mL, about 25% v/v polyethylene glycol 300, about 12.5% v/v dehydrated ethyl alcohol, about 5% v/v benzyl benzoate, about 57.5% v/v propylene glycol and less than about 0.5% v/v water.

32. The method of claim 29 wherein the composition comprises 16α-bromoepiandrosterone at a concentration of about 85-105 mg/mL, about 27-33% w/w benzyl benzoate, about 27-33% w/w polyethylene glycol 300, about 25-30% w/w propylene glycol and about 1-3% w/w benzyl alcohol.

33. The composition of claim 32 wherein the composition comprises 16α-bromoepiandrosterone at a concentration of about 100 mg/mL, about 30.4% w/w benzyl benzoate, about 30.7% w/w polyethylene glycol 300, about 28% w/w propylene glycol and about 1.9% w/w benzyl alcohol.

34. A method to enhance phagocytosis of *Plasmodium* or *Trypanosoma* infected cells in an infected subject comprising administering to the infected subject an effective amount of a compound of formula 1



1

wherein

Q_1 is $-C(R_1)_2-$ or $-C(O)-$;

Q_2 is $-C(R_1)_2-$, $-C(R_1)(Y)-$, $-C(Y)-$ or $-CH_2-CH_2-$;

Q_3 is -H or $-C(R_1)_3$-;

Q_4 is $-C(R_1)_2$-, -C(O)-, hydroxyvinylidine or methyl methylene;

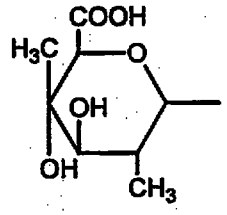
Q_5 is $-C(R_1)_2$- or -C(O)-;

X and Y independently are -OH, -H, lower alkyl, $-O-C(O)-R_5$, $-C(O)-OR_5$, halogen or =O;

each R_1 independently is -H, halogen, -OH, C_{1-6} alkoxy, or C_{1-6} alkyl;

R_2 is -H, -OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-OR_3$, an ester, a thioester, a thioacetal, a sulfate ester, a sulfonate ester or a carbamate or R_2, together with the R_1 that is bonded to the same carbon atom is =O;

R_3 is $-S(O)(O)-OM$, $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6$, $-P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7$, a glucuronide group of structure (A)



(A),

or R_3 is C_{1-18} alkyl, C_{2-18} alkenyl, C_{2-18} alkynyl, a C_{1-18} ester or a C_{1-18} thioester, where any of the foregoing C_{1-18} or C_{2-18} moieties are optionally substituted at one or more hydrogen atoms with one or more independently selected $-OR^{PR}$, $-NHR^{PR}$, or $-SR^{PR}$, groups, or R_3 is a C_{1-18} fatty acid, C_{2-10} alkynyl, $(J)_n$-phenyl-C_{1-5}-alkyl, $(J)_n$-phenyl-C_{2-5}-alkenyl;

each R_5 independently is straight or branched C_{1-14} alkyl;

each R_6 independently is C_{1-14} straight or branched alkyl; and

each R_7 independently is C_{1-14} straight or branched alkyl or a glucuronide group of structure (A);

each R^{PR} independently is -H or an independently selected protecting group;

n is 0, 1, 2 or 3;

each J independently is halogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, carboxy, nitro, sulfate, sulfonyl, a C_{1-6} carboxyl ester or a C_{1-6} sulfate ester;

M is hydrogen, sodium, $-S(O)(O)-O-CH_2-CH(O-C(O)-R_6)-CH_2-O-C(O)-R_6$, $-P(O)(O)-O-CH_2-CH(O-C(O)-R_7)-CH_2-O-C(O)-R_7$ or a glucuronide group of structure (A); and

the dotted lines represent an optional double bond, provided that there are not double bonds at both the 4-5 and 5-6 positions and provided that when a double bond is present, zero or 1 R_1 group is bonded to carbon atoms at the 1-, 2-, 4-, 5-, 6- or 17- positions so that these carbon atoms are tetravalent; and

the salts, stereoisomers, positional isomers, metabolites, analogs, precursors, hydrates, tautomers, ionized forms and solvates thereof.

35. The method of claim 34 wherein the formula 1 compound is a 16-haloepiandrosterone or a 16-halodehydroepiandrosterone.

36. The method of claim 35 wherein the 16-haloepiandrosterone or 16-halo-dehydroepiandrosterone is 16α-bromoepiandrosterone or 16α-bromo-dehydroepiandrosterone.

5