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(54) **TRIARYL METHANE COMPOUNDS FOR THE TREATMENT OF CANCER, ACTINIC KERATOSIS AND KAPOSÍ'S SARCOMA**

TRIARYLMETHANVERBINDUNGEN ZUR BEHANDLUNG VON KREBS, AKTINISCHER KERATOSE UND KAPOSISARKOM

COMPOSES DE TRIARYLE METHANE POUR LE TRAITEMENT DU CANCER, DES KERATOSES ACTINIQUES ET DU SARCOMME DE KAPOSÍ

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Description**1. CROSS-REFERENCE TO RELATED APPLICATIONS**

5 **[0001]** This application is a continuation-in-part of application Serial No. 08/618,952, filed March 20, 1996, now pending and 08/618,760, filed March 20, 1996, now pending, each of which is a continuation-in-part of application Serial No. 08/307,874, filed September 16, 1994, now abandoned. The application is also a continuation-in-part of application Serial No. 08/618,762, filed March 20, 1996, now pending and application Serial No. 08/618,759, filed March 20, 1996, now pending, each of which is a continuation-in-part of application Serial No. 08/307,887, filed September 16, 1994, now abandoned. Each of these applications is incorporated herein in its entirety by reference.

2. FIELD OF THE INVENTION

15 **[0002]** The present invention relates to aromatic organic compounds which are specific, potent and safe inhibitors of the Ca²⁺-activated potassium channel (Gardos channel) of erythrocytes and/or of mammalian cell proliferation. The compounds can be used to inhibit mammalian cell proliferation *in situ* as a therapeutic approach towards the treatment or prevention of diseases characterized by abnormal cell proliferation.

3. BACKGROUND OF THE INVENTION

20 **[0003]** Cell proliferation is a normal part of mammalian existence, necessary for life itself. However, cell proliferation is not always desirable, and has recently been shown to be the root of many life-threatening diseases such as cancer, certain skin disorders, inflammatory diseases, fibrotic conditions and arteriosclerotic conditions.

25 **[0004]** Cell proliferation is critically dependent on the regulated movement of ions across various cellular compartments, and is associated with the synthesis of DNA. Binding of specific polypeptide growth factors to specific receptors in growth-arrested cells triggers an array of early ionic signals that are critical in the cascade of mitogenic events eventually leading to DNA synthesis (Rozengurt, 1986, *Science* 234: 161-164). These include (1) a rapid increase in cytosolic Ca²⁺, mostly due to rapid release of Ca²⁺ from intracellular stores; (2) capacitative Ca²⁺ influx in response to opening of ligand-bound and hyperpolarization-sensitive Ca²⁺ channels in the plasma membrane that contribute further to increased intracellular Ca²⁺ concentration (Tsien and Tsien, 1990, *Annu. Rev. Cell Biol.* 6:715-760; Peppelenbosch et al., 1991, *J. Biol. Chem.* 266:19938-19944); and (3) activation of Ca²⁺-dependent K⁺ channels in the plasma membrane with increased K⁺ conductance and membrane hyperpolarisation (Magni et al., 1991, *J. Biol. Chem.* 261:9321-9327). These mitogen induced early ionic changes, considered critical events in the signal transduction pathways, are powerful therapeutic targets for inhibition of cell proliferation in normal and malignant cells.

35 **[0005]** One therapeutic approach towards the treatment of diseases characterized by unwanted or abnormal cell proliferation via alteration of the ionic fluxes associated with early mitogenic signals involves the actrainistration of Clotrimazole. As discussed above, Clotrimazole has been shown to inhibit the Ca²⁺ activated potassium channel of erythrocytes. In addition, Clotrimazole inhibits voltage- and ligand-stimulated Ca²⁺ influx mechanisms in nucleated cells (villalobos et al., 1992, *FASEB J.* 6:2742-2747; Montero et al., 1991, *Biochem. J.* 277:73-79) and inhibits cell proliferation both *in vitro* and *in vivo* (Benzaquen et al., 1995, *Nature Medicine* 1:534-540). Recently, Clotrimazole and other imidazole-containing antimycotic agents capable of inhibiting Ca²⁺-activated potassium channels have been shown to be useful in the treatment of arteriosclerosis (U.S. Patent No. 5,358,959 to Halperin et al.), as well as other disorders characterized by unwanted or abnormal cell proliferation.

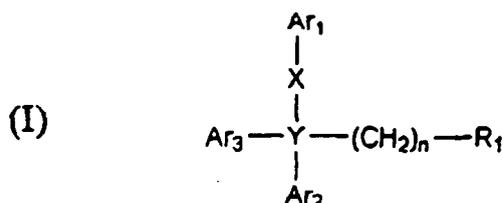
45 **[0006]** As can be seen from the above discussion, inhibiting mammalian cell proliferation *via* alteration of ionic fluxes associated with early mitogenic signals is a powerful therapeutic approach towards the treatment and/or prevention of diseases characterized by unwanted or abnormal cell proliferation. Compounds capable of inhibiting mammalian cell proliferation are highly desirable, and are therefore also an object of the present invention.

4. SUMMARY OF THE INVENTION

50 **[0007]** These and other objects are provided by the present invention, which in one aspect provides a class of organic compounds which are potent, selective and safe inhibitors of the Ca²⁺-activated potassium channel (Gardos channel) of erythrocytes, particularly sickle erythrocytes, and/or of mammalian cell proliferation. The compounds are generally substituted triaryl methane compounds, or analogues thereof wherein one or more of the aryl moieties is replaced with a heteroaryl, cycloalkyl or heterocycloalkyl moiety and/or wherein the tertiary carbon is replaced with another atom such as Si, Ge, N, or P and are set out in the claims thereafter.

55 **[0008]** In one illustrative embodiment, the compounds capable of inhibiting mammalian cell proliferation according to the invention are:

compounds having the structural formula:



or a pharmaceutically acceptable salt or hydrate thereof wherein:

n is 0, 1, 2, 3 or 4;

X is absent, (C₁-C₃) alkyl, (C₁-C₃) alkenyl or (C₁-C₃) alkynyl;

Y is C, N, Si or Ge;

R₁ is absent, -halo, -R, -OR, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂ or aryl;

Ar₁ is aryl, substituted aryl, heteroaryl other than imidazole, nitroimidazole and triazole, heteroarylium other than imidazolium, nitroimidazolium and triazolium, (C₅-C₆) cycloalkyl or (C₅-C₆) heterocycloalkyl;

Ar₂ is aryl or substituted aryl;

Ar₃ is aryl, substituted aryl, biaryl or heteroaryl other than imidazole, nitroimidazole and triazole;

each R is independently selected from the group of -H, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

the aryl substituents are each independently selected from the group of -halo, trihalomethyl, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' and -C(S)SR';

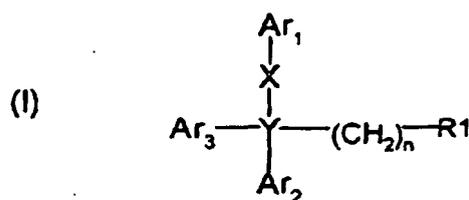
the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of -halo, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryl, γ-butyrolactonyl, pyrrolidinyl, pyrrolidinonyl and succinic anhydridyl;

each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl and (C₁-C₆) alkynyl-;

except that the compound is other than 1-(2-chlorophenyl)-1,1-diphenyl methanol, 1-(2-chlorophenyl)-1,1-diphenyl methane, 1-(2-chlorophenyl)-1-1(4-hydroxyphenyl)-1-phenyl methane;

or

compounds having the structural formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

X is absent, (C₁-C₃) alkyl, (C₁-C₂) alkenyl, or (C₁-C₃) alkynyl;

Y is C, N, P, Si or Ge;

R₁ is absent, -halo, -OR, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(S)R, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, or -CH[C(S)SR];

Ar₁ is aryl, substituted aryl, heteroaryl other than imidazole, nitroimidazole and triazole, heteroaryliums other than imidazolium, nitroimidazolium and triazolium, (C₅-C₆) cycloalkyl or (C₅-C₆) heterocycloalkyl;

Ar₂ is aryl or substituted aryl;

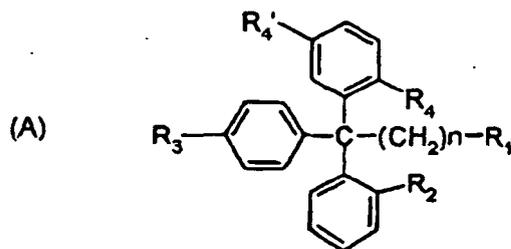
Ar₃ is aryl, substituted aryl, biaryl or heteroaryl other than imidazole, nitroimidazole and triazole;

each R is independently selected from the group of -H, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl,

substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;
 the aryl substituents are each independently selected from the group of -halo, trihalomethyl, -R, -R', -OR', -SR', N
 (R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' and -C(S)SR';
 the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of halo, -R', -OR', -SR',
 5 N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryl, γ -butyrolactonyl, pyrrolidinyl,
 pyrrolidinonyl and succinic anhydridyl; and
 each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl and (C₁-C₆) alkynyl.

[0009] In another aspect, the present invention provides:

a) a compound having the formula (A):



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

25 n is 0, 1, 2, 3 or 4;

R₁ is -H, -OR, -SR, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -CH
 [C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂;

R₂ is -F, -Cl, -Br or -I;

R₃ is -R, -OR or -SR;

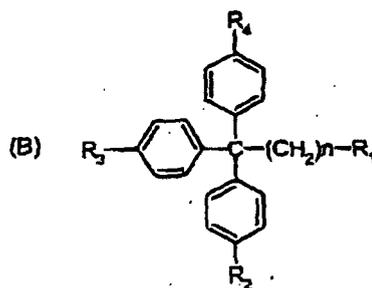
30 R₄ is -H or -N(R)₂;

R₄' is -H, -F, -Cl, -Br or -I; and

each R is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and
 (C₁-C₆) alkoxy,

with the provisos that (i) when n is 0 and R₁ is -H or -OH, R₃ is other than -H; and (ii) when n is 0 and R₁ is -H,
 35 R₃ is other than -OH;

b) a compound of formula (B) :



or a pharmaceutically acceptable salt, or hydrate thereof, wherein:

50 n is 0, 1, 2, 3 or 4;

R₁ is -N(R)₂, -C(O)R, -C(S)R, -C(O)N(R')₂ or -C(S)N(R')₂;

R₂ is -F, -Cl, -Br or -I;

R₃ is -F, -Cl, -Br or -I;

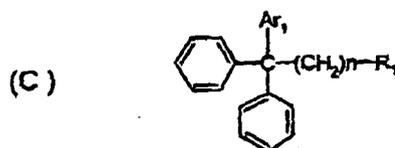
55 R₄ is -F, -Cl, -Br or -I;

each R is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and (C₁-C₆)

alkoxy; and
 each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;
 with the proviso that when R₂ = R₃ = R₄ = Cl, and R₁ = NH₂, then n = 1, 3 or 4;

and

c) compound of formula (C):



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

Ar₁ is phenyl or cyclohexyl;

R₁ is -N(R)₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -C(O)N(R)₂ or -C(S)N(R)₂; and each R is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and (C₁-C₆) alkoxy, with the proviso that when R₁ is -NH₂ or -C(O)NH₂, then n is 1, 2 or 3 and when:

(i) when Ar₁ = Ph, and R₁ = -NHR, wherein R is (C₁-C₄) alkyl, -CH(CH₃)(CH₂)₂CH₃, -CH(C₂H₅)₂, -CH(CH₃)CH(CH₃)CH₂CH₃, -CH(CH₃)CH₂CH(CH₃)CR₃, cyclohexyl; -OCH₃; -(CH₂)₅CH₃; -(CH₂)₄CH₃; -CH₂CH=CH₂, -CH(CH₃)CH=CH₂, -CH[CH₂CH(CH₃)₂]CH=CH₂, then n = 1, 2, 3 or 4;

(ii) when Ar₁ = Ph, and R₁ = -NR₂, wherein one of the R group is -CH(C≡CH)₂ and the other R group is -CH₂C≡CH or -CH₂CH₂C≡CH, then n = 1, 2, 3 or 4;

(iii) when Ar₁ = Ph, and R₁ = -NR₂, wherein one of the R group is -CH₂CH₃ and the other R group is -CH₃ or -CH₂C(CH₃)=CH₂, then n = 1, 2, 3 or 4;

(iv) when Ar₁ = Ph, and R₁ = N(CH₃)₂ or N(CH₂CH₃)₂, then n = 2, 3 or 4;

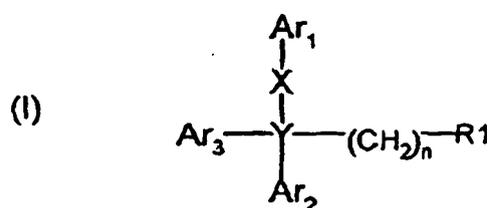
(v) when Ar₁ = Ph, and R₁ = NH(*t*-Bu) or C(O)NH₂, then n = 0, 2, 3 or 4;

(vi) when Ar₁ = Ph, and R₁ = NH₂, then n = 3 or 4;

(vii) when Ar₁ = Ph, and R₁ = -C(O)N(CH₃)₂ or -C(O)N(CH₃)cyclohexane or -CH[C(O)OC₂H₅]₂, then n = 1, 2, 3 or 4;

(viii) when Ar₁ = cyclohexyl, R₁ = N(CH₂CH₃)₂, then n = 0, 1, 2, or 4.

[0010] In another aspect, the present invention provides pharmaceutical compositions comprising one or more compounds according to the invention in admixture with a pharmaceutically acceptable carrier, excipient or diluent. Such a preparation can be administered in the methods of the invention. The compositions of the instant invention comprise: one or more compounds having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

X is absent, (C₁-C₃) alkyl, (C₁-C₃) alkenyl, or (C₁-C₃) alkynyl;

Y is C or Si;

R₁ is -halo, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂,

-C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, or -CH[C(S)SR]₂;

Ar₁ is aryl, substituted aryl, heteroaryl other than imidazole, nitroimidazole and triazole, heteroaryliums other than imidazolium, nitroimidazolium and triazolium, (C₅-C₈) cycloalkyl or (C₅-C₈) heterocycloalkyl;

Ar₂ is aryl or substituted aryl;

Ar₃ is aryl, substituted aryl, biaryl or heteroaryl other than imidazole, nitroimidazole and triazole;

each R is independently selected from the group of -H, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

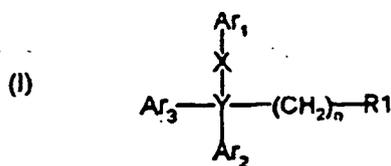
the aryl substituents are each independently selected from the group of -halo, trihalomethyl, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' and -C(S)SR';

the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of -halo, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryl, γ-butyrolactonyl, pyrrolidinyl, pyrrolidinonyl and succinic anhydridyl; and

each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl and (C₁-C₆) alkynyl;

or

one or more compounds having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

X is absent, (C₁-C₃) alkyl, (C₁-C₃) alkenyl, or (C₁-C₃) alkynyl;

Y is C, N, P, Si or Ge;

R₁ is absent, -halo, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(S)R, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, or -CH[C(S)SR]₂;

Ar₁ is aryl, substituted aryl, heteroaryl other than imidazole, nitroimidazole and triazole, heteroaryliums other than imidazolium, nitroimidazolium and triazolium, (C₅-C₈) cycloalkyl or (C₅-C₈) heterocycloalkyl;

Ar₂ is aryl or substituted aryl;

Ar₃ is aryl, substituted aryl, biaryl or heteroaryl other than imidazole, nitroimidazole and triazole;

each R is independently selected from the group of -H, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

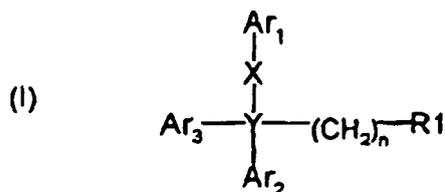
the aryl substituents are each independently selected from the group of -halo, trihalomethyl, -R, -R', -OR', -SR', -N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' and -C(S)SR';

the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of -halo, -R', -OR', -SR', -N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryl, γ-butyrolactonyl, pyrrolidinyl, pyrrolidinonyl and succinic anhydridyl; and

each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl and (C₁-C₆) alkynyl;

or

one or more compounds having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

x is absent, (C₁-C₃) alkyl, (C₁-C₃) alkenyl, or (C₁-C₃) alkynyl;

Y is N, Si or Ge;

15 R₁ is absent, -halo, -R, -OR, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂ or aryl;

Ar₁ is aryl, substituted aryl, heteroaryl other than imidazole, nitroimidazole and triazole, heteroaryliums other than imidazolium, nitroimidazolium and triazolium, (C₅-C₈) cycloalkyl or (C₅-C₈) heterocycloalkyl;

20 Ar₂ is aryl or substituted aryl;

Ar₃ is aryl, substituted aryl, biaryl or heteroaryl other than imidazole, nitroimidazole and triazole;

each R is independently selected from the group of -H, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

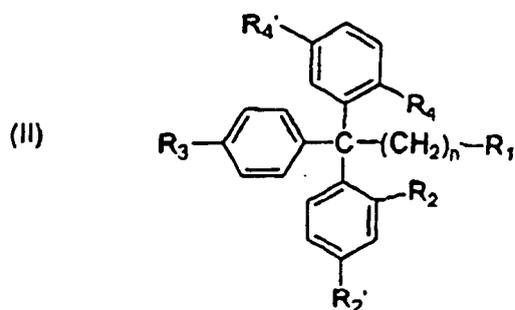
25 the aryl substituents are each independently selected from the group of -halo, trihalomethyl, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' and -C(S)SR';

the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of -halo, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryl, γ-butyrolactonyl, pyrrolidinyl pyrrolidinonyl and succinic anhydridyl; and

30 each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl and (C₁-C₆) alkynyl;

or

one or more compounds having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

R₁ is -H, -OR, -SR, -CN, -C(O)R, -C(O)OR, -C(O)N(R)₂, -CH[C(O)R]₂ or -CH[C(O)OR]₂;

50 R₂ is -F, -Cl, -Br, -I, -OR, -SR, -C(O)R or -C(O)N(R)₂;

R₂' is -H or -NO₂;

R₃ is -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, -OR or -SR;

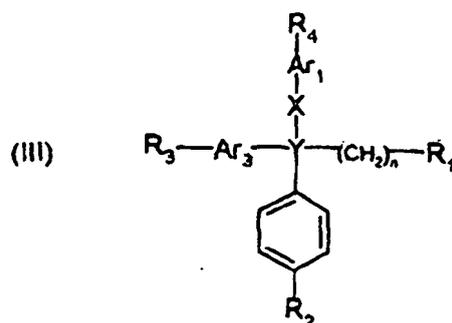
R₄ is -H or -N(R)₂;

55 R₄' is -H, -F, -Cl, -Br or -I; and

each R_i is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl or (C₁-C₆) alkoxy;

except that the compound is other than 1-(2-chlorophenyl)-1,1-diphenyl methanol, 1-(2-chlorophenyl)-1,1-diphenyl methane or 1-(2-chlorophenyl)-1-(4-hydroxyphenyl)-1-phenyl methane;

or
one or more compounds having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is absent or -C≡C-;

Y is C, Si or Ge;

n is 0, 1, 2, 3 or 4;

Ar₁ is phenyl, substituted phenyl, cycloalkyl or heteroarylium other than imidazolium, nitroimidazolium or triazolium;

Ar₃ is phenyl, naphthyl, piperidyl or cyclohexyl;

R₁ is -R, -OR, -SR, -CN, -N(R)₂, -ONR₂, -C(O)R, -C(O)OR, -C(O)N(R)₂, -CH[C(O)R]₂, -CH[C(O)OR]₂, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₅) alkynyl, cyclopenta-2,4-diene-1-ylidene or phenyl;

each of R₂, R₃ and R₄ is independently selected from the group of -H, -F, -Cl, -Br, -I, -OR, -SR, -N(R)₂, -NO₂, -C(O)R, -C(O)OR, -C(O)N(R)₂, trihalomethyl, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and phenyl;

each R is independently selected from the group of -H, halo, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

the alkyl, alkenyl or alkynyl substituents are each independently selected from the group of aryl, -C(O)OR, pyrrolidinyl, pyrrolidinonyl, butyrolactonyl, -F, -Cl, -Br, -I and -CN; and

the phenyl substituents are each independently -R: except that the compound is other than 1-(2-chlorophenyl)-1,1-diphenyl methanol, 1-(2-chlorophenyl)-1,1-diphenyl methane or 1-(2-chlorophenyl)-1-(4-hydroxyphenyl)-1-phenyl methane.

[0011] The compound or composition may act either cytostatically, cytotoxicity or by a combination of both mechanisms to inhibit proliferation. Mammalian cells in this manner include vascular smooth muscle cells, fibroblasts, endothelial cells, various types of pre-cancer cells and various types of cancer cells.

[0012] In still another aspect, the invention enables treating and/or preventing unwanted or abnormal cell proliferation in a subject, such as a human. In the method, at least one compound according to the invention, or a pharmaceutical composition thereof, is to be administered to a subject in need of such treatment in an amount effective to inhibit the unwanted or abnormal mammalian cell proliferation. The compound and/or composition may be applied locally to the proliferating cells, or may be administered to the subject systemically. Preferably, the compound and/or composition is to be administered to a subject that has a disorder characterized by unwanted or abnormal cell proliferation. Such disorders include, but are not limited to, cancer, epithelial precancerous lesions or non-cancerous angiogenic conditions.

[0013] In another aspect, the invention enables the treatment and/or prevention of diseases that are characterized by unwanted and/or abnormal mammalian cell proliferation. This involves a prophylactically or therapeutically effective amount of at least one compound according to the invention, or a pharmaceutical composition thereof, to be administered to a subject in need of such treatment. Diseases that are characterized by abnormal mammalian cell proliferation which can be treated or prevented by using the compounds or pharmaceutical compositions of the invention include, but are not limited to, cancer, actinic keratosis, Kaposi's sarcoma, blood vessel proliferative disorders, and fibrotic disorders.

[0014] In yet another aspect, the invention enables use of the compounds of the invention for the manufacture of a medicament for treating diseases that are characterized by abnormal mammalian cell proliferation. Such diseases include, but are not limited to, cancer, actinic keratosis, Kaposi's sarcoma, blood vessel proliferative disorders, and fibrotic disorders.

4.1 Definitions

[0015] As used herein, the following terms shall have the following meanings:

5 "Alkyl:" refers to a saturated branched, straight chain or cyclic hydrocarbon radical. Typical alkyl groups include methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, t-butyl, cyclobutyl, pentyl, isopentyl, cyclopentyl, hexyl, cyclohexyl and the like.

10 "Heterocycloalkyl:" refers to a saturated cyclic hydrocarbon radical wherein one or more of the carbon atoms is replaced with another atom such as Si, Ge, N, O, S or P. Typical heterocycloalkyl groups include, but are not limited to, morpholino, thiolino, piperidyl, pyrrolidinyl, piperazyl, pyrazolidyl, imidazolidinyl, and the like.

15 "Alkenyl:" refers to an unsaturated branched, straight chain or cyclic hydrocarbon radical having at least one carbon-carbon double bond. The radical may be in either the *cis* or *trans* conformation about the double bond(s). Typical alkenyl groups include ethenyl, propenyl, isopropenyl, cyclopropenyl, butenyl, isobutenyl, cyclobutenyl, *tert*-butenyl, pentenyl, hexenyl and the like.

20 "Alkynyl:" refers to an unsaturated branched, straight chain or cyclic hydrocarbon radical having at least one carbon-carbon triple bond. Typical alkynyl groups include ethynyl, propynyl, butynyl, isobutynyl, pentynyl, hexynyl and the like.

"Alkoxy:" refers to an -OR radical, where R is alkyl, alkenyl or alkynyl, as defined above.

25 "Aryl:" refers to an unsaturated cyclic hydrocarbon radical having a conjugated π electron system. Typical aryl groups include, but are not limited to, penta-2,4-diene, phenyl, naphthyl, anthracyl, azulenyl, indacenyl, and the like.

30 "Heteroaryl:" refers to an aryl group wherein one or more of the ring carbon atoms is replaced with another atom such as N, O or S. Typical heteroaryl groups include, but are not limited to, furanyl, thienyl, indolyl, pyrrolyl, pyranyl, pyridyl, pyrimidyl, pyrazyl, pyridazyl, and the like.

"Heteroarylium:" refers to a heteroaryl group wherein one or more hydrogens has been added to any position of the neutral parent ring. Typical heteroarylium groups include, but are not limited to, pyridinium, pyrazinium, pyrimidinium, pyridazinium, 1,3,5-triazinium, and the like.

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

40 5. DETAILED DESCRIPTION OF THE INVENTION

[0016] As discussed in the Background section, the modulation of early ionic mitogenic signals and inhibition of cell proliferation are powerful therapeutic approaches towards the treatment and/or prevention of disorders characterized by abnormal cell proliferation. It has been shown that Clotrimazole, in addition to inhibiting the Gardos channel of erythrocytes, also modulates ionic mitogenic signals and inhibits cell proliferation both *in vitro* and *in vivo*.

45 **[0017]** For example, Clotrimazole inhibits the rate of cell proliferation of normal and cancer cell lines in a reversible and dose-dependent manner *in vitro* (Benzaquen *et al.*, 1995 *Nature Medicine* 1:534-540). Clotrimazole also depletes the intracellular Ca^{2+} stores and prevents the rise in cytosolic Ca^{2+} that normally follows mitogenic stimulation. Moreover, in mice with severe combined immunodeficiency disease (SCID) and inoculated with MM-RU human melanoma cells, daily administration of Clotrimazole resulted in a significant reduction in the number of lung metastases observed (Benzaquen *et al.*, *supra*).

50 **[0018]** Quite surprisingly, it has now been discovered that the imidazole-like ring moieties of Clotrimazole and the other above-mentioned antimycotic agents, which are well-recognized as the essential functionality underlying their antimycotic and other biological activities, is not the underlying functionality responsible for effecting inhibition of the Gardos channel or inhibition of mitogen-induced mammalian cell proliferation. Thus, based in part on this surprising discovery, in one aspect the present invention provides a new class of organic compounds that are capable of inhibiting mammalian cell proliferation, particularly mitogen-induced cell proliferation.

[0019] The compounds of the invention are potent, specific inhibitors of mammalian cell proliferation. Thus, in another

aspect, the invention enables inhibiting mammalian cell proliferation as a therapeutic approach towards the treatment or prevention of diseases characterized by unwanted or abnormal cell proliferation. In its broadest sense, this involves an effective amount of at least one pharmacologically active compound according to the invention to be administered to a mammalian cell in situ. The compound may act cytostatically, cytotoxically, or by a combination of both mechanisms to inhibit cell proliferation. Mammalian cells treatable in this manner include vascular smooth muscle cells, fibroblasts, endothelial cells, various pre-cancer cells and various cancer cells. In a preferred embodiment, cell proliferation is to be inhibited in a subject suffering from a disorder that is characterized by unwanted or abnormal cell proliferation. Such diseases are described more fully below.

[0020] Based in part on the surmised role of mammalian cell proliferation in certain diseases, the invention enables the treatment or prevention of diseases characterized by abnormal cell proliferation. This involves, an effective amount of at least one compound according to the invention, or a pharmaceutical composition thereof, is to be administered to a patient suffering from a disorder that is characterized by abnormal cell proliferation. While not intending to be bound by any particular theory, it is believed that administration of an appropriate amount of a compound according to the invention to a subject inhibits cell proliferation by altering the ionic fluxes associated with early mitogenic signals. Such alteration of ionic fluxes is thought to be due to the ability of the compounds of the invention to inhibit potassium channels of cells, particularly Ca^{2+} -activated potassium channels. The described method can be used prophylactically to prevent unwanted or abnormal cell proliferation, or may be used therapeutically to reduce or arrest proliferation of abnormally proliferating cells. The compound, or a pharmaceutical formulation thereof, can be applied locally to proliferating cells to arrest or inhibit proliferation at a desired time, or may be administered to a subject systemically to arrest or inhibit cell proliferation.

[0021] Diseases which are characterized by abnormal cell proliferation that can be treated or prevented by means of the present invention include blood vessel proliferative disorders, fibrotic disorders, and various cancers.

[0022] Blood vessel proliferation disorders refer to angiogenic and vasculogenic disorders generally resulting in abnormal proliferation of blood vessels. The formation and spreading of blood vessels, or vasculogenesis and angiogenesis, respectively, play important roles in a variety of physiological processes such as embryonic development, corpus luteum formation, wound healing and organ regeneration. They also play a pivotal role in cancer development. Other examples of blood vessel proliferative disorders include arthritis, where new capillary blood vessels invade the joint and destroy cartilage and ocular diseases such as diabetic retinopathy, where new capillaries in the retina invade the vitreous, bleed and cause blindness and neovascular glaucoma.

[0023] Another example of abnormal neovascularization is that associated with solid tumors. It is now established that unrestricted growth of tumors is dependent upon angiogenesis and that induction of angiogenesis by liberation of angiogenic factors can be an important step in carcinogenesis. For example, basic fibroblast growth factor (bFGF) is liberated by several cancer cells and plays a crucial role in cancer angiogenesis. The demonstration that certain animal tumors regress when angiogenesis is inhibited has provided the most compelling evidence for the role of angiogenesis in tumor growth. Other cancers that are associated with neovascularization include hemangioendotheliomas, hemangiomas and Kaposi's sarcoma.

[0024] Proliferation of endothelial and vascular smooth muscle cells is the main feature of neovascularization. The invention is useful in inhibiting such proliferation, and therefore in inhibiting or arresting altogether the progression of the angiogenic condition which depends in whole or in part upon such neovascularization. The invention is particularly useful when the condition has an additional element of endothelial or vascular smooth muscle cell proliferation that is not necessarily associated with neovascularization. For example, psoriasis may additionally involve endothelial cell proliferation that is independent of the endothelial cell proliferation associated with neovascularization. Likewise, a solid tumor which requires neovascularization for continued growth may also be a tumor of endothelial or vascular smooth muscle cells. In this case, growth of the tumor cells themselves, as well as the neovascularization, is inhibited by the compounds described herein.

[0025] The invention is also useful for the treatment of fibrotic disorders such as fibrosis and other medical complications of fibrosis which result in whole or in part from the proliferation of fibroblasts. Medical conditions involving fibrosis (other than atherosclerosis, discussed below) include undesirable tissue adhesion resulting from surgery or injury.

[0026] Vascular injury can also result in endothelial and vascular smooth muscle cell proliferation. The injury can be caused by any number of traumatic events or interventions, including vascular surgery and balloon angioplasty. Restenosis is the main complication of successful balloon angioplasty of the coronary arteries. It is believed to be caused by the release of growth factors as a result of mechanical injury to the endothelial cells lining the coronary arteries. Thus, by inhibiting unwanted endothelial and smooth muscle cell proliferation, the compounds described herein can be used to delay, or even avoid, the onset of restenosis.

[0027] Other conditions which can be treated or prevented by means of the present invention include diseases of the arterial walls that involve proliferation of endothelial and/or vascular smooth muscle cells, such as complications of diabetes, diabetic glomerulosclerosis and diabetic retinopathy.

[0028] The compounds described herein are also useful in treating or preventing various types of cancers. Cancers

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

[0029] The compounds of the invention are useful with hormone dependent and also with nonhormone dependent cancers. They also are useful with prostate and nonprostate cancers and with breast and nonbreast cancers. They further are useful with multidrug resistant strains of cancer.

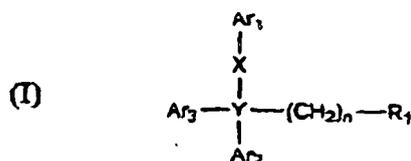
[0030] In addition to the particular disorders enumerated above, the invention is also useful in treating or preventing dermatological diseases including keloids, hypertrophic scars, seborrheic dermatosis, papilloma virus infection (e.g., producing verruca vulgaris, verruca plantaris, verruca plan, condylomata, etc.), eczema and epithelial precancerous lesions such as actinic keratosis; other inflammatory diseases including proliferative glomerulonephritis; lupus erythematosus; scleroderma; temporal arthritis; thromboangiitis obliterans; mucocutaneous lymph node syndrome; and other pathologies mediated by growth factors including uterine leiomyomas.

[0031] The compounds of the invention provide myriad advantages over agents commonly used to treat sickle cell disease and/or cell proliferative disorders. The compounds of the invention also provide myriad advantages over the treatment of cell proliferative disorders with Clotrimazole or other antimycotic agents. For example, many of the compounds of the invention are more potent than Clotrimazole in *in vitro* tests, and therefore may provide consequential therapeutic advantages in clinical settings.

[0032] Most significantly, the compounds of the invention have reduced toxicity as compared with these other agents. For Clotrimazole, it is well-known that the imidazole moiety is responsible for inhibiting a wide range of cytochrome P-450 isozyme catalyzed reactions, which constitutes their main toxicological effects (Pappas and Franklin, 1993, *Toxicology* 80:27-35; Matsuura *et al.*, 1991, *Biochemical Pharmacology* 41:1949-1956). Analogues and metabolites of Clotrimazole do not induce cytochrome P-450 (Matsuura *et al.*, 1991, *Biochemical Pharmacology* 41:1949-1956), and therefore do not share Clotrimazole's toxicity.

5.1 The Compounds

[0033] The compounds which are capable of inhibiting mammalian cell proliferation according to the invention are generally triaryl methane compounds or analogues thereof wherein one or more of the aryl moieties is replaced with a heteroaryl, cycloalkyl or heterocycloalkyl moiety and/or wherein the tertiary carbon is replaced with another atom such as Si, Ge, N or P and are set out in the claims thereafter. In one illustrative embodiment, the compounds of the invention are compounds having the formula:



or a pharmaceutically acceptable salt or hydrate thereof wherein:

n is 0, 1, 2, 3 or 4:

X is absent, (C₁-C₃) alkyl, (C₁-C₃) alkenyl or (C₁-C₃) alkynyl;

Y is C, N, Si or Ge;

R₁ is absent, -halo, -R, -OR, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂ or aryl;

Ar₁ is aryl, substituted aryl, heteroaryl other than imidazole, nitroimidazole and triazole, heteroarylium other than

imidazolium, nitroimidazolium and triazolium, (C₅-C₈) cycloalkyl or (C₅-C₆) heterocycloalkyl;

Ar₂ is aryl or substituted aryl;

Ar₃ is aryl, substituted aryl, biaryl or heteroaryl other than imidazole, nitroimidazole and triazole;

each R is independently selected from the group of -H, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

the aryl substituents are each independently selected from the group of -halo, trihalomethyl, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' and -C(S)SR';

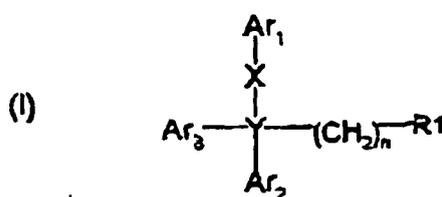
the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of -halo, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryl, γ-butyrolactonyl, pyrrolidinyl, pyrrolidinonyl and succinic anhydridyl;

each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl and (C₁-C₆) alkynyl-;

except that the compound is other than 1-(2-chlorophenyl)-1,1-diphenyl methanol, 1-(2-chlorophenyl)-1,1-diphenyl methane, 1-(2-chlorophenyl)-1-1(4-hydroxyphenyl)-1-phenyl methane;

or

compounds having the structural formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

X is absent, (C₁-C₃) alkyl, (C₁-C₃) alkenyl, or (C₁-C₃) alkynyl;

Y is C, N, P, Si or Ge;

R₁ is absent, -halo, -OR, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(S)R, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, or -CH[C(S)SR];

Ar₁ is aryl, substituted aryl, heteroaryl other than imidazole, nitroimidazole and triazole, heteroaryliums other than imidazolium, nitroimidazolium and triazolium, (C₅-C₆) cycloalkyl or (C₅-C₆) heterocycloalkyl;

Ar₂ is aryl or substituted aryl;

Ar₂ is aryl, substituted aryl, biaryl or heteroaryl other than imidazole, nitroimidazole and triazole;

each R is independently selected from the group of -H, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₅) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

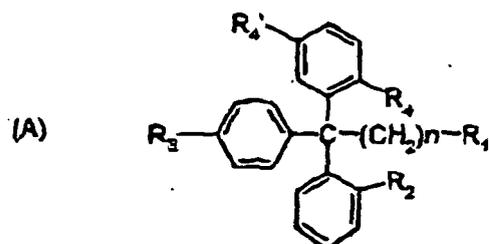
the aryl substituents are each independently selected from the group of -halo, trihalomethyl, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' and -C(S)SR';

the alkyl, alkenyl and alkynyl- substituents are each independently selected from the group of halo, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryl, γ-butyrolactonyl, pyrrolidinyl, pyrrolidinonyl and succinic anhydridyl; and

each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl and (C₁-C₆) alkynyl.

[0034] In another aspect, the present invention provides:

a) a compound having the formula (A):



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4:

15 R_1 is -H, -OR, -SR, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -CH [C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂;

R_2 is -F, -Cl, -Br or -I;

R_3 is -R, -OR or -SR;

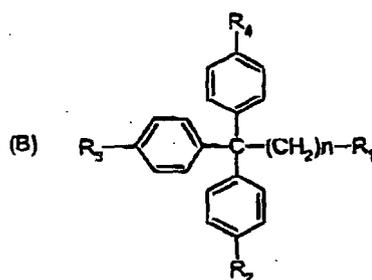
R_4 is -H or -N(R)₂;

R_4' is -H, -F, -Cl, -Br or -I; and

20 each R is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and (C₁-C₆) alkoxy,

with the provisos that (i) when n is 0 and R_1 is -H or -OH, R_3 is other than -H; and (ii) when n is 0 and R_1 is -H, R_3 is other than -OH;

25 b) a compound of formula (B):



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

40 n is 0, 1, 2, 3 or 4;

R_1 is -N(R)₂, -C(O)R, -C(S)R, -C(O)N(R')₂ or -C(S)N(R')₂;

R_2 is -F, -Cl, -Br or -I;

R_3 is -F, -Cl, -Br or -I;

R_4 is -F, -Cl, -Br or -I;

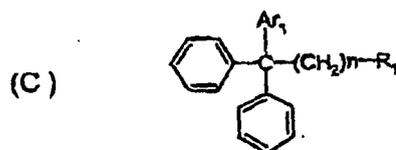
45 each R is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and (C₁-C₆) alkoxy; and

each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

50 with the proviso that when $R_2 = R_3 = R_4 = \text{Cl}$, and $R_1 = \text{NH}_2$, then n = 1, 3 or 4;

and

c) compound of formula (C) :



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

Ar₁ is phenyl or cyclohexyl;

R₁ is -N(R)₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -C(O)N(R)₂ or -C(S)N(R)₂; and each R is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and (C₁-C₆) alkoxy, with the proviso that when R₁ is -NH₂ or -C(O)NH₂, then n is 1, 2 or 3; and when:

(i) when Ar₁ = Ph, and R₁ = -NHR, wherein R is (C₁-C₄) alkyl, -CH(CH₃)(CH₂)₂CH₃, -CH(C₂H₅)₂, -CH(CH₃)CH(CH₃)CH₂CH₃, -CH(CH₃)CH₂CH(CH₃)CH₃, cyclohexyl; -OCH₃; -(CH₂)₅CH₃; -(CH₂)₄CH₃; -CH₂CH=CH₂, -CH(CH₃)CH=CH₂, -CH[CH₂CH(CH₃)₂]CH=CH₂, then n = 1, 2, 3 or 4;

(ii) when Ar₁ = Ph, and R₁ = -NR₂, wherein one of the R group is -CH(C≡CH)₂ and the other R group is -CH₂C≡CH or -CH₂CH₂C≡CH, then n = 1, 2, 3 or 4;

(iii) when Ar₁ = Ph, and R₁ = -NR₂, wherein one of the R group is -CH₂CH₃ and the other R group is -CH₃ or -CH₂C(CH₃)=CH₂, then n = 1, 2, 3 or 4;

(iv) when Ar₁ = Ph, and R₁ = N(CH₃)₂ or N(CH₂CH₃)₂, then n = 2, 3 or 4;

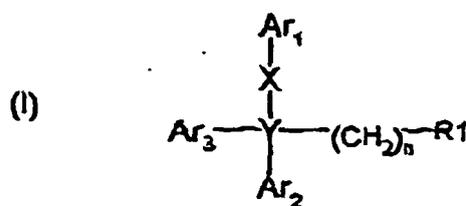
(v) when Ar₁ = Ph, and R₁ = NH(t-Bu) or C(O)NH₂, then n = 0, 2, 3 or 4;

(vi) when Ar₁ = Ph, and R₁ = NH₂, then n = 3 or 4;

(vii) when Ar₁ = Ph, and R₁ = -C(O)N(CH₃)₂ or -C(O)N(CH₃)cyclohexane or -CH[C(O)OC₂H₅]₂, then n = 1, 2, 3 4;

(viii) when Ar₁ = cyclohexyl, R₁ = N(CH₂CH₂)₂, then n = 0, 1, 2, or 4.

[0035] In another aspect, the present invention provides pharmaceutical compositions comprising one or more compounds according to the invention in admixture with a pharmaceutically acceptable carrier, excipient or diluent. Such a preparation can be administered in the methods of the invention. The compositions of the instant invention comprise: one or more compounds having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

X is absent, (C₁-C₃) alkyl, (C₁-C₃) alkenyl, or (C₁-C₃) alkynyl;

Y is C or Si;

R₁ is -halo, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)-OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, or -CH[C(S)SR]₂;

Ar₁ is aryl, substituted aryl, heteroaryl other than imidazole, nitroimidazole and triazole, heteroaryliums other than imidazolium, nitroimidazolium and triazolium, (C₅-C₆) cycloalkyl or (C₅-C₈) heterocycloalkyl;

Ar₂ is aryl or substituted aryl;

Ar₃ is aryl, substituted aryl, biaryl or heteroaryl other than imidazole, nitroimidazole and triazole;

each R is independently selected from the group of -H, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

the aryl substituents are each independently selected from the group of -halo, trihalomethyl, -R, -R', -OR', -SR', N

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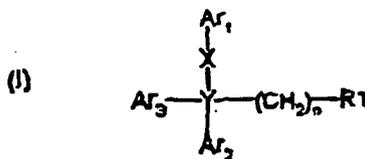
(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' and -C(S)SR';

the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of -halo, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryl, γ-butyrolactonyl, pyrrolidinyl, pyrrolidinonyl and succinic anhydridyl; and

each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl and (C₁-C₆) alkynyl;

or

one or more compounds having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

X is absent, (C₁-C₃) alkyl, (C₁-C₃) alkenyl, or (C₁-C₃) alkynyl;

Y is C, N, P, Si or Ge;

R₁ is absent, -halo, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(S)R, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, or -CH[C(S)SR]₂

Ar₁ is aryl, substituted aryl, heteroaryl other than imidazole, nitroimidazole and triazole, heteroaryliums other than imidazolium, nitroimidazolium and triazolium, (C₅-C₈) cycloalkyl or (C₅-C₈) heterocycloalkyl;

Ar₂ is aryl or substituted aryl;

Ar₃ is aryl, substituted aryl, biaryl or heteroaryl other than imidazole, nitroimidazole and triazole;

each R is independently selected from the group of -H, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

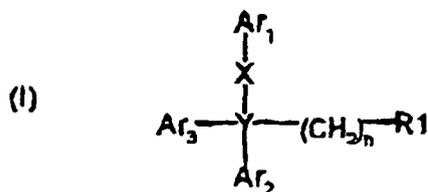
the aryl substituents are each independently selected from the group of -halo, trihalomethyl, -R, -R', -OR', -SR', -N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' and -C(S)SR';

the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of -halo, -R', -OR', -SR', -N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryl, γ-butyrolactonyl, pyrrolidinyl, pyrrolidinonyl and succinic anhydridyl; and

each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl and (C₁-C₆) alkynyl;

or

one or more compounds having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

x is absent, (C₁-C₃) alkyl, (C₁-C₃) alkenyl, or (C₁-C₃) alkynyl;

Y is N, Si or Ge;

R₁ is absent, -halo, -R, -OR, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂ or aryl;

Ar₁ is aryl, substituted aryl, heteroaryl other than imidazole, nitroimidazole and triazole, heteroaryliums other than imidazolium, nitroimidazolium and triazolium, (C₅-C₈) cycloalkyl -or (C₅-C₈) heterocycloalkyl;

Ar₂ is aryl or substituted aryl;

Ar₃ is aryl, substituted aryl, biaryl or heteroaryl other than imidazole, nitroimidazole and triazole;

5 each R is independently selected from the group of -H, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

the aryl substituents are each independently selected from the group of -halo, trihalomethyl, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' and -C(S)SR';

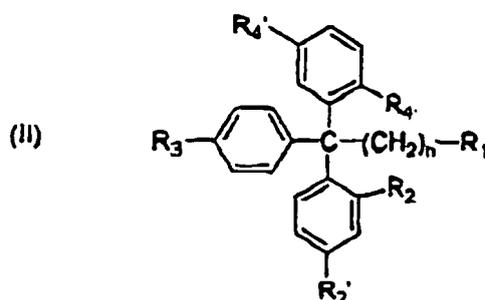
10 the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of -halo, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryl, γ-butyrolactonyl, pyrrolidinyl pyrrolidinonyl and succinic anhydridyl; and

each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl and (C₁-C₆) alkynyl;

or

15 one or more compounds having the formula:

20



25

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

30

n is 0, 1, 2, 3 or 4;

R₁ is -H, -OR, -SR, -CN, -C(O)R, -C(O)OR, -C(O)N(R)₂, -CH[C(O)R]₂ or -CH[C(O)OR]₂;

R₂ is -F, -Cl, -Br, -I, -OR, -SR, -C(O)R or -C(O)N(R)₂;

R₂' is -H or -NO₂;

35

R₃ is -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, -OR or -SR;

R₄ is -H or -N(R)₂;

R₄' is -H, -F, -Cl, -Br or -I; and

each R is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl or (C₁-C₆) alkoxy;

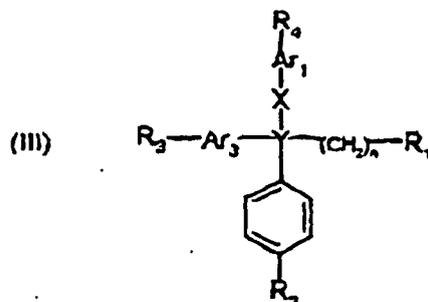
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except that the compound is other than 1-(2-chlorophenyl)-1,1-diphenyl methanol, 1-(2-chlorophenyl)-1,1-diphenyl methane or 1-(2-chlorophenyl)-1-(4-hydroxyphenyl)-1- phenyl methane;

or

one or more compounds having the formula:

45



50

55

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is absent or $-C\equiv C-$;

Y is C, Si or Ge;

n is 0, 1, 2, 3 or 4;

Ar_1 is phenyl, substituted phenyl, cycloalkyl or heteroaryl other than imidazolium, nitroimidazolium or triazolium;

Ar_1 is phenyl, naphthyl, piperidyl or cyclohexyl;

R_1 is $-R$, $-OR$, $-SR$, $-CN$, $-N(R)_2$, $-ONR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)N(R)_2$, $-CH[C(O)R]_2$, $-CH[C(O)OR]_2$, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, cyclopenta-2,4-diene-1-ylidene or phenyl;

each of R_2 , R_3 and R_4 is independently selected from the group of $-H$, $-F$, $-Cl$, $-Br$, $-I$, $-OR$, $-SR$, $-N(R)_2$, $-NO_2$, $-C(O)R$, $-C(O)OR$, $-C(O)N(R)_2$, trihalomethyl, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl and phenyl;

each R is independently selected from the group of $-H$, halo, (C_1-C_6) alkyl, substituted (C_1-C_6) alkyl, (C_1-C_6) alkenyl, substituted (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, substituted (C_1-C_6) alkynyl and (C_1-C_6) alkoxy;

the alkyl, alkenyl or alkynyl substituents are each independently selected from the group of aryl, $-C(O)OR$, pyrrolidinyl, pyrrolidinonyl, butyrolactonyl, $-F$, $-Cl$, $-Br$, $-I$ and $-CN$; and

the phenyl substituents are each independently $-R$; except that the compound is other than 1-(2-chlorophenyl)-1,1-diphenyl methanol, 1-(2-Chlorophenyl)-1,1-diphenyl-methane or 1-(2-chlorophenyl)-1-(4-hydroxyphenyl)-1-phenyl methane.

[0036] The compound or composition may act either cytostatically, cytotoxically or a by a combination of both mechanisms to inhibit proliferation. Mammalian cells in this manner include vascular smooth muscle cells, fibroblasts, endothelial cells, various types of pre-cancer cells and various types of cancer cells.

[0037] In still another aspect, the invention enables treating and/or preventing unwanted or abnormal cell proliferation in a subject, such as a human. In the method, at least one compound according to the invention, or a pharmaceutical composition thereof, is to be administered to a subject in need of such treatment in an amount effective to inhibit the unwanted or abnormal mammalian cell proliferation. The compound and/or composition may be applied locally to the proliferating cells, or may be administered to the subject systemically. Preferably, the compound and/or composition is to be administered to a subject that has a disorder characterized by unwanted or abnormal cell proliferation. Such disorders include, but are not limited to, cancer, epithelial precancerous lesions or non-cancerous angiogenic conditions.

[0038] In another aspect, the invention enables the treatment and/or prevention of diseases that are characterized by unwanted and/or abnormal mammalian cell proliferation. This involves a prophylactically or therapeutically effective amount of at least one compound according to the invention, or a pharmaceutical composition thereof, to be administered to a subject in need of such treatment. Diseases that are characterized by abnormal mammalian cell proliferation which can be treated or prevented by using the compounds or pharmaceutical compositions of the invention include, but are not limited to, cancer, actinic keratosis, Kaposi's sarcoma, blood vessel proliferative disorders, and fibrotic disorders.

[0039] In yet another aspect, the invention enables use of the compounds of the invention for the manufacture of a medicament for treating diseases that are characterized by abnormal mammalian cell proliferation. Such diseases include, but are not limited to, cancer, actinic keratosis, Kaposi's sarcoma, blood vessel proliferative disorders, and fibrotic disorders.

[0040] Exemplary preferred compounds according to formula (I) include those listed in TABLE A, below.

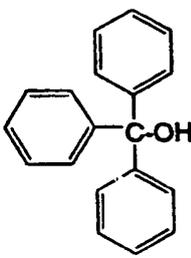
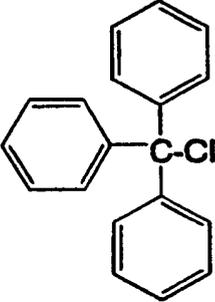
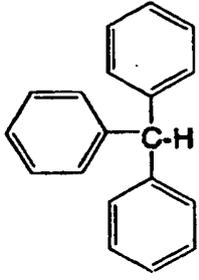
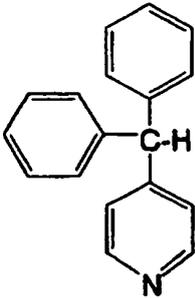
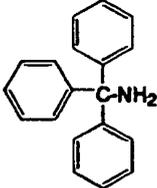
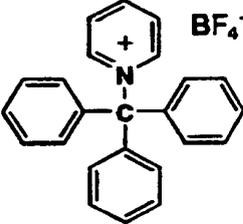
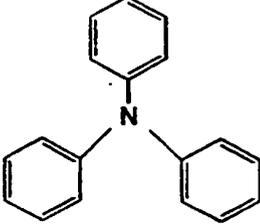
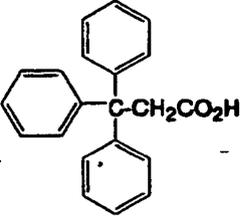
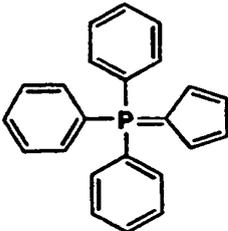
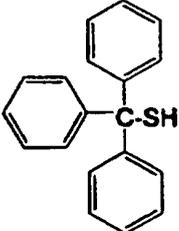
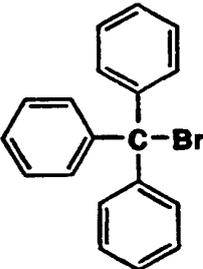
TABLE A		
Exemplary Compounds		
 <p>(1)</p>	 <p>(2)</p>	 <p>(3)</p>

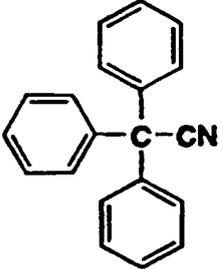
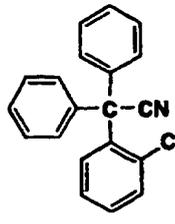
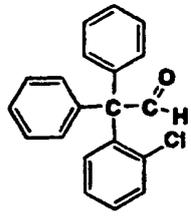
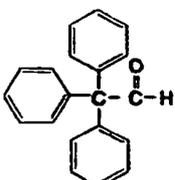
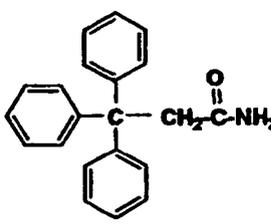
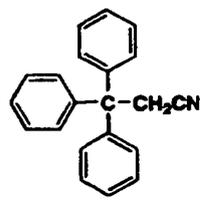
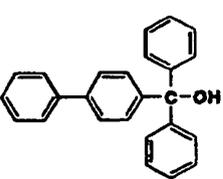
TABLE A
Exemplary Compounds

5 10 15  (4)	 (5)	
20 25 30  (7)	 (8)	 (9)
35 40 45  (10)	 (11)	 (12)

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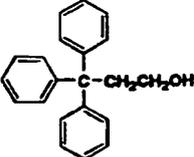
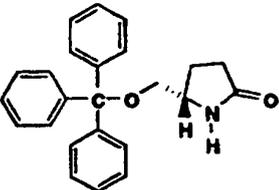
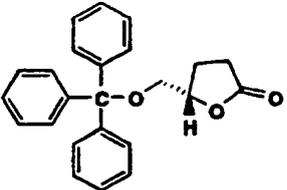
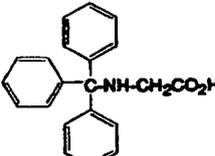
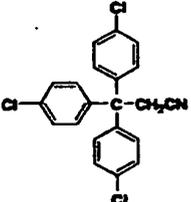
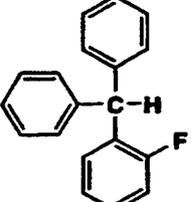
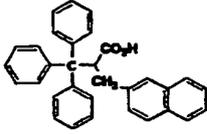
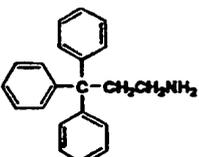
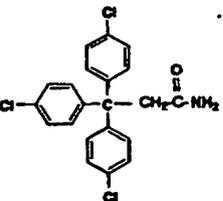
TABLE A
Exemplary Compounds

<p>5</p> <p>10</p> <p>15</p>  <p>(13)</p>	 <p>(14)</p>	 <p>(15)</p>
<p>20</p> <p>25</p>  <p>(16)</p>		 <p>(18)</p>
<p>35</p> <p>40</p> <p>45</p>  <p>(19)</p>	 <p>(20)</p>	 <p>(21)</p>

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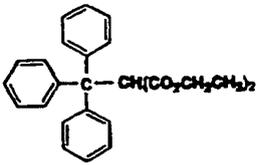
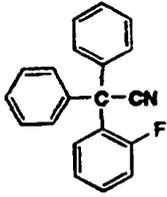
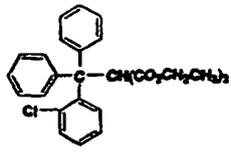
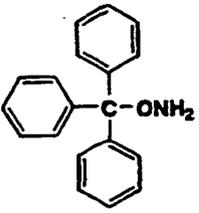
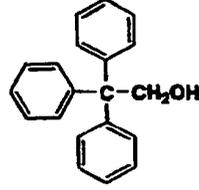
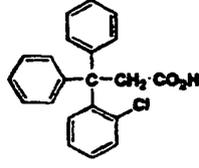
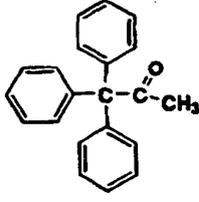
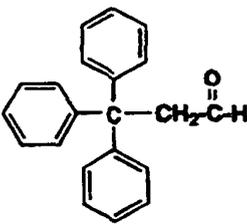
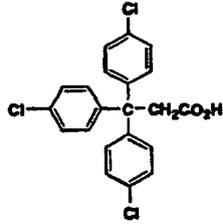
TABLE A
Exemplary Compounds

5 10 15	 (22)	 (23)	 (24)
20 25 30	 (25)	 (26)	 (27)
35 40 45	 (28)	 (29)	 (30)

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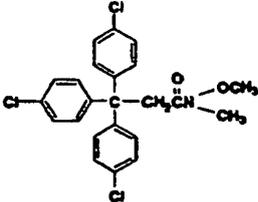
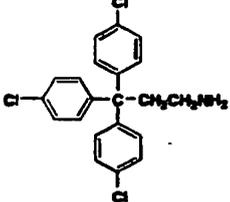
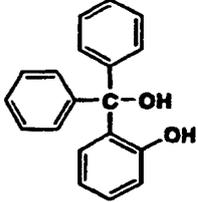
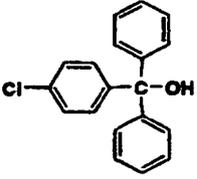
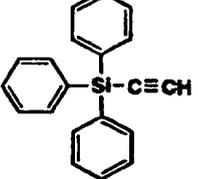
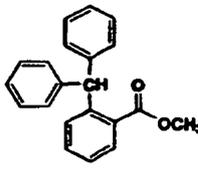
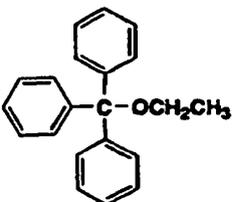
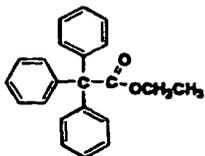
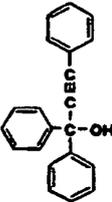
TABLE A
Exemplary Compounds

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<p>20</p> <p>25</p>  <p>(34)</p>	 <p>(35)</p>	 <p>(36)</p>
<p>35</p> <p>40</p>  <p>(37)</p>	 <p>(38)</p>	 <p>(39)</p>

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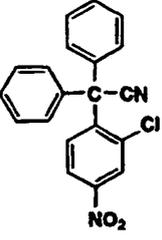
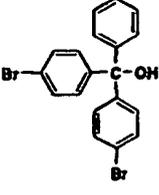
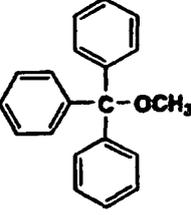
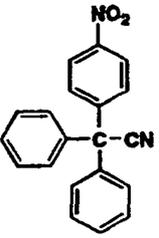
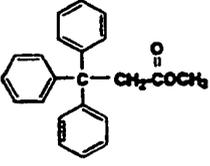
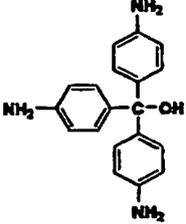
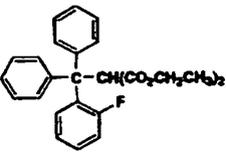
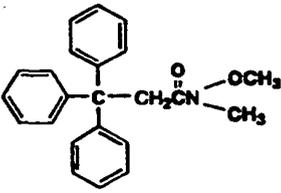
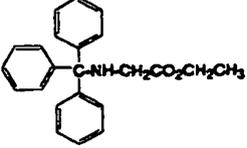
TABLE A
Exemplary Compounds

<p>5</p> <p>10</p> <p>15</p>  <p>(40)</p>	 <p>(41)</p>	 <p>(42)</p>
<p>20</p> <p>25</p>  <p>(43)</p>	 <p>(44)</p>	 <p>(45)</p>
<p>35</p> <p>40</p>  <p>(46)</p>	 <p>(47)</p>	 <p>(48)</p>

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TABLE A
Exemplary Compounds

<p>5</p> <p>10</p> <p>15</p>  <p>(49)</p>	 <p>(50)</p>	 <p>(51)</p>
<p>20</p> <p>25</p> <p>30</p>  <p>(52)</p>	 <p>(53)</p>	 <p>(54)</p>
<p>35</p> <p>40</p> <p>45</p>  <p>(55)</p>	 <p>(56)</p>	 <p>(57)</p>

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TABLE A
Exemplary Compounds

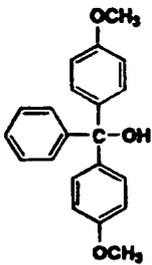
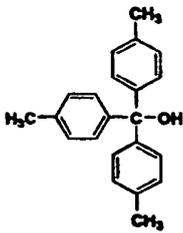
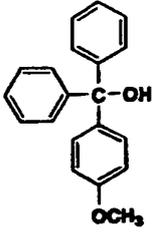
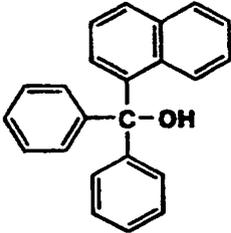
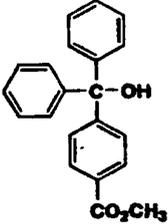
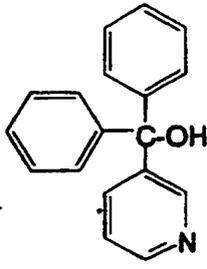
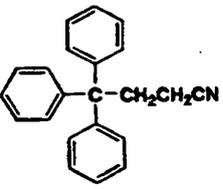
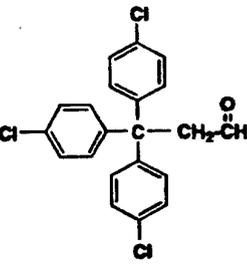
<p>5</p> <p>10</p> <p>15</p>  <p>(58)</p>	 <p>(59)</p>	 <p>(60)</p>
<p>20</p> <p>25</p>  <p>(61)</p>	 <p>(62)</p>	 <p>(63)</p>
<p>35</p> <p>40</p>  <p>(64)</p>	 <p>(65)</p>	 <p>(66)</p>

TABLE A
Exemplary Compounds

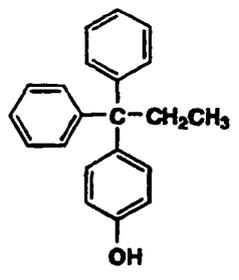
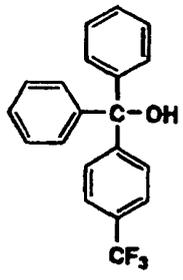
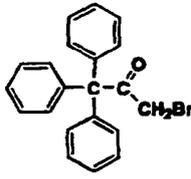
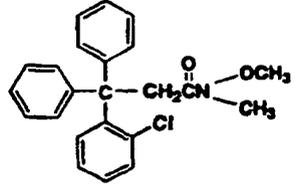
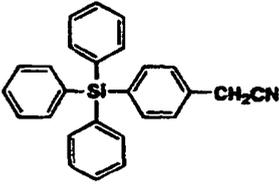
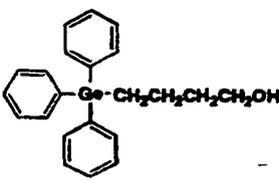
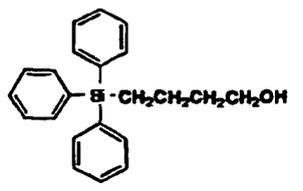
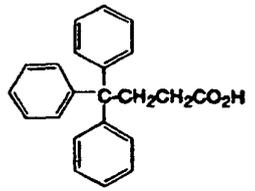
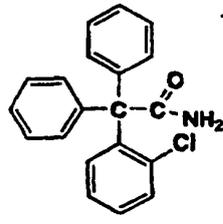
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<p>20</p> <p>25</p> <p>30</p>  <p>(70)</p>	 <p>(71)</p>	 <p>(72)</p>
<p>35</p> <p>40</p> <p>45</p>  <p>(73)</p>	 <p>(74)</p>	 <p>(75)</p>

TABLE A
Exemplary Compounds

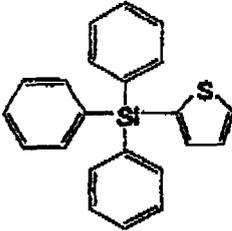
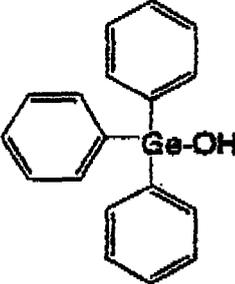
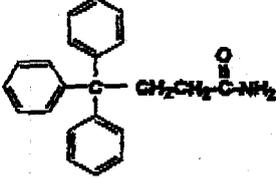
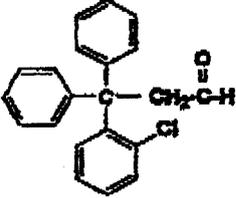
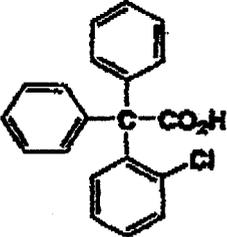
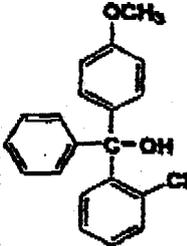
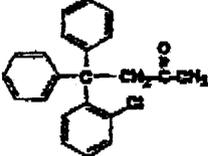
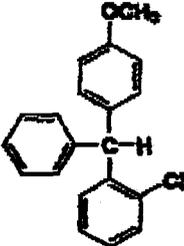
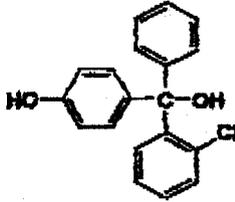
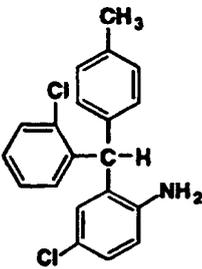
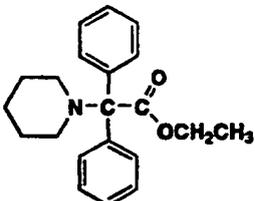
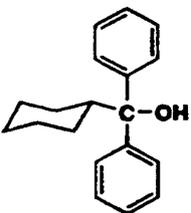
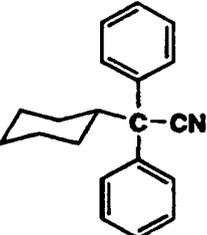
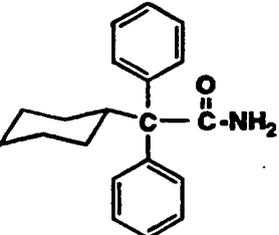
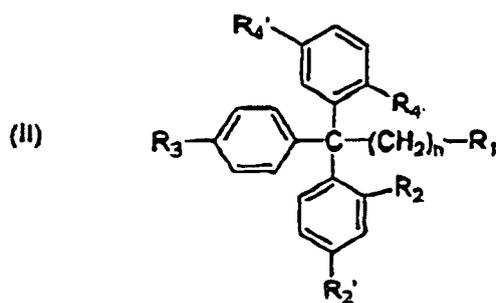
<p>5</p> <p>10</p> <p>15</p>  <p>(76)</p>	 <p>(77)</p>	 <p>(78)</p>
<p>20</p> <p>25</p>  <p>(79)</p>	 <p>(80)</p>	 <p>(81)</p>
<p>35</p> <p>40</p>  <p>(82)</p>	 <p>(83)</p>	 <p>(84)</p>

TABLE A
Exemplary Compounds

<p>5</p> <p>10</p> <p>15</p>	 <p>(86)</p>	 <p>(87)</p>	
<p>20</p> <p>25</p> <p>30</p>	 <p>(88)</p>	 <p>(89)</p>	 <p>(90)</p>

[0041] The compounds will be referred to herein by way of compound numbers as presented in TABLE A, above.

[0042] In another preferred embodiment, the compounds of the invention are compounds having the structural formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

R₁ is -H, -OR, -SR, -CN, -C(O)R, -C(O)OR, -C(O)N(R)₂, -CH[C(O)R]₂ or -CH[C(O)OR]₂;

R₂ is -F, -Cl, -Br, -I, -OR, -SR, -C(O)R or -C(O)N(R)₂;

R₂' is -H or -NO₂;

R_a is -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, -OR or -SR;

R₄ is -H or -N(R)₂;

R₄' is -H, -F, -Cl, -Br or -I; and

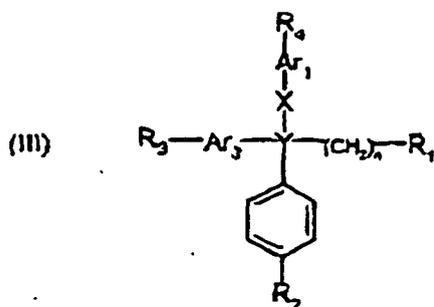
each R is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl or (C₁-C₆)

alkoxy;

except that the compound is other than 1-(2-chlorophenyl)-1,1-diphenyl methanol, 1-(2-chlorophenyl)-1,1-diphenyl methane or 1-(2-chlorophenyl)-1-(4-hydroxyphenyl)-1-phenyl methane;

5 [0043] Exemplary preferred compounds according to formula (II) include the following: **14, 15, 20, 27, 32, 33, 36, 42, 45, 49, 55, 70, 75, 79, 80, 81, 82, 83, and 86.**

[0044] In another preferred embodiment, the compounds of the invention are compounds having the structural formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

X is absent or $-C\equiv C-$;

Y is C, Si or Ge;

n is 0, 1, 2, 3 or 4;

Ar₁ is phenyl, substituted phenyl, cycloalkyl or heteroaryl other than imidazolium, nitroimidazolium or triazolium;

Ar₂ is phenyl, naphthyl, piperidyl or cyclohexyl;

R₁ is $-R$, $-OR$, $-SR$, $-CN$, $-N(R)_2$, $-ONR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)N(R)_2$, $-CH[C(O)R]_2$, $-CH[C(O)OR]_2$, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₅) alkynyl, cyclopenta-2,4-diene-1-ylidene or phenyl;

each of R₂, R₃ and R₄ is independently selected from the group of $-H$, $-F$, $-Cl$, $-Br$, $-I$, $-OR$, $-SR$, $-N(R)_2$, $-NO_2$, $-C(O)R$, $-C(O)OR$, $-C(O)N(R)_2$, trihalomethyl, (C₂-C₆) alkyl, (C₂-C₆) alkenyl, (C₁-C₆) alkynyl and phenyl;

each R is independently selected from the group of $-H$, halo, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

the alkyl, alkenyl or alkynyl substituents are each independently selected from the group of aryl, $-C(O)OR$, pyrrolidinyl, pyrrolidinonyl, butyrolactonyl, $-F$, $-Cl$, $-Br$, $-I$ and $-CN$; and

the phenyl substituents are each independently $-R$; except that the compound is other than 1-(2-chlorophenyl)-1,1-diphenyl methanol, 1-(2-chlorophenyl)-1,1-diphenyl methane or 1-(2-chlorophenyl)-1-(4-hydroxyphenyl)-1-phenyl methane.

40 [0045] Exemplary preferred compounds according to formula (III) include the following: **7, 12, 13, 16, 18, 19, 21, 22, 23, 24, 26, 28, 29, 30, 31, 34, 35, 37, 38, 40, 41, 44, 46, 47, 48, 50, 51, 52, 53, 54, 56, 58, 59, 60, 61, 62, 64, 65, 67, 68, 69, 71, 72, 73, 78, 87, 88, 89 and 90.**

[0046] The chemical formulae referred to herein may exhibit the phenomena of tautomerism or conformational isomerism. As the formulae drawings within this specification can represent only one of the possible tautomeric or conformational isomeric forms, it should be understood that the invention encompasses any tautomeric or conformational isomeric forms which exhibit biological or pharmacological activity as described herein.

[0047] The compounds of the invention may be in the form of free acids, free bases or pharmaceutically effective salts thereof. Such salts can be readily prepared by treating a compound with an appropriate acid. Such acids include, by way of example and not limitation, inorganic acids such as hydrohalic acids (hydrochloric, hydrobromic, etc.), sulfuric acid, nitric acid, phosphoric acid, etc.; and organic acids such as acetic acid, propanoic acid, 2-hydroxyacetic acid, 2-hydroxypropanoic acid, 2-oxopropanoic acid, propandioic acid, butandioic acid, etc. Conversely, the salt can be converted into the free base form by treatment with alkali.

[0048] In addition to the above-described compounds and their pharmaceutically acceptable salts, the invention may employ, where applicable, solvated as well as unsolvated forms of the compounds (e.g. hydrated forms).

[0049] The compounds described herein may be prepared by any processes known to be applicable to the preparation of chemical compounds. Suitable processes are well known in the art. Preferred processes are illustrated by the representative examples. Necessary starting materials may be obtained commercially or by standard procedures of organic chemistry. Moreover, many of the compounds are commercially available.

[0050] An individual compound's relevant activity and potency as an agent to affect mammalian cell proliferation may be determined using standard techniques. Preferentially, a compound is subject to a series of screens to determine its pharmacological activity.

[0051] In most cases, the active compounds of the invention exhibit two pharmacological activities: inhibition of the Gardos channel of erythrocytes and inhibition of mammalian cell proliferation. However, in some cases, the compounds of the invention may exhibit only one of these pharmacological activities. Any compound encompassed by formula (I) which exhibits at least one of these pharmacological activities is considered to be within the scope of the present invention.

[0052] In general, the active compounds of the invention are those which induce at least about 25% inhibition of the Gardos channel of erythrocytes (measured at about 10 μ M) and/or about 25% inhibition of mammalian cell proliferation (measured at about 10 μ M), as measured using *in vitro* assays that are commonly known in the art (see, e.g., Brugnara *et al.*, 1993, *J. Biol. Chem.* 268(12):8760-8768; Benzaquen *et al.*, 1995, *Nature Medicine* 1:534-540). Alternatively, or in addition, the active compounds of the invention generally will have an IC₅₀ (concentration of compound that yields 50% inhibition) for inhibition of the Gardos channel of less than about 10 μ M and/or an IC₅₀ for inhibition of cell proliferation of less than about 10 μ M, as measured using *in vitro* assays that are commonly known in the art (see, e.g., Brugnara *et al.*, 1993, *J. Biol. Chem.* 268(12):8760-8768; Benzaquen *et al.*, 1995, *Nature Medicine* 1:534-540).

[0053] Representative active compounds according to the invention are those listed in TABLE A, *supra*.

[0054] In certain embodiments of the invention, compounds which exhibit only one pharmacological activity, or a higher degree of one activity, may be preferred.

[0055] When the compound is to be used in methods to treat or prevent disorders characterized by abnormal cell proliferation or in methods to inhibit cell proliferation *in situ*, it is preferable that the compound exhibit at least about 75% inhibition of mitogen-induced cell proliferation (measured at about 10 μ M) and/or have an IC₅₀ of cell proliferation of less than about 3 μ M, with at least about 90% inhibition and/or an IC₅₀ of less than about 1 μ M being particularly preferred.

[0056] Exemplary preferred compounds for use in methods inhibiting mammalian cell proliferation or for the treatment or prevention of diseases characterized by abnormal cell proliferation include compound numbers **13, 14, 15, 16, 18, 19, 21, 26, 27, 28, 30, 31, 36, 38, 40, 41, 42, 43, 45, 46, 47, 48, 49, 50, 52, 54, 59, 61, 65, 67, 68, 70, 71, 72, 73, 79, 82, 83, 86, 89** and **90**.

[0057] Exemplary particularly preferred compounds for use in methods of inhibiting mammalian cell proliferation or for the treatment or prevention of diseases characterized by abnormal cell proliferation include compound numbers **16, 28, 30, 36, 43, 45, 47, 48, 49, 50, 54** and **84**, noting that **84** is not covered in the compound claims hereinafter.

[0058] Certain compounds of formula (I) are commercially available. For example, compound numbers **1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 19, 20, 21, 23, 24, 25, 26, 28, 34, 37, 38, 39, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 54, 57, 59, 60, 61, 62, 66, 67, 69, 71, 72, 73, 76, 77** and **87** are commercially available. However, no biological activity has been reported for these compounds (see, e.g., Hanessian *et al.*, 1976, *Methods Carbohydr. Chem.* 7:63; Paike, 1992, *Mater. Sci.* 18:53-57; Liu & Paike, 1987, *Tetrahedron Lett.* 28(3):3763-3766; Tomioka *et al.*, 1981, *Chem. Lett.* 11:1621-1624; Glidewell *et al.*, 1994, *Acta Crystallogr., Sect C: Cryst. Struct. Commun.* C50:1362-1366; Ponnuswamy *et al.*, 1984, *Acta Crystallogr., Sect C: Cryst. Struct. Commun.* C40(1):142-144; Lewis *et al.*, 1980, *J. Am. Chem. Soc.* 102(14):4659-4664 and CA 083:018922; Illes *et al.*, 1988, *Acta Phytopathologica et Entomologia Hungarica* 23:243-255; and Matsuura *et al.*, 1991, *Biochem. Pharmacol.* 41:1949-1956).

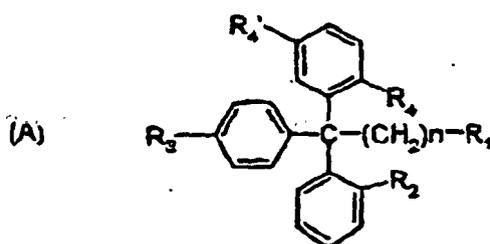
[0059] Apart from the inventions disclosed and claimed herein, additional active compounds of formula (I) for which no biological activity has been previously reported include Compound **13** (U.S. Patent No. 4,006,023); Compound **25** (WO 96/36631); Compound **26** (Fan *et al.*, 1983, *Yiyao Gongye* 9:2-4); Compound **60** (Ethridge *et al.*, 1990, *J. Production Agriculture* 3(2):246-252); Compound **76** (CAS No. 18740-94-8); Compound **77** (Ferguson *et al.*, 1992, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* C48(7):1228-1231); and Compound **90** (1957, *Comptes. Rendus.* 245(1):73-75).

[0060] Apart from the inventions disclosed and claimed herein, other compounds of formula (I) for which no biological activity has been reported include 1,1-diphenyl-1-(2-hydroxynaphthyl)-methanol (Lewis *et al.*, 1980, *J. Am. Chem. Soc.* 102(14):4659-4664; CA 083:018922); 1,1-diphenyl-1-(pyrid-2-yl)-methanol, 1-(4-chlorophenyl)-1-phenyl-1-(pyrid-2-yl)-methanol, 1-(4-methoxyphenyl)-1-phenyl-1-(pyrid-3-yl)-methanol and 1,1-di-(4-methoxyphenyl)-1-(pyrid-3-yl)-methanol (Illes *et al.*, 1988, *Acta Phytopathologica et Entomologia Hungarica* 23:243-255); 1,1,1-triphenyl-1-aminomethane and 1,1-diphenyl-1-(N-pyridyl)-methane (Matsuura *et al.*, 1991, *Biochem. Pharmacol.* 41:1949-1956); 4,4'-dimethoxytrityl chloride, pixyl chloride, di-*o*-anisyl-1-naphthyl-methyl chloride and *p*-anisyl-1-naphthyl-methyl chloride (Gait, 1984, *Oligonucleotide Synthesis: A Practical Approach*, IRL Press, Oxford).

[0061] Additionally, Compounds **6, 17** and **85** are known metabolites of Clotrimazole (Duhm *et al.*, 1974, *Postgraduate Medical Journal July Suppl.*:13-16). However, unlike Clotrimazole, no biological or pharmacological activity has been reported for these compounds. For example, unlike Clotrimazole, Compound **6** does not induce hepatic microsomal cytochrome P450 in rats (Matsuura *et al.*, 1991, *Biochem. Pharmacol.* 41:1949-1956).

[0062] The pharmaceutical compositions of the invention embrace all of the compounds of formula (I). Certain compounds of formula (I) which are included in the invention apart from any pharmaceutical excipients, carriers or diluents are represented by formulae (A), (B) and (C), below.

[0063] In a preferred embodiment, compounds of the invention are compounds having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

15 n is 0, 1, 2, 3 or 4;

R₁ is -H, -OR, -SR, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂;

R₂ is -F, -Cl, -Br or -I;

R₃ is -R, -OR or -SR;

20 R₄ is -H or -N(R)₂;

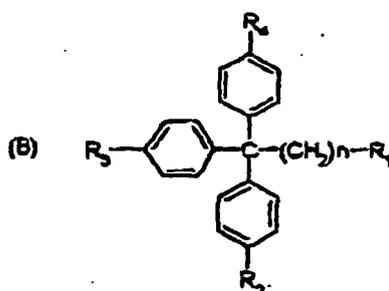
R₄' is -H, -F, -Cl, -Br or -I; and

each R is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and (C₁-C₆) alkoxy,

with the provisos that (i) when n is 0 and R₁ is -H or -OH, R₃ is other than -H; and (ii) when n is 0 and R₁ is -H, R₃

25 [0064] Representative compounds according to formula (A) include Compounds 14, 15, 32, 33, 36, 55, 70, 75, 79, 80, 81, 82, 83, and 86.

[0065] In another preferred embodiment, the compounds of the invention are compounds having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

45 n is 0, 1, 2, 3 or 4;

R₁ is -NR₂, -C(O)R, -C(S)R, -C(O)NR'₂ or -C(S)NR'₂;

R₂ is -F, -Cl, -Br or -I;

R₃ is -F, -Cl, -Br or -I;

R₄ is -F, -Cl, -Br or -I;

50 each R is independently selected from the group of -H, (C₁-C₅) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and (C₁-C₆) alkoxy; and

each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

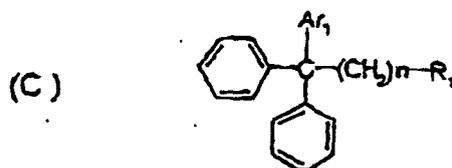
with the proviso that when R₂ = R₃ = R₄ = Cl, R₁ = NH₂, then n = 1, 3 or 4;

55 [0066] Representative preferred compounds according to formula (B) include Compounds 30, 40, and 65.

[0067] In another preferred embodiment, the compounds of the invention are compounds having the formula:

c) a compound of formula (C):

[0068]



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

Ar₁ is phenyl or cyclohexyl;

R₁ is -N(R)₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -C(O)N(R)₂ or -C(S)N(R)₂; and

each R is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and (C₁-C₆) alkoxy,

with the proviso that when R₁ is -NH₂ or -C(O)NH₂, then n is 1, 2 or 3

and when:

(i) when Ar₁=Ph, R₁=-NHR, wherein R is (C₁-C₆) alkyl, -CH(CH₃)(CH₂)₂CH₃, -CH(C₂H₅)₂, -CH(CH₂)CH(CH₃)CH₂CH₂, -CH(CH₃)CH₂CH(CH₃)CH₃, cyclohexyl, -OCH₃, -(CH₂)₃CH₃, -(CH₂)₄CH₃, -CH₂CH=CH₂, -CH(CH₃)CH=CH₂, -CH[CH₂CH(CH₃)₂]CH=CH₂, then n = 1, 2, 3 or 4;

(ii) when Ar₁=Ph, R₁=-NR₂, wherein one of the R group is -CH(C/CH)₂ and the other R group is -CH₂C/CH or -CH₂CH₂C/CH, then n=1, 2, 3 or 4;

(iii) when Ar₁=Ph, R₁=-NR₂, wherein one of the R group is -CH₂CH₃ and the other R group is -CH₃ or -CH₂C(CH₃)=CH₂, then n = 1, 2, 3 or 4;

(iv) when Ar₁=Ph, R₁=N(CH₂)₂ or N(CH₂CH₂)₂, then n=2, 3 or 4;

(v) when Ar₁=Ph, R₁=NH(t-Bu) or C(O)NH₂, then n=0, 2, 3 or 4;

(vi) when Ar₁=Ph, R₁=NH₂, then n=3 or 4;

(vii) when Ar₁=Ph, R₁=-C(O)N(CH₂)₂ or -C(O)N(CH₃) cyclohexane or -CH[C(O)OC₂H₅]₂, then n=1, 2, 3 or 4;

(viii) when Ar₁ = cyclohexyl, R₁ = N(CH₂CH₂)₂, then n = 0, 1, 2, or 4.

[0069] Representative preferred compounds according to formula (C) include compounds 56 and 78.

5.2 Formulation and Routes of Administration

[0070] The compounds described herein, or pharmaceutically acceptable addition salts or hydrates thereof, can be delivered to a patient using a wide variety of routes or modes of administration. Suitable routes of administration include, but are not limited to, inhalation, transdermal, oral, rectal, transmucosal, intestinal and parenteral administration, including intramuscular, subcutaneous and intravenous injections.

[0071] The compounds described herein, or pharmaceutically acceptable salts and/or hydrates thereof, may be administered singly, in combination with other compounds of the invention, and/or in cocktails combined with other therapeutic agents. Of course, the choice of therapeutic agents that can be co-administered with the compounds of the invention will depend, in part, on the condition being treated.

[0072] When administered to a patient undergoing cancer treatment, the compounds may be administered in cocktails containing other anti-cancer agents and/or supplementary potentiating agents. The compounds may also be administered in cocktails containing agents that treat the side-effects of radiation therapy, such as anti-emetics, radiation protectants, etc.

[0073] Anti-cancer drugs that can be co-administered with the compounds of the invention include, e.g., Aminoglutethimide; Asparaginase; Bleomycin; Busulfan; Carboplatin; Carmustine (BCNU); Chlorambucil; Cisplatin (cis-DDP); Cyclophosphamide; Cytarabine HCl; Dacarbazine; Dactinomycin; Daunorubicin HCl; Doxorubicin HCl; Estramustine phosphate sodium; Etoposide (VP-16); Floxuridine; Fluorouracil (5-FU); Flutamide; Hydroxyurea (hydroxycarbamide); Ifosfamide; Interferon Alfa-2a, Alfa 2b, Lueprolide acetate (LHRH-releasing factor analogue); Lomustine (CCNU); Mechlorethamine HCl (nitrogen mustard); Melphalan; Mercaptopurine; Mesna; Methotrexate (MTX); Mitomycin; Mitotane (o.p'-

DDD); Mitoxantrone HCl; Octreotide; Plicamycin; Procarbazine HCl; Streptozocin; Tamoxifen citrate; Thioguanine; Thiotepea; Vinblastine sulfate; Vincristine sulfate; Amsacrine (m-AMSA); Azacitidine; Hexamethylmelamine (HMM); Interleukin 2; Mitoguanone (methyl-GAG; methyl glyoxal bis-guanylhydrazone; MGBG); Pentostatin; Semustine (methyl-CCNU); Teniposide (VM-26); paclitaxel and other taxanes; and Vindesine sulfate.

5 **[0074]** Supplementary potentiating agents that can be co-administered with the compounds of the invention include, e.g., Tricyclic anti-depressant drugs (e.g., imipramine, desipramine, amitriptyline, clomipramine, trimipramine, doxepin, nortriptyline, protriptyline, amoxapine and maprotiline); non-tricyclic and anti-depressant drugs (e.g., sertraline, trazodone and citalopram); Ca⁺⁺ antagonists (e.g., verapamil, nifedipine, nitrendipine and caroverine); Amphotericin (e.g., Tween 80 and perhexiline maleate); Triparanol analogues (e.g., tamoxifen); antiarrhythmic drugs (e.g., quinidine); antihypertensive drugs (e.g., reserpine); Thiol depleters (e.g., buthionine and sulfoximine); and calcium leucovorin.

10 **[0075]** The active compound(s) may be administered per se or in the form of a pharmaceutical composition wherein the active compound(s) is in admixture with one or more pharmaceutically acceptable carriers, excipients or diluents. Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon 15 the route of administration chosen.

[0076] For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally 20 known in the art.

[0077] For oral administration, the compounds can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained solid excipient, optionally grinding 25 a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or 30 alginic acid or a salt thereof such as sodium alginate.

[0078] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

35 **[0079]** Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. 40 All formulations for oral administration should be in dosages suitable for such administration.

[0080] For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

[0081] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

50 **[0082]** The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multidose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[0083] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation 55

of highly concentrated solutions.

[0084] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0085] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

[0086] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or transcutaneous delivery (for example subcutaneously or intramuscularly), intramuscular injection or a transdermal patch. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0087] The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

5.3 Effective Dosages

[0088] Pharmaceutical compositions suitable for use with the present invention include compositions wherein the active ingredient is contained in a therapeutically effective amount, i.e., in an amount effective to achieve its intended purpose. Of course, the actual amount effective for a particular application will depend, inter alia, on the condition being treated. When administered in methods to inhibit cell proliferation, such compositions will contain an amount of active ingredient effective to achieve this result. When administered to patients suffering from disorders characterized by abnormal cell proliferation, such compositions will contain an amount of active ingredient effective to, *inter alia*, prevent the development of or alleviate the existing symptoms of, or prolong the survival of, the patient being treated. For use in the treatment of cancer, a therapeutically effective amount further includes that amount of compound which arrests or regresses the growth of a tumor. Determination of an effective amount is well within the capabilities of those skilled in the art, especially in light of the detailed disclosure herein.

[0089] For any compound described herein the therapeutically effective amount can be initially determined from cell culture arrays. Target plasma concentrations will be those concentrations of active compound(s) that are capable of inducing at least about 25% inhibition of cell proliferation in cell culture assays, depending, of course, on the particular desired application. Target plasma concentrations of active compound(s) that are capable of inducing at least about 50%, 75%, or even 90% or higher inhibition of the cell proliferation in cell culture assays are preferred. The percentage of inhibition of the cell proliferation in the patient can be monitored to assess the appropriateness of the plasma drug concentration achieved, and the dosage can be adjusted upwards or downwards to achieve the desired percentage of inhibition.

[0090] Therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a circulating concentration that has been found to be effective in animals. A particularly useful animal model for sickle cell disease is the SAD mouse model (Trudel *et al.*, 1991, EMBO J. 11: 315725-3165). Useful animal models for diseases characterized by abnormal cell proliferation are well-known in the art. In particular, the following references provide suitable animal models for cancer xenografts (Corbett *et al.*, 1996, J. Exp. Ther. Oncol. 1:95-108; Dykes *et al.*, 1992, Contrib. oncol. Basel 42:1-22), restenosis (Carter *et al.*, 1994, J. Am. Coll. Cardiol. 24(5):1398-1405), atherosclerosis (Zhu *et al.*, 1994, Cardiology 85(6):370-377) and neovascularization (Epstein *et al.*, 1987, Cornea 6(4):250-257). The dosage in humans can be adjusted by monitoring inhibition of cell proliferation and adjusting the dosage upwards or downwards, as described above.

[0091] A therapeutically effective dose can also be determined from human data for compounds which are known to exhibit similar pharmacological activities, such as Clotrimazole and other antimycotic agents (see, e.g., Brugnara *et al.*, 1995, JPET 273:266-272; Benzaquen *et al.*, 1995, Nature Medicine 1:534-540; Brugnara *et al.*, 1996, J. Clin. Invest. 97(5):1227-1234). The applied dose can be adjusted based on the relative bioavailability and potency of the administered compound as compared with Clotrimazole.

[0092] Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods as are well-known in the art is well within the capabilities of the ordinarily skilled artisan.

[0093] Of course, in the case of local administration, the systemic circulating concentration of administered compound will not be of particular importance. In such instances, the compound is administered so as to achieve a concentration at the local area effective to achieve the intended result.

[0094] For use in the treatment of disorders characterized by abnormal cell proliferation, including cancer, arteriosclerosis and angiogenic conditions such as restenosis, a circulating concentration of administered compound of about 0.001 μM to 20 μM is considered to be effective, with about 0.1 μM to 5 μM being preferred.

[0095] Patient doses for oral administration of the compounds described herein for the treatment or prevention of cell proliferative disorders typically range from about 80 mg/day to 16,000 mg/day, more typically from about 800 mg/day to

8000 mg/day, and most typically from about 800 mg/day to 4000 mg/day. Stated in terms of patient body weight, typical dosages range from about 1 to 200 mg/kg/day, more typically from about 10 to 100 mg/kg/day, and most typically from about 10 to 50 mg/kg/day. Stated in terms of patient body surface areas, typical dosages range from about 40 to 8000 mg/m²/day, more typically from about 400 to 4000 mg/m²/day, and most typically from about 400 to 2000 mg/m²/day.

[0096] For other modes of administration, dosage amount and interval can be adjusted individually to provide plasma levels of the administered compound effective for the particular clinical indication being treated.

[0097] For use in the treatment of tumorigenic cancers, the compounds can be administered before, during or after surgical removal of the tumor. For example, the compounds can be administered to the tumor via injection into the tumor mass prior to surgery in a single or several doses. The tumor, or as much as possible of the tumor, may then be removed surgically. Further dosages of the drug at the tumor site can be applied post removal. Alternatively, surgical removal of as much as possible of the tumor can precede administration of the compounds at the tumor site.

[0098] Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and preferred mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial toxicity and yet is entirely effective to treat the clinical symptoms demonstrated by the particular patient. Of course, many factors are important in determining a therapeutic regimen suitable for a particular indication or patient. Severe indications such as cancer may warrant administration of higher dosages as compared with less severe indications such as sickle cell disease.

5.4 Toxicity

[0099] The ratio between toxicity and therapeutic effect for a particular compound is its therapeutic index and can be expressed as the ratio between LD₅₀ (the amount of compound lethal in 50% of the population) and ED₅₀ (the amount of compound effective in 50% of the population). Compounds which exhibit high therapeutic indices are preferred.

Therapeutic index data obtained from cell culture assays and/or animal studies can be used in formulating a range of dosages for use in humans. The dosage of such compounds preferably lies within a range of plasma concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See *e.g.* Fingl *et al.*, 1975, *In: The Pharmacological Basis of Therapeutics*, Ch. 1 pl).

[0100] The invention having been described, the following examples are intended to illustrate, not limit, the invention.

6. EXAMPLE: Compound Syntheses

[0101] This Example demonstrates general methods of synthesis for many of the preferred compounds of the invention, as well as preferred methods of synthesis for certain exemplary compounds of the invention.

6.1 Synthesis of Triphenylmethanols

[0102] A general method of synthesis of triphenylmethanol derivatives is as follows: A mixture of substituted benzoyl chloride (1 equivalent), substituted benzene (1 equivalent), and aluminum chloride (1.1 equivalent), in methylene chloride was stirred at room temperature for 1 hour. The reaction mixture was cooled in an ice bath and water was added. The layers were separated and the aqueous layer extracted with methylene chloride. The combined methylene chloride extracts were washed with water and saturated aqueous sodium bicarbonate and then dried over sodium sulfate. Evaporation of the solvent gave the substituted benzophenone in 80-95% yield. The substituted benzophenone (1 equivalent) and substituted phenylmagnesium bromide (1.1 equivalent) in tetrahydrofuran was refluxed for 5 hours, cooled in an ice bath and water added. The reaction mixture was extracted with methylene chloride and the combined extracts were dried over sodium sulfate. Evaporation of the solvent followed by column chromatography gave the substituted triphenylmethanol in 45-90% yield.

6.2 Synthesis of Triphenylpropionic acids

6.2.1 Method A

[0103] One method of synthesis of triphenylpropionic acid derivatives is as follows: A mixture of substituted triphenylmethanol (1 equivalent) and malonic acid (2-3 equivalents) was stirred without solvent at 170 °C for 3 hour. After cooling, aqueous 1.0 M sodium hydroxide was added to the reaction mixture. This mixture was stirred at 90 °C for 4 hours and then filtered hot. Acidification of the cooled filtrate with 1.0 M hydrochloric acid caused precipitation of a white product

which was collected by suction filtration in 20-40% yield.

6.2.2 Method B

5 **[0104]** A second method of synthesis of triphenylpropionic acid derivatives is as follows: A mixture of magnesium (1.1 equivalent) and diethyl malonate (1.1 equivalent) in anhydrous ethanol was heated at reflux until all the magnesium was consumed (approximately 2 hours). Evaporation of the solvent gave a clear oil to which substituted triphenylmethane (obtained by reduction of the substituted triphenylmethanol by the method of Ando & Ikeno, 1979, *Tetrahedron. Lett.* 51:4941) (1 equivalent) and benzene was added. The mixture was refluxed for 5 minutes and then stirred at ambient
10 temperature for 3 hours. Hydrochloric acid (0.1 M) was added and the mixture stirred at room temperature overnight. The organic layer was separated, washed with water and dried over sodium sulfate. Evaporation gave the intermediate diethyl-substituted-diphenyl-benzylmalonate in 50-90% yield. In the final step, this intermediate (1 equivalent) and potassium hydroxide (6 equivalents) in ethanol was refluxed for 9 hours. The solvent was removed in vacuo, water added, and the solution stirred at 65 °C for 1 hour. The cooled solution was acidified with 1.0 M hydrochloric acid causing
15 precipitation of a white solid. The solid was collected by suction filtration to give the desired substituted triphenylpropionic acid in 60-90% yield.

6.3 Synthesis of 2-Chlorophenyl-diphenylmethanol

20 **[0105]** A preferred method of synthesis of 2-chlorophenyl-diphenylmethanol (Compound **6**) is as follows: A mixture of 25 g (0.073 mole) of Clotrimazole in 100 mL of 1.0M HCl was refluxed for 2.5 hours. After cooling to room temperature the mixture was extracted with ethyl acetate and the combined organics dried over sodium sulfate. The solvent was removed *in vacuo* and the residue crystallized from hexane to give 19.5 g (91% yield) of a yellow crystalline product having a melting point of 92-93.5 °C.

25 **[0106]** The product gave the following analytical data: NMR (CDCl₃): δ 4.48 ppm (1H, s, OH); δ 6.70 ppm (1H, d, J = 7 Hz, aryl); δ 7.13 ppm (1H, t, J = 8 Hz, aryl); δ 7.28 ppm (5H, m, aryl); δ 7.34 ppm (6H, m, aryl); δ 7.52 ppm (1H, d, J = 9 Hz, aryl).

[0107] Anal. C₁₉H₁₅ClO (CH calculated: 77.42, 5.13; found: 77.33, 5.17).

30 6.4 Synthesis of (2-Chlorophenyl)-diphenylacetonitrile

[0108] A preferred method of synthesis of (2-chlorophenyl)-diphenylacetonitrile (Compound **14**) is as follows: A mixture of 1 g (0.003 mole) of chloro-(2-chlorophenyl)-diphenylmethane and 0.3 g (0.004 mole) of copper cyanide was heated for 2 hours at 150 °C without solvent. The mixture was allowed to cool slightly, 10 mL of toluene added, the mixture
35 filtered, and the solvent removed *in vacuo*. The resulting brown solid was crystallized from 2-propanol to give 0.64 g (66% yield) of a light brown crystalline product having a melting point of 145-147 °C.

[0109] The product gave the following analytical data: NMR (CDCl₃): δ 6.58 ppm (1H, d, J = 8 Hz, aryl); δ 7.16 ppm (1H, t, J = 10 Hz, aryl); δ 7.24 ppm (4H, m, aryl); δ 7.32 ppm (1H, d, J = 7 Hz, aryl); δ 7.37 ppm (6H, m, aryl); δ 7.48 ppm (1H, d, J = 8 Hz, aryl).

40 **[0110]** Anal. C₂₀H₁₄ClN (CHNCl calculated: 79.07, 4.65, 4.61, 11.67; found: 79.08, 4.72, 4.58, 11.58).

6.5 Synthesis of 2-Chlorophenyl-diphenylacetaldehyde

[0111] A preferred method of synthesis of 2-chlorophenyl-diphenylacetaldehyde (Compound **15**) is as follows: A mixture of 7.5 g (0.025 mole) of 2-chlorophenyl-diphenylacetonitrile, and 56 mL (0.056 mole) of DIBAL-H in 100 mL of toluene was stirred for 1 hour at -78 °C. Ethyl acetate (7 mL), silica gel (65 g), and water (5 mL) was added and the mixture stirred at -78 °C for 2 hours. The mixture was then allowed to warm to room temperature and stirred at room temperature for 4 hours. Ethyl acetate (200 mL) was added and the mixture filtered. The organic layer was dried over sodium sulfate and the solvent removed *in vacuo*. The resulting solid was crystallized from 2-propanol to give 6.0 g (77
50 % yield) of a white crystalline product having a melting point of 126-129 °C.

[0112] The product gave the following analytical data: NMR (CDCl₃): δ 6.69 ppm (1H, d, J = 9 Hz, aryl); δ 7.13 ppm (2H, d, J = 9 Hz, aryl); δ 7.19 ppm (1H, d, J = 6 Hz, aryl); δ 7.26 ppm (1H, s, aryl); δ 7.28 ppm (1H, d, J = 8 Hz, aryl); δ 7.36 ppm (7H, m, aryl); δ 7.46 ppm (1H, d, J = 9 Hz, aryl); δ 10.49 ppm (1H, s, CHO).

[0113] Anal. C₂₀H₁₅ClO (CHCl calculated: 78.30, 4.93, 11.56; found: 77.90, 5.28, 11.39).

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6.6 Synthesis of Triphenylacetaldehyde

[0114] A preferred method of synthesis of triphenylacetaldehyde (Compound **16**) is as follows: A mixture of 1 g (0.003

mole) of 2-chlorophenyl-diphenylacetonitrile, and 8 mL (0.008 mole) of DIBAL-H in 15 mL of toluene was stirred for 1 hour at -78 °C. Ethyl acetate (4 mL), silica gel (10 g), and water (0.5 mL) was added and the mixture stirred at -78 °C for 30 min. The mixture was then allowed to warm to room temperature and stirred at room temperature for 4 hours. Ethyl acetate (100 mL) was added and the mixture filtered. The organic layer was dried over sodium sulfate. Evaporation gave 0.9 g (95 % yield) of a white powder having a melting point of 91-96 °C.

[0115] The product gave the following analytical data: NMR (CDCl₃): δ 7.05 ppm (6H, d, J = 9 Hz, aryl); δ 7.44 ppm (9H, m, aryl); δ 10.28 ppm (1H, s, CHO).

[0116] Anal. C₂₀H₁₅O (CH calculated: 88.20, 5.92; found: 88.06, 5.99).

6.7 Synthesis of 2-Chlorophenyl-diphenylmethane

[0117] A preferred method of synthesis of 2-chlorophenyl-diphenylmethane (Compound 17) is as follows: A mixture of 5 g (0.017 mole) of 2-chlorophenyl-diphenylmethanol (Compound 6), 15 g (0.1 mole) of sodium iodide, 12.7 mL (0.1 mole) of chlorotrimethylsilane and 5 mL (0.1 mole) acetonitrile in 30 mL of dichloromethane was stirred at room temperature for 2 days. The reaction mixture was diluted with 50 mL of water and extracted with ethyl acetate. The combined organics were dried over sodium sulfate and the solvent removed *in vacuo*. The resultant oil was passed through a silica gel column using ethyl acetate:hexane (1:5) as eluent. The first fraction collected contained the product which was obtained as a solid after removal of the solvent *in vacuo*. This solid was crystallized from ethanol/water to give 3.67 g (78% yield) of a white crystalline product having a melting point of 74-76°C.

[0118] The product gave the following analytical data: NMR (DMSO-d₆) δ 5.91 ppm (1H, s, CH); δ 6.92 ppm (1H, d, J=9 Hz, aryl); δ 7.06 ppm (4H, d, J=8 Hz, aryl); δ 7.24 ppm (8H, m, aryl); δ 7.48 ppm (1H, d, J=9 Hz, aryl).

[0119] Anal. C₁₉H₁₅Cl (CH calculated: 81.86, 5.42; found: 81.69, 5.51).

6.8 Synthesis of Tris(4-chlorophenyl)propionamide

[0120] A preferred method of synthesis of tris(4-chlorophenyl)propionamide (Compound 30) is as follows: A mixture of 5.2 g (0.012 mole) of tris(4-chlorophenyl)propionic acid chloride in 25 mL of tetrahydrofuran was cooled to 0-5 °C and 25 mL of ammonium hydroxide (0.4 mole NH₃) was added. The solution was stirred at 0-5 °C for 15 minutes and then extracted with ethyl acetate (5 x 25 mL). The combined organics were dried over magnesium sulfate. Evaporation gave 4.5 g (91 % yield) of an off-white powder which was crystallized from hexane to give 3.7 g (74% yield) of a white powder having a melting point of 158-160 °C.

[0121] The product gave the following analytical data: NMR (CDCl₃): δ 3.50 ppm (2H, s, CH₂); δ 4.91 ppm (1H, s, NH₂); δ 5.29 ppm (1H, s, NH₂); δ 7.15 ppm (6H, d, J = 8 Hz, aryl); δ 7.26 ppm (6H, d, J = 8 Hz, aryl).

[0122] Anal. C₂₁H₁₆Cl₃NO (CHNCl calculated: 62.53, 4.00, 3.47, 26.03; found: 62.31, 4.03, 3.45, 26.20).

6.9 Synthesis of (2-Fluorophenyl)-diphenylacetonitrile

[0123] A preferred method of synthesis of (2-fluorophenyl)-diphenylacetonitrile (Compound 32) is as follows: A mixture of 0.5 g (0.002 mole) of chloro-(2-fluorophenyl)-diphenylmethane and 0.15 g (0.002 mole) of copper cyanide was heated for 2 hours at 150 °C without solvent. The mixture was allowed to cool slightly, 10 mL of toluene added, the mixture filtered, and the solvent removed *in vacuo*. The resulting off-white solid was crystallized from 2-propanol to give 0.31g (64% yield) of a clear crystalline product having a melting point of 144-145 °C.

[0124] The product gave the following analytical data: NMR (CDCl₃): δ 6.67 ppm (1H, t, J = 9 Hz, aryl); δ 7.03-7.17 ppm (4H, m, aryl); δ 7.24 ppm (3H, m, aryl); δ 7.48 ppm (6H, m, aryl).

[0125] Anal. C₂₀H₁₄FN (CHN calculated: 83.60, 4.91, 4.87; found: 83.41, 4.97, 4.84).

6.10 Synthesis of 3-(2-Chlorophenyl)-3,3-diphenylpropionic acid

[0126] A preferred method of synthesis of 3-(2-chlorophenyl)-3,3-diphenylpropionic acid (Compound 36) is as follows: A mixture of 1.7 g (0.07 mole) of magnesium and 11.2 g (0.07 mole) of diethyl malonate in 25 mL anhydrous ethanol was heated at reflux until all the magnesium was consumed (approximately 2 hours). Evaporation of the solvent gave a clear oil to which 20 g (0.064) of chloro-(2-chlorophenyl)-diphenylmethane and 100 mL benzene was added. The mixture was refluxed for 5 minutes and then stirred at ambient temperature for 3 hours. Water (90 mL) and 10 mL of 1.0 M hydrochloric acid was added and the mixture stirred at room temperature for 14 hours. The organic layer was separated, washed with water and dried over sodium sulfate. Evaporation gave 14.6 g (51 % yield) of pale yellow solid. In the final step, 12.5 g (0.028 mole) of this solid and 9.5 g (0.17 mole) potassium hydroxide in 100 mL of ethanol refluxed for 9 hours. The solvent was removed *in vacuo*, 400 mL of water added and the solution stirred at 65 °C for 1 hour. The cooled solution was acidified with 1.0 M hydrochloric acid causing precipitation of a white solid. The solid was collected by

filtration, boiled in hexane and filtered hot. The resulting white solid weighed 8.5g (90% yield) and had a melting point of 180-182 °C.

[0127] The product gave the following analytical data: NMR (DMSO- d_6): δ 4.01 ppm (2H, s, CH₂); δ 6.98 ppm (1H, d, J = 9 Hz, aryl); δ 7.19 ppm (6H, m, aryl); δ 7.28 ppm (6H, m, aryl); δ 7.36 ppm (1H, d, J = 9 Hz, aryl); δ 11.92 ppm (1H, br, COOH).

[0128] Anal. C₂₁H₁₇ClO₂ • 0.1 H₂O (CH calculated: 74.49, 5.12; found: 74.37, 5.27).

6.11 Synthesis of Diethyl-(α,α -diphenyl)-2-fluorobenzyl)malonate

[0129] A preferred method of synthesis of diethyl-(α,α -diphenyl)-2-fluorobenzyl)malonate (Compound 55) is as follows: A mixture of 0.1 g (0.0035 mole) of magnesium, 0.64 g (0.004 mole) of diethyl malonate, a catalytic amount of iodine, and 1 drop of carbon tetrachloride in 10 mL anhydrous ethanol was heated at reflux until all the magnesium was consumed (2 hours). Evaporation of the solvent gave a clear oil to which 1 g (0.0034 mole) of chloro-(2-fluorophenyl)-diphenylmethane and 40 mL benzene was added. The mixture was refluxed for 5 minutes and then stirred at ambient temperature for 4 hours. Water (10 mL) and 1 mL of 1.0 M hydrochloric acid was added and the mixture stirred at room temperature for 14 hours. The organic layer was separated, washed with water, dried over sodium sulfate and the solvent removed in vacuo. The resulting red solid was crystallized from ethanol to give a pale yellow solid which weighed 1.0 g (67% yield) and had a melting point of 133.5-135 °C.

[0130] The product gave the following analytical data: NMR (CDCl₃): δ 1.03 ppm (6H, t, J = 8 Hz, CH₃); δ 3.92 ppm (4H, m, CH₂); δ 5.50 ppm (1H, s, CH); δ 6.87 ppm (1H, dd, J = 9, 11 Hz, aryl); δ 7.06 ppm (1H, m, aryl); δ 7.26 ppm (8H, m, aryl); δ 7.42 ppm (4H, d, J = 9 Hz, aryl).

[0131] Anal. C₂₆H₂₅FO₄ • 0.25 H₂O (CH calculated: 73.48, 6.05; found: 73.44, 5.96).

6.12 Synthesis of 4,4,4-Triphenylbutronitrile

[0132] A preferred method of synthesis of 4,4,4-triphenylbutronitrile (Compound 64) is as follows: A mixture of 5.0 g (0.017 mole) of 3,3,3-triphenylpropanol, 2.2 g (0.019 mole) of methanesulfonyl chloride, and 3.6 mL (0.026 mole) of triethylamine in 100 mL of methylene chloride was stirred at -15 °C for 30 minutes. The reaction mixture was then washed sequentially with 50 mL water, 100 mL 1.0 M hydrochloric acid, 100 mL saturated aqueous sodium carbonate, and 100 mL brine. Evaporation of the solvent gave 6.4 g (80% yield) of a white solid (3,3,3-triphenylpropyl mesylate). A mixture of 5.3 g (0.0145 mole) of this mesylate and 0.85 g (0.017 mole) of sodium cyanide was refluxed in 100 mL of methyl sulfoxide for 2.5 hours. To the cooled reaction mixture was added 500 mL of water and 500 mL of ethyl acetate, the layers separated and the aqueous layer extracted three times with 100 mL of ethyl acetate each time. The combined organics were washed with 200 mL of water and dried over magnesium sulfate. The solvent was removed in vacuo and the resultant white solid crystallized from 2-propanol to give 2.3 g (45% yield) of white crystals having a melting point of 130-133 °C.

[0133] The product gave the following analytical data: NMR (DMSO- d_6): δ 2.06 ppm (2H, t, J = 8.5 Hz, CH₂); δ 3.00 ppm (2H, t, J = 8.5 Hz, CH₂); δ 7.20-7.36 ppm (15H, m, aryl).

[0134] Infrared (KBr) 3018 cm⁻¹; 2246 cm⁻¹; 1592 cm⁻¹; 1489 cm⁻¹.

[0135] Anal. C₂₂H₁₉N • 0.1 H₂O (CHN calculated: 88.32, 6.46, 4.68; found: 88.24, 6.45, 4.35).

6.13 Synthesis of (2-Chlorophenyl)-diphenylacetamide.

[0136] A preferred method of synthesis of (2-chlorophenyl)-diphenylacetamide (Compound 75) is as follows: (2-chlorophenyl)-diphenylacetonitrile (Compound 14), 2.0 g (0.007 mole), was dissolved in 15 mL of sulfuric acid and 15 mL of acetic acid and heated for 12 hours at 100 °C. The cooled reaction mixture was neutralized with ammonium hydroxide and extracted with methylene chloride. The organic layer was dried over sodium sulfate and the solvent removed *in vacuo*. The resulting brown solid was crystallized from acetone to give 0.9 g (42% yield) of a light brown solid having a melting point of 197-198.5 °C.

[0137] The product gave the following analytical data: NMR (CDCl₃): δ 5.90 ppm (1H, s, NH₂); δ 6.07 ppm (1H, s, NH₂); δ 6.93 ppm (1H, d, J = 7 Hz, aryl); δ 7.20 ppm (1H, t, J = 8 Hz, aryl); δ 7.31 ppm (11H, m, aryl); δ 7.49 ppm (1H, d, J = 7 Hz, aryl).

[0138] Infrared (KBr) 1690 cm⁻¹; 1240 cm⁻¹; 1020 cm⁻¹.

[0139] Anal. C₂₀H₁₆ClN • 0.3 H₂O (CHN calculated: 73.41, 5.11, 4.28; found: 73.13, 5.12, 4.24).

6.14 Synthesis of 3-(2'-Chlorophenyl)-3,3-diphenylpropanal

[0140] A preferred method of synthesis of 3-(2'-chlorophenyl)-3,3-diphenylpropanal (Compound 79) is as follows: A

mixture of 1.8 g (0.0053 mole) of 3-(2-chlorophenyl)-3,3-diphenylpropionic acid (Compound 36), 0.68 g (0.007 mole) of N-methyl-N-methoxyhydroxylamine hydrochloride, 0.91 g (0.0059 mole) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.97 mL (0.007 mole) of triethylamine in 25 mL of dimethylformamide was stirred at 0-5 °C for 2 hours followed by stirring at room temperature for 15 hours. Water (15 mL) was added and the mixture stirred at room temperature for 1.5 hours before an additional 30 mL of water was added and the mixture extracted with ethyl acetate (3 x 50 mL) which was then dried over sodium sulfate. Evaporation of the solvent gave an orange oil (0.99g, 0.0026 mole, 49 % yield of N-methyl-N-methoxy-3-(2'-chlorophenyl)-3,3-diphenylpropyl amide). This amide was dissolved in 25 mL of tetrahydrofuran and cooled to 0-5 °C with stirring. A slurry of 0.20 g (0.0053 mole) of lithium aluminum hydride in 5 mL of tetrahydrofuran was added dropwise to this cold, stirring solution. The mixture was stirred at 0-5 °C for 1 hour and quenched with a solution of 9.9 g (0.073 mole) of potassium hydrogen sulfate in 70 mL of water. Ethyl acetate (50 mL) was added and the layers separated. The aqueous layer was extracted with 30 mL of ethyl acetate and the combined organic fractions were dried over sodium sulfate. The solvent was removed in vacuo and the yellow residue crystallized from ethyl acetate to give 0.29g (91% yield) of a white crystalline product having a melting point of 92-93 °C.

[0141] The product gave the following analytical data: NMR (CDCl₃): δ 3.99 ppm (2H, d, J = 3 Hz, CH₂); δ 6.94 ppm (1H, d, J = 9 Hz, aryl); δ 7.10 ppm (4H, d, J = 8 Hz, aryl); δ 7.18 ppm (1H, d, J = 9 Hz, aryl); δ 7.29 ppm (8H, m, aryl); δ 7.40 ppm (1H, d, J = 8 Hz, aryl); δ 9.48 ppm (1H, t, J = 3 Hz, CHO).

[0142] Anal. C₂₁H₁₇ClO (CH calculated: 78.62, 5.34; found: 78.46, 5.53).

6.15 Synthesis of 4-(2-Chlorophenyl)-4,4-diphenyl-2-butanone

[0143] A preferred method of synthesis of 4-(2-chlorophenyl)-4,4-diphenyl-2-butanone (Compound 82) is as follows: A solution of 1.05 g (0.0027 mole) of N-methyl-N-methoxy 3-(2-chlorophenyl) 3,3-diphenylpropionamide, in 20 mL of tetrahydrofuran was cooled to 0 °C and 1.01 mL of methyl magnesium bromide (3.0 M solution in tetrahydrofuran, 0.00303 mole) was added to the cooled solution. The mixture was stirred at room temperature overnight. The reaction was quenched with cold aqueous hydrochloric acid solution (25 mL, 1.0 M) and then extracted with dichloromethane (2 x 20 mL). The organic solution was washed with 20 mL of saturated aqueous sodium bicarbonate and 15 mL of brine. The organic layer was dried over sodium sulfate. Evaporation gave 0.89 g of the crude product as a yellow solid. Purification of the crude product by flash column chromatography (silica gel, 1: 5 ethyl acetate : hexane) gave 0.385 g (41 % yield) of a white solid having a melting point of 120-123 °C.

[0144] The product gave the following analytical data: NMR (CDCl₃): δ 2.20 ppm (3H, s, CH₃); δ 4.28 ppm (2H, s, CH₂); δ 6.85 ppm (1H, m, aryl); δ 7.04-7.32 ppm (13H, m, aryl).

[0145] Anal. C₂₂H₁₉ClO (CH calculated: 78.91, 5.72; found: 78.52, 5.65)

6.16 Synthesis of α-(2-Chlorophenyl)-α-(4-hydroxyphenyl) benzyl alcohol

[0146] A preferred method of synthesis of α-(2-chlorophenyl)-α-(4-hydroxyphenyl)benzyl alcohol (Compound 84) is as follows: A solution of 0.5 g (0.0015 mole) of α-(2-chlorophenyl)-α-(4-methoxyphenyl)benzyl alcohol, in 10 mL of dichloromethane, was cooled to -15 °C and 4.5 mL of boron tribromide (1.0 M solution in dichloromethane, 0.0045 mole) was added to the cooled solution. The mixture was stirred at room temperature overnight and then refluxed for 8 hours. The reaction mixture was quenched with water and neutralized by adding aqueous sodium bicarbonate. The mixture was extracted with dichloromethane (3 x 20 mL). The organic layer was dried over magnesium sulfate. Evaporation gave 0.47 g of the crude product as a thick red oil. Purification of the crude product by flash column chromatography (silica gel, 1:5 ethyl acetate : hexane) gave 0.182 g (39 % yield) of a yellow solid having a melting point of 56.5-60 °C.

[0147] The product gave the following analytical data: NMR (CDCl₃): δ 5.76 ppm (1H, bs, OH); δ 6.45 ppm (2H, dd, aryl); δ 6.78 ppm (2H, m, aryl); δ 7.12 ppm (4, m, aryl); δ 7.24-7.62 ppm (5H, m, aryl).

6.17 Synthesis of Cyclohexyl-diphenylmethanol

[0148] A preferred method of synthesis of cyclohexyl-diphenylmethanol (Compound 88) is as follows: A solution of 3.0 g (0.0021 mole) of methylcyclohexyl carboxylate in 20 mL of tetrahydrofuran (THF) was added dropwise, with stirring, to 46 mL (0.0046 mole) of phenylmagnesium bromide (1.0 M in THF) at room temperature. The solution was refluxed for 6 hours and then allowed to cool. Water (15 mL) was added causing a white precipitate to form. The mixture was extracted with ethyl acetate (3 x 25 mL) and the combined organics dried over sodium sulfate. Evaporation of the solvent gave a clear oil which crystallized from ethanol. The white crystals were collected by filtration to give 4.0 g (75% yield) of a product having a melting point of 76-78°C.

[0149] The product gave the following analytical data: NMR (CDCl₃): δ 1.00-1.40 ppm (5H, m, aliphatic); δ 1.58 ppm (2H, d, J=12 Hz, aliphatic); δ 1.64-1.82 ppm (3H, m, aliphatic); δ 1.58 ppm (1H, s, OH); δ 2.45 ppm (1H, t, J=13 Hz, CH); δ 7.16 ppm (2H, t, J=9 Hz, aryl); δ 7.30 ppm (4H, m, aryl); δ 7.48 ppm (4H, d, J=9 Hz, aryl).

[0150] Anal. C₁₉H₂₂O • 0.75 ethanol (CH calculated: 82.83, 8.44; found: 82.07, 8.62).

6.18 Synthesis of Cyclohexyl-diphenylacetonitrile

5 **[0151]** A preferred method of synthesis of cyclohexyl-diphenylacetonitrile (Compound 89) is as follows: A mixture of 0.94 g (0.024 mole) of sodium amide and 3.85 g (0.02 mole) of diphenylacetonitrile in 25 mL of toluene was stirred at reflux for 3 hours. To this refluxing mixture was added 2.6 mL (0.022 mole) of cyclohexyl chloride. The mixture was stirred at reflux an additional 3 hours and then allowed to cool. To the cool solution was added 50 mL of a 1.0 M HCl solution. The layers were separated and the organic layer was washed with brine and then dried over sodium sulfate.
10 The toluene was removed in vacuo to give a yellow solid (4.9 g). This solid was crystallized from ethanol to give 3.6 g of a white crystalline product having a melting point of 117.5-119°C.

[0152] The product gave the following analytical data: NMR (CDCl₃): δ 1.29 ppm (5H, m, aliphatic); δ 1.73 ppm (5H, m, aliphatic); δ 2.50 ppm (1H, t, J=12 Hz, CH); δ 7.26 ppm (2H, d, J=9 Hz, aryl); δ 7.32 ppm (4H, t, J=9 Hz, aryl); δ 7.50 ppm (4H, d, J=9 Hz, aryl).

15 **[0153]** Anal. C₂₀H₂₁N (CHN calculated: 87.23, 7.69, 5.09; found: 87.28, 7.68, 5.05).

6.19 Synthesis of Cyclohexyl-diphenylacetamide

20 **[0154]** A preferred method of synthesis of Cyclohexyl-diphenylacetamide (Compound 90) is as follows: Cyclohexyl-diphenylacetonitrile (Compound 89), 0.155 g (0.0056 mole), was stirred in 1 mL of sulfuric acid and 1 mL of acetic acid and heated for 9 hours at 110°C. The cooled reaction mixture was diluted with an equal volume of water and extracted with methylene chloride. Separation of the product from the unreacted starting material was accomplished by flash chromatography (7:3 hexane:ethyl acetate on silica gel). Evaporation of the fractions *in vacuo* gave 0.044 g (27% yield) of a white solid.

25 **[0155]** The product gave the following analytical data: NMR (CDCl₃): δ 0.60 ppm (2H, q, J=9 Hz, CH₂); δ 0.93 ppm (1H, q, J=9 Hz, CH₂); δ 1.42 ppm (2H, q, J=12 Hz, CH₂); δ 1.67 ppm (3H, m, CH₂); δ 1.83 ppm (2H, d, J=10 Hz, CH₂); δ 2.89 ppm (1H, t, J=12 Hz, CH₂); δ 5.58 ppm (1H, br s, NH); δ 6.00 ppm (1H, br s, NH); δ 7.23-7.48 ppm (10H, m, aryl).

6.20 Other Compounds

30 **[0156]** Other compounds of the invention can be synthesized by routine modification of the above-described syntheses, or by other methods that are well known in the art. Compounds **1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 19, 20, 21, 23, 24, 25, 26, 28, 34, 37, 38, 39, 42, 43, 44, 45, 46, 47, 48, 50, 51, 54, 57, 59, 60, 61, 62, 66, 67, 69, 71, 72, 73, 76, 77** and **87** are available from Aldrich Chemical Co.

35 **[0157]** Compounds **49** and **52** are available from Maybridge Chemical Co.

7. EXAMPLE: In Vitro Activity

40 **[0158]** This Example demonstrates the ability of several exemplary compounds of formula (I) to inhibit the Gardos channel of erythrocytes and/or mitogen-induced cell proliferation *in vitro*. The assays are generally applicable for demonstrating the *in vitro* activity of other compounds of formula (I).

7.1 Experimental Protocol

45 **[0159]** The percent inhibition of the Gardos channel (10 μM compound) and the IC₅₀ were determined as described in Brugnara *et al.*, 1993, *J. Biol. Chem.* **268**(12):8760-8768. The percent inhibition of mitogen-induced cell proliferation (10 μM compound) and the IC₅₀ were determined or described in Benzaquen *et al.* (1995, *Nature Medicine* **1**:534-540) with NIH 3T3 mouse fibroblast cells (ATCC No. CRL 1658). Clotrimazole is reported for purposes of comparison. Other cell lines, e.g., cancer cells, endothelial cells and fibroblasts, as well as many others, may be used in the cell proliferation
50 assay. Selection of a particular cell line will depend in part on the desired application, and is well within the capabilities of an ordinarily skilled artisan.

7.2 Results

55 **[0160]** The results of the *in vitro* assays are provided in TABLE 1, below. All of the compounds tested exhibited significant activity in at least one of the assays. Most of the compounds tested exhibited significant activity in both of the assays.

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TABLE 1

Pharmacological Activities of Various Compounds (Inhibition measured at 10 μ M)				
Compound No.	Mitogen-induced cell proliferation		Gardos Channel	
	IC ₅₀ (μ M)	% Inhibition	IC ₅₀ (μ M)	% Inhibition
Clotrimazole	0.626	93.0	0.046	99.3
(1)	-	-	0.755	97.0
(2)	-	64.8	0.459	99.4
(3)	-	53.0	1.205	86.6
(4)	-	37.7	2.86	91.0
(5)	1.28	66.0	1.653	86.0
(6)	2.10	31.0	0.961	98.0
(7)	-	6.6	0.410	98.2
(8)	-	28.3	2.851	95.6
(9)	-	32.7	21.803	77.2
(10)	4.80	25.5	0.957	89.7
(11)	2.31	52.0	2.16	99.2
(12)	1.70	72.8	0.252	99.0
(13)	0.92	87.0	0.133	72.4
(14)	2.20	95.8	0.048	98.8
(15)	2.60	88.63	0.0968	100.0
(16)	0.40-2.0	99.4	0.087	98.0
(17)	3.90	91.8	0.860	100.0
(18)	10.0	76.09	0.431	98.0
(19)	5.8	80.0	1.129	97.0
(20)	-	39.0	0.795	98.1
(21)	2.8	99.0	0.725	97.3
(22)	6.8	85.0	0.302	82.0
(23)	3.8	77.0	0.216	97.9
(24)	-	29.0	0.135	97.9
(25)	-	70.0	-	34.4
(26)	1.30	99.0	-	10.0
(27)	3.00	99.0	0.449	100.0
(28)	0.70	99.0	5.22	98.0
(29)	3.10	99.0	0.649	100.0
(30)	0.90	99.0	0.272	97.0
(31)	2.60	89.0	0.445	99.0
(32)	-	54.0	0.068	95.7
(33)	-	45.0	0.125	100.0
(34)	-	68.0	0.939	96.3

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Table continued

Pharmacological Activities of Various Compounds (Inhibition measured at 10 μ M)				
Compound No.	Mitogen-induced cell proliferation		Gardos Channel	
	IC ₅₀ (μ M)	% Inhibition	IC ₅₀ (μ M)	% Inhibition
(35)	-	38.0	0.430	95.8
(36)	0.60	92.0	3.11	78.6
(37)	-	31.0	0.057	100.0
(38)	0.80-2.30	99.0	0.22	92.0
(39)	3.30	99.0	1.682	97.0
(40)	1.0-1.20	99.0	-	(16.9)
(41)	1.40	99.0	2.071	97.0
(42)	3.30	99.0	0.615	99.0
(43)	0.80	99.0	0.061	99.0
(44)	-	82.0	0.388	79.4
(45)	0.80	99.0	0.320	98.0
(46)	2.20	99.0	0.076	99.5
(47)	0.80	99.0	0.193	100.0
(48)	0.40	98.0	1.29	100.0
(49)	0.30	94.0	0.336	88.0
(50)	0.50	99.0	0.288	100.0
(51)	-	37.0	0.551	100.0
(52)	1.70	93.0	0.255	94.0
(53)	-	74.0	0.101	98.0
(54)	0.20	99.0	-	17.4
(55)	-	5.0	0.058	98.0
(56)	3.20	99.0	0.275	91.0
(57)	-	21.0	1.506	89.0
(58)	-	99.0	0.247	99.6
(59)	3.00	98.0	0.489	100.0
(60)	-	31.0	0.304	98.0
(61)	1.6	99.0	2.372	85.0
(62)	-	31.0	0.098	98.0
(63)	-	37.0	1.017	69.0
(64)	5.80	63.0	0.088	100.0
(65)	1.60	99.0	0.435	98.0
(66)	-	73.0	0.384	67.2
(67)	1.40	98.0	0.43	96.1
(68)	3.1	98.0	0.236	97.5
(69)	-	99.0	0.025	100.0
(70)	1.20	92.0	0.459	99.6

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Table continued

Pharmacological Activities of Various Compounds (Inhibition measured at 10 μ M)				
Compound No.	Mitogen-induced cell proliferation		Gardos Channel	
	IC ₅₀ (μ M)	% Inhibition	IC ₅₀ (μ M)	% Inhibition
(71)	1.10	97.0	-	0.4
(72)	2.40	99.0	1.075	72.6
(73)	2.50	99.0	0.371	98.9
(74)	-	70.0	1.405	97.5
(75)	-	90.0	0.006	98.0
(76)	-	84.0	-	(30.4)
(77)	-	83.0	-	16.4
(78)	-	72.0	0.22	95.0
(79)	2.70	99.0	0.083	96.0
(80)	-	62.0	0.206	97.0
(81)	-	53.0	0.187	100.0
(82)	5.0	98.0	0.027	99.5
(83)	6.4	80.0	0.918	96.7
(84)	1.0	99.0	1.274	95.3
(85)	7.0	91.0	0.739	98.0
(86)	2.4	99.0	0.237-0.455	93.9
(87)	2.2	96.0	0.068	99.0
(88)	9.5	94.0	0.862	99.0
(89)	0.90	98.0	6.128	70.2
(90)	3.0	86.0	0.072	98.3

8. EXAMPLE: Clotrimazole Metabolite B (Compound 6) Displaces Bound ¹²⁵I-ChTX

[0161] Charybdotoxin (ChTX), a peptide of 37 amino acids in length, is a potent inhibitor of many Ca²⁺-activated and voltage-gated K⁺ channels, including the Gardos channel (Miller *et al.*, 1985, *Nature* 313:316-318; Bontems *et al.*, 1992, *Biochemistry* 31:7756-7764; Park *et al.*, 1991, *Proc. Natl. Acad. Sci. U.S.A.* 88:2046-2050; Vazquez *et al.*, 1989, *J. Biol. Chem.* 264:20902-20909; Grinstein and Smith, 1990, *J. Gen. Physiol.* 95:97-120; Brugnara *et al.*, 1993, *J. Biol. Chem.* 268:8760-8768). Because bound ChTX inhibitor may be competitively displaced by other Gardos channel inhibitors, ChTX is an important tool for understanding Gardos channel function and activation. This example demonstrates displacement of ChTX by CLT metabolite B (Compound 6). The method described herein is generally applicable for demonstrating the ability of other compounds of formula (I) to competitively displace ChTX.

8.1 ¹²⁵IChTX binding to red cells

[0162] White cells were removed by passing 0.8 mL of packed red cells through a 5 mL syringe containing a mixture of equal parts of alpha-cellulose and microcrystalline cellulose as originally described by Beutler and West, 1976, *J. Lab. Clin. Med.* 88:328-333. Red cells were washed three times in binding medium containing 18mM NaCl, 2mM KCl, 10mM tris-Cl, pH 8.0, 230 mM sucrose and 0.25% bovine serum albumin. A suspension was then made in the same medium at 15% Hematocrit (Hct). Cells were added to 3.5 ml of binding medium containing ¹²⁵IChTX to a final concentration of 1 X 10⁷ cells/mL, in the absence or presence of the specified drugs. Tubes containing cell suspension were gently rotated for 90 min. at room temperature. At the end of the incubation, aliquots of 1 ml were pelleted by microfuge and washed 3 times at 4°C with a solution containing 200 mM NaCl, 10mM tris-Cl, pH 8.0. The washed red cell pellet was then lysed in 1 ml of 0.01% Acationox (American scientific Products), and counted in a gamma counter. Aliquots

of binding medium were counted prior to addition of cells at the end of the binding assay.

8.2 Displacement by Metabolite B (Compound 6)

5 [0163] Metabolite B (Compound 6) was added to the red cells from a stock solution in acetonitrile. A similar amount of acetonitrile was added to each control tube. Specific binding was estimated on the basis of displacement of ^{125}I -ChTX by 50 nM unlabeled ChTX. Various concentrations of metabolite B (Compound 6) or unlabeled ChTX were added to the cell suspension (1×10^7 cells/mL) prior to the addition of ^{125}I -ChTX.

10 8.3 Results

[0164] The results of the assay are depicted in TABLE 2. Metabolite B (Compound 6) specifically displaces ^{125}I ChTX binding.

15 TABLE 2
Displacement of ^{125}I -ChTX Binding by Metabolite B (Compound 6)

	^{125}I -ChTX Binding	Displacement		
		σ	(%)	σ (%)
20 control	1.279	0.030	0.0	2.3
50 nM ChTX	0.608	0.002	100.0	0.3
10 μM CLT	1.000	0.06	41.6	6.0
1 nM B	1.403	0.13	(18.5)	9.3
25 10 nM B	1.399	0.15	(17.9)	10.7
100 nM B	1.239	0.35	6.0	28.1
500 nM B	1.134	0.07	21.6	6.1
1 μM B	1.327	0.05	(7.2)	4.1
5 μM B	1.016	0.07	39.2	7.0
30 10 μM B	0.790	0.04	72.9	5.1

σ is standard deviation

B is CLT Metabolite B (Compound 6)

35 9. EXAMPLE: Clotrimazole and Its Metabolites Inhibit Ca^{2+} -Activated Potassium Transport *In Vivo* In Humans

[0165] This Example demonstrates the ability of Clotrimazole (CLT) and CLT metabolites A and B (Compounds 17 and 6, respectively) to inhibit the Gardos channel of erythrocytes *in vivo* in humans. The methods described herein are generally applicable for demonstrating the *in vivo* activity of other compounds of formula (I) when administered to humans.

40 9.1 Experimental Protocol

[0166] Two subjects, one male (A, 72 Kg) and one female (D, 56 Kg), ingested one 500mg CLT tablet every twelve hours for six days, corresponding to a daily CLT dose of 14 and 18 mg/kg, respectively. Blood was collected six hours after the AM dose of CLT on days 3 and 6 for measurement of inhibition of red cell calcium-activated potassium transport.

9.2 Results

50 [0167] TABLE 3 depicts the results of the measurement of the red cell calcium-activated potassium transport in the two normal subjects. As shown in TABLE 3, there was significant inhibition of calcium-activated potassium transport during CLT administration, which persisted for at least 7 days after the drugs were discontinued. At day 6, plasma CLT concentration was 0.2 μM with combined metabolite levels of 2.9 μM (subject A) and 3.85 μM (subject D). There was no evidence of CLT or CLT-metabolites in plasma two days after CLT administration was stopped.

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TABLE 3

Effect of 6-Day Course of Oral Clotrimazole Blood Levels and Red Cells Ca²⁺-Activated K⁺ Transport in Two Subjects

	CLT Levels Plasma			Blood Cells		Ca ²⁺ -activated ⁸⁶ Rb influx inhibition %
	CLT μM	Met-B μM	Met-A μM	CLT μmol/L cells	Met A+B μM	
Subject A						
Baseline	0	0	0	0	0	0±4
CLT day 3	0.2	1.1	0.7	0.45	4.45	74±5
CLT day 6	0.2	1.1	1.8	0.8	4.15	73±4
Wash-out day 6	0	<0.1	<0.1	0.4	0	71±7
Wash-out day 10	0	<0.1	<0.1	ND	0	75±11
Wash-out day 13	0	0	0	0.85	0	58±9
Wash-out day 20	0	0	0	0	0	0±10
Subject B						
Baseline	0	0	0	0	0	0±10
CLT day 3	0.25	0.8	1.65	0.2	4.2	80±28
CLT day 6	0.2	1.35	2.5	1.1	7.3	83±7
Wash-out day 8	0	<0.1	<0.1	0.6	0	79±21
Wash-out day 10	0	<0.1	<0.1	0.65	0	82±4
Wash-out day 13	0	0	0	0.7	0	37±30
Wash-out day 20	0	0	0	0.25	0	0±13

[0168] Measurements of whole blood CLT levels allowed estimation of "blood cell-associated" CLT levels. As shown in TABLE 3, significant levels of "blood cell-associated CLT were detected up to 7 days (subject A) and 14 days (subject D) following CLT withdrawal. There were no metabolites detectable in blood cells 2 days after CLT was discontinued. These data suggest that red cells and possibly other blood elements bind or contain a significant amount of CLT for an extended period of time, even in the absence of measurable plasma levels. CLT metabolites show a different behavior, disappearing at the same time from both plasma and cells.

[0169] There was a significant correlation between summed levels of CLT and its metabolites in cells and the percent inhibition of the Gardos channel measured in whole blood [% inhibition = 31.7 log (CLT + Met A + Met B, μM) + 56.4; r²=0.439, t=3.06, p<0.02, n=14].

[0170] Metabolite B (Compound 6) specifically inhibits potassium transport via the red cell Gardos channel. CLT and metabolite B (Compound 6) were incubated with a red cell suspension at 20% Hct. Comparison of the inhibitory effect on the red cell Gardos channel of CLT and metabolite B (Compound 6) shows IC₅₀ values of 310 ± 63 nM for CLT and 720 ± 190nM for metabolite B (Compound 6). The value for the inhibition of K⁺ transport by metabolite B (Compound 6) is two to three fold lower than the IC₅₀ for displacement of ¹²⁵I-ChTX by metabolite B (Compound 6). It has previously been shown, (Brugnara, 1993, supra) for ChTX that there is a two to three fold increase in the IC₅₀ value for displacement of ¹²⁵I-ChTX by ChTX compared with the inhibition of K⁺ transport by ChTX.

[0171] Inhibition of K⁺ transport was measured by varying concentrations of metabolite B (Compound 6) and CLT, and the results are depicted in TABLE 4. The percent inhibition of K-transport was greater than 50% when the cells were treated with 500 nM CLT or 1 μM metabolite B (Compound 6) and reached maximal levels at 5 μM CLT and 10 μM metabolite B (Compound 6).

[0172] Oral administration of CLT was not associated with significant side effects in any of the subject studied. In particular no nausea, vomiting or diarrhea were observed. No changes were observed in liver function tests, plasma creatine or blood urea nitrogen (BUN).

TABLE 4

[drug]	flux	% control	% inhibition
Control	1.152	100.0%	0.0%
CLT:			
1 nM	1.155	100.3%	-0.3%

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Table continued

CLT:			
10 nM	1.124	97.6%	2.4%
100 nM	0.892	77.4%	22.6%
500 nM	0.518	45.0%	55.0%
1 μ M	0.248	21.5%	78.5%
5 μ M	0.038	3.3%	96.7%
10 μ M	0.043	3.7%	96.3%
2-chlorophenyl-bis-phenyl-methanol (Compound 6):			
1 nM	1.444	125.3%	-25.3%
10 nM	1.115	96.8%	3.2%
100 nM	0.952	82.6%	17.4%
500 nM	0.717	62.2%	37.8%
1 μ M	0.437	37.9%	62.1%
5 μ M	0.25	21.7%	78.3%
10 μ M	0.113	9.8%	90.2%

10. EXAMPLE: Metabolite B (compound 6) Inhibits Mitogen-Induced Cell Proliferation *In Vitro* In Various Cell Lines

[0173] This Example demonstrates the ability of Clotrimazole (CLT) metabolite B (Compound 6) to inhibit mitogen-induced cell proliferation in various cell lines, including cancer cells. Such assays are generally applicable for demonstrating the activities of other compounds of formula (I) in various cell lines.

10.1 Experimental Protocol

[0174] Human melanoma cells (MM-RU) and colon adenocarcinoma cells (HT29) were cultured in the presence and absence of 10 μ M CLT metabolite B (Compound 6) as described in Benzaquen *et al.*, 1995, Nature Medicine 1:534-540 and the level of DNA synthesis determined by measuring [³H]thymidine uptake.

10.2 Results

[0175] CLT metabolite B (Compound 6) was a potent inhibitor of proliferation of these cell lines *in vitro*. Specifically, CLT metabolite B (Compound 6) inhibited [³H]thymidine uptake by about 60% versus controls in MM-RU cells and by about 50% versus controls in HT29 cells.

11. EXAMPLE: CLT Inhibits Cell Proliferation *In Vivo*

[0176] This Example demonstrates the ability of Clotrimazole (CLT) to inhibit cell proliferation in an *in vivo* animal model of human melanoma. Such an animal model is contemplated to be applicable for demonstrating the *in vivo* activity of compounds of formula (I) which inhibit MM-RU cells *in vitro*.

11.1 Experimental Protocol

[0177] Mice with severe combined immunodeficiency disease (SCID) were inoculated via the lateral tail vein with approximately 2.5×10^6 MM-RU human melanoma cells, a cell line that produces metastases only in the lungs (Byers *et al.*, 1993, Melanoma Res. 3:247-253). Starting on the day of inoculation, subcutaneous injections of either vehicle (control group, n=9) or CLT (120 mg/Kg; treatment group, n=10) was administered daily for a period of 10 weeks. At the end of the 10 week treatment period, the mice were sacrificed and examined for metastases.

11.2 Results

[0178] Ten weeks after inoculation of MM-RU cells, all animals in the control group had developed pleural macroscopic and microscopic lung metastases. In stark contrast, half of the CLT-treated animals were free of macroscopic metastases, and two did not even exhibit evidence of microscopic metastases.

[0179] Despite the variability in the number of metastases observed within each group, animals in the CLT-treated group exhibited significantly fewer pleural (14 ± 4 in control vs. 2 ± 1 in treated animals; $P < 0.05$) and microscopic (27 ± 9 in control vs. 7 ± 2 in treated animals; $P < 0.05$) metastases than those in the control group. A greater number of metastases were counted in the microscopic sections than on the pleural surface, as is typical of the SCID-mice/MM-RU-cells model. There was an excellent correlation between both methods of counting ($r = 0.90$). Consistent with the high organ specificity for lung tissue of the MM-RU melanoma cells, other organs did not show any histological evidence of metastatic lesions.

[0180] Animals in the control and treatment groups did not show any evidence of systemic metastatic disease or toxicity; both control and CLT-treated animals gained weight in comparable amounts.

[0181] *In vivo* efficacy in this mouse melanoma model can be demonstrated with other compounds of formula (I) which inhibit MM-RU cells *in vitro* as well.

12. EXAMPLE: Formulations

[0182] The following examples provide exemplary, not limiting, formulations for administering the compounds of the invention to mammalian, especially human, patients. Any of the compounds described herein, or pharmaceutical salts or hydrates thereof, may be formulated as provided in the following examples.

12.1 Tablet Formulation

[0183] Tablets each containing 60 mg of active ingredient are made up as follows:

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

[0184] The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules are dried at 50° - 60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules, which, after mixing are compressed by a tablet machine to yield tablets each weighing 150 mg.

[0185] Tablets can be prepared from the ingredients listed by wet granulation followed by compression.

12.2 Gelatin Capsules

[0186] Hard gelatin capsules are prepared using the following ingredients:

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

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[0187] The above ingredients are mixed and filled into hard. gelatin capsules in 460 mg quantities.

12.3 Aerosol Solution

5 [0188] An aerosol solution is prepared containing the following components:

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

10 [0189] The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

12.4 Suppositories

15 [0190] Suppositories each containing 225 mg of active ingredient are made as follows:

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

20 [0191] The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

12.5 Suspensions

25 [0192] Suspensions each containing 50 mg of medicament per 5 mL dose are made as follows:

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

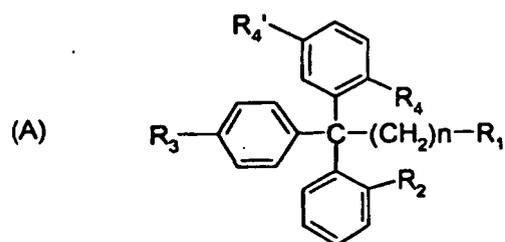
30 [0193] The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and some color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

35 [0194] The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention.

Claims

40 1. A compound of formula (A):

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or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

15 R₁ is -H, -OR, -SR, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂;

R₂ is -F, -Cl, -Br or -I;

R₃ is -R, -OR or -SR;

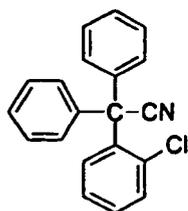
R₄ is -H or -N(R)₂;

R₄' is -H, -F, -Cl, -Br or -I; and

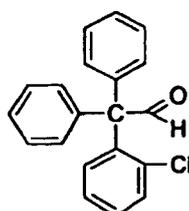
20 each R is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and (C₁-C₆) alkoxy,

with the provisos that (i) when n is 0 and R₁ is -H or -OH, R₃ is other than -H; and (ii) when n is 0 and R₁ is -H, R₃ is other than -OH;

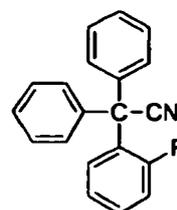
- 25 2. The compound according to Claim 1, wherein said compound is selected from the group of compounds 14, 15, 32, 33, 36, 55, 70, 75, 79, 80, 81, 82, 83 and 86.



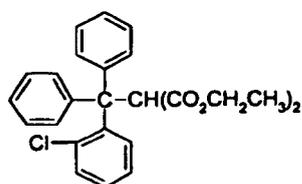
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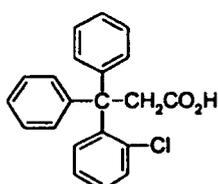
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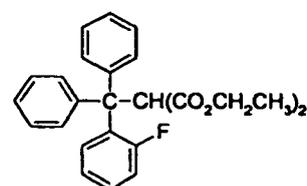
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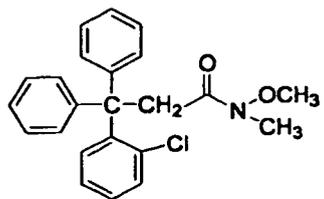


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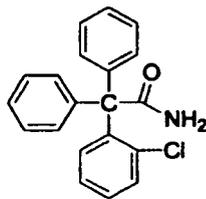
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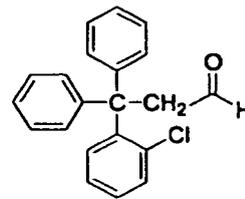
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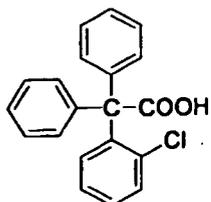
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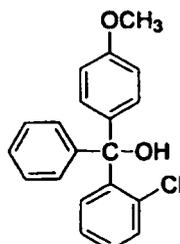
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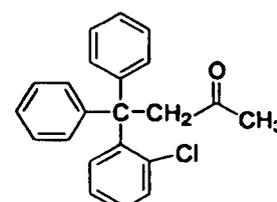
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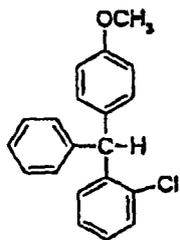


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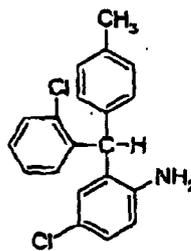
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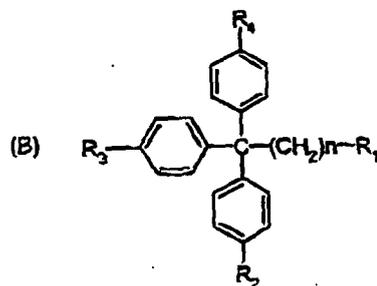


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3. A compound of formula (B):

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or a pharmaceutically acceptable salt or hydrate thereof, wherein:

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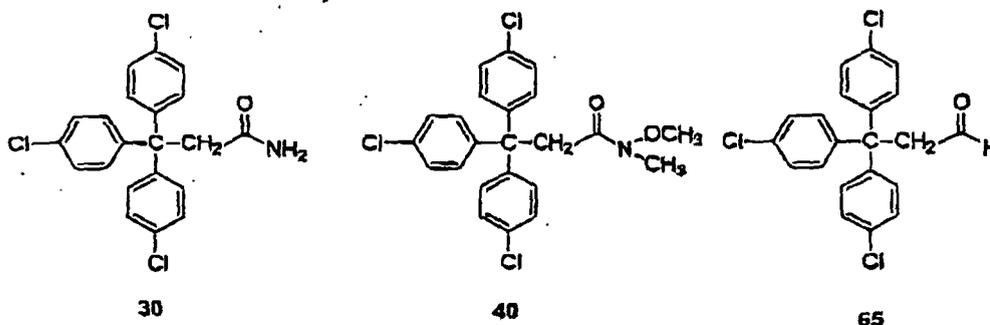
- n is 0, 1, 2, 3 or 4;
- R₁ is -N(R)₂, -C(O)R, -C(S)R, -C(O)N(R')₂ or -C(S)N(R')₂;
- R₂ is -F, -Cl, -Br or -I;
- R₃ is -F, -Cl, -Br or -I;
- R₄ is -F, -Cl, -Br or -I;

each R is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and (C₁-C₆) alkoxy; and

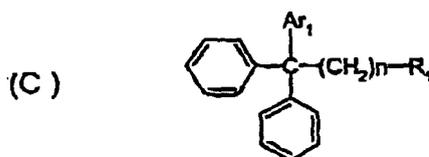
each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

with the proviso that when R₂ = R₃ = R₄ = Cl, and R₁ = NH₂, then n = 1, 3 or 4.

4. The compound according to Claim 3, wherein said compound is selected from the group of compounds 30, 40 and 65.



5. A compound of formula (C):



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

Ar₁ is phenyl or cyclohexyl;

R₁ is -N(R)₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -C(O)N(R)₂ or -C(S)N(R)₂; and each R is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl and (C₁-C₆) alkoxy, with the proviso that when R₁ is -NH₂ or -C(O)NH₂, then n is 1, 2 or 3 and when:

(i) when Ar₁ = Ph, and R₁ = -NHR, wherein R is (C₁-C₄) alkyl, -CH(CH₃)(CH₂)₂CH₃, -CH(C₂H₅)₂, -CH(CH₃)CH(CH₃)CH₂CH₃, -CH(CH₃)CH₂CH(CH₃)CH₃, cyclohexyl; -OCH₃; -(CH₂)₅CH₃; -(CH₂)₄CH₃; -CH₂CH=CH₂, -CH(CH₃)CH=CH₂, or -CH[CH₂CH(CH₃)₂]CH=CH₂, then n = 1, 2, 3 or 4;

(ii) when Ar₁ = Ph, and R₁ = -NR₂, wherein one of the R group is -CH(C≡CH)₂ and the other R group is -CH₂C≡CH or -CH₂CH₂C≡CH, then n = 1, 2, 3 or 4;

(iii) when Ar₁ = Ph, and R₁ = -NR₂, wherein one of the R group is -CH₂CH₃ and the other R group is -CH₃ or -CH₂C(CH₃)=CH₂, then n = 1, 2, 3 or 4;

(iv) when Ar₁ = Ph, and R₁ = N(CH₃)₂ or N(CH₂CH₃)₂, then n = 2, 3 or 4;

(v) when Ar₁ = Ph, and R₁ = NH(*t*-Bu) or C(O)NH₂, then n = 0, 2, 3 or 4;

(vi) when Ar₁ = Ph, and R₁ = NH₂, then n = 3 or 4;

(vii) when Ar₁ = Ph, and R₁ = -C(O)N(CH₃)₂ or -C(O)N(CH₃)cyclohexane or -CH[C(O)OC₂H₅]₂, then n = 1, 2, 3 or 4;

(viii) when Ar₁ = cyclohexyl, and R₁ = N(CH₂CH₃)₂, then n = 0, 1, 2, or 4.

6. The compound according to Claim 5, wherein said compound is selected from the group of compounds 56 and 78.

X is absent, (C₁-C₃) alkyl, (C₁-C₃) alkenyl, or (C₁-C₃) alkynyl;

Y is C, N, P, Si or Ge;

R₁ is absent, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, C(S)R, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂,
-C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)
OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, or -CH[C(S)SR]₂;

Ar₁ is aryl, substituted aryl, heteroaryl other than imidazole, nitroimidazole and triazole, heteroarylium other than imidazolium, nitroimidazolium and triazolium, (C₅-C₈) cycloalkyl or (C₅-C₈) heterocycloalkyl;

Ar₂ is aryl or substituted aryl;

Ar₃ is aryl, substituted aryl, biaryl or heteroaryl other than imidazole, nitroimidazole and triazole;

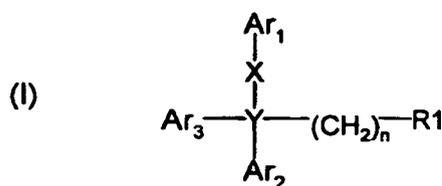
each R is independently selected from the group of -H, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

the aryl substituents are each independently selected from the group of -halo, trihalomethyl, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' and -C(S)SR';

the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of -halo, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryl, γ-butyrolactonyl, pyrrolidinyl, pyrrolidinonyl and succinic anhydridyl; and

each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl and (C₁-C₆) alkynyl.

9. A pharmaceutical composition comprising a compound in admixture with a pharmaceutically acceptable excipient, carrier or diluent, said compound having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

X is absent, (C₁-C₃) alkyl, (C₁-C₃) alkenyl, or (C₁-C₃) alkynyl;

Y is N, Si or Ge;

R₁ is absent, -halo, -R, -OR, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH
[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂ or aryl;

Ar₁ is aryl, substituted aryl, heteroaryl other than imidazole, nitroimidazole and triazole, heteroarylium other than imidazolium, nitroimidazolium and triazolium, (C₅-C₈) cycloalkyl or (C₅-C₈) heterocycloalkyl;

Ar₂ is aryl or substituted aryl;

Ar₃ is aryl, substituted aryl, biaryl or heteroaryl other than imidazole, nitroimidazole and triazole;

each R is independently selected from the group of -H, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

the aryl substituents are each independently selected from the group of -halo, trihalomethyl, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' and -C(S)SR';

the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of -halo, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryl, γ-butyrolactonyl, pyrrolidinyl, pyrrolidinonyl and succinic anhydridyl; and

each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl and (C₁-C₆) alkynyl.

10. The pharmaceutical composition of claim 7, wherein the substituents are as follows:

n is 0, 1, 2, 3 or 4;

X is absent or -C≡C-;

Y is C or Si;

R₁ is -F, -Cl, -Br, SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, -C(O)OR, -C(O)N(R)₂, -C(O)NR(OR), or -CH[C(O)
OR]₂;

Ar₁ is phenyl, substituted phenyl, heteroaryl other than imidazole, nitroimidazole and triazole, cyclohexyl, pip-

eridyl or pyridinium;

Ar₂ is phenyl or substituted phenyl;

Ar₃ is phenyl, substituted phenyl, biphenyl, naphthyl or pyridyl;

R is -H, (C₁-C₃) alkyl, substituted (C₁-C₃) alkyl, (C₁-C₃) alkenyl, substituted (C₁-C₃) alkenyl, (C₁-C₃) alkynyl, substituted (C₁-C₃) alkynyl and (C₁-C₃) alkoxy;

the phenyl substituents are each independently selected from the group of -F, -Cl, -Br, -CF₃, -R, -R', -OR', -SR', -N(R')₂, -NO₂, -CN, -C(O)R' and -C(O)OR';

the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of -F, -Cl, -Br, -R', -OR', -SR', -N(R')₂, -NO₂, -CN, -C(O)R',

-C(O)OR', naphthyl, γ -butyrolactonyl, pyrrolidinyl, pyrrolidinonyl; and succinic anhydridyl; and

each R' is independently selected from the group of -H, (C₁-C₃) alkyl, (C₁-C₃) alkenyl and (C₁-C₃) alkynyl.

11. The pharmaceutical composition of claim 9, wherein:

n is 0, 1, 2, 3 or 4;

X is absent or -C \equiv C-;

Y is N, Si, or Ge;

R₁ is absent, -F, -Cl, -Br, -R, -OR, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, -C(O)OR, -C(O)N(R)₂, -C(O)NR(OR), -CH[C(O)OR]₂ or cyclo-penta-2, 4-dien-1-ylidene,

Ar₁ is phenyl, substituted phenyl, heteroaryl other than imidazole, nitroimidazole and triazole, cyclohexyl, piperidyl or pyridinium;

Ar₂ is phenyl or substituted phenyl;

Ar₃ is phenyl, substituted phenyl, biphenyl, naphthyl or pyridyl;

R is -H, (C₁-C₃) alkyl, substituted (C₁-C₃) alkyl, (C₁-C₃) alkenyl, substituted (C₁-C₃) alkenyl, (C₁-C₃) alkynyl, substituted (C₁-C₃) alkynyl and (C₁-C₃) alkoxy;

the phenyl substituents are each independently selected from the group of -F, -Cl, -Br, -CF₃, -R, -R', -OR', -SR', -N(R')₂, -NO₂, -CN, -C(O)R' and -C(O)OR';

the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of -F, -Cl, -Br, -R', -OR', -SR', -N(R')₂, -NO₂, -CN, -C(O)R', -C(O)OR', naphthyl, γ -butyrolactonyl, pyrrolidinyl, pyrrolidinonyl; and succinic anhydridyl; and

each R' is independently selected from the group of -H, (C₁-C₃) alkyl, (C₁-C₃) alkenyl and (C₁-C₃) alkynyl.

12. The pharmaceutical composition of claim 8, wherein:

n is 0, 1, 2, 3 or 4;

X is absent or -C \equiv C-;

Y is C, N, P, Si, or Ge;

R₁ is absent, -F, -Cl, -Br, SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)N(R)₂, -C(O)NR(OR), or -CH[C(O)OR]₂,

Ar₁ is phenyl, substituted phenyl, heteroaryl other than imidazole, nitroimidazole and triazole, cyclohexyl, piperidyl or pyridinium;

Ar₂ is phenyl or substituted phenyl;

Ar₃ is phenyl, substituted phenyl, biphenyl, naphthyl or pyridyl;

R is -H, (C₁-C₃) alkyl, substituted (C₁-C₃) alkyl, (C₁-C₃) alkenyl, substituted (C₁-C₃) alkenyl, (C₁-C₃) alkynyl, substituted (C₁-C₃) alkynyl and (C₁-C₃) alkoxy;

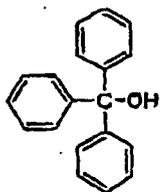
the phenyl substituents are each independently selected from the group of -F, -Cl, -Br, -CF₃, -R, -R', -OR', -SR', -N(R')₂, -NO₂, -CN, -C(O)R' and -C(O)OR';

the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of -F, -Cl, -Br, -R', -OR', -SR', -N(R')₂, -NO₂, -CN, -C(O)R', -C(O)OR', naphthyl, γ -butyrolactonyl, pyrrolidinyl, pyrrolidinonyl; and succinic anhydridyl; and

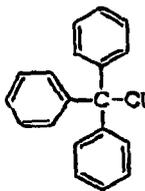
each R' is independently selected from the group of -H, (C₁-C₃) alkyl, (C₁-C₃) alkenyl and (C₁-C₃) alkynyl.

13. A pharmaceutical composition comprising a compound in admixture with a pharmaceutically acceptable excipient, carrier or diluent, wherein said compound is selected from the group of compounds 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 86, 87, 88, 89 and 90:

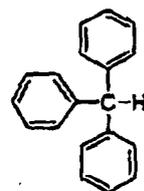
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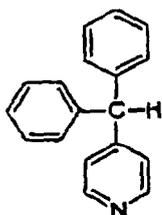
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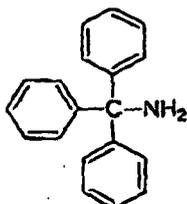
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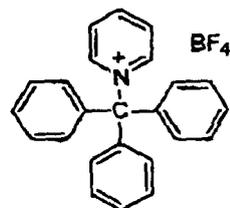
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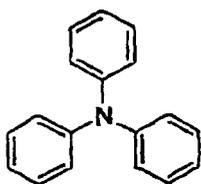
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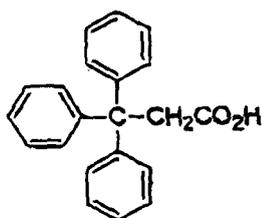
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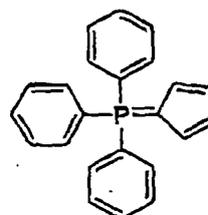
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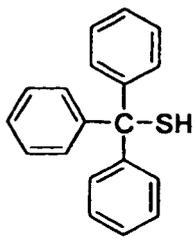
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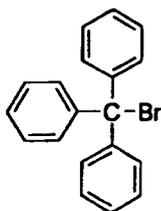
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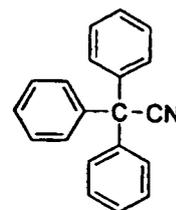
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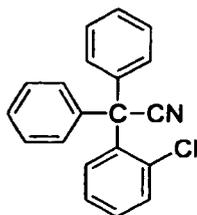
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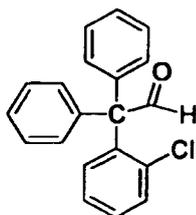
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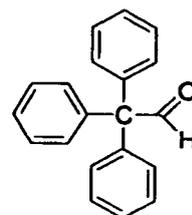
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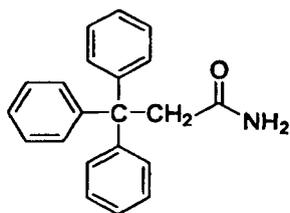
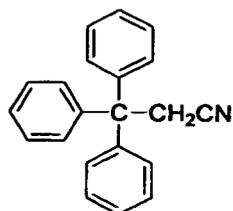


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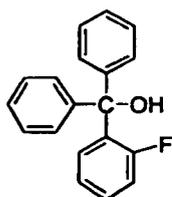
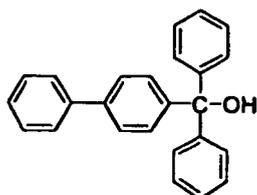
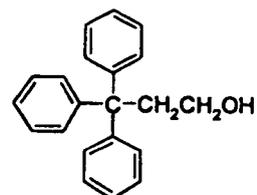
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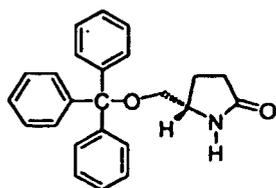
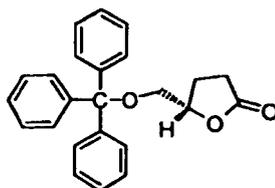
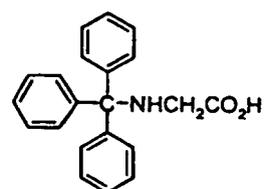
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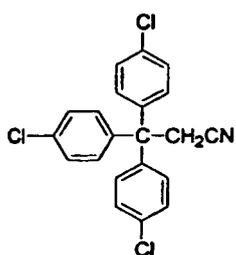
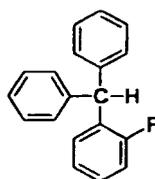
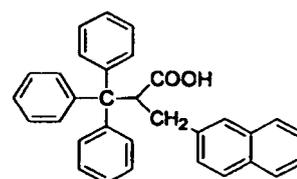
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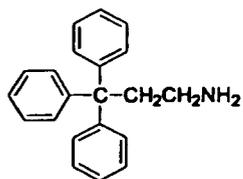
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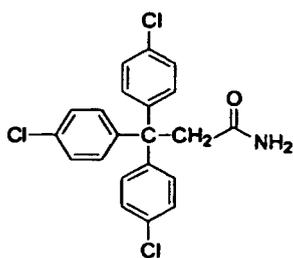
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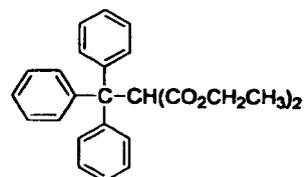
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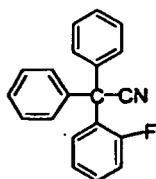
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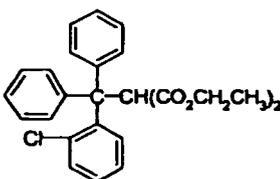
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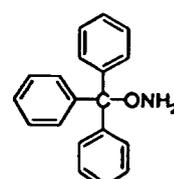
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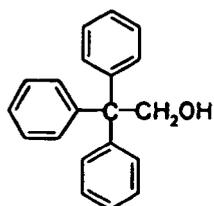
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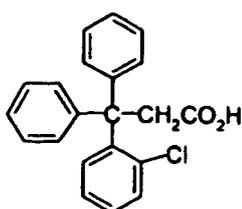
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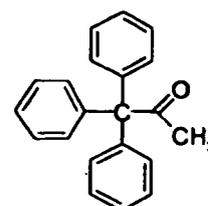
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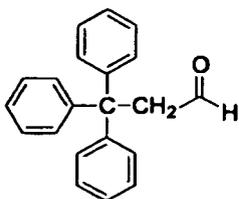


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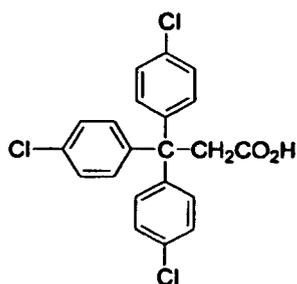
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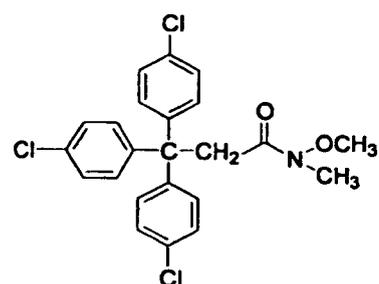
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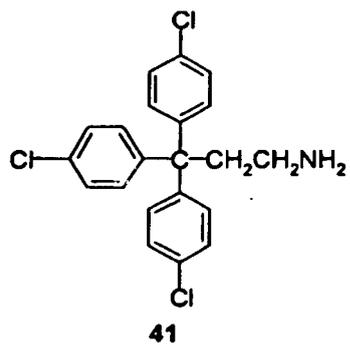
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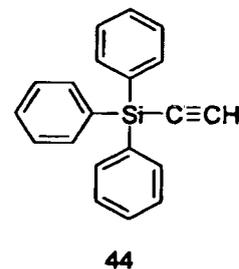
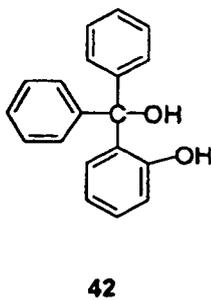
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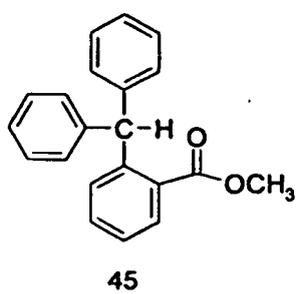


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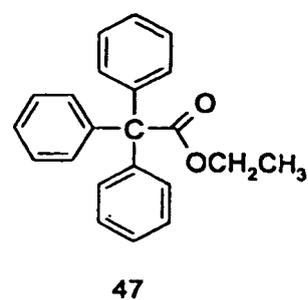
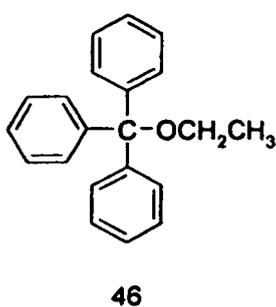


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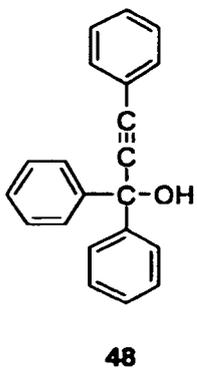


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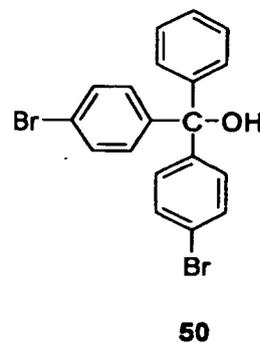
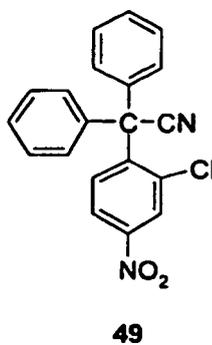


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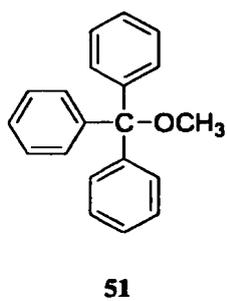


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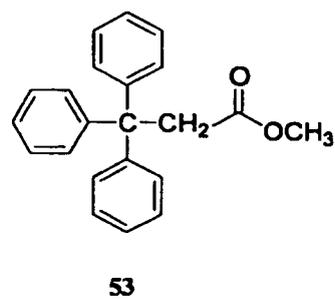
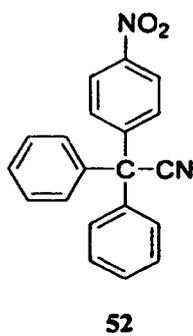


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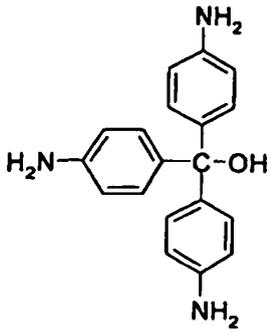
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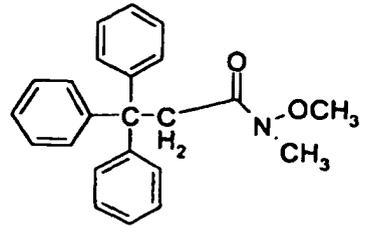


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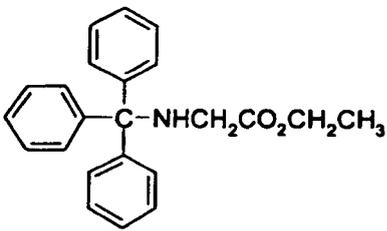
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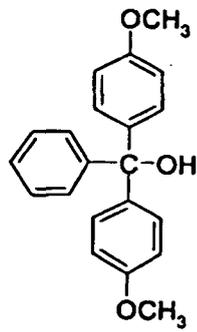
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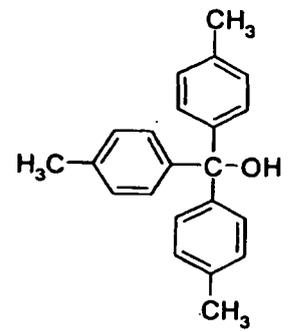


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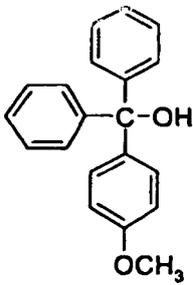
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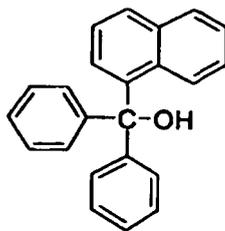
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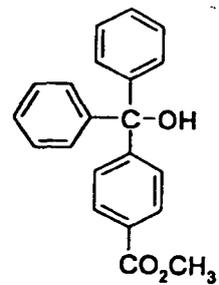
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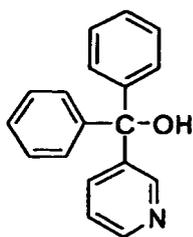


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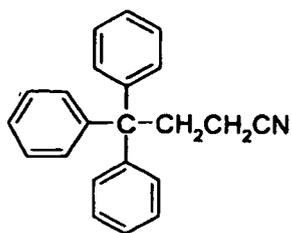
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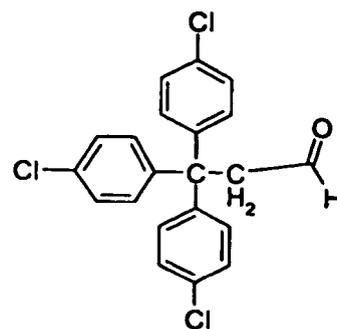


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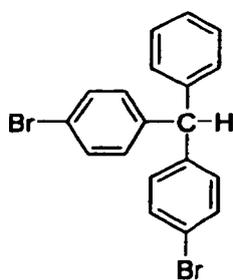
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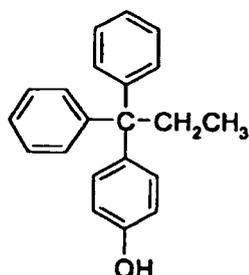
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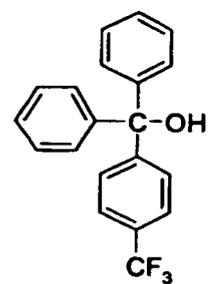
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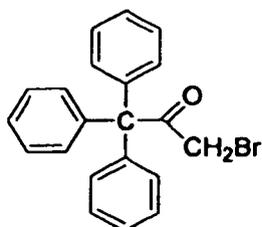
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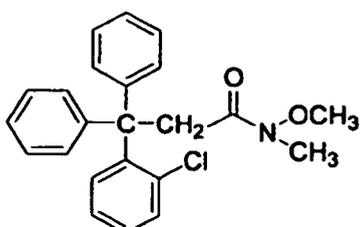
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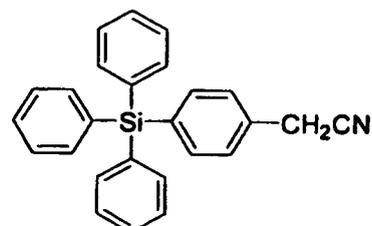


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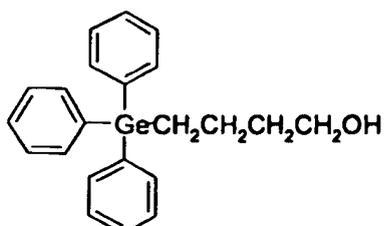
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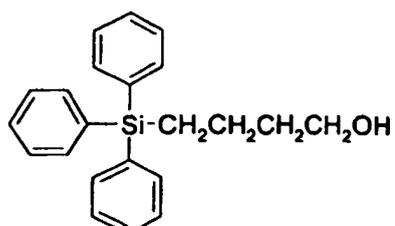
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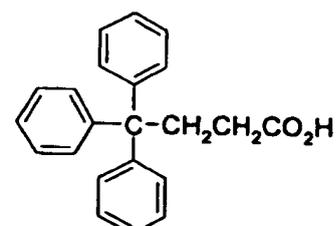


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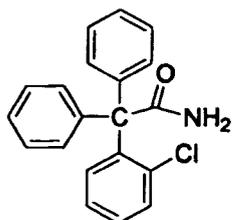


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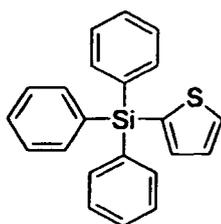


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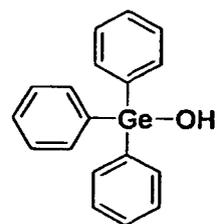
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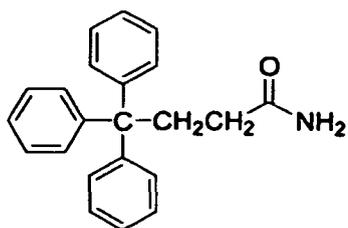
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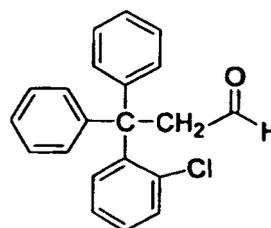
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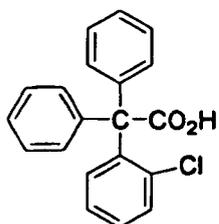


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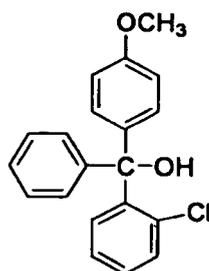
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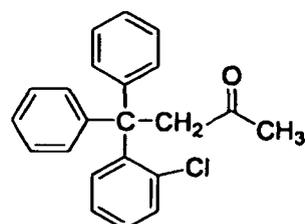


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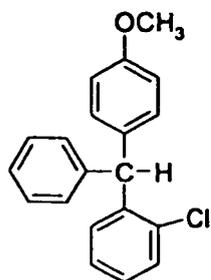
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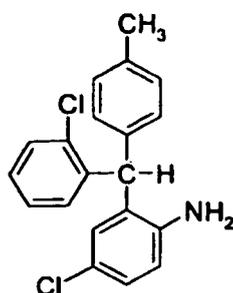
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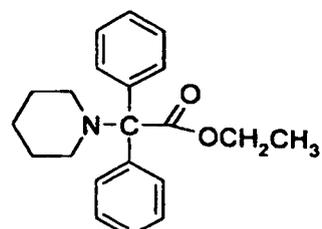


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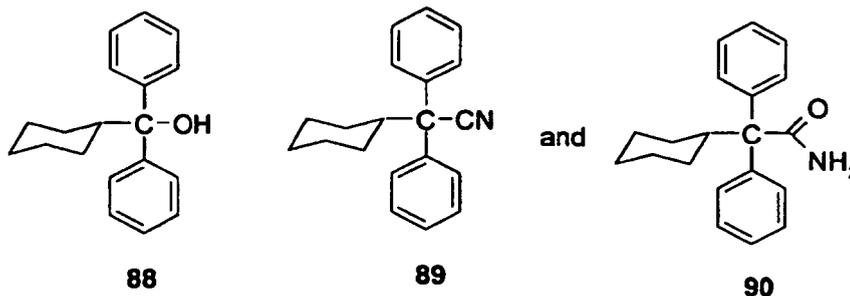
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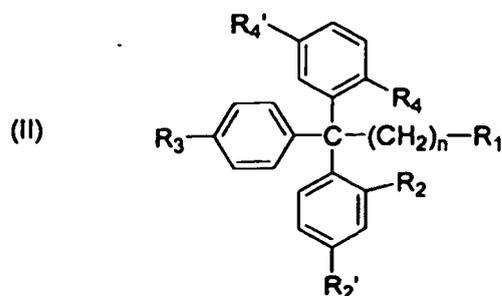
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14. The pharmaceutical composition of Claim 13, wherein said compound is selected from the group of compounds 7, 10, 12, 13, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 40, 41, 42, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 58, 59, 60, 61, 62, 64, 65, 67, 68, 69, 70, 71, 72, 73, 75, 78, 79, 80, 81, 82, 83, 86, 87, 88, 89 and 90.

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15. A pharmaceutical composition comprising a compound in admixture with a pharmaceutically acceptable excipient, carrier or diluent, wherein said compound has the structural formula:

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or a pharmaceutically acceptable salt or hydrate thereof, wherein:

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n is 0, 1, 2, 3 or 4;

R₁ is -H, -OR, -SR, -CN, -C(O)R, -C(O)OR, -C(O)N(R)₂, -CH[C(O)R]₂ or -CH[C(O)OR]₂;

R₂ is -F, -Cl, -Br, -I, -OF, -SR, -C(O)R or -C(O)N(R)₂;

R₂' is -H or -NO₂;

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R₃ is -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, -OR or -SR;

R₄ is -H or -N(R)₂;

R₄' is -H, -F, -Cl, -Br or -I; and

each R is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl or (C₁-C₆) alkoxy;

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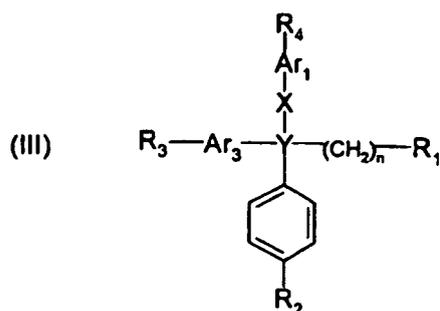
except that the compound is other than 1-(2-chlorophenyl)-1,1-diphenyl methanol, 1-(2-chlorophenyl)-1,1-diphenyl methane or 1-(2-chlorophenyl)-1-(4-hydroxyphenyl)-1-phenyl methane.

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16. The pharmaceutical composition of Claim 15, wherein said compound is selected from the group of compounds 14, 15, 20, 27, 32, 33, 36, 42, 45, 49, 55, 70, 75, 79, 80, 81, 82, 83 and 86.

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17. A pharmaceutical composition comprising a compound in admixture with a pharmaceutically acceptable excipient, carrier or diluent, wherein said compound has the structural formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

15 X is absent or $-C\equiv C-$;

Y is C, Si or Ge;

n is 0, 1, 2, 3 or 4;

Ar₁ is phenyl, substituted phenyl, cycloalkyl or heteroaryl other than imidazolium, nitroimidazolium or triazolium;

20 Ar₃ is phenyl, naphthyl, piperidyl or cyclohexyl;

R₁ is $-R$, $-OR$, $-SR$, $-CN$, $-N(R)_2$, $-ONR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)N(R)_2$, $-CH[C(O)R]_2$, $-CH[C(O)OR]_2$, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, cyclopenta-2,4-diene-1-ylidene or phenyl;

each of R₂, R₃ and R₄ is independently selected from the group of $-H$, $-F$, $-Cl$, $-Br$, $-I$, $-OR$, $-SR$, $-N(R)_2$, $-NO_2$, $-C(O)R$, $-C(O)OR$, $-C(O)N(R)_2$, trihalomethyl, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl and phenyl;

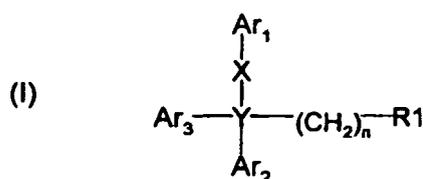
25 each R is independently selected from the group of $-H$, halo, (C_1-C_6) alkyl, substituted (C_1-C_6) alkyl, (C_1-C_6) alkenyl, substituted (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, substituted (C_1-C_6) alkynyl and (C_1-C_6) alkoxy;

the alkyl, alkenyl or alkynyl substituents are each independently selected from the group of aryl, $-C(O)OR$, pyrrolidinyl, pyrrolidinonyl, butyrolactonyl, $-F$, $-Cl$, $-Br$, $-I$ and $-CN$; and

30 the phenyl substituents are each independently $-R$; except that the compound is other than 1-(2-chlorophenyl)-1, 1-diphenyl methanol, 1-(2-chlorophenyl)-1,1-diphenyl methane or 1-(2-chlorophenyl)-1-(4-hydroxyphenyl)-1-phenyl methane.

18. The pharmaceutical composition of Claim 17, wherein said compound is selected from the group of compounds 7, 12, 13, 16, 18, 19, 21, 22, 23, 24, 26, 28, 29, 30, 31, 34, 35, 37, 38, 40, 41, 44, 46, 47, 48, 50, 51, 52, 53, 54, 56, 58, 59, 60, 61, 62, 64, 65, 67, 68, 69, 71, 72, 73, 78, 87, 88, 89 and 90.

19. Use of a compound of formula (I):



or a pharmaceutically acceptable salt or hydrate thereof in the preparation of a medicament for treating or preventing a disorder selected from cancer, actinic keratosis or Kaposi's sarcoma, wherein:

50 n is 0, 1, 2, 3 or 4;

X is absent, (C_1-C_3) alkyl, (C_1-C_3) alkenyl or (C_1-C_3) alkynyl;

Y is C, N, Si or Ge;

55 R₁ is absent, $-halo$, $-R$, $-OR$, $-SR$, $-N(R)_2$, $-ON(R)_2$, $-NO_2$, $-CN$, $-C(O)R$, $-C(S)R$, $-C(O)OR$, $-C(S)OR$, $-C(O)SR$, $-C(S)SR$, $-C(O)N(R)_2$, $-C(S)N(R)_2$, $-C(O)NR(OR)$, $-C(S)NR(OR)$, $-C(O)NR(SR)$, $-C(S)NR(SR)$, $-CH(CN)_2$, $-CH[C(O)R]_2$, $-CH[C(S)R]_2$, $-CH[C(O)OR]_2$, $-CH[C(S)OR]_2$, $-CH[C(O)SR]_2$, $-CH[C(S)SR]_2$ or aryl;

Ar₁ is aryl, substituted aryl, heteroaryl other than imidazole, nitroimidazole and triazole, heteroaryl other than imidazolium, nitroimidazolium and triazolium, (C_5-C_8) cycloalkyl or (C_5-C_8) heterocycloalkyl;

Ar₂ is aryl or substituted aryl;

Ar₃ is aryl, substituted aryl, biaryl or heteroaryl other than imidazole, nitroimidazole and triazole;

each R is independently selected from the group of -H, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

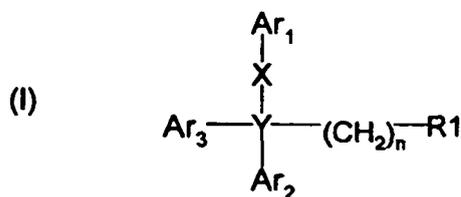
the aryl substituents are each independently selected from the group of -halo, trihalomethyl, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' and -C(S)SR';

the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of -halo, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryl, γ-butyrolactonyl, pyrrolidinyl, pyrrolidinonyl and succinic anhydridyl;

each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl and (C₁-C₆) alkynyl; and

each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl and (C₁-C₆) alkynyl, except that the compound is other than 1-(2-chlorophenyl)-1,1-diphenyl methanol, 1-(2-chlorophenyl)-1,1-diphenyl methane, 1-(2-chlorophenyl)-1-(4-hydroxyphenyl)-1-phenyl methane.

20. Use of a compound in admixture with a pharmaceutically acceptable excipient, carrier or diluent, in the preparation of a medicament for treating a disorder selected from cancer, actinic keratosis and Kaposi's sarcoma, wherein said compound having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2, 3 or 4;

X is absent, (C₁-C₃) alkyl, (C₁-C₃) alkenyl, or (C₁-C₃) alkynyl;

Y is C, N, P, Si or Ge;

R₁ is absent, -halo, OR, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(S)R, C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, or -CH[C(S)SR]₂;

Ar₁ is aryl, substituted aryl, heteroaryl other than imidazole, nitroimidazole and triazole, heteroarylium other than imidazolium, nitroimidazolium and triazolium, (C₅-C₈) cycloalkyl or (C₅-C₈) heterocycloalkyl;

Ar₂ is aryl or substituted aryl;

Ar₃ is aryl, substituted aryl, biaryl or heteroaryl other than imidazole, nitroimidazole and triazole;

each R is independently selected from the group of -H, (C₁-C₆) alkyl, substituted (C₁-C₆) alkyl, (C₁-C₆) alkenyl, substituted (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, substituted (C₁-C₆) alkynyl and (C₁-C₆) alkoxy;

the aryl substituents are each independently selected from the group of -halo, trihalomethyl, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' and -C(S)SR';

the alkyl, alkenyl and alkynyl substituents are each independently selected from the group of -halo, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryl, γ-butyrolactonyl, pyrrolidinyl, pyrrolidinonyl and succinic anhydridyl; and

each R' is independently selected from the group of -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl and (C₁-C₆) alkynyl.

21. The use according to Claim 19, wherein said compound is selected from the group of compounds 13, 14, 15, 16, 18, 19, 21, 26, 27, 28, 30, 31, 36, 38, 40, 41, 42, 43, 45, 46, 47, 48, 49, 50, 52, 54, 59, 61, 65, 67, 68, 70, 71, 72, 73, 79, 82, 83, 84, 86, 89 and 90.

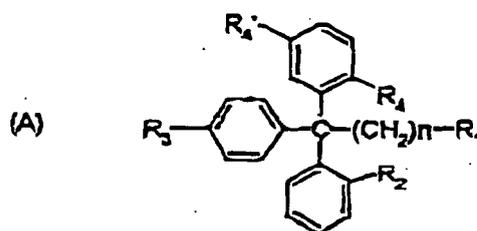
22. The use according to Claim 19, wherein said compound is selected from the group of compounds 16, 28, 30, 36, 38, 45, 47, 48, 49, 50, 52, 54, and 84.

23. The use according to any one of Claims 19, 21 or 22 wherein said compound is for oral, parenteral, intravenous or transdermal administration.

24. The use according to any one of Claims 19, 21 or 22 wherein said disorder is cancer and said compound is for oral, parenteral or intravenous administration.
25. The use according to any one of Claims 19, 21 or 22, wherein said disorder is selected from actinic keratosis or Kaposi's sarcoma and said compound is for transdermal administration.
26. The compound according to any one claims 1 to 6 for use in the treatment or prevention of a disorder selected from cancer, actinic keratosis and Kaposi's sarcoma.
27. The pharmaceutical composition according to any one claims 13 to 18 for use in the treatment or prevention of a disorder selected from cancer, actinic keratosis and Kaposi's sarcoma.

Patentansprüche

1. Verbindung der Formel (A):



oder ein pharmazeutisch verträgliches Salz oder Hydrat davon, wobei:

n 0, 1, 2, 3 oder 4 ist;

R₁ -H, -OR, -SR, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂ ist;

R₂ -F, -Cl, -Br oder -I ist;

R₃ -R, -OR oder -SR ist;

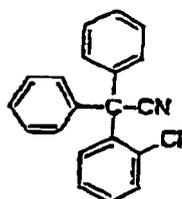
R₄ -H oder -N(R)₂ ist;

R₄' -H, -F, -Cl, -Br oder -I ist; und

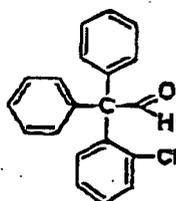
jedes R unabhängig aus der Gruppe von -H, (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl, (C₁-C₆)-Alkynyl und (C₁-C₆)-Alkoxy ausgewählt ist,

mit den Maßgaben, daß (i), wenn n 0 ist und R₁ -H oder -OH ist, R₃ anders als -H ist; und (ii), wenn n 0 ist und R₁ -H ist, R₃ anders als -OH ist.

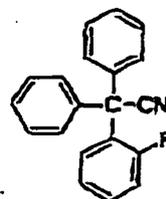
2. Verbindung nach Anspruch 1, wobei die Verbindung aus der Gruppe von Verbindungen 14, 15, 32, 33, 36, 55, 70, 75, 79, 80, 81, 82, 83 und 86 ausgewählt ist.



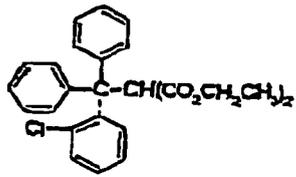
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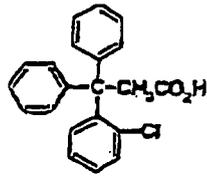
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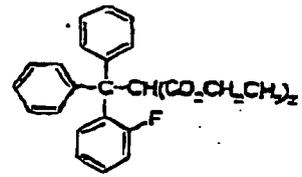
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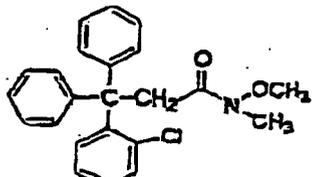
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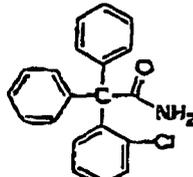
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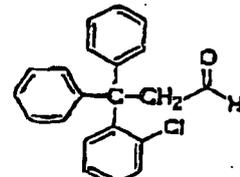
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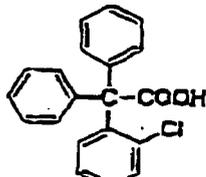
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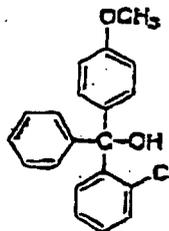
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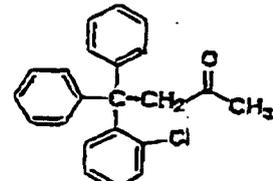
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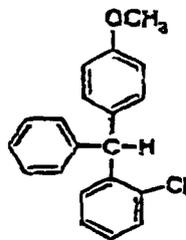
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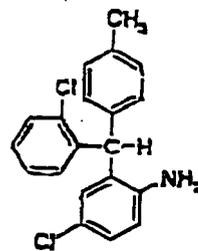
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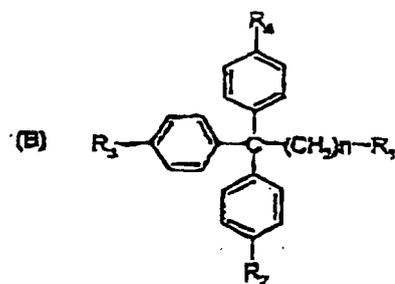


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45 3. Verbindung der Formel (B):



oder ein pharmazeutisch verträgliches Salz oder Hydrat davon, wobei:

n 0, 1, 2, 3 oder 4 ist;

R_1 -NR₂, -C(O)R, -C(S)R, -C(O)NR'₂ oder -C(S)NR'₂ ist;

R₂ -F, -Cl, -Br oder -I ist;

R₃ -F, -Cl, -Br oder -I ist;

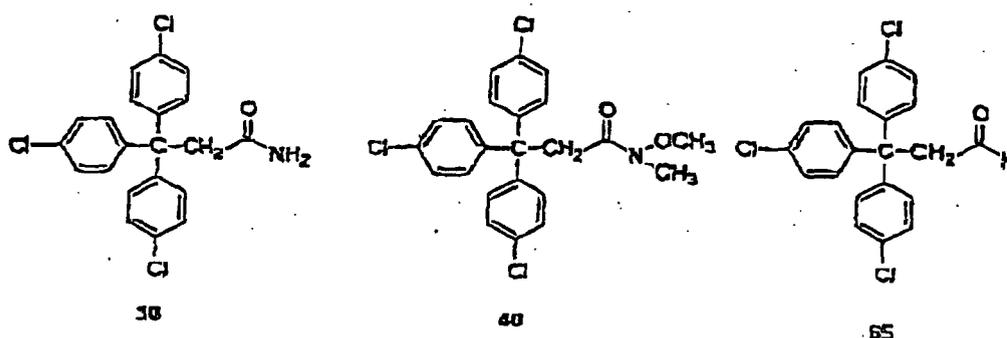
R₄ -F, -Cl, -Br oder -I ist;

jedes R unabhängig aus der Gruppe von -H, (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl, (C₁-C₆)-Alkynyl und (C₁-C₆)-Alkoxy ausgewählt ist; und

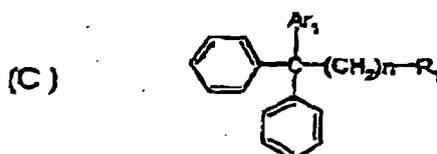
jedes R' unabhängig aus der Gruppe von -H, (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl, (C₁-C₆)-Alkynyl und (C₁-C₆)-Alkoxy ausgewählt ist;

mit der Maßgabe, daß, wenn R₂ = R₃ = R₄ = Cl, R₁ = NH₂, dann n = 1, 3 oder 4.

4. Verbindung nach Anspruch 3, wobei die Verbindung aus der Gruppe von Verbindungen 30, 40 und 65 ausgewählt ist.



5. Verbindung der Formel (C):



oder ein pharmazeutisch verträgliches Salz oder Hydrat davon, wobei:

n 0, 1, 2, 3 oder 4 ist;

Ar₁ Phenyl oder Cyclohexyl ist;

R₁ N(R)₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -C(O)N(R)₂ oder -C(S)N(R)₂ ist; und jedes R unabhängig aus der Gruppe von -H, (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl, (C₁-C₆)-Alkynyl und (C₁-C₆)-Alkoxy ausgewählt ist,

mit der Maßgabe, daß, wenn R₁ -NH₂ oder -C(O)NH₂ ist, dann n 1, 2 oder 3 ist, und wenn:

(i) wenn Ar₁ = Ph, R₁ = -NHR, wobei R (C₁-C₄)-Alkyl, -CH(CH₃)(CH₂)₂CH₃, -CH(C₂H₅)₂, -CH(CH₃)CH(CH₃)CH₂CH₃, -CH(CH₃)CH₂CH(CH₃)CH₃, Cyclohexyl; -OCH₃; -(CH₂)₅CH₃; -(CH₂)₄CH₃; -CH₂CH=CH₂, -CH(CH₃)CH=CH₂, -CH[CH₂CH(CH₃)₂]CH=CH₂ ist, dann n = 1, 2, 3 oder 4;

(ii) wenn Ar₁ = Ph, R₁ = -NR₂, wobei eine der R-Gruppen -CH(C≡CH)₂ ist und die andere R-Gruppe -CH₂C≡CH oder -CH₂CH₂C≡CH ist, dann n = 1, 2, 3, 4;

(iii) wenn Ar₁ = Ph, R₁ = -NR₂, wobei eine der R-Gruppen -CH₂CH₃ ist und die andere R-Gruppe -CH₃ oder -CH₂C(CH₃)=CH₂ ist, dann n = 1, 2, 3 oder 4;

(iv) wenn Ar₁ = Ph, R₁ = N(CH₃)₂ oder N(CH₂CH₃)₂, dann n = 2, 3 oder 4;

(v) wenn Ar₁ = Ph, R₁ = NH(t-Bu) oder C(O)NH₂, dann n = 0, 2, 3 oder 4;

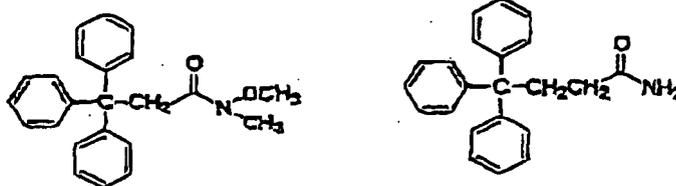
(vi) wenn Ar₁ = Ph, R₁ = NH₂, dann n = 3 oder 4;

(vii) wenn Ar₁ = Ph, R₁ = -C(O)N(CH₃)₂ oder -C(O)N(CH₃)-Cyclohexan oder -CH[C(O)OC₂H₅]₂, dann n = 1, 2, 3 oder 4;

(viii) wenn Ar₁ = Cyclohexyl, R₁ = N(CH₂CH₃)₂, dann n = 0, 1, 2 oder 4.

6. Verbindung nach Anspruch 5, wobei die Verbindung aus der Gruppe von Verbindungen 56 und 78 ausgewählt ist.

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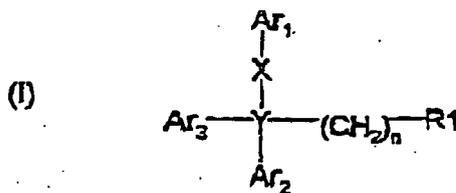
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und

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7. Pharmazeutische Zusammensetzung, umfassend eine Verbindung im Gemisch mit einem pharmazeutisch verträglichen Excipienten, Träger oder Verdünnungsmittel, wobei die Verbindung die Formel:

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hat, oder ein pharmazeutisch verträgliches Salz oder Hydrat davon, wobei:

n 0, 1, 2, 3 oder 4 ist;

X abwesend, (C₁-C₃)-Alkyl, (C₁-C₃)-Alkenyl oder (C₁-C₃)-Alkynyl ist;

Y C oder Si ist;

30

R₁ -Halogen, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂ oder -CH[C(S)SR]₂ ist;

Ar₁ Aryl, substituiertes Aryl, Heteroaryl anders als Imidazol, Nitroimidazol und Triazol, Heteroarylium anders als Imidazolium, Nitroimidazolium und Triazolium, (C₅-C₈)-Cycloalkyl oder (C₅-C₈)-Heterocycloalkyl ist;

35

Ar₂ Aryl oder substituiertes Aryl ist;

Ar₃ Aryl, substituiertes Aryl, Biaryl oder Heteroaryl anders als Imidazol, Nitroimidazol und Triazol ist;

jedes R unabhängig aus der Gruppe von -H, (C₁-C₆)-Alkyl, substituiertem (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl, substituiertem (C₁-C₆)-Alkenyl, (C₁-C₆)-Alkynyl, substituiertem (C₁-C₆)-Alkynyl und (C₁-C₆)-Alkoxy ausgewählt ist;

40

die Arylsubstituenten jeweils unabhängig aus der Gruppe von -Halogen, Trihalogenmethyl, -R, -R', -OR', -SR', N(R)₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' und -C(S)SR' ausgewählt sind;

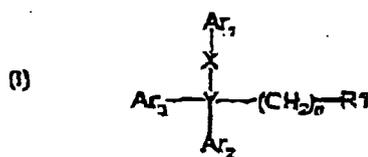
die Alkyl-, Alkenyl- und Alkynylsubstituenten jeweils unabhängig aus der Gruppe von -Halogen, -R', -OR', -SR', N(R)₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(S)OF, -, -C(O)SR', -C(S)SR', Aryl, γ-Butyrolactonyl, Pyrrolidinyl, Pyrrolidinonyl und Succinanhydridyl ausgewählt sind; und

jedes R' unabhängig aus der Gruppe von -H, (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl und (C₁-C₆)-Alkynyl ausgewählt ist.

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8. Pharmazeutische Zusammensetzung, umfassend eine Verbindung im Gemisch mit einem pharmazeutisch verträglichen Excipienten, Träger oder Verdünnungsmittel, wobei die Verbindung die Formel:

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hat, oder ein pharmazeutisch verträgliches Salz oder Hydrat davon, wobei:

n 0, 1, 2, 3 oder 4 ist;

X abwesend, (C₁-C₃)-Alkyl, (C₁-C₃)-Alkenyl oder (C₁-C₃)-Alkynyl ist;

Y C, N, P, Si oder Ge ist;

R₁ abwesend, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(S)R, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂ oder -CH[C(S)SR]₂ ist;

Ar₁ Aryl, substituiertes Aryl, Heteroaryl anders als Imidazol, Nitroimidazol und Triazol, Heteroarylium anders als Imidazolium, Nitroimidazolium und Triazolium, (C₅-C₈)-Cycloalkyl oder (C₅-C₈)-Heterocycloalkyl ist;

Ar₂ Aryl oder substituiertes Aryl ist;

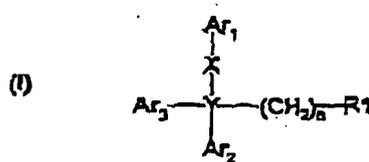
Ar₃ Aryl, substituiertes Aryl, Biaryl oder Heteroaryl anders als Imidazol, Nitroimidazol und Triazol ist;

jedes R unabhängig aus der Gruppe von -H, (C₁-C₆)-Alkyl, substituiertem (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl, substituiertem (C₁-C₆)-Alkenyl, (C₁-C₆)-Alkynyl, substituiertem (C₁-C₆)-Alkynyl und (C₁-C₆)-Alkoxy ausgewählt ist; die Arylsubstituenten jeweils unabhängig aus der Gruppe von -Halogen, Trihalogemethyl, -R, R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' und -C(S)SR' ausgewählt sind;

die Alkyl-, Alkenyl- und Alkynylsubstituenten jeweils unabhängig aus der Gruppe von -Halogen, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', Aryl, γ-Butyrolactonyl, Pyrrolidinyl, Pyrrolidinonyl und Succinanhydridyl ausgewählt sind; und

jedes R' unabhängig aus der Gruppe von -H, (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl und (C₁-C₆)-Alkynyl ausgewählt ist.

9. Pharmazeutische Zusammensetzung, umfassend eine Verbindung im Gemisch mit einem pharmazeutisch verträglichen Exeipienten, Träger oder Verdünnungsmittel, wobei die Verbindung die Formel:



hat, oder ein pharmazeutisch verträgliches Salz oder Hydrat davon, wobei:

n 0, 1, 2, 3 oder 4 ist;

X abwesend, (C₁-C₃)-Alkyl, (C₁-C₃)-Alkenyl oder (C₁-C₃)-Alkynyl ist;

Y N, Si oder Ge ist;

R₁ abwesend, -Halogen, -R, -OR, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂ oder Aryl ist;

Ar₁ Aryl, substituiertes Aryl, Heteroaryl anders als Imidazol, Nitroimidazol und Triazol, Heteroarylium anders als Imidazolium, Nitroimidazolium und Triazolium, (C₅-C₈)-Cycloalkyl oder (C₅-C₈)-Heterocycloalkyl ist;

Ar₂ Aryl oder substituiertes Aryl ist;

Ar₃ Aryl, substituiertes Aryl, Biaryl oder Heteroaryl anders als Imidazol, Nitroimidazol und Triazol ist;

jedes R unabhängig aus der Gruppe von -H, (C₁-C₆)-Alkyl, substituiertem (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl, substituiertem (C₁-C₆)-Alkenyl, (C₁-C₆)-Alkynyl, substituiertem (C₁-C₆)-Alkynyl und (C₁-C₆)-Alkoxy ausgewählt ist; die Arylsubstituenten jeweils unabhängig aus der Gruppe von -Halogen, Trihalogenmethyl, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' und -C(S)SR' ausgewählt sind;

die Alkyl-, Alkenyl- und Alkynylsubstituenten jeweils unabhängig aus der Gruppe von -Halogen, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', Aryl, γ-Butyrolactonyl, Pyrrolidinyl, Pyrrolidinonyl und Succinanhydridyl ausgewählt sind; und

jedes R' unabhängig aus der Gruppe von -H, (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl und (C₁-C₆)-Alkynyl ausgewählt ist.

10. Pharmazeutische Zusammensetzung nach Anspruch 7, wobei die Substituenten wie folgt sind:

n 0, 1, 2, 3 oder 4 ist;

X abwesend oder -C≡C- ist;

Y C oder Si ist;

R₁ -F, -Cl, -Br, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, -C(O)OR, -C(O)N(R)₂, -C(O)NR(OR) oder -CH[C(O)OR]₂ ist;

Ar₁ Phenyl, substituiertes Phenyl, Heteroaryl anders als Imidazol, Nitroimidazol und Triazol, Cyclohexyl, Piperidyl oder Pyridinium ist;

Ar₂ Phenyl oder substituiertes Phenyl ist;
 Ar₃ Phenyl, substituiertes Phenyl, Biphenyl, Naphthyl oder Pyridyl ist;
 R-H, (C₁-C₃)-Alkyl, substituiertes (C₁-C₃)-Alkyl, (C₁-C₃)-Alkenyl, substituiertes (C₁-C₃)-Alkenyl, (C₁-C₃)-Alkyl,
 substituiertes (C₁-C₃)-Alkyl und (C₁-C₃)-Alkoxy ist;
 5 die Phenylsubstituenten jeweils unabhängig aus der Gruppe von -F, -Cl, -Br, -CF₃, R, -R', -OR', -SR', -N(R')₂,
 -NO₂, -CN, -C(O)R' und -C(O)OR' ausgewählt sind;
 die Alkyl-, Alkenyl- und Alkylsubstituenten jeweils unabhängig aus der Gruppe von -F, -Cl, Br, -R', -OR', -SR',
 -N(R')₂, -NO₂, -CN, -C(O)R', -C(O)OR', Naphthyl, γ -Butyrolactonyl, Pyrrolidinyl, Pyrrolidinonyl; und Succinan-
 10 hydridyl ausgewählt sind; und
 jedes R' unabhängig aus der Gruppe von -H, (C₁-C₃)-Alkyl, (C₁-C₃)-Alkenyl und (C₁-C₃)-Alkyl ausgewählt ist.

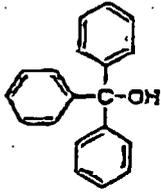
11. Pharmazeutische Zusammensetzung nach Anspruch 9, wobei:

n 0, 1, 2, 3 oder 4 ist;
 15 X abwesend oder -C \equiv C- ist;
 Y N, Si oder Ge ist;
 R₁ abwesend, -F, -Cl, -Br, R, -OR, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, -C(O)OR, -C(O)N(R)₂, -C(O)NR
 (OR), -CH[C(O)OR]₂ oder Cyclopenta-2,4-dien-1-yliden ist;
 Ar₁ Phenyl, substituiertes Phenyl, Heteroaryl anders als Imidazol, Nitroimidazol und Triazol, Cyclohexyl, Pipe-
 20 ridyl oder Pyridinium ist;
 Ar₂ Phenyl oder substituiertes Phenyl ist;
 Ar₃ Phenyl, substituiertes Phenyl, Biphenyl, Naphthyl oder Pyridyl ist;
 R-H, (C₁-C₃)-Alkyl, substituiertes (C₁-C₃)-Alkyl, (C₁-C₃)-Alkenyl, substituiertes (C₁-C₃)-Alkenyl, (C₁-C₃)-Alkyl,
 substituiertes (C₁-C₃)-Alkyl und (C₁-C₃)-Alkoxy ist;
 25 die Phenylsubstituenten jeweils unabhängig aus der Gruppe von -F, -Cl, -Br, -CF₃, -R, -R', -OR', -SR', -N(R')₂.
 -NO₂, -CN, -C(O)R' und -C(O)OR' ausgewählt sind;
 die Alkyl-, Alkenyl- und Alkylsubstituenten jeweils unabhängig aus der Gruppe von -F, -Cl, -Br, -R', -OR', -SR',
 -N(R')₂, -NO₂, -CN, -C(O)R', -C(O)OR', Naphthyl, γ -Butyrolactonyl, Pyrrolidinyl, Pyrrolidinonyl; und Succinan-
 30 hydridyl ausgewählt sind; und
 jedes R' unabhängig aus der Gruppe von -H, (C₁-C₃)-Alkyl, (C₁-C₃)-Alkenyl und (C₁-C₃)-Alkyl ausgewählt ist.

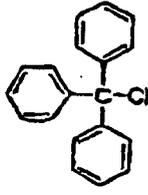
12. Pharmazeutische Zusammensetzung nach Anspruch 8, wobei:

n 0, 1, 2, 3 oder 4 ist;
 35 X abwesend oder -C \equiv C- ist;
 Y C, N, P, Si oder Ge ist;
 R₁ abwesend, -F, -Cl, -Br, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)N(R)₂, -C(O)NR(OR) oder -CH[C(O)OR]₂ ist;
 Ar₁ Phenyl, substituiertes Phenyl, Heteroaryl anders als Imidazol, Nitroimidazol und Triazol, Cyclohexyl, Pipe-
 40 ridyl oder pyridinium ist;
 Ar₂ Phenyl oder substituiertes Phenyl ist;
 Ar₃ Phenyl, substituiertes Phenyl, Biphenyl, Naphthyl oder Pyridyl ist;
 R-H, (C₁-C₃)-Alkyl, substituiertes (C₁-C₃)-Alkyl, (C₁-C₃)-Alkenyl, substituiertes (C₁-C₃)-Alkenyl, (C₁-C₃)-Alkyl,
 substituiertes (C₁-C₃)-Alkyl und (C₁-C₃)-Alkoxy ist,
 45 die Phenylsubstituenten jeweils unabhängig aus der Gruppe von -F, -Cl, -Br, -CF₃, -R, -R', -OR', -SR', -N(R')₂,
 -NO₂, -CN, -C(O)R' und -C(O)OR' ausgewählt sind;
 die Alkyl-, Alkenyl- und Alkylsubstituenten jeweils unabhängig aus der Gruppe von F, -Cl, -Br, -R', -OR', -SR',
 -N(R')₂, -NO₂, -CN, -C(O)R', -C(O)OR', Naphthyl, γ -Butyrolactonyl, Pyrrolidinyl, Pyrrolidinonyl; und Succinan-
 50 hydridyl ausgewählt sind; und
 jedes R' unabhängig aus der Gruppe von -H, (C₁-C₃)-Alkyl, (C₁-C₃)-Alkenyl und (C₁-C₃)-Alkyl ausgewählt ist.

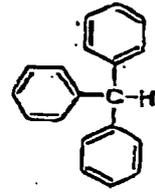
13. Pharmazeutische Zusammensetzung, umfassend eine Verbindung im Gemisch mit einem pharmazeutisch verträglichen Excipienten, Träger oder Verdünnungsmittel, wobei die Verbindung aus der Gruppe von Verbindungen 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 86, 87, 88, 89 und 90;



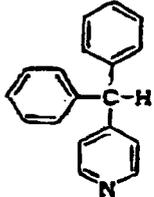
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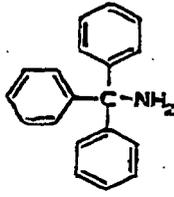
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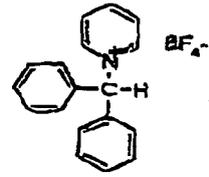
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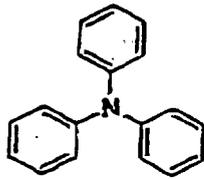
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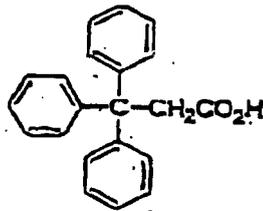
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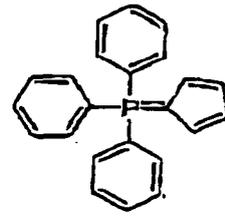
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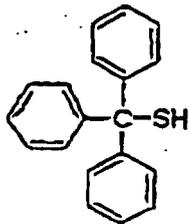
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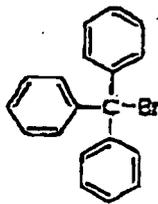
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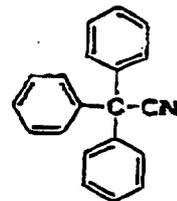
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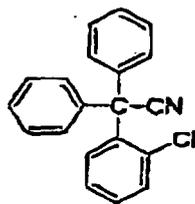
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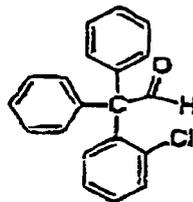
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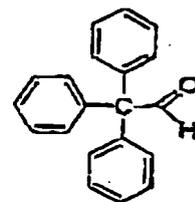
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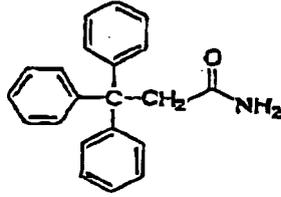


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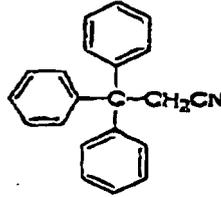


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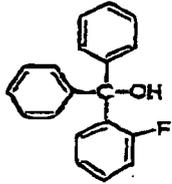
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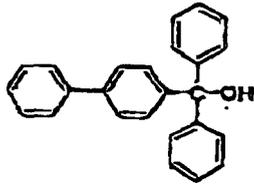
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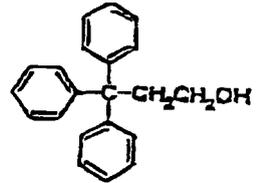
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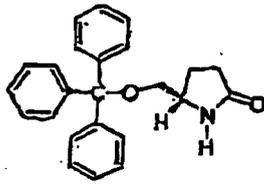
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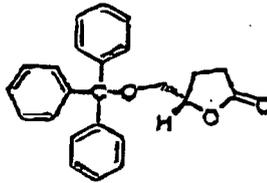
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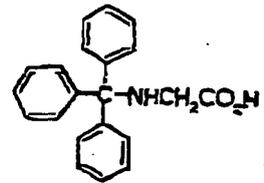
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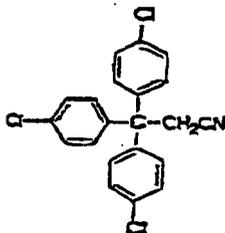
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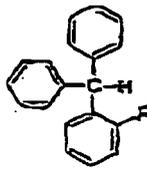
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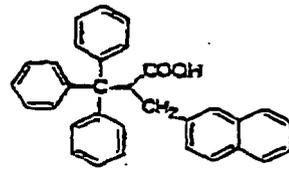
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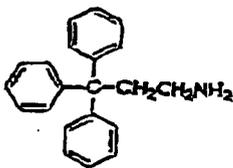
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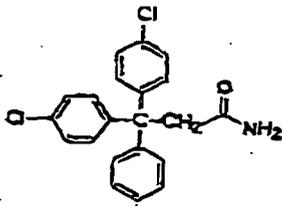
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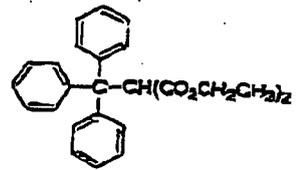
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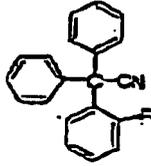


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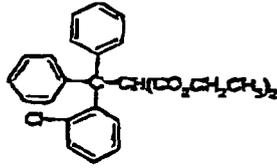


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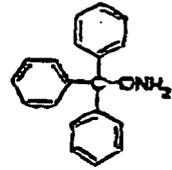
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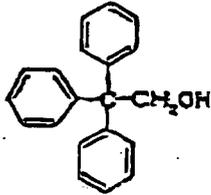
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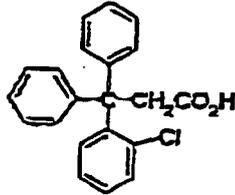
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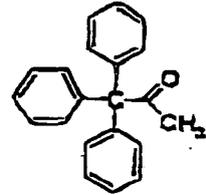
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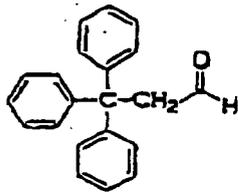
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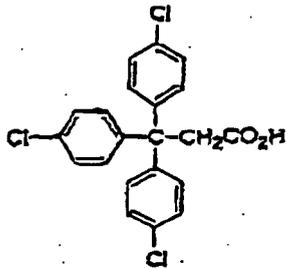
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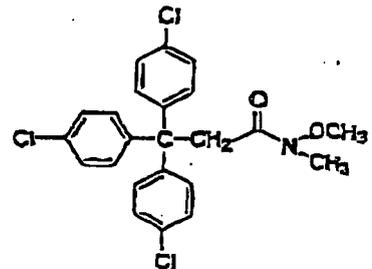
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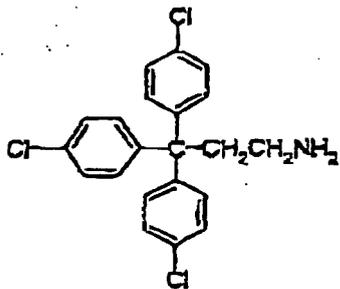
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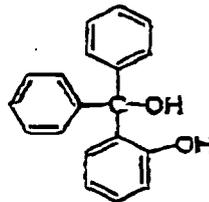
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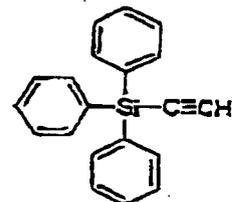
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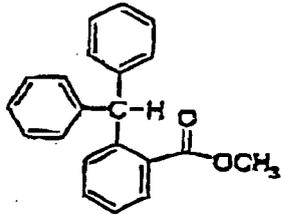


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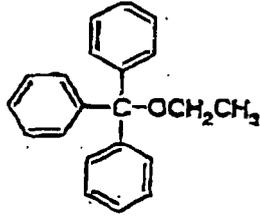
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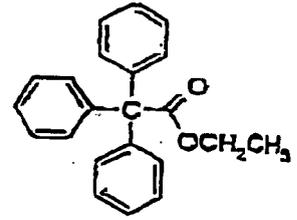


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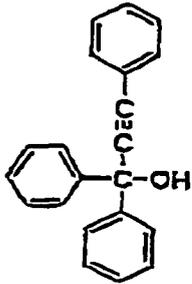


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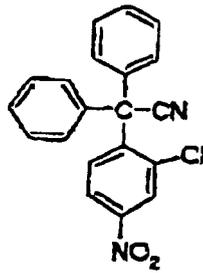
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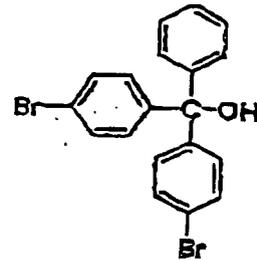


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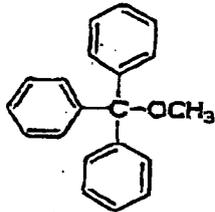
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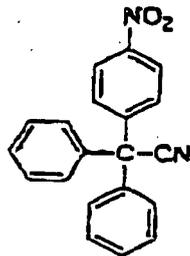
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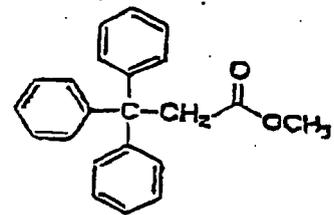


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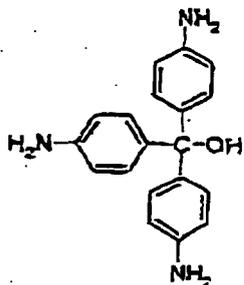


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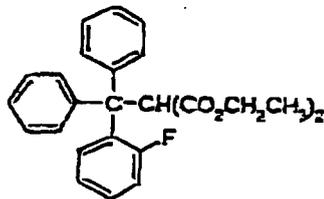
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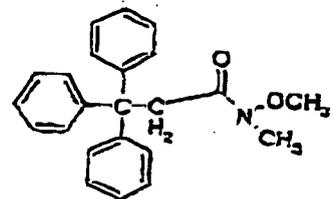
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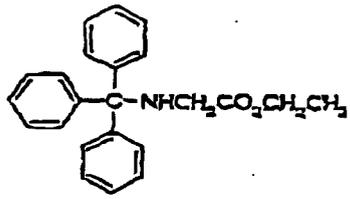
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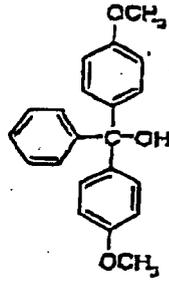
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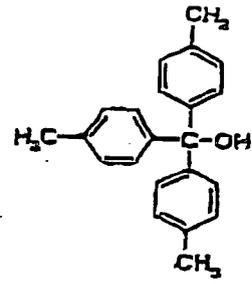


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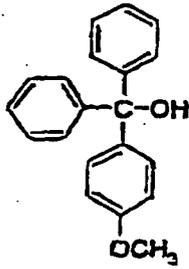


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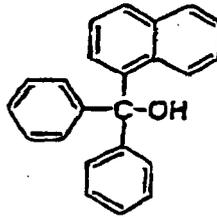
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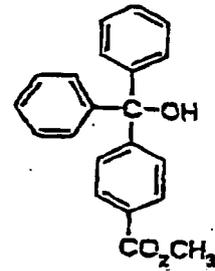


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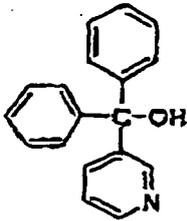
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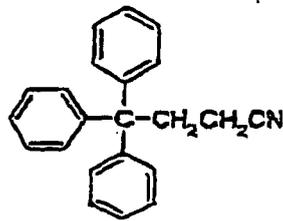
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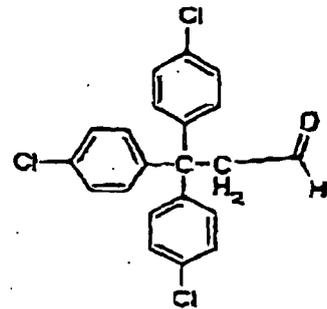


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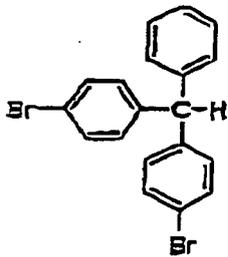
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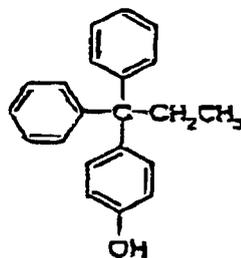
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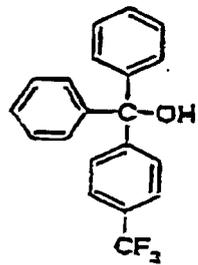


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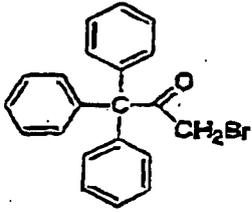
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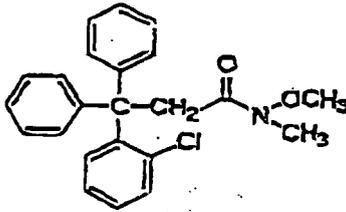
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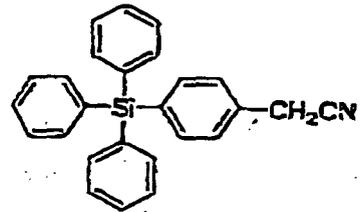
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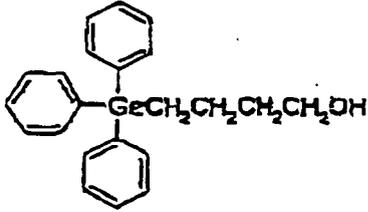


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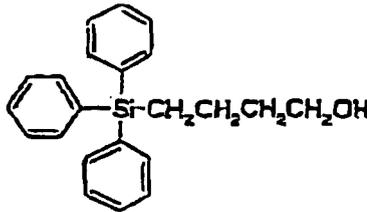


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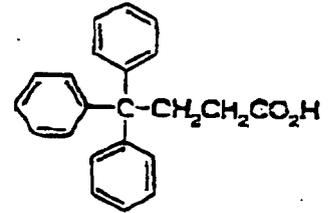
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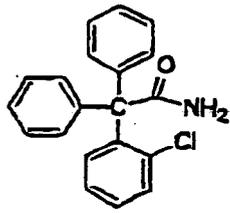
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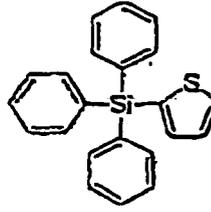
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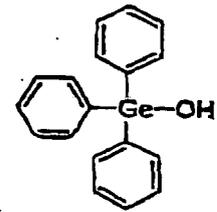
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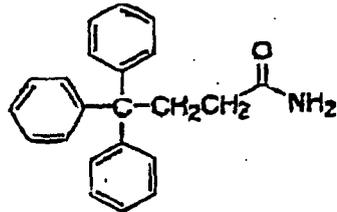
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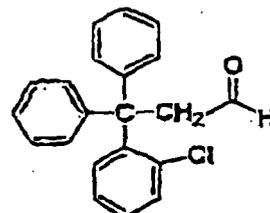
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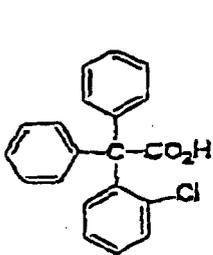
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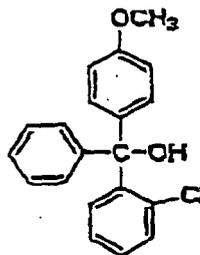
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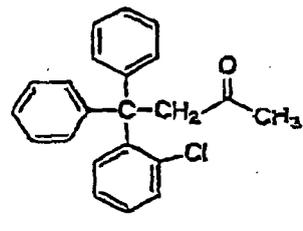
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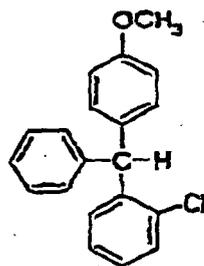


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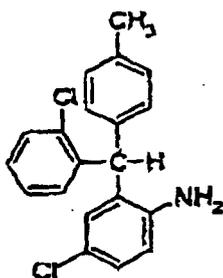


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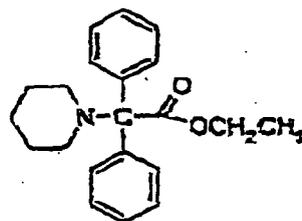
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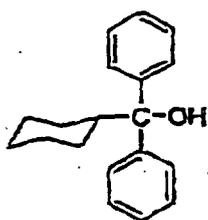
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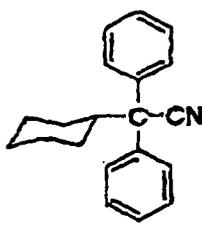
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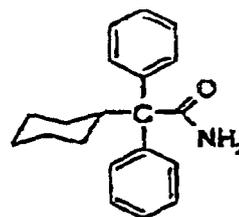
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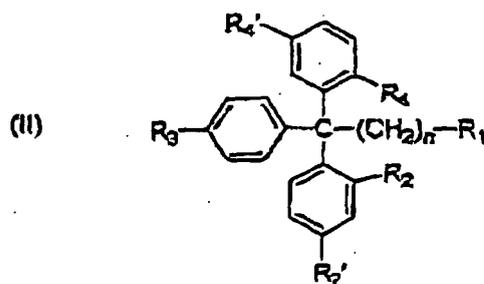
90

und

ausgewählt ist.

14. Pharmazeutische Zusammensetzung nach Anspruch 13, wobei die Verbindung aus der Gruppe von Verbindungen 7, 10, 12, 13, 14, 15, 16, 18, 19, 24, 21, 22, 23, 24, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 40, 41, 42, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 58, 59, 60, 61, 62, 64, 65, 67, 68, 69, 70, 71, 72, 73, 75, 78, 79, 80, 81, 82, 83, 86, 87, 88, 89 und 90 ausgewählt ist.

15. Pharmazeutische Zusammensetzung, umfassend eine Verbindung im Gemisch mit einem pharmazeutisch verträglichen Excipienten, Träger oder Verdünnungsmittel, wobei die Verbindung die Strukturformel:



hat, oder ein pharmazeutisch verträgliches Salz oder Hydrat davon, wobei:

n 0, 1, 2, 3 oder 4 ist;

R_1 -H, -OR, -SR, -CN, -C(O)R, -C(O)OR, -C(O)N(R)₂, -CH[C(O)R]₂ oder -CH[C(O)OR]₂ ist;

R_2 -F, -Cl, -Br, -I, -OR, -SR, -C(O)R oder -C(O)N(R)₂ ist;

R_2' -H oder -NO₂ ist;

R_3 -H, (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl, (C₁-C₆)-Alkynyl, -OR oder -SR ist;

R_4 -H oder -N(R)₂ ist;

R_4' -H, -F, -Cl, -Br oder -I ist; und

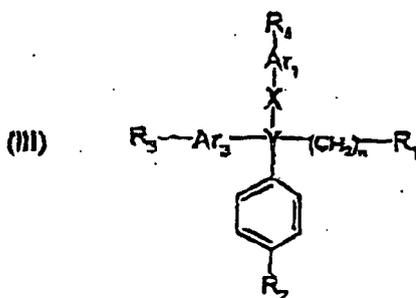
jedes R unabhängig aus der Gruppe von -H, (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl, (C₁-C₆)-Alkynyl und (C₁-C₆)-Alkoxy ausgewählt ist;

außer, daß die Verbindung anders als 1-(2-Chlorphenyl)-1,1-diphenylmethanol, 1-(2-Chlorphenyl)-1,1-diohe-

nylmethan oder 1-(2-Chlorphenyl)-1-(4-hydroxyphenyl)-1-phenylmethan ist.

16. Pharmazeutische Zusammensetzung nach Anspruch 15, wobei die Verbindung aus der Gruppe von Verbindungen 14, 15, 20, 27, 32, 33, 36, 42, 45, 49, 55, 70, 75, 79, 80, 81, 82, 83 und 86 ausgewählt ist.

17. Pharmazeutische Zusammensetzung, umfassend eine Verbindung im Gemisch mit einem pharmazeutisch verträglichen Excipienten, Träger oder Verdünnungsmittel, wobei die Verbindung die Strukturformel:



hat, oder ein pharmazeutisch verträgliches Salz oder Hydrat davon, wobei:

X abwesend oder -C≡C- ist;

Y C, Si oder Ge ist;

n 0, 1, 2, 3 oder 4 ist;

Ar₁ Phenyl, substituiertes Phenyl, Cycloalkyl oder Heteroarylium anders als Imidazolium, Nitroimidazolium oder Triazolium ist;

Ar₃ Phenyl, Naphthyl, Piperidyl oder Cyclohexyl ist;

R₁ -R, -OR, -SR, -CN, -N(R)₂, -ONR₂, -C(O)R, -C(O)OR, -C(O)N(R)₂, -CH[C(O)R]₂, -CH[C(O)OR]₂, (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl, (C₁-C₆)-Alkynyl, Cyclopenta-2,4-dien-1-yliden oder Phenyl ist;

jedes von R₂, R₃ und R₄ unabhängig aus der Gruppe von -H, -F, -Cl, -Br, -I, -OR, -SR, -N(R)₂, -NO₂, -C(O)R, -C(O)OR, -C(O)N(R)₂, -C(O)N(R)₂, Trihalomethyl, (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl, (C₁-C₆)-Alkynyl und Phenyl ausgewählt ist;

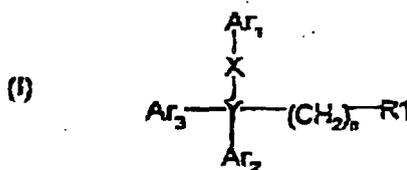
jedes R unabhängig aus der Gruppe von -H, Halogen, (C₁-C₆)-Alkyl, substituiertem (C₁-C₆)-Alkyl, (C₁-C₆)-Alkenyl, substituiertem (C₁-C₆)-Alkenyl, (C₁-C₆)-Alkynyl, substituiertem (C₁-C₆)-Alkynyl und (C₁-C₆)-Alkoxy ausgewählt ist;

die Alkyl-, Alkenyl- oder Alkynylsubstituenten jeweils unabhängig aus der Gruppe von Aryl, -C(O)OR, Pyrrolidinyl, Pyrrolidinonyl, γ-Butyrolactonyl, -F, -Cl, -Br, -I und -CN ausgewählt sind; und

die Phenylsubstituenten jeweils unabhängig -R sind, außer, daß die Verbindung anders als 1-(2-Chlorphenyl)-1,1-diphenylmethanol, 1-(2-Chlorphenyl)-1,1-diphenylmethan oder 1-(2-Chlorphenyl)-1-(4-hydroxyphenyl)-1-phenylmethan ist.

18. Pharmazeutische Zusammensetzung nach Anspruch 17, wobei die Verbindung aus der Gruppe von Verbindungen 7, 12, 13, 16, 18, 19, 21, 22, 23, 24, 26, 28, 29, 30, 31, 34, 35, 37, 38, 40, 41, 44, 46, 47, 48, 50, 51, 52, 53, 54, 56, 58, 59, 60, 61, 62, 64, 65, 67, 68, 69, 71, 72, 73, 78, 87, 88, 89 und 90 ausgewählt ist.

19. Verwendung einer Verbindung der Formel (I):

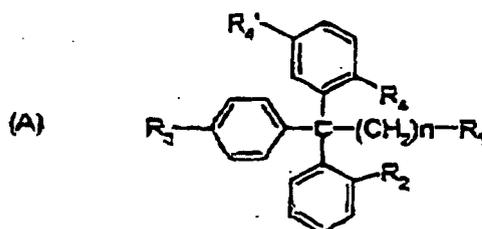


oder eines pharmazeutisch verträglichen Salzes oder Hydrats davon bei der Herstellung eines Medikaments zum Behandeln oder Verhindern einer Erkrankung, ausgewählt aus Krebs, aktinischer Keratose oder Kaposi-Sarkom,

21. Utilisation selon la revendication 19, dans laquelle la molécule est choisie dans le groupe de molécules 13, 14, 15, 16, 18, 19, 21, 26, 27, 28, 30, 31, 36, 38, 40, 41, 42, 43, 45, 46, 47, 48, 49, 50, 52, 54, 59, 61, 65, 67, 68, 70, 71, 72, 73, 79, 82, 83, 84, 86, 89 et 90.
- 5 22. Utilisation selon la revendication 19, dans laquelle la molécule est choisie dans le groupe de molécules 16, 28, 30, 36, 38, 45, 47, 48, 49, 50, 52, 54 et 84.
23. Utilisation selon l'une des revendications 19, 21 ou 22, dans laquelle la molécule est destinée à une administration orale, parentérale, intraveineuse ou transdermique.
- 10 24. Utilisation selon l'une des revendications 19, 21 ou 22, dans laquelle la maladie est le cancer et la molécule est destinée à une administration orale, parentérale ou intraveineuse.
- 15 25. Utilisation selon l'une des revendications 19, 21 ou 22, dans laquelle la maladie est l'actinocératose ou le sarcome de Kaposi et la molécule est destinée à une administration transdermique.
26. Molécule selon l'une des revendications 1 à 6 pour l'utilisation dans le traitement ou la prévention d'une maladie, choisie dans le cancer, l'actinocératose et le sarcome de Kaposi.
- 20 27. Composition pharmaceutique selon l'une des revendications 13 à 18 pour l'utilisation dans le traitement ou la prévention d'une maladie, choisie dans le cancer, l'actinocératose et le sarcome de Kaposi.

Revendications

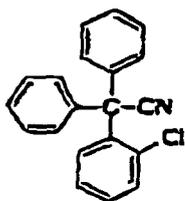
1. Composé de la formule (A):



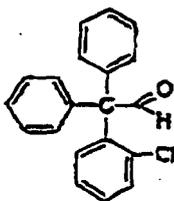
ou sel ou hydrate pharmaceutiquement acceptable de celui-ci, dans lequel:

- n est 0, 1, 2, 3 ou 4;
 R₁ est -H, -OR, -SR, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂;
 R₂ est -F, -Cl, -Br ou -I;
 R₃ est -R, -OR ou -SR;
 R₄ est -H ou -N(R)₂;
 R_{4'} est -H, -F, -Cl, -Br ou -I; et
 chaque R est indépendamment choisi dans le groupe de -H, radical alkyle (C₁-C₆), alcényle (C₁-C₆), alcynyle (C₁-C₆) et alkoxy (C₁-C₆),
 sous réserve que (i) lorsque n est 0 et R₁ est -H ou -OH, R₃ soit différent de -H; et (ii) lorsque n est 0 et R₁ est -H, R₃ soit différent de -OH.
2. Composé suivant la revendication 1, où ledit composé est choisi dans le groupe des composés 14, 15, 32, 33, 36, 55, 70, 75, 79, 80, 81, 82, 83 et 86.

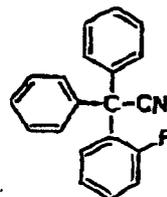
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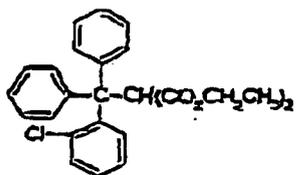


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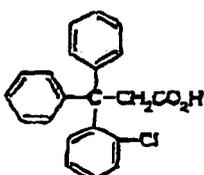


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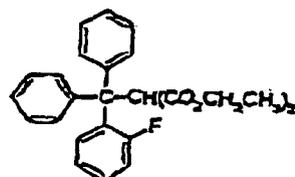
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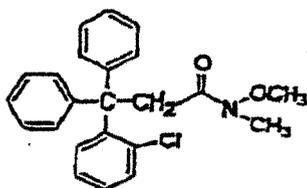


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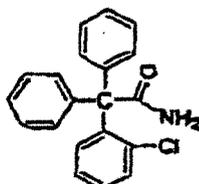
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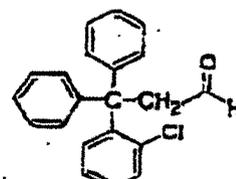
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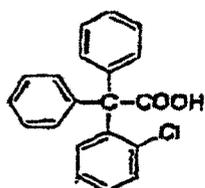
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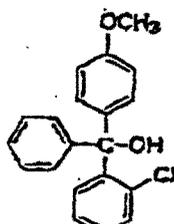
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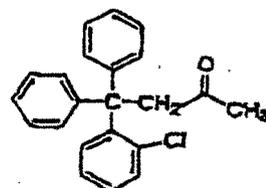
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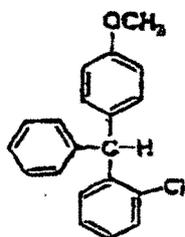
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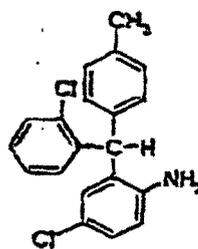
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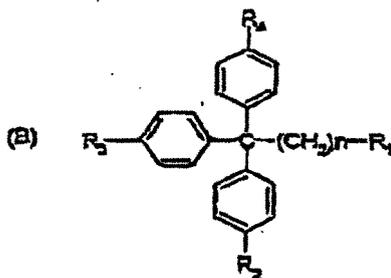


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3. Composé de la formule (B):



ou sel ou hydrate pharmaceutiquement acceptable de celui-ci, dans lequel:

n est 0, 1, 2, 3 ou 4;

R₁ est -NR₂, -C(O)R, -C(S)R, -C(O)NR'₂ ou -C(S)NR'₂;

R₂ est -F, -Cl, -Br ou -I;

R₃ est -F, -Cl, -Br ou -I;

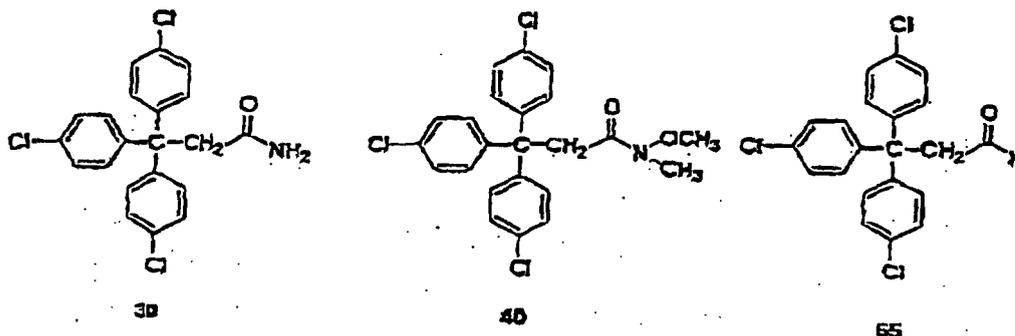
R₄ est -F, -Cl, -Br ou -I;

chaque R est indépendamment choisi dans le groupe de -H, radical alkyle (C₁-C₆), alcényle (C₁-C₆), alcynyle (C₁-C₆) et alkoxy (C₁-C₆); et

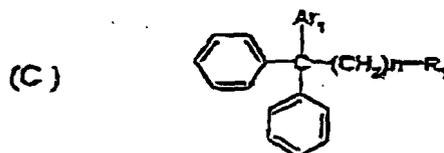
chaque R' est indépendamment choisi dans le groupe de -H, radical alkyle (C₁-C₆), alcényle (C₁-C₆), alcynyle (C₁-C₆) et alkoxy (C₁-C₆);

sous réserve que lorsque R₂ = R₃ = R₄ = Cl, R₁ = NH₂, alors n = 1, 3 ou 4,

- 25 4. Composé suivant la revendication 3, où ledit composé est choisi dans le groupe des composés 30, 40 et 65.



- 40 5. Composé de la formule (C):



ou sel ou hydrate pharmaceutiquement acceptable de celui-ci, dans lequel:

n est 0, 1, 2, 3 ou 4;

Ar₁ est un radical phényle ou cyclohexyle;

R₁ est -NR₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -C(O)N(R)₂ ou -C(S)N(R)₂; et

chaque R est indépendamment choisi dans le groupe de -H, radical alkyle (C₁-C₆), alcényle (C₁-C₆), alcynyle (C₁-C₆) et alkoxy (C₁-C₆);

sous réserve que lorsque R₁ est -NH₂ ou -C(O)NH₂, alors n soit 1, 2 ou 3; et:

- (i) lorsque Ar₁ = Ph, R₁ = -NHR, où R est un radical alkyle (C₁-C₄), -CH(CH₃)(CH₂)₂CH₃, -CH(C₂H₅)₂, -CH

(C₅-C₈);

Ar₂ est un radical aryle ou aryle substitué;

Ar₃ est un radical aryle, aryle substitué, biaryle ou hétéroaryle différent d'imidazole, de nitroimidazole et de triazole;

5 chaque R est indépendamment choisi dans le groupe de -H, radical alkyle (C₁-C₆), alkyle (C₁-C₆) substitué; alcényle (C₁-C₆), alcényle (C₁-C₆) substitué, alcynyle (C₁-C₆), alcynyle (C₁-C₆) substitué et alkoxy (C₁-C₆); les substituants des radicaux aryles sont chacun indépendamment choisis dans le groupe de radical halo, trihalométhyle, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' et -C(S)SR';

10 les substituants des radicaux alkyles, alcényles et alcynyles sont chacun indépendamment choisis dans le groupe de radical halo, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryle, γ-butyrolactonyle, pyrrolidinyle, pyrrolidinonyle et anhydridyle succinique; et chaque R' est indépendamment choisi dans le groupe de -H, radical alkyle (C₁-C₆), alcényle (C₁-C₆) et alcynyle (C₁-C₆).

15 **10.** Composition pharmaceutique suivant la revendication 7, dans laquelle les substituants sont comme suit:

n est 0, 1, 2, 3 ou 4;

X est absent ou -C≡C-;

20 Y est C ou Si;

R₁ est -F, -Cl, -Br, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, -C(O)OR, -C(O)N(R)₂, -C(O)NR(OR) ou -CH[C(O)OR]₂;

Ar₁ est un radical phényle, phényle substitué, hétéroaryle différent d'imidazole, de nitroimidazole et de triazole, cyclohexyle, pipéridyle ou pyridinium;

25 Ar₂ est un radical phényle ou phényle substitué;

Ar₃ est un radical phényle, phényle substitué, biphényle, naphthyle ou pyridyle;

Rest -H, un radical alkyle (C₁-C₃), alkyle (C₁-C₃) substitué, alcényle (C₁-C₃), alcényle (C₁-C₃) substitué, alcynyle (C₁-C₃), alcynyle (C₁-C₃) substitué et alkoxy (C₁-C₃);

30 les substituants des radicaux phényles sont chacun indépendamment choisis dans le groupe de F, -Cl, -Br, -CF₃, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R' et -C(O)OR';

les substituants des radicaux alkyles, alcényles et alcynyles sont chacun indépendamment choisis dans le groupe de -F, -Cl, -Br, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(O)OR', radical naphthyle, γ-butyrolactonyle, pyrrolidinyle, pyrrolidinonyle et anhydridyle succinique; et

35 chaque R' est indépendamment choisi dans le groupe de -H, radical alkyle (C₁-C₃), alcényle (C₁-C₃) et alcynyle (C₁-C₃).

11. Composition pharmaceutique suivant la revendication 9, dans laquelle:

n est 0, 1, 2, 3 ou 4;

40 X est absent ou -C≡C-;

Y est N, Si ou Ge;

R₁ est absent, -F, -Cl, -Br, -R, -OR, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, C(O)OR, -C(O)N(R)₂, -C(O)NR(OR), -CH[C(O)OR]₂ ou un radical cyclopenta-2,4-diène-1-ylidène;

45 Ar₁ est un radical phényle, phényle substitué, hétéroaryle différent d'imidazole, de nitroimidazole et de triazole, cyclohexyle, pipéridyle ou pyridinium;

Ar₂ est un radical phényle ou phényle substitué;

Ar₃ est un radical phényle phényle substitué, biphényle, naphthyle ou pyridyle;

Rest -H, un radical alkyle (C₁-C₃), alkyle (C₁-C₃) substitué, alcényle (C₁-C₃), alcényle (C₁-C₃) substitué, alcynyle (C₁-C₃), alcynyle (C₁-C₃) substitué et alkoxy (C₁-C₃);

50 les substituants des radicaux phényles sont chacun indépendamment choisis dans le groupe de -F, -Cl, -Br, -CF₃, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R' et -C(O)OR';

les substituants des radicaux alkyles, alcényles et alcynyles sont chacun indépendamment choisis dans le groupe de -F, -Cl, -Br, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(O)OR', radical naphthyle, γ-butyrolactonyle, pyrrolidinyle, pyrrolidinonyle et anhydridyle succinique; et

55 chaque R' est indépendamment choisi dans le groupe de -H, radical alkyle (C₁-C₃), alcényle (C₁-C₃) et alcynyle (C₁-C₃).

12. Composition pharmaceutique suivant la revendication 8, dans laquelle:

n est 0, 1, 2, 3 ou 4;

X est absent ou $-C\equiv C-$;

Y est C, N, P, Si ou Ge;

R_1 est absent, -F, -Cl, -Br, -SR, $-N(R)_2$, $-ON(R)_2$, $-NO_2$, -CN, $-C(O)N(R)_2$, $-C(O)NR(OR)$ ou $-CH[C(O)OR]_2$;

Ar_1 est un radical phényle, phényle substitué, hétéroaryle différent d'imidazole, de nitroimidazole et de triazole, cyclohexyle, pipéridyle ou pyridinium;

Ar_2 est un radical phényle ou phényle substitué;

Ar_3 est un radical phényle, phényle substitué, biphényle, naphthyle ou pyridyle;

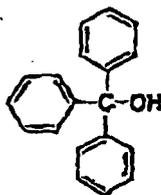
Rest -H, un radical alkyle (C_1-C_3), alkyle (C_1-C_3) substitué, alcényle (C_1-C_3), alcényle (C_1-C_3) substitué, alcynyle (C_1-C_3), alcynyle (C_1-C_3) substitué et alkoxy (C_1-C_3);

les substituants des radicaux phényles sont chacun indépendamment choisis dans le groupe de -F, -Cl, -Br, $-CF_3$, -R, $-R'$, $-OR'$, $-SR'$, $N(R')_2$, $-NO_2$, -CN, $-C(O)R'$ et $-C(O)OR'$;

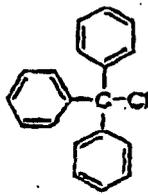
les substituants des radicaux alkyles, alcényles et alcynyles sont chacun indépendamment choisis dans le groupe de -F, -Cl, Br, $-R'$, $-OR'$, $-SR'$, $N(R')_2$, $-NO_2$, -CN, $-C(O)R'$, $-C(O)OR'$, radical naphthyle, γ -butyrolactonyle, pyrrolidinyle, pyrrolidinonyle et anhydridyle succinique; et

chaque R' est indépendamment choisi dans le groupe de -H, radical alkyle (C_1-C_3), alcényle (C_1-C_3) et alcynyle (C_1-C_3).

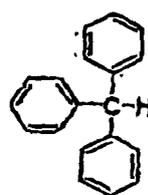
13. Composition pharmaceutique comprenant un composé dans un mélange avec un excipient, un véhicule ou un diluant pharmaceutiquement acceptable, dans laquelle ledit composé est choisi dans le groupe des composés 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 86, 87, 88, 89 et 90:



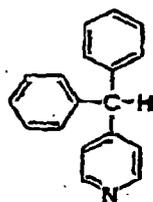
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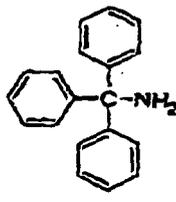
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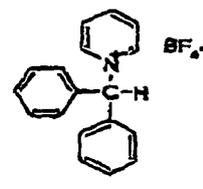
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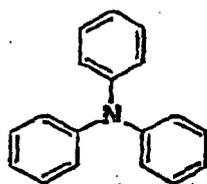
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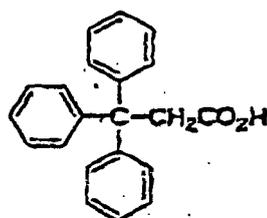
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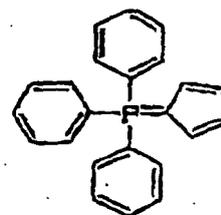
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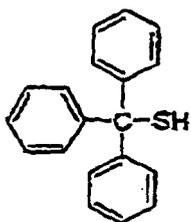


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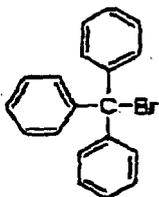


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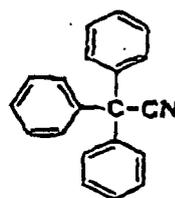
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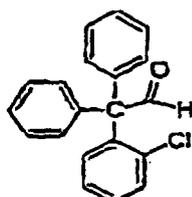
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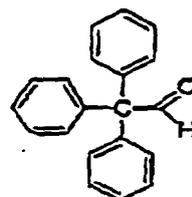
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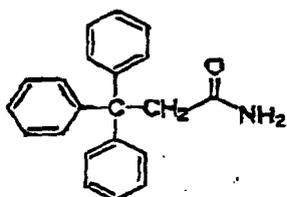
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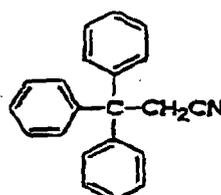
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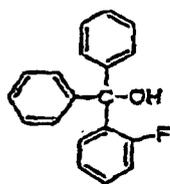
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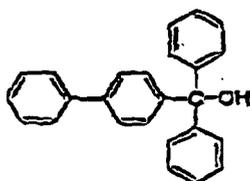
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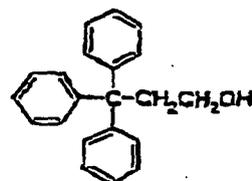
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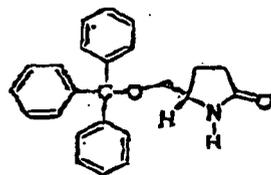
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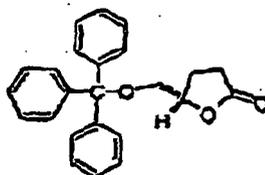
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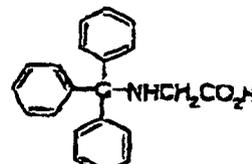
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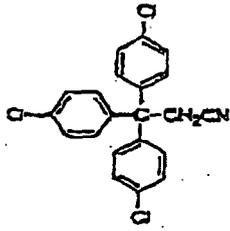


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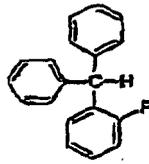


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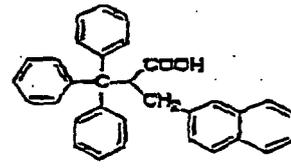
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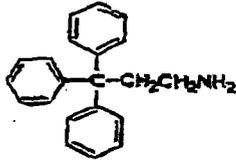


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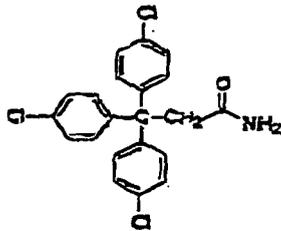


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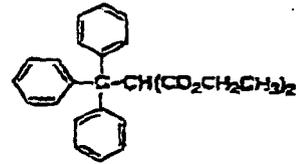
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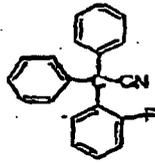


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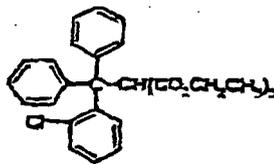
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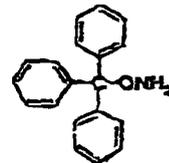
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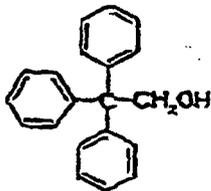
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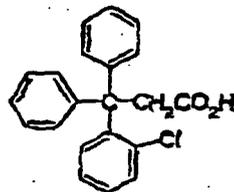
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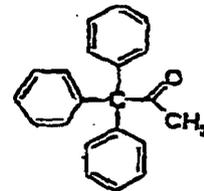
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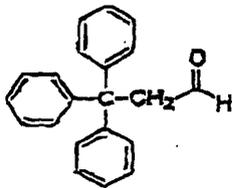
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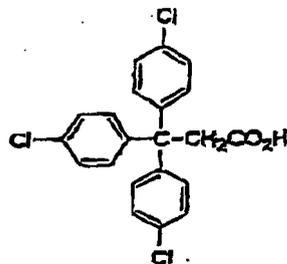
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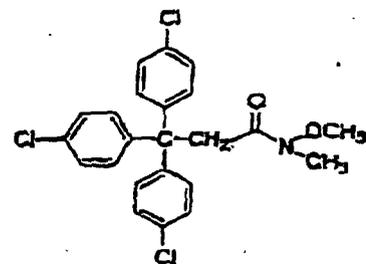
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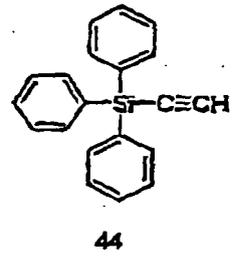
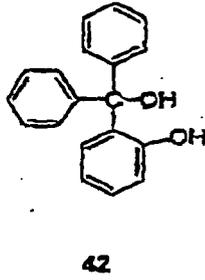
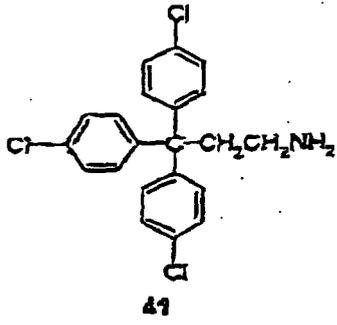


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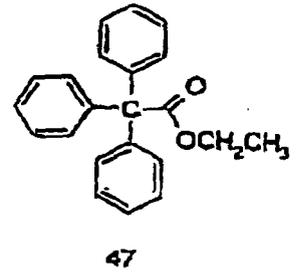
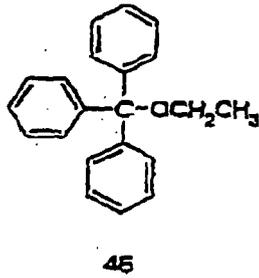
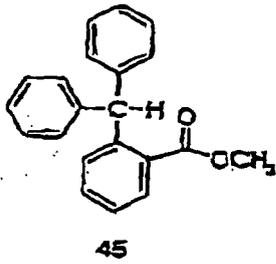
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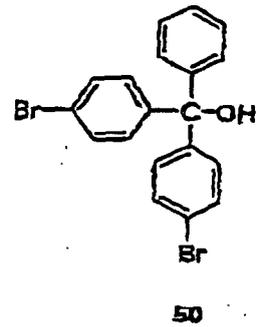
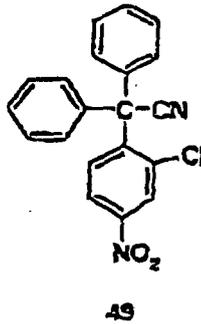
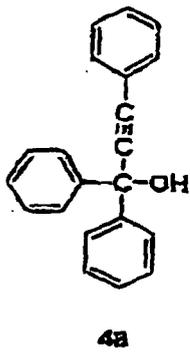
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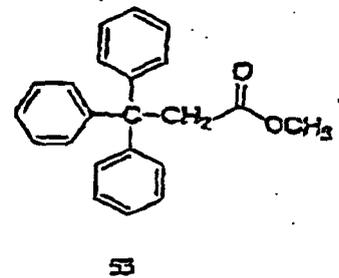
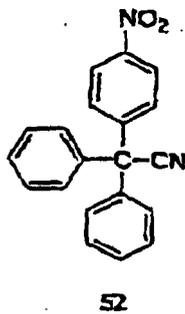
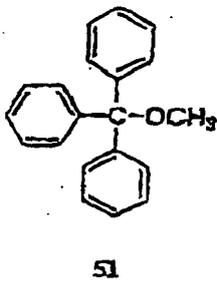
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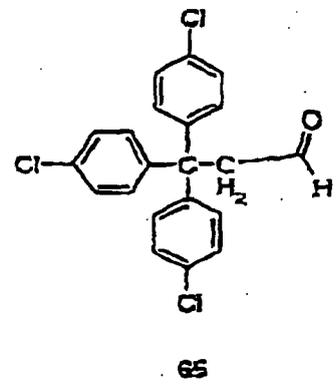
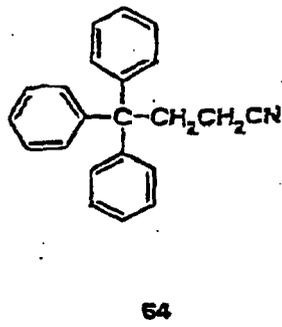
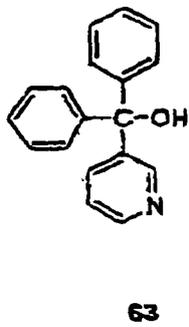
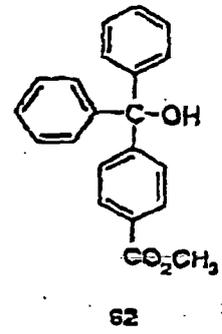
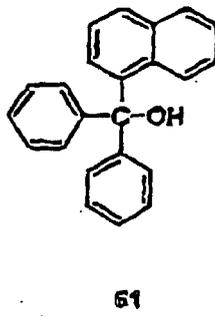
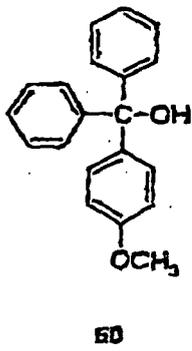
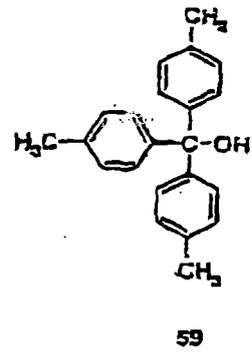
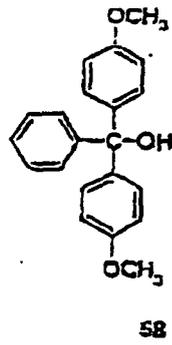
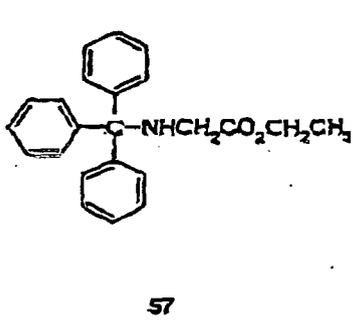
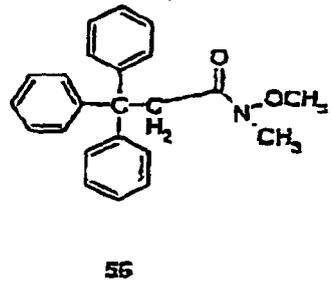
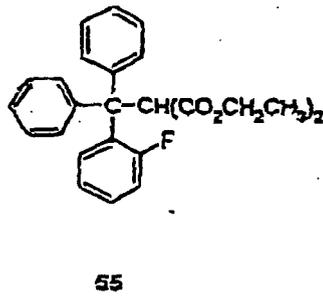
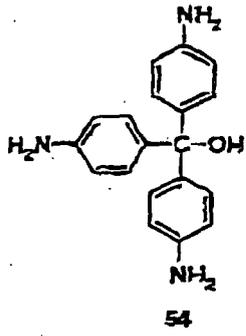
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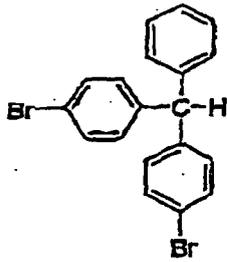


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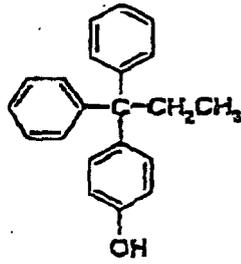
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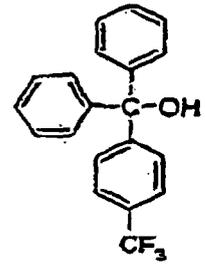
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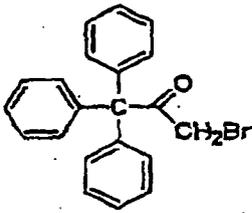
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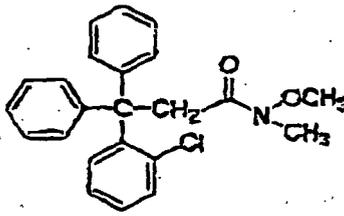
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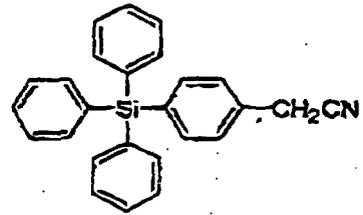
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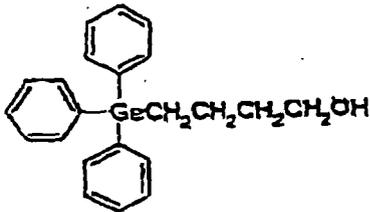


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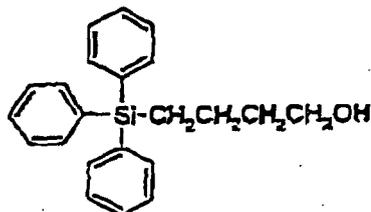
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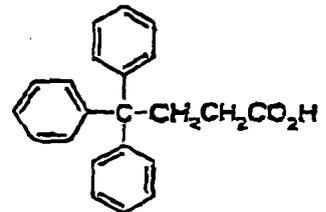
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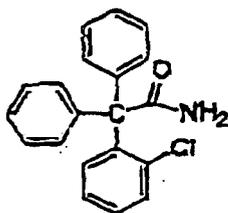
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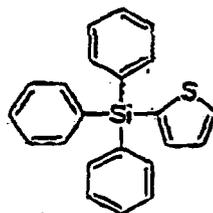
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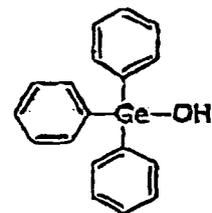
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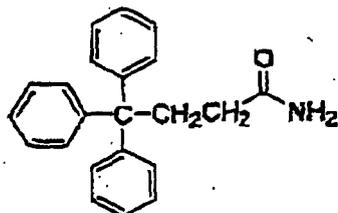
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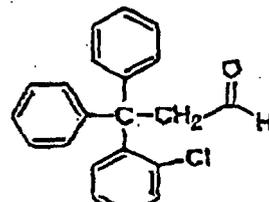
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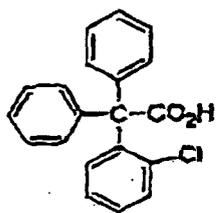
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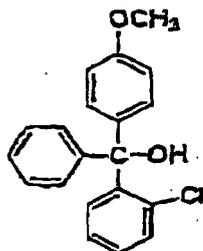
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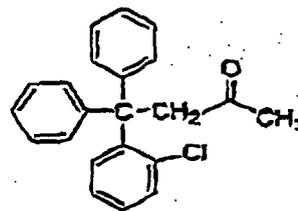
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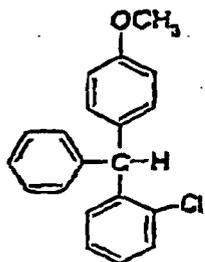
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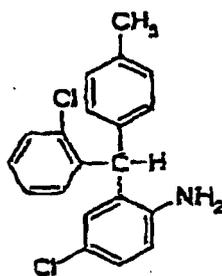
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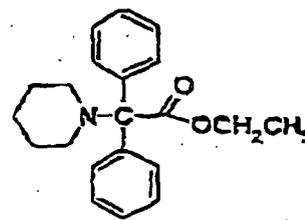
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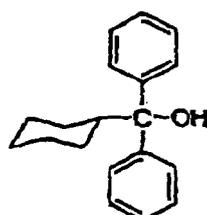


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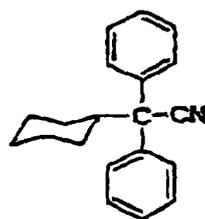
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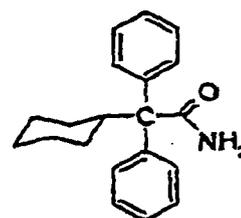
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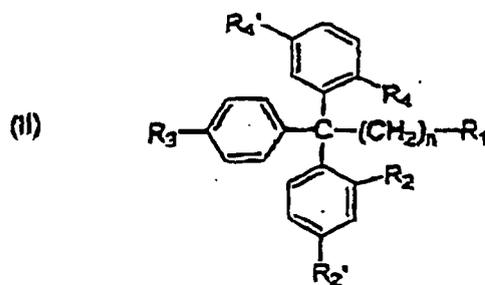
et

14. Composition pharmaceutique suivant la revendication 13, dans laquelle ledit composé est choisi dans le groupe des composés 7, 10, 12, 13, 14, 15, 16, 18, 19, 20, 21, 22, 23, 24, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 40, 41, 42, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 58, 59, 60, 61, 62, 64, 65, 67, 68, 69, 70, 71, 72, 73, 75, 78, 79, 80, 81, 82, 83, 86, 87, 88, 89 et 90.

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15. Composition pharmaceutique comprenant un composé dans un mélange avec un excipient, un véhicule ou un diluant pharmaceutiquement acceptable, dans laquelle ledit composé présente la formule structurale:

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ou est un sel ou un hydrate pharmaceutiquement acceptable de celui-ci, dans lequel:

n est 0, 1, 2, 3 ou 4;

R₁ est -H, -OR, -SR, -CN, -C(O)R, -C(O)OR, -C(O)N(R)₂, CH[C(O)R]₂ ou CH[C(O)OR]₂;

R₂ est -F, -Cl, -Br, -I, -OR, -SR, -C(O)R ou -C(O)N(R)₂;

R₂' est -H ou -NO₂;

R₃ est -H, un radical alkyle (C₁-C₆), alcényle (C₁-C₆), alcynyle (C₁-C₆), -OR ou -SR;

R₄ est -H ou -N(R)₂;

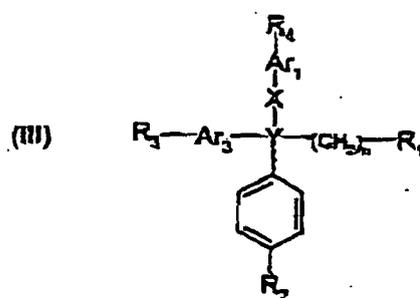
R₄' est -H, -F, -Cl, -Br ou -I; et

chaque R est indépendamment choisi dans le groupe de -H, radical alkyle (C₁-C₆), alcényle (C₁-C₆), alcynyle (C₁-C₆), ou alkoxy (C₁-C₆);

excepté le fait que le composé est différent de 1-(2-chlorophényl)-1,1-diphénylméthanol, de 1-(2-chlorophényl)-1,1-diphénylméthane ou de 1-(2-chlorophényl)-1-(4-hydroxyphényl)-1-phénylméthane.

16. Composition pharmaceutique suivant la revendication 15, dans laquelle ledit composé est choisi dans le groupe des composés 14, 15, 20, 27, 32, 33, 36, 42, 45, 49, 55, 70, 75, 79, 80, 81, 82, 83 et 86.

17. Composition pharmaceutique comprenant un composé dans un mélange avec un excipient, un véhicule ou un diluant pharmaceutiquement acceptable, dans laquelle ledit composé présente la formule structurale:



ou est un sel ou un hydrate pharmaceutiquement acceptable de celui-ci, dans lequel:

X est absent ou -C≡C-;

Y est C, Si ou Ge;

n est 0, 1, 2, 3 ou 4;

Ar₁ est un radical phényle, phényle substitué, cycloalkyle ou hétéroarylium différent d'imidazolium, de nitroimidazolium ou de triazolium;

Ar₃ est un radical phényle, naphthyle, pipéridyle ou cyclohexyle;

R₁ est -R, -OR, -SR, -CN, -N(R)₂, -ON(R)₂, -C(O)R, -C(O)OR, -C(O)N(R)₂, -CH[C(O)R]₂, -CH[C(O)OR]₂, un radical alkyle (C₁-C₆), alcényle (C₁-C₆), alcynyle (C₁-C₆), cyclopenta-2,4-diène-1-ylidène ou phényle;

chacun de R₂, R₃ et R₄ est indépendamment choisi dans le groupe de -H, -F, -Cl, -Br, -I, -OR, -SR, -N(R)₂, -NO₂, -C(O)R, -C(O)OR, -C(O)N(R)₂, radical trihalométhyle, alkyle (C₁-C₆), alcényle (C₁-C₆), alcynyle (C₁-C₆) et phényle;

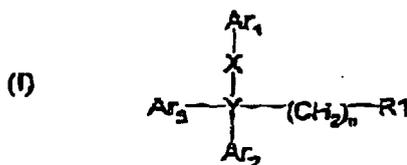
chaque R est indépendamment choisi dans le groupe de -H, un radical halo, alkyle (C₁-C₆), alkyle (C₁-C₆) substitué, alcényle (C₁-C₆), alcényle (C₁-C₆) substitué, alcynyle (C₁-C₆), alcynyle (C₁-C₆) substitué et alkoxy (C₁-C₆);

les substituants des radicaux alkyles, alcényles ou alcynyles sont chacun indépendamment choisis dans le groupe de radical aryle, -C(O)OR, pyrrolidinyle, pyrrolidinonyl, butyrolactonyl, -F, -Cl, -Br, -I et -CN; et

les substituants des radicaux phényles sont chacun indépendamment -R; excepté le fait que le composé est différent de 1-(2-chlorophényl)-1,1-diphénylméthanol, de 1-(2-chlorophényl)-1,1-diphénylméthane ou de 1-(2-chlorophényl)-1-(4-hydroxyphényl)-1-phénylméthane.

18. Composition pharmaceutique suivant la revendication 17, dans laquelle ledit composé est choisi dans le groupe des composés 7, 12, 13, 16, 18, 19, 21, 22, 23, 24, 26, 28, 29, 30, 31, 34, 35, 37, 38, 40, 41, 44, 46, 47, 48, 50, 51, 52, 53, 54, 56, 58, 59, 60, 61, 62, 64, 65, 67, 68, 69, 71, 72, 73, 78, 87, 88, 89 et 90.

19. Utilisation d'un composé de la formule (I):



ou d'un sel ou d'un hydrate pharmaceutiquement acceptable de celui-ci dans la préparation d'un médicament pour le traitement ou la prévention d'un trouble choisi parmi un cancer, une kératose actinique ou un sarcome de Kaposi, dans lequel:

n est 0, 1, 2, 3 ou 4;

X est absent, un radical alkyle (C₁-C₃), alcényle (C₁-C₃) ou alcynyle (C₁-C₃);

Y est C, N, Si ou Ge;

R₁ est absent, un radical halo, -R, -OR, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂ ou aryle;

Ar₁ est un radical aryle, aryle substitué, hétéroaryle différent d'imidazole, de nitroimidazole et de triazole, hétéroarylium différent d'imidazolium, de nitroimidazolium et de triazolium, cycloalkyle (C₅-C₈) ou hétérocycloalkyle (C₅-C₈);

Ar₂ est un radical aryle ou aryle substitué;

Ar₃ est un radical aryle, aryle substitué, biaryle ou hétéroaryle différent d'imidazole, de nitroimidazole et de triazole;

chaque R est indépendamment choisi dans le groupe de -H, radical alkyle (C₁-C₆), alkyle (C₁-C₆) substitué, alcényle (C₁-C₆), alcényle (C₁-C₆) substitué, alcynyle (C₁-C₆), alcynyle (C₁-C₆) substitué et alkoxy (C₁-C₆);

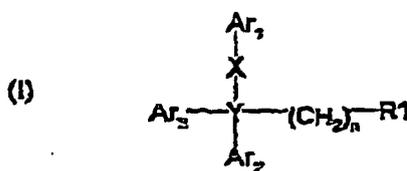
les substituants des radicaux ayles sont chacun indépendamment choisis dans le groupe de radical halo, trihalométhyle, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' et -C(S)SR';

les substituants des radicaux alkyles, alcényles et alcynyles sont chacun indépendamment choisis dans le groupe de radical halo, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryle, γ-butyrolactonyle, pyrrolidinyle, pyrrolidinonyle et anhydridyle succinique;

chaque R' est indépendamment choisi dans le groupe de -H, radical alkyle (C₁-C₆), alcényle (C₁-C₆) et alcynyle (C₁-C₆); et

chaque R' est indépendamment choisi dans le groupe de -H, radical alkyle (C₁-C₆), alcényle (C₁-C₆) et alcynyle (C₁-C₆), excepté le fait que le composé est différent de 1-(2-chlorophényl)-1,1-diphénylméthanol, de 1-(2-chlorophényl)-1,1-diphénylméthane, de 1-(2-chlorophényl)-1-(4-hydroxyphényl)-1-phenylméthane.

20. Utilisation d'un composé dans un mélange avec un excipient, un véhicule ou un diluant pharmaceutiquement acceptable, dans la préparation d'un médicament pour le traitement d'un trouble choisi parmi un cancer, une kératose actinique et un sarcome de Kaposi, dans laquelle ledit composé présente la formule:



ou est un sel ou un hydrate pharmaceutiquement acceptable de celui-ci, dans lequel:

n est 0, 1, 2, 3 ou 4;

X est absent, un radical alkyle (C₁-C₃), alcényle (C₁-C₃) ou alcynyle (C₁-C₃);

Y est C, N, P, Si ou Ge;

R₁ est absent, un radical halo, -OR, -SR, -N(R)₂, -ON(R)₂, -NO₂, -CN, -C(S)R, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)N(R)₂, -C(S)N(R)₂, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂ ou -CH[C(S)SR]₂;

Ar₁ est un radical aryle, aryle substitué, hétéroaryle différent d'imidazole, de nitroimidazole et de triazole, hétéroarylium différent d'imidazolium, de nitroimidazolium et de triazolium, cycloalkyle (C₅-C₈) ou hétérocycloalkyle (C₅-C₈);

Ar₂ est un radical aryle ou aryle substitué;

Ar₃ est un radical aryle, aryle substitué, biaryle ou hétéroaryle différent d'imidazole, de nitroimidazole et de triazole;

chaque R est indépendamment choisi dans le groupe de -H, radical alkyle (C₁-C₆), alkyle (C₁-C₆) substitué, alcényle (C₁-C₆), alcényle (C₁-C₆) substitué, alcynyle (C₁-C₆), alcynyle (C₁-C₆) substitué et alkoxy (C₁-C₆);

les substituants des radicaux aryles sont chacun indépendamment choisis dans le groupe de radical halo, trihalométhyle, -R, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR' et -C(S)SR';

les substituants des radicaux alkyles, alcényles et alcynyles sont chacun indépendamment choisis dans le groupe de radical halo, -R', -OR', -SR', N(R')₂, -NO₂, -CN, -C(O)R', -C(S)R', -C(O)OR', -C(S)OR', -C(O)SR', -C(S)SR', aryle, γ-butyrolactonyle, pyrrolidinyle, pyrrolidinonyle et anhydridyle succinique; et

chaque R' est indépendamment choisi dans le groupe de -H, radical alkyle (C₁-C₆), alcényle (C₁-C₆) et alcynyle (C₁-C₆).

21. Utilisation suivant la revendication 19, dans laquelle ledit composé est choisi dans le groupe des composés 13, 14, 15, 16, 18, 19, 21, 26, 27, 28, 30, 31, 36, 38, 40, 41, 42, 43, 45, 46, 47, 48, 49, 50, 52, 54, 59, 61, 65, 67, 68, 70, 71, 72, 73, 79, 82, 83, 84, 86, 89 et 90.

22. Utilisation suivant la revendication 19, dans laquelle ledit composé est choisi dans le groupe des composés 16, 28, 30, 36, 38, 45, 47, 48, 49, 50, 52, 54 et 84.

23. Utilisation suivant l'une quelconque des revendications 19, 21 et 22, dans laquelle ledit composé est destiné à une administration orale, parentérale, intraveineuse ou transdermique.

24. Utilisation suivant l'une quelconque des revendications 19, 21 et 22, dans laquelle ledit trouble est un cancer et ledit composé est destiné à une administration orale, parentérale ou intraveineuse.

25. Utilisation suivant l'une quelconque des revendications 19, 21 et 22, dans laquelle ledit trouble est choisi parmi une kératose actinique ou un sarcome de Kaposi et ledit composé est destiné à une administration transdermique.

26. Composé suivant l'une quelconque des revendications 1 à 6, pour une utilisation dans le traitement ou la prévention d'un trouble choisi parmi un cancer, une kératose actinique et un sarcome de Kaposi.

27. Composition pharmaceutique suivant l'une quelconque des revendications 13 à 18, pour une utilisation dans le traitement ou la prévention d'un trouble choisi parmi un cancer, une kératose actinique et un sarcome de Kaposi.