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(54) **NOVEL THERAPEUTIC AGENTS FOR THE TREATMENT OF CANCER, METABOLIC DISEASES AND SKIN DISORDERS**

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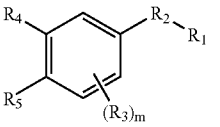
C07F 5/02	(2006.01)

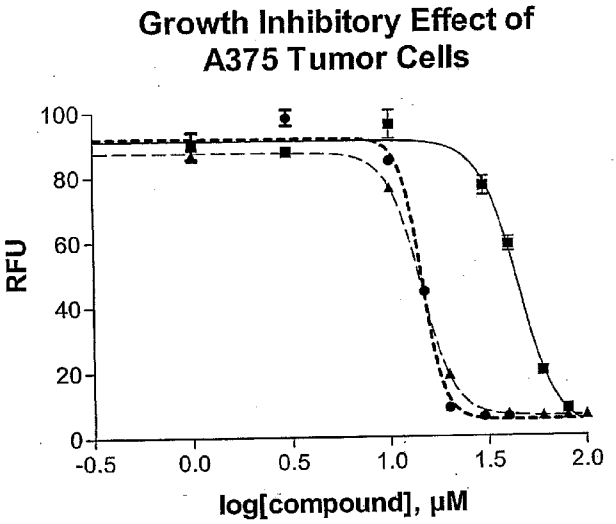
(52) **U.S. Cl.** **514/64**; 568/328; 514/682; 568/6

(57) **ABSTRACT**

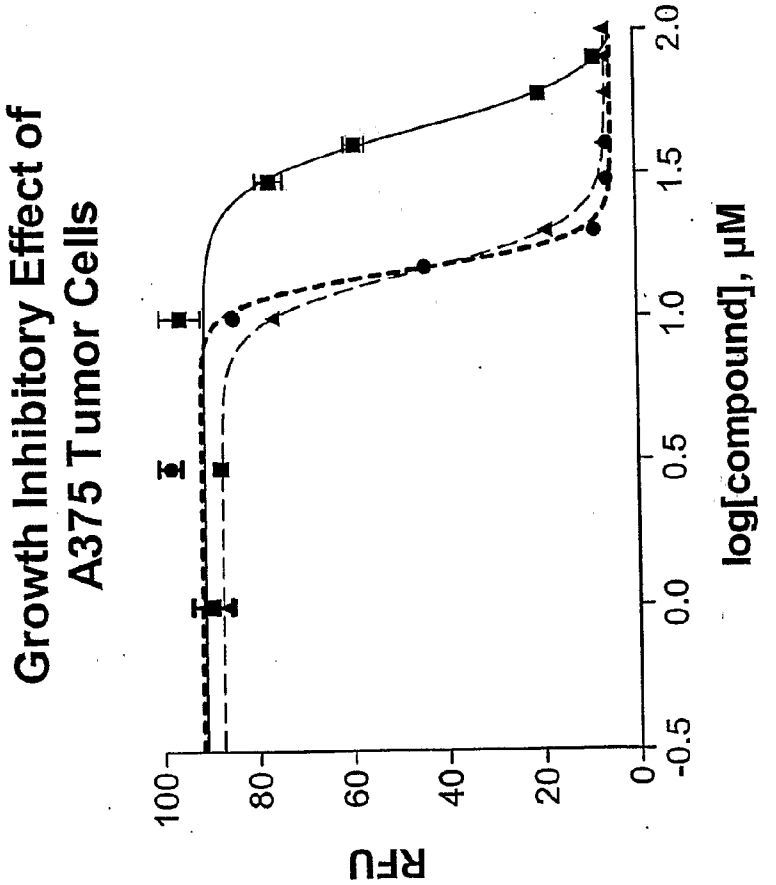
The present invention is directed to compounds having the structure Formula (I) wherein R_1, R_2, R_3, R_4, R_5 and m are as defined herein. The compounds of this invention are novel therapeutic agents for the treatment of cancer, metabolic diseases and skin disorders in mammalian subjects. These compounds are also useful modulators of gene expression. They exert their activity by interfering with certain cellular signal transduction cascades. The compounds of the invention are thus also useful for regulating cell differentiation and cell cycle processes that are controlled or regulated by various hormones or cytokines. In particular, the invention relates to compounds that induce apoptosis of cancer cells and therefore may be used for the treatment or prevention of cancer, including advanced cancers and pre-cancerous cells. The invention also discloses pharmaceutical compositions and methods of treatment of disease in mammals.



(I)

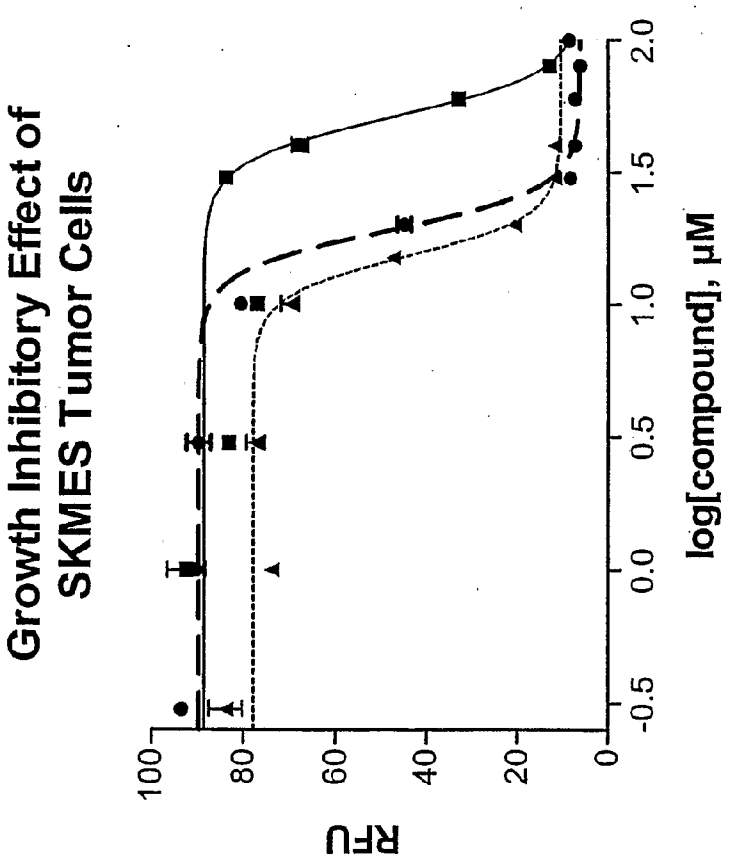


Compound	EC_{50} (µM)
Targretin	45
Example 4	14
Example 5	14



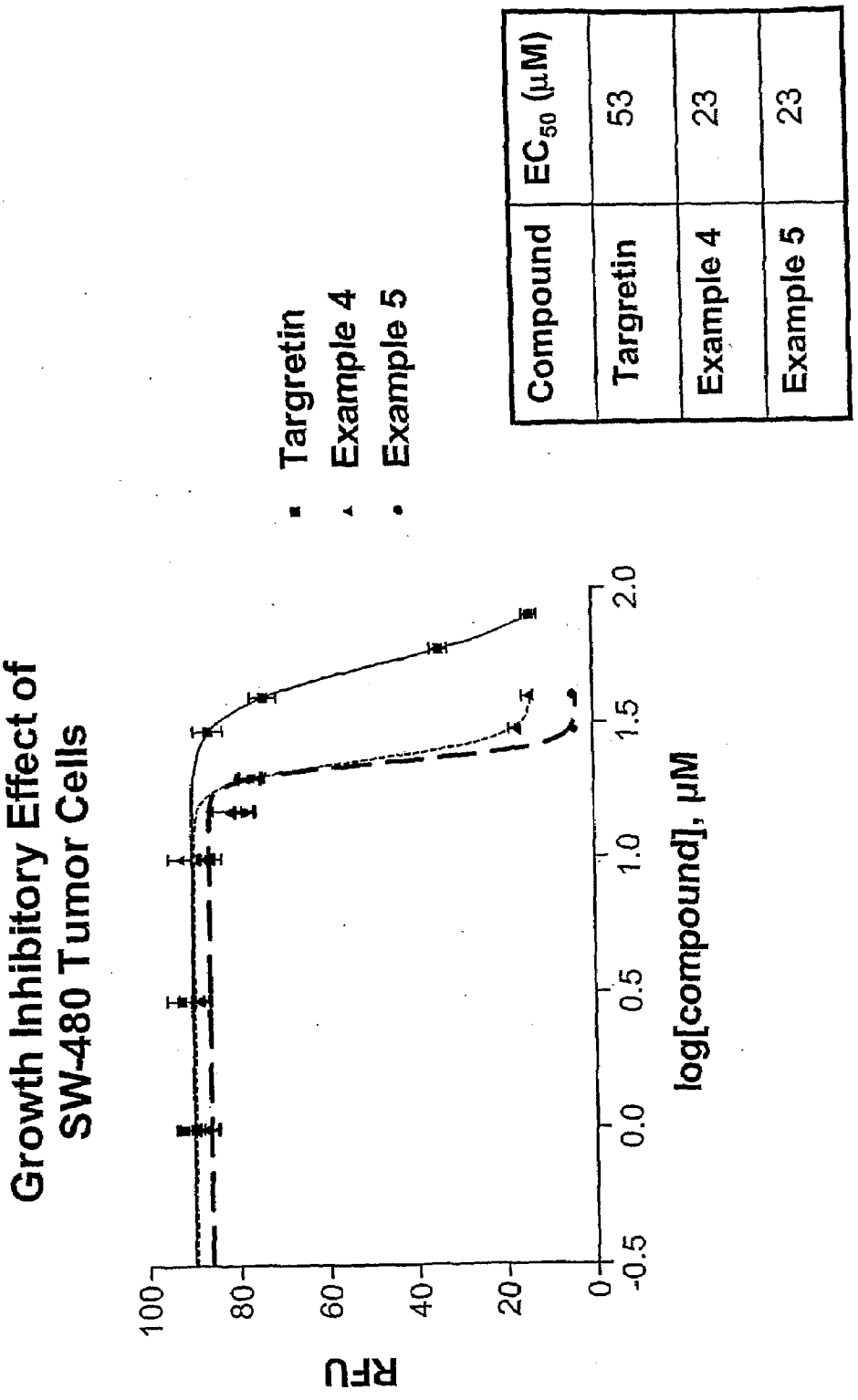
Compound	EC_{50} (µM)
Targretin	45
Example 4	14
Example 5	14

Figure 1



Compound	EC_{50} (μM)
Targretin	51
Example 4	19
Example 5	15

Figure 2



Compound	EC_{50} (μM)
Targretin	53
Example 4	23
Example 5	23

Figure 3

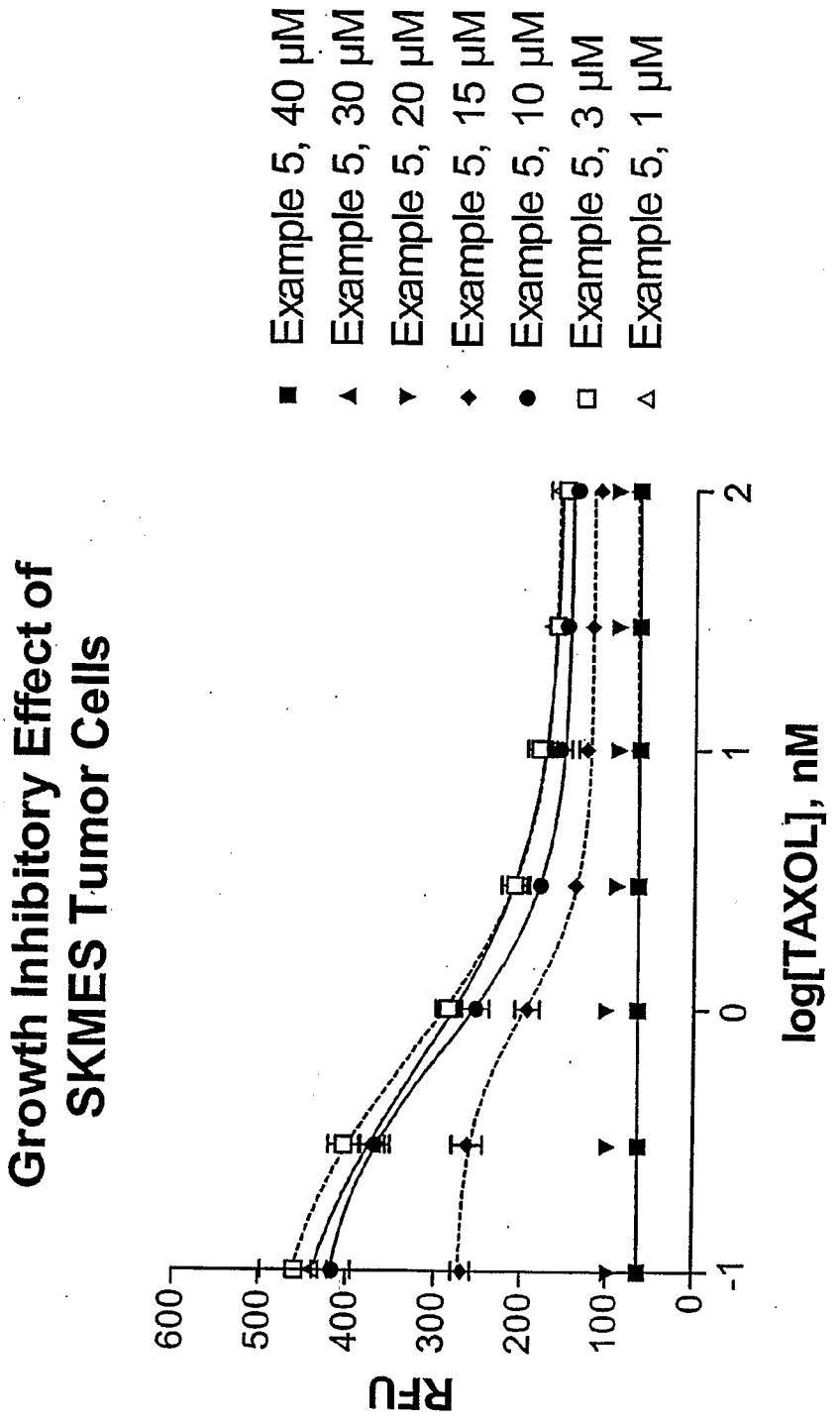

Growth Inhibitory Effect of SKMES Tumor Cells
Example 5, 40 µM
Example 5, 30 µM
Example 5, 20 µM
Example 5, 15 µM
Example 5, 10 µM
Example 5, 3 µM
Example 5, 1 µM
RFU
600
500
400
300
200
100
0
-1
0
1
2
log[TAXOL], nM

Figure 4

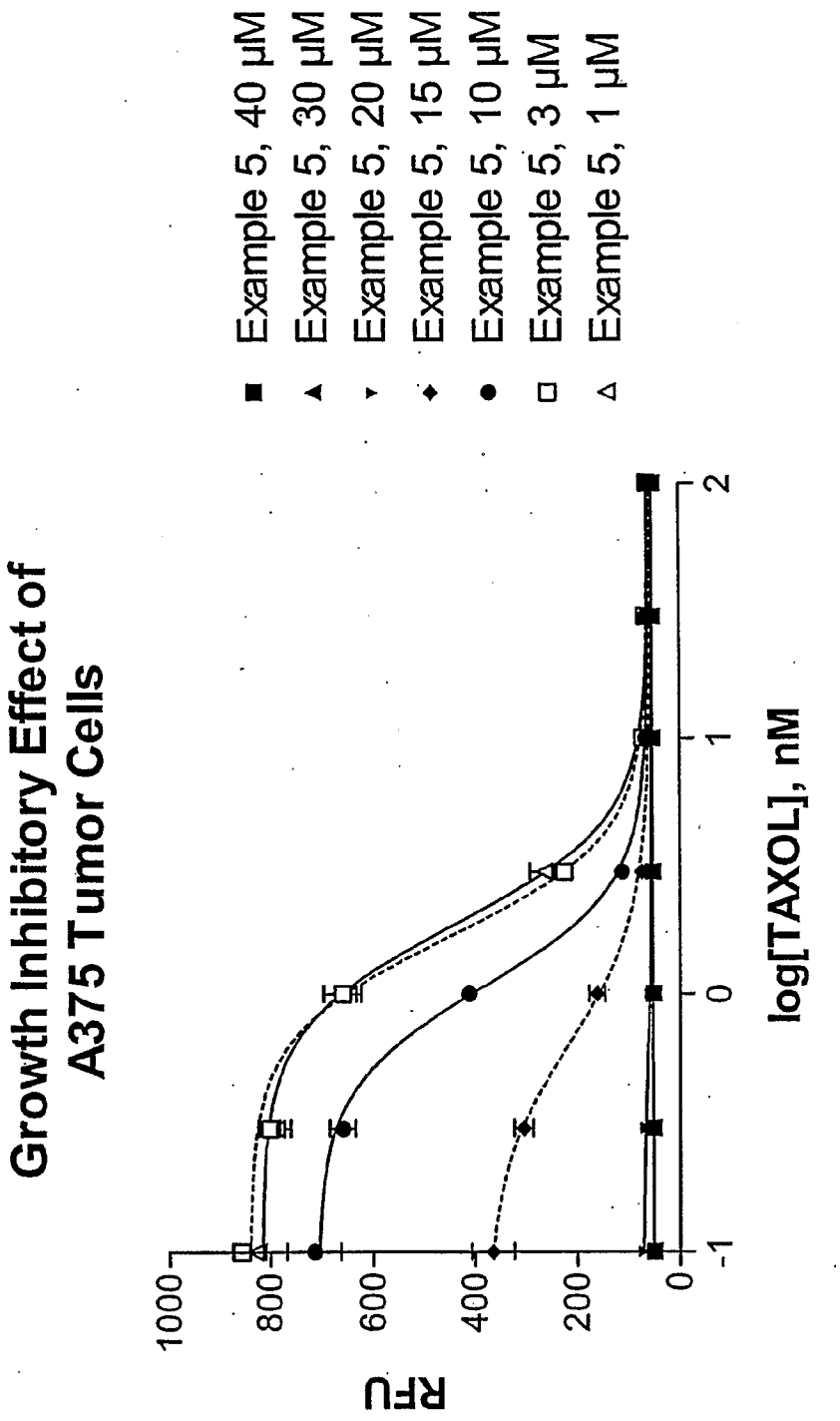

Growth Inhibitory Effect of A375 Tumor Cells
Example 5, 40 µM
Example 5, 30 µM
Example 5, 20 µM
Example 5, 15 µM
Example 5, 10 µM
Example 5, 3 µM
Example 5, 1 µM
RFU
1000
800
600
400
200
0
-1
0
1
2
log[TAXOL], nM

Figure 5

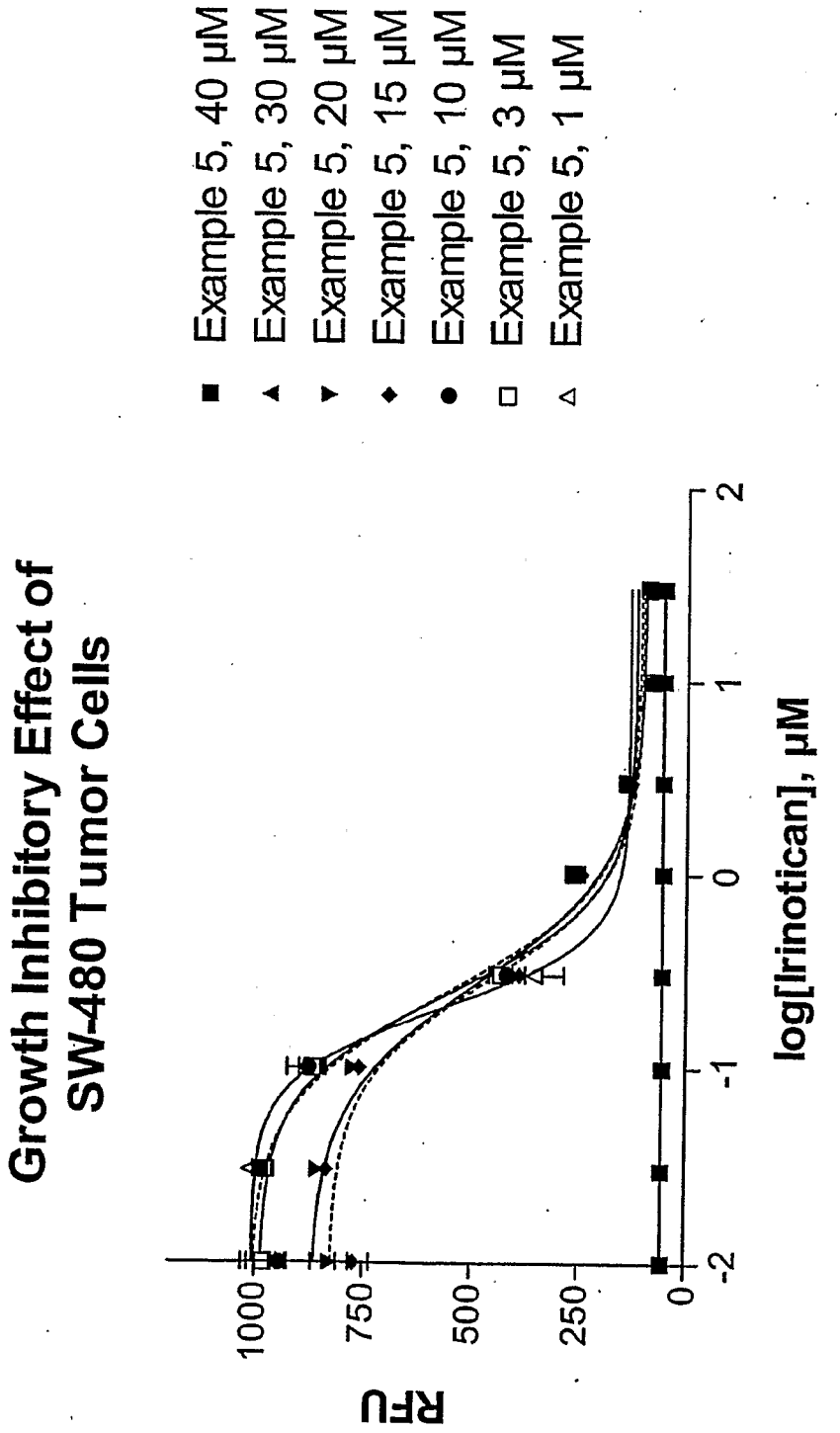

Growth Inhibitory Effect of SW-480 Tumor Cells
Example 5, 40 µM
Example 5, 30 µM
Example 5, 20 µM
Example 5, 15 µM
Example 5, 10 µM
Example 5, 3 µM
Example 5, 1 µM
RFU
1000
750
500
250
0
-2
-1
0
1
2
log[Irinotican], µM

Figure 6

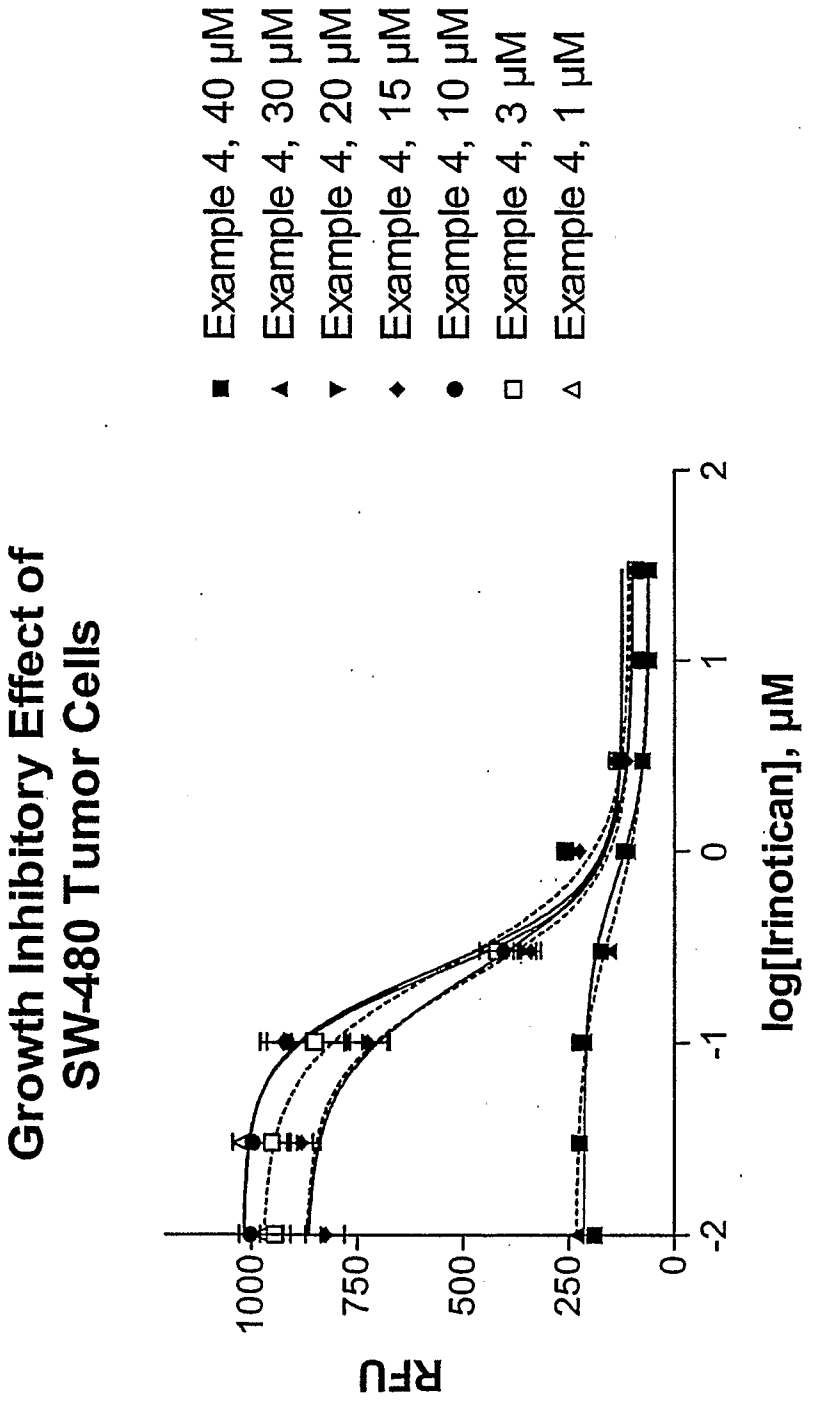

Growth Inhibitory Effect of SW-480 Tumor Cells
Example 4, 40 µM
Example 4, 30 µM
Example 4, 20 µM
Example 4, 15 µM
Example 4, 10 µM
Example 4, 3 µM
Example 4, 1 µM
RFU
1000
750
500
250
0
2
1
0
-1
-2
log[Irinotican], µM

Figure 7

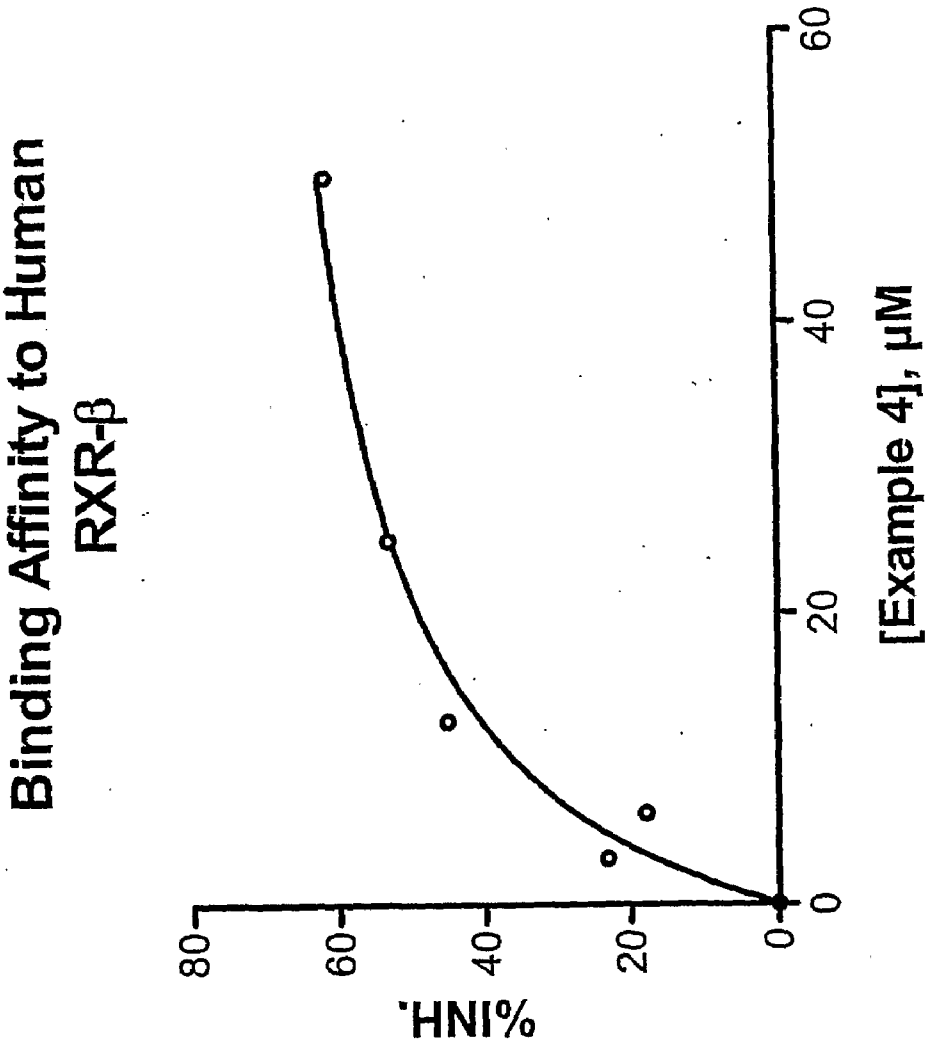

Binding Affinity to Human
RXR-β
%INH
80
60
40
20
0
0
20
40
60
[Example 4], μM

Figure 8

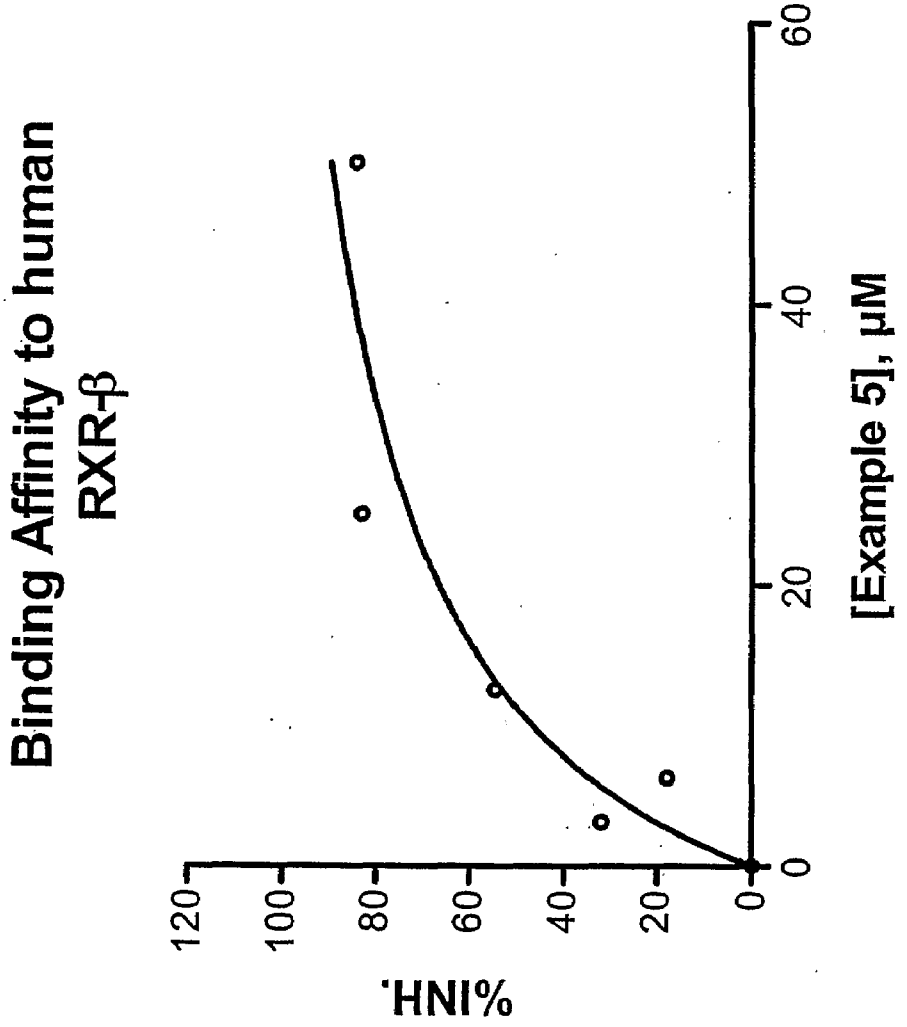

Binding Affinity to human
RXR-β
'HNI%
120
100
80
60
40
20
0
0
20
40
60
[Example 5], μM

Figure 9

NOVEL THERAPEUTIC AGENTS FOR THE TREATMENT OF CANCER, METABOLIC DISEASES AND SKIN DISORDERS

FIELD OF INVENTION

[0001] The invention relates generally to a novel class of retinoids and more specifically to methods of preparation, pharmaceutical compositions, and methods of disease treatment utilizing pharmaceutical compositions comprising these compounds.

BACKGROUND OF THE INVENTION

[0002] Cancer is a complex disease characterized by genetic mutations that lead to uncontrolled cell growth. Cancerous cells are present in all organisms and under normal circumstances their excessive growth is tightly regulated by various physiological factors. One such regulatory process is apoptosis or programmed cell death. When the internal machinery of a cell detects abnormalities in cell division and growth, a signal is propagated within the cell, activating suicide proteins that kill the afflicted cell and prevent its proliferation. Such an apoptotic signal can be triggered, for example, when a ligand or drug interacts with a receptor or protein in the cell.

[0003] Most agents that induce apoptosis in cancer cells (e.g. Doxorubicin and Vincristine) are extremely toxic and cause a number of undesirable side effects. The toxicity associated with these therapies is a result of the non-specific interaction of the drug with the DNA of non-cancerous cells (e.g. intestinal and red blood cells). In order to circumvent such undesirable side effects, more selective compounds have been designed that inhibit one or more signaling proteins, growth factors and/or receptors involved in cancer cell proliferation. Examples include monoclonal antibodies for breast cancer (e.g. Herceptin) and Non-Hodgkin's Lymphoma (e.g. Rituxan), as well anti-angiogenic drugs for chronic myeloid leukemia (e.g. Gleevec). Since patient populations are genetically heterogeneous, it follows that a single selective therapy will not work in all cases, and as a result, cancer drugs are often used in combination. As such, there is a continual need for improved treatments.

[0004] Retinoids are analogs of vitamin A and regulate cell growth, differentiation, and apoptosis. Retinoids bind to and activate two classes of Nuclear Retinoid receptors: the retinoic acid receptors (RARα, RARβ, RARγ) and retinoic X receptors (RXRα, RXRβ, RXRγ). These receptors bind to specific sequences of DNA and thereby regulate gene expression. The RAR and RXR receptor isoforms are expressed differently during development and differentiation. These various isoforms can either homodimerize or heterodimerize leading to a variety of protein complexes that regulate different sets of retinoid-induced genes. Activation of each receptor class results in modulation of various biological functions such as cell differentiation, embryonic development, and cell proliferation. Clinical studies have shown that retinoic acid and its synthetic analogs can inhibit the growth and invasion of cancer cells, and induce them to undergo apoptosis, thereby eradicating various types of cancers.

[0005] The novel compounds of this invention modulate the activity of nuclear retinoid receptors. These novel compounds are thus useful for regulating cell differentiation and cell cycle processes as well as other cellular signaling processes controlled or regulated by hormones and vitamins such as the thyroid hormone, vitamin D, all-trans retinoic acid and 9-cis-retinoic acid. Hence, conditions and/or diseases that are regulated by the aforementioned entities may be treated using the compounds of this invention. Examples of such conditions include for example cancer, mammary cancer, prostate cancer, kidney cancer, Karposi's sarcoma, colon cancer, cervical cancer, lung cancer, cutaneous T-cell lymphoma, cancer of the head and neck, cancers of the aerodigestive pathway, skin cancer, bladder cancer, sarcomas, leukoplakias, acute promyelocytic leukemia, acne, psoriasis, aging, wrinkling, diabetes, hyperglycemia, bone calcification, thyroid conditions, and the like.

[0006] Compounds that modulate the activity of RAR receptors are structural analogs of all-trans-retinoic acid. On the other hand compounds that modulate the activity of RXR receptors are structural analogs of 9-cis-retinoic acid (e.g. Bexarotene). The aforementioned modulators of Nuclear Retinoid receptors bear a carboxylic acid group in a specific position of the molecule. This acidic group forms a salt bridge to a basic residue in the binding pocket of the Nuclear Retinoid receptors. Research in this field indicates that removal of this acidic group drastically reduces the potency or the modulator. There are however, other amino acid residues in the binding pocket that can interact with the modulator. None of the modulators of nuclear retinoid receptors described to date take advantage of these critical interactions.

[0007] Another drawback of the current state of the art is the limited aqueous solubility of the selective nuclear retinoid receptor modulators. Said modulators mimic the structures of retinoic acids in order to conform to the three-dimensional structure and the hydrophobic nature of the respective binding pockets. In general, introduction of solubilizing substituents has resulted in lower in vitro binding affinity or increased in vivo metabolism and toxicity.

[0008] There exists therefore a need to improve upon the prior art in order to enhance the clinical profile of such therapeutics. Such improvements may be carried out by introducing specially designed functional groups at specific positions on the molecular backbone of the modulator. The novel compounds of this invention address this issue and display enhanced in vitro profiles when compared to compounds of the prior art.

BRIEF DESCRIPTION OF THE FIGURES

[0009] FIG. **1** depicts the growth inhibitory effect of Targretin, example 4 and example 5 on human A375 carcinoma cells. The figure clearly shows the enhanced activity of examples 4 and 5 when compared to Targretin (4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid).

[0010] FIG. **2** depicts the growth inhibitory effect of Targretin, example 4 and example 5 on human SKMES carcinoma cells. The figure clearly shows the enhanced activity of examples 4 and 5 when compared to Targretin (4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid).

[0011] FIG. **3** depicts the growth inhibitory effect of Targretin, example 4 and example 5 on human SW480 carcinoma cells. The figure clearly shows the enhanced activity of examples 4 and 5 when compared to Targretin (4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-benzoic acid).

[0012] FIG. **4** depicts the growth inhibitory effect of varying concentrations of example 5 on human SKMES carcinoma cells in the presence of Taxol. The figure clearly shows a synergism between example 5 and Taxol as evidenced by the enhancement in the activity of Taxol with increasing concentrations of example 5.

[0013] FIG. **5** depicts the growth inhibitory effect of varying concentrations of example 5 on human A375 carcinoma cells in the presence of Taxol. The figure clearly shows a synergism between example 5 and Taxol as evidenced by the enhancement in the activity of Taxol with increasing concentrations of example 5.

[0014] FIG. **6** depicts the growth inhibitory effect of varying concentrations of example 5 on human SW480 carcinoma cells in the presence of Irinotican. The figure clearly shows a synergism between example 5 and Irinotican as evidenced by the enhancement in the activity of Irinotican with increasing concentrations of example 5.

[0015] FIG. **7** depicts the growth inhibitory effect of varying concentrations of example 4 on human SW480 carcinoma cells in the presence of Irinotican. The figure clearly shows a synergism between example 4 and Irinotican as evidenced by the enhancement in the activity of Irinotican with increasing concentrations of example 4.

[0016] FIG. **8** depicts the binding affinity of example 4 to the human retinoic acid receptor subtype RXR-beta.

[0017] FIG. **9** depicts the binding affinity of example 5 to the human retinoic acid receptor subtype RXR-beta.

SUMMARY OF THE INVENTION

[0018] The present invention provides novel therapeutic agents for the treatment of cancer, metabolic diseases and skin disorders in mammalian subjects. These novel agents bear specially designed functional groups at specific positions on the molecular backbone of the modulator. As a result, the compounds of this invention show enhanced in vitro profiles.

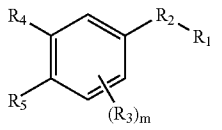
[0019] The invention also provides novel compounds that interact with one or more cellular receptors and are useful in the modulation of gene expression.

[0020] Furthermore, the invention also provides novel compounds that are useful in controlling cell cycle, and cell differentiation processes regulated by certain hormones, such as for example the thyroid hormone and the like, and/or certain vitamins, such as for example vitamin D and the like, and/or certain retinoids, such as for example 9-cis-retinoic acid and the like.

[0021] Furthermore, the invention also provides novel compounds that are useful in inducing apoptosis in mammalian cells.

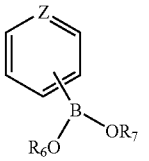
[0022] Furthermore, the invention also provides novel chemical compositions and discloses synthetic methodologies to prepare the same.

[0023] In one aspect, the invention relates to novel compounds having the structural formula A



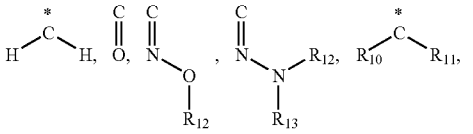
A

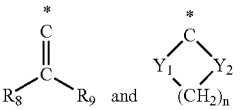
[0024] wherein R_1 is



[0025] wherein Z is CH or nitrogen, R_6 and R_7 are selected from the group consisting of hydrogen, alkyl, aryl and heteroaryl; R_6 and R_7 may be linked together to form a substituted or unsubstituted 5- or 6-membered cycloalkyl or cycloalkenyl ring, where said substituents are described as herein;

[0026] R_2 is selected from the group consisting of





wherein:

[0027] R_8, R_9, R_{10} and R_{11} are independently selected from the group consisting of hydrogen, halogen and alkyl. Y_1 and Y_2 are independently O, S, NH, or CH_2, or Y_1 is O, S or NH, and Y_2 is CH_2, with the proviso that Y_1 and Y_2 cannot both be O S, or NH if n is 0 or 1, R_{12} and R_{13} are independently selected from the group consisting of hydrogen, alkyl, and aryl and "*" represents the point of attachment of the R_2 to the molecule of formula A;

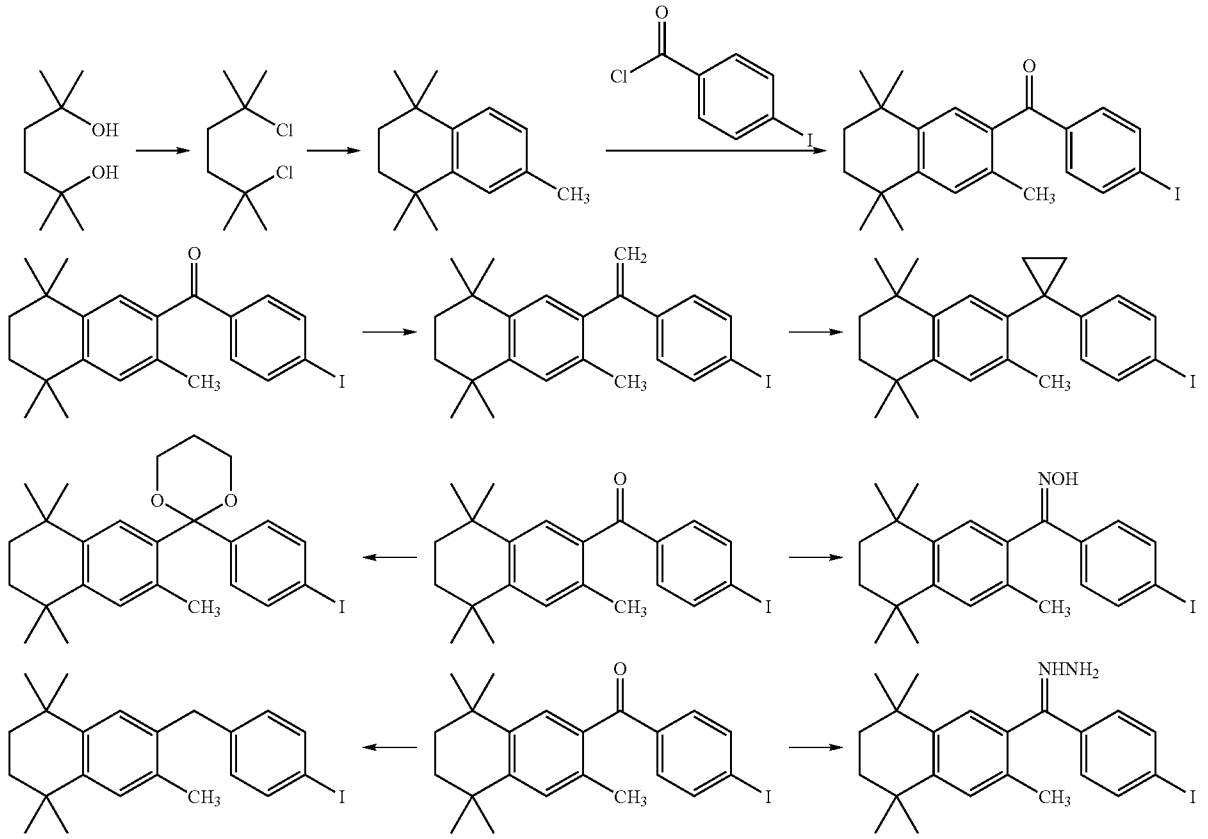
[0028] R_3 substituents are independently selected from the group consisting of halogen, alkyl, and alkyloxy;

[0029] R_4 is selected from the group consisting of alkyl, aryl, heteroaryl, and adamantyl; R_5 is selected from the group consisting of alkyl, alkyloxy, alkylthio, aryl, and heteroaryl; or R_4 and R_5 may be linked together to form a substituted or unsubstituted 5- or 6-membered cycloalkyl or cycloalkenyl ring, where said substituents are selected from the group consisting of —OH, =O, halogen, alkyl, and where 1 or 2 of the carbon atoms on said 5- or 6-membered cycloalkyl or cycloalkenyl ring may be optionally replaced by W where W is selected from the group consisting of O, S, N, NH, alkylamino, and arylamino; and

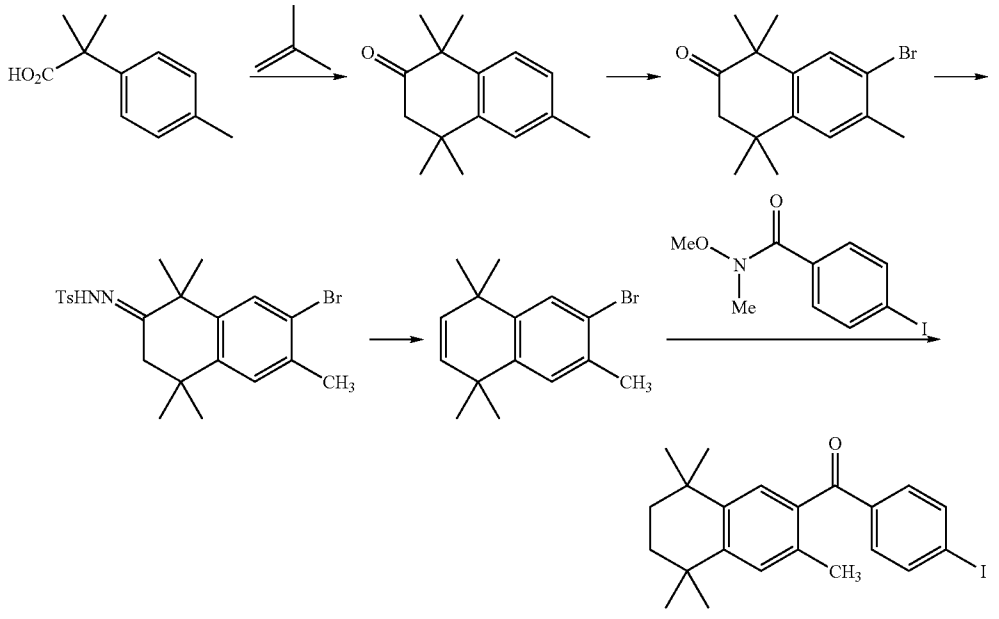
[0030] m and n are independently 0, 1, 2 or 3, and pharmaceutically acceptable salts, solvates, and prodrugs thereof.

[0031] The non-limiting exemplary synthetic schemes 1-3 shown below illustrate some methods that can be used for carrying out the preparative process of the invention.

Scheme 1



Scheme 2



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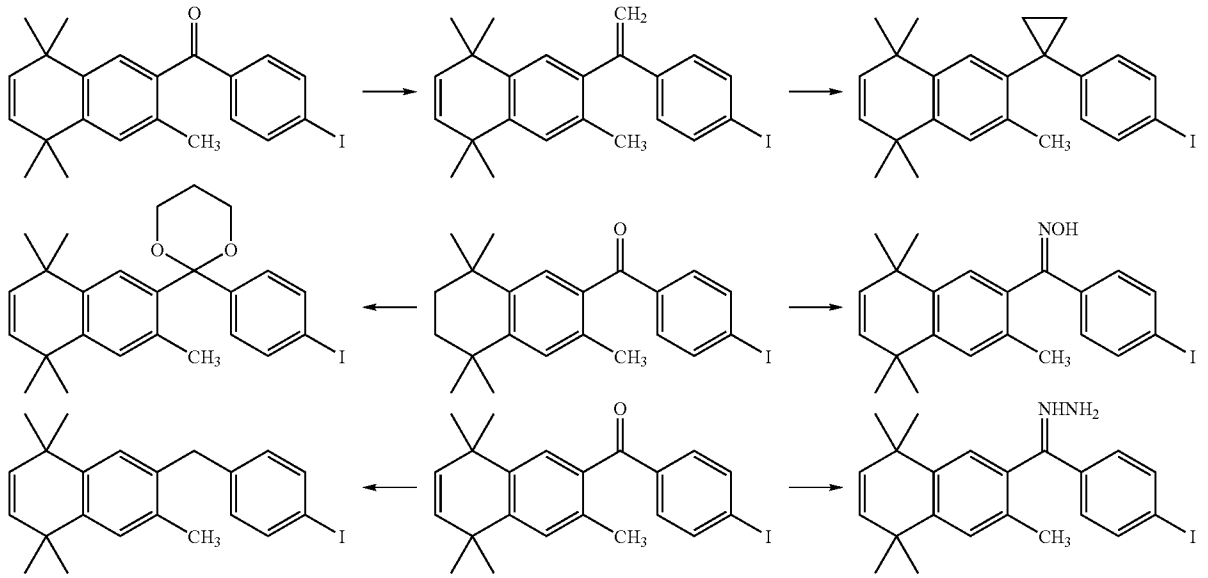
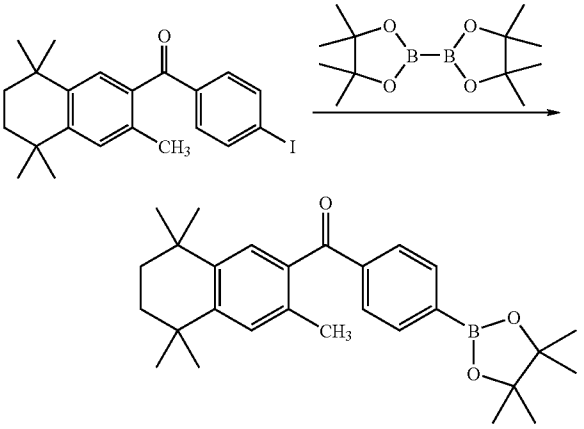


Scheme 3



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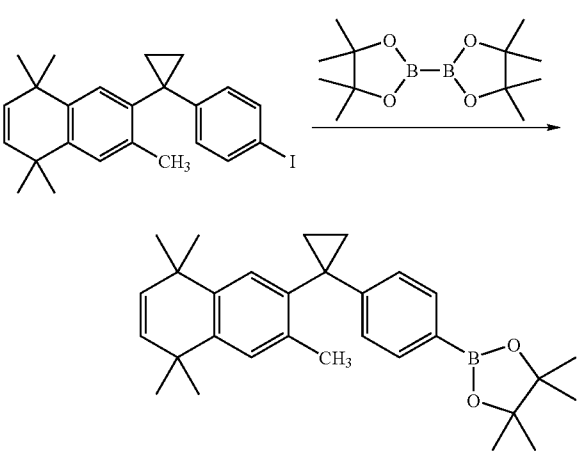

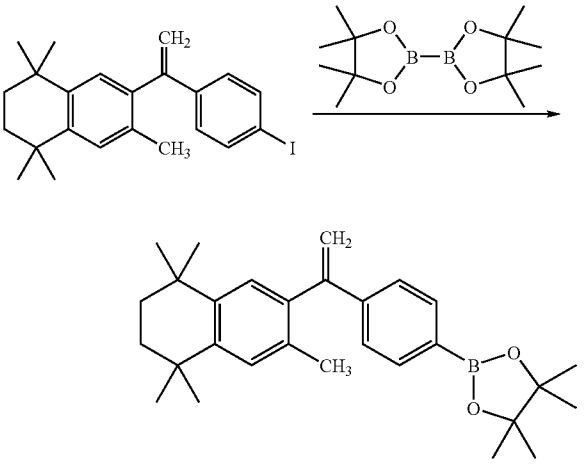

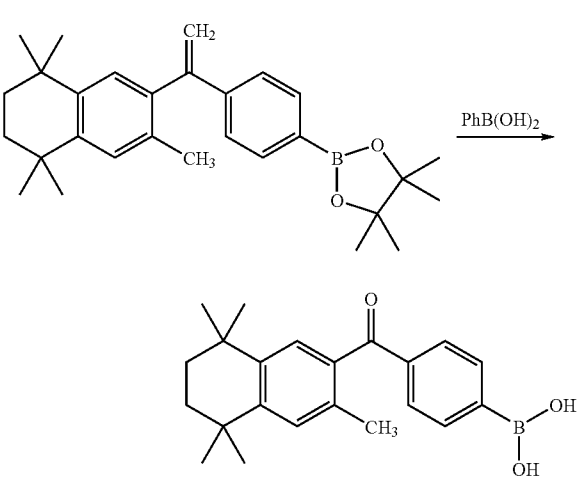

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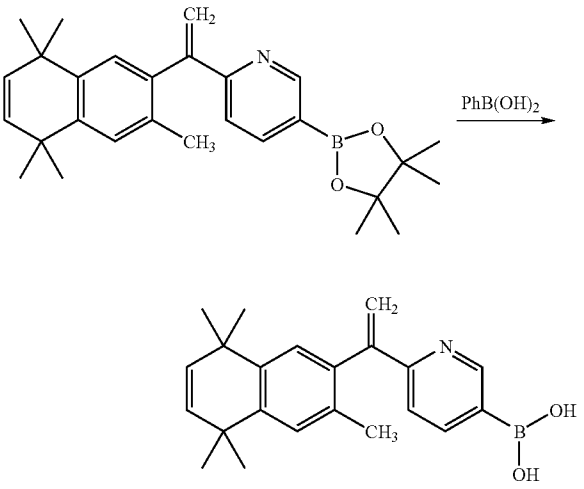


[0032] In another aspect, the invention relates to pharmaceutical compositions containing the novel compounds of the invention and to methods of using these compounds for modulating and controlling cell cycle, cell differentiation and apoptosis processes regulated by certain hormones, such as for example the thyroid hormone and the like, and/or certain vitamins, such as for example vitamin D and the like, and/or certain retinoids, such as for example 9-cis-retinoic acid and the like.

[0033] In another aspect, the invention relates to pharmaceutical compositions containing the novel compounds of the invention and to methods of using these compounds for modulating and controlling cell cycle, cell differentiation and apoptosis processes regulated by certain genes, such as for example the Fibroblast Growth Fact Binding Protein mRNA, and the like, and/or certain Signal Transducers and Activators of Transcription, such as for example STAT3, and the like, and/or certain proteins, such as for example Cyclin Dependent Kinase (CDK), Transforming Growth Factor alpha (TGF-α), and the like, and/or certain receptors, such as for example Transforming Growth Factor Receptor (TGFR), Endothelial Growth Factor Receptor (EGFR), Retinoid X Receptor (RXR) and the like.

[0034] In another aspect, the invention relates to pharmaceutical compositions containing the novel compounds of the invention and to methods of using these compounds to modulate selective gene expression by one or more cellular receptors.

[0035] In another aspect, the invention relates to pharmaceutical compositions containing the novel compounds of the invention and to methods of treating diseases and/or conditions using the same. Examples of such disorders include proliferative disorders, differentiation disorders, cancer, inflammatory diseases, cardiovascular diseases, plasma HDL levels, apolipoprotein A1 metabolism, hyperlipidemia, lipid metabolism, lipid homeostasis, hyperlipidemia, skin-related processes, autoimmune diseases, fatty acid metabolism, malignant cell development, premalignant lesions, programmed cell death, endocrinological processes, AP-1 metabolism and the like.

[0036] In another aspect, the invention relates to pharmaceutical compositions containing the novel compounds of the invention and to methods of treating diseases and/or conditions using the same. Example of diseases and/or conditions include cancer, mammary cancer, prostate cancer, kidney cancer, Karposi's sarcoma, colon cancer, cervical cancer, lung cancer, cutaneous T-cell lymphoma, cancer of the head and neck, cancers of the aerodigestive pathway, skin cancer, bladder cancer, sarcomas, leukoplakias, acute promyelocytic leukemia, acne, psoriasis, aging, wrinkling, diabetes, hyperglycemia, bone calcification, thyroid conditions, and the like.

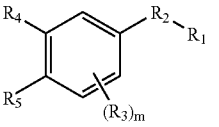
[0037] In yet another aspect, the invention relates to pharmaceutical compositions containing the novel compounds of the invention in combination with other therapeutic agents and to methods of treating diseases and/or conditions using the same. Example of diseases and/or conditions include cancer, mammary cancer, prostate cancer, kidney cancer, Karposi's sarcoma, colon cancer, cervical cancer, lung cancer, cutaneous T-cell lymphoma, cancer of the head and neck, cancers of the aerodigestive pathway, skin cancer, bladder cancer, sarcomas, leukoplakias, acute promyelocytic leukemia and the like. Examples of other therapeutic agents include Busulfan, Carboplatin, Cisplatin, Cyclophosphamide, Cytosine arabinoside, Etoposide, 5-Fluorouracil, Melphalan, Methotrexate, Mitoxantrone, Taxol, Gemzar, Irinotican, Interferon, Fareston, Arzoxifene, Evista, Tamoxifen, and the like.

[0038] The invention further provides pharmaceutical compositions containing one or more of the novel compounds as well as pharmaceutically acceptable pro-drugs and salts of such compounds.

[0039] Additional features of the invention will be set forth in part in the detailed description which follows, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention.

DETAILED DESCRIPTION OF THE INVENTION

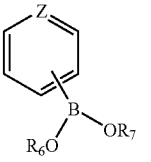
[0040] In one embodiment of the invention, there are provided compounds having the structural formula A:



A

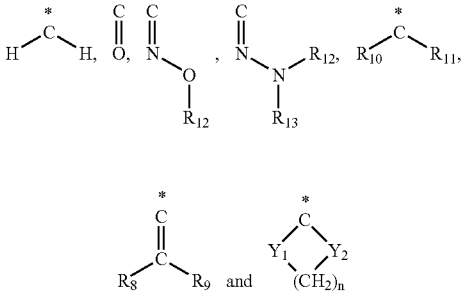
wherein:

[0041] a. R_1 is



[0042] wherein Z is CH or nitrogen, R_6 and R_7 are selected from the group consisting of hydrogen, alkyl, aryl and heteroaryl; R_6 and R_7 may be linked together to form a substituted or unsubstituted 5- or 6-membered cycloalkyl or cycloalkenyl ring, where said substituents are described as herein.

[0043] b. R_2 is selected from the group consisting of



wherein:

[0044] i) R_8, R_9, R_{10} and R_{11} are independently selected from the group consisting of hydrogen, halogen and alkyl,

[0045] ii) R_{12} and R_{13} are independently selected from the group consisting of hydrogen, alkyl, and aryl,

[0046] iii) Y_1 and Y_2 are independently O, S, NH, or CH_2, or Y_1 is O, S or NH, and Y_2 is CH_2, with the proviso that Y_1 and Y_2 cannot both be O S, or NH if n is 0 or 1, and

[0047] iv) * represents the point of attachment of the R_2 to the molecule of formula A

[0048] c. R_3 substituents are independently selected from the group consisting of alkyl, alkyloxy, and halogen,

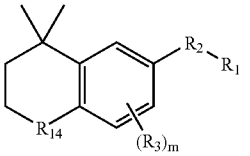
[0049] d. R_4 is selected from the group consisting of alkyl, aryl, heteroaryl, and adamantyl; R_5 is selected from the group consisting of alkyl, alkyloxy, alkylthio, aryl, and heteroaryl; or R_4 and R_5 may be linked together to form a substituted or unsubstituted 5- or 6-membered cycloalkyl or cycloalkenyl ring, where said substituents are selected from the group consisting of —OH, =O, halogen, alkyl, and where 1 or 2 of the carbon atoms on said 5- or 6-membered cycloalkyl or cycloalkenyl ring may be optionally replaced by W where W is selected from the group consisting of O, S, N, NH, alkylamino, and arylamino;

[0050] e. m and n are independently 0, 1, 2 or 3,

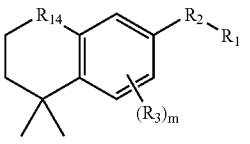
and pharmaceutically acceptable salts, solvates, and prodrugs thereof.

[0051] In another embodiment of the invention, there are provided compounds having the structure, selected from the group consisting of compounds having formulae B_1, B_2, B_3, B_4, B_5, B_6, B_7, B_8, B_9, and B_{10}

B_1



B_2



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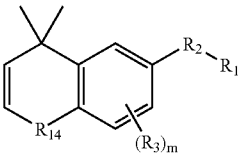
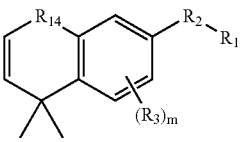
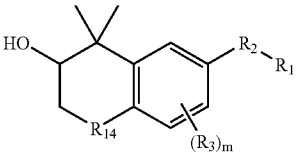
B_3



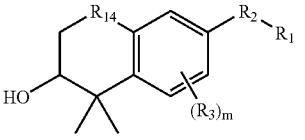
B_4



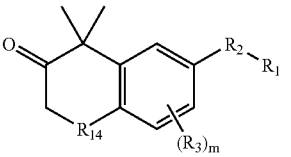
B_5



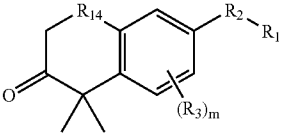
B_6



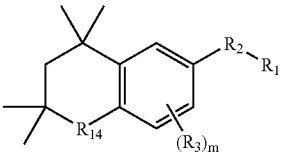
B_7



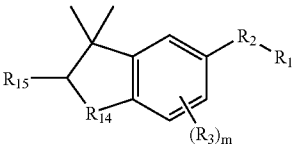
B_8



B_9



B_{10}



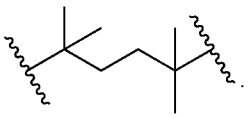
wherein R_1, R_2 and R_3 are as described above and R_{14} is selected from the group consisting of O, S, $(CH_3)_2C$ and CH_2, and R_{15} is hydrogen or methyl.

[0052] In some embodiments of the invention, Z is CH. In other embodiments of the invention, Z is nitrogen.

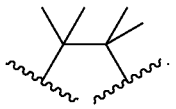
[0053] In certain embodiments of the invention, R_2 is C=O. In other embodiments of the invention, R_2 is CH_2. In other embodiments of the invention, R_2 is $C{=}CH_2$. In yet other embodiments of the invention, R_2 is $C{=}C(CH_3)_2$. In still other embodiments of the invention, R_2 is $C{=}NNH_2$. In other embodiments of the invention, R_2 is C=NOH. In still

other embodiments of the invention, R_2 is cyclopropane. In certain embodiments of the invention, R_2 is oxirane.

[0054] In certain embodiments of the invention, R_4 is alkyl. In other embodiments of the invention, R_5 is alkyl. In still other embodiments of the invention, R_4 and R_5 are linked together to form a substituted or unsubstituted 5- or 6-membered cycloalkyl. In yet other embodiments of the invention, R_4 and R_5 are linked together to form



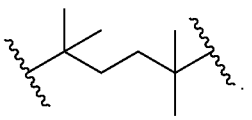
[0055] In certain embodiments of the invention, R_6 is hydrogen. In other embodiments of the invention, R_7 is Hydrogen. In yet other embodiments of the invention, R_6 and R_7 are both hydrogens. In certain embodiments of the invention, R_6 is alkyl. In other embodiments of the invention, R_7 is alkyl. In still other embodiments of the invention, R_6 and R_7 are linked together to form a substituted or unsubstituted 5- or 6-membered cycloalkyl. In yet other embodiments of the invention, R_6 and R_7 are linked together to form



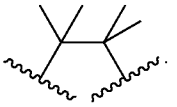
[0056] In some embodiments of the invention, Z is not CH. In other embodiments of the invention, Z is not nitrogen.

[0057] In certain embodiments of the invention, R_2 is not C═O. In other embodiments of the invention, R_2 is not CH_2. In other embodiments of the invention, R_2 is not C═CH_2. In yet other embodiments of the invention, R_2 is not C═$C(CH_3)_2$. In still other embodiments of the invention, R_2 is not C═NNH_2. In other embodiments of the invention, R_2 is not C═NOH. In still other embodiments of the invention, R_2 is not cyclopropane. In certain embodiments of the invention, R_2 is not oxirane.

[0058] In certain embodiments of the invention, R_4 is not alkyl. In other embodiments of the invention, R_5 is not alkyl. In still other embodiments of the invention, R_4 and R_5 are not linked together to form a substituted or unsubstituted 5- or 6-membered cycloalkyl. In yet other embodiments of the invention, R_4 and R_5 are not linked together to form



[0059] In certain embodiments of the invention, R_6 is not hydrogen. In other embodiments of the invention, R_7 is not Hydrogen. In yet other embodiments of the invention, R_6 and R_7 are both hydrogens. In certain embodiments of the invention, R_6 is not alkyl. In other embodiments of the invention, R_7 is not alkyl. In still other embodiments of the invention, R_6 and R_7 are not linked together to form a substituted or unsubstituted 5- or 6-membered cycloalkyl. In yet other embodiments of the invention, R_6 and R_7 are not linked together to form



[0060] The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium (D) and tritium (T). Isotopes of carbon include ^{13}C and ^{14}C. Isotopes of sulfur include ^{32}S, ^{33}S, ^{34}S, and ^{36}S. Isotopes of nitrogen include ^{14}N and ^{15}N. Isotopes of oxygen include ^{16}O, ^{17}O, and ^{18}O.

[0061] Isotopic hydrogen can be introduced into organic molecules by synthetic techniques and exchange techniques. Synthetic techniques, where tritium or deuterium is directly and specifically inserted, may yield high tritium or deuterium abundance, but can be limited by the chemistry required. In addition, the molecule being labeled may be changed, depending upon the severity of the synthetic reaction employed. Exchange techniques may yield lower tritium or deuterium incorporation, often with the isotope being distributed over many sites on the molecule, but offer the advantage that they do not require separate synthetic steps and are less likely to disrupt the structure of the molecule being labeled.

[0062] Unless otherwise indicated, when a substituent is deemed to be "optionally substituted," it is meant that the substituent is a group that may be substituted with one or more group(s) individually and independently selected from the group consisting of hydrogen, deuterium, cycloalkyl, aryl, heteroaryl, heterocyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art and may be found in references such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, N.Y., 1999, which is incorporated by reference herein in its entirety.

[0063] The compounds according to this invention may contain one or more asymmetric carbon atoms and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures or individual diastereomers. The term "stereoisomer" refers to a chemical compound having the same molecular weight, chemical composition, and constitution as another, but with the atoms grouped differently. That is, certain identical chemical moieties are at different orientations in space and, therefore, when pure, have the ability to rotate the plane of polarized light. However, some pure stereoisomers may have an optical rotation that is so slight that it is undetectable with present instrumentation. The compounds described herein may have one or more asymmetrical carbon atoms and therefore include various stereoi-

somers. All such isomeric forms of these compounds are expressly included in the present invention.

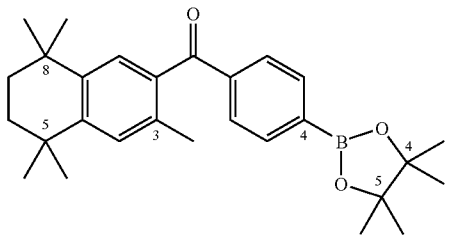
[0064] Each stereogenic carbon may be of R or S configuration. Although the specific compounds exemplified in this application may be depicted in a particular configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned. When chiral centers are found in the derivatives of this invention, it is to be understood that this invention encompasses all possible stereoisomers.

[0065] The terms "optically pure compound" or "optically pure isomer" refers to a single stereoisomer of a chiral compound regardless of the configuration of the said compound.

[0066] For the purposes of this application, all sugars are referenced using conventional three-letter nomenclature. All sugars are assumed to be in the D-form unless otherwise noted, except for fucose, which is in the L-form. Further, all sugars are in the pyranose form.

[0067] The compounds according to this invention may occur as a mixture of tautomers. The terms "tautomer" or "tautomerism" refer to one of two or more structural isomers that exist in equilibrium and are readily converted from one isomeric form to another. Examples of include keto-enol tautomers, such as acetone/propen-2-ol and the like, ring-chain tautomers, such as glucose/2,3,4,5,6-pentahydroxy-hexanal and the like. The compounds described herein may have one or more tautomers and therefore include various isomers. All such isomeric forms of these compounds are expressly included in the present invention.

[0068] The following example of nomenclature and numbering system is provided for reference.



(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methanone

[0069] The term "substantially homogeneous" refers to collections of molecules wherein at least 80%, preferably at least about 90% and more preferably at least about 95% of the molecules are a single compound or a single stereoisomer thereof.

[0070] The term "substantially homogeneous" also refers to collections of molecules wherein at least 80%, preferably at least about 90% and more preferably at least about 95% of the molecules are a single compound or a single stereoisomer thereof, or to collections of molecules wherein at least 80%, preferably at least about 90% and more preferably at least about 95% of the molecules are fully deuterated at the positions stated.

[0071] As used herein, the term "attached" signifies a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art.

[0072] The terms "optional" or "optionally" refer to occurrence or non-occurrence of the subsequently described event or circumstance, and that the description includes instances where said event or circumstance occurs and instances where it does not. In such context, the sentence "optionally substituted alkyl group" means that the alkyl group may or may not be substituted and the description includes both a substituted and an unsubstituted alkyl group.

[0073] The term "effective amount" of a compound refers to a non-toxic but sufficient amount of the compound that provides a desired effect. This amount may vary from subject to subject, depending on the species, age, and physical condition of the subject, the severity of the disease that is being treated, the particular compound used, its mode of administration, and the like. Therefore, it is difficult to generalize an exact "effective amount," yet, a suitable effective amount may be determined by one of ordinary skill in the art.

[0074] The term "pharmaceutically acceptable" refers to a compound, additive or composition that is not biologically or otherwise undesirable. For example, the additive or composition may be administered to a subject along with a compound of the invention without causing any undesirable biological effects or interacting in an undesirable manner with any of the other components of the pharmaceutical composition in which it is contained.

[0075] The term "pharmaceutically acceptable salts" includes hydrochloric salt, hydrobromic salt, hydroiodic salt, hydrofluoric salt, sulfuric salt, citric salt, maleic salt, acetic salt, lactic salt, nicotinic salt, succinic salt, oxalic salt, phosphoric salt, malonic salt, salicylic salt, phenylacetic salt, stearic salt, pyridine salt, ammonium salt, piperazine salt, diethylamine salt, nicotinamide salt, formic salt, urea salt, sodium salt, potassium salt, calcium salt, magnesium salt, zinc salt, lithium salt, cinnamic salt, methylamino salt, methanesulfonic salt, picric salt, tartaric salt, triethylamino salt, dimethylamino salt, tris(hydroxymethyl)aminomethane salt and the like. Additional pharmaceutically acceptable salts are known to those of skill in the art.

[0076] When used in conjunction with a compound of this invention, the terms "elicite," "eliciting," modulator," "modulate," "modulating," "regulator," "regulate," or "regulating" selective gene expression refer to a compound that can act as an activator, an agonist, a pan-agonist or an antagonist of gene expression by a particular receptor, such as for example a Retinoid X Receptor and the like.

[0077] The terms "drug," "therapeutic agent," and "chemotherapeutic agent" refer to a compound or compounds and pharmaceutically acceptable compositions thereof that are administered to mammalian subjects as prophylactic or remedy in the treatment of a disease or medical condition. Such compounds may be administered to the subject via oral formulation, transdermal formulation or by injection.

[0078] The term "subject" refers to an animal, preferably a mammal, and most preferably a human, who is the object of treatment, observation or experiment. The mammal may be selected from the group consisting of mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, primates, such as monkeys, chimpanzees, and apes, and humans.

[0079] The term "therapeutically effective amount" is used to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. This response may occur in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

[0080] The terms "treating," "treatment," "therapeutic," or "therapy" do not necessarily mean total loss of symptoms or nociception. Any alleviation of any undesired signs or symptoms of a disease, such as cancer, acne, psoriasis, or a subset of these conditions, to any extent can be considered treatment or therapy. Furthermore, treatment may include acts that may worsen the patient's overall feeling of well being or appearance.

[0081] The term "Lewis acid" refers to a molecule that can accept an unshared pair of electrons and as such would be obvious to one of ordinary skill and knowledge in the art. The definition of "Lewis acid" includes but is not limited to: boron trifluoride, boron trifluoride etherate, boron trifluoride tetrahydrofuran complex, boron trifluoride tert-butyl-methyl ether complex, boron trifluoride dibutyl ether complex, boron trifluoride dihydrate, boron trifluoride di-acetic acid complex, boron trifluoride dimethyl sulfide complex, boron trichloride, boron trichloride dimethyl sulfide complex, boron tribromide, boron tribromide dimethyl sulfide complex, boron triiodide, triimethoxyborane, triethoxyborane, trimethylaluminum, triethylaluminum, aluminum trichloride, aluminum trichloride tetrahydrofuran complex, aluminum tribromide, titanium tetrachloride, titanium tetrabromide, titanium iodide, titanium tetraethoxide, titanium tetraisopropoxide, scandium (III) trifluoromethanesulfonate, yttrium (III) trifluoromethanesulfonate, ytterbium (III) trifluoromethanesulfonate, lanthanum (III) trifluoromethanesulfonate, zinc (II) chloride, zinc (II) bromide, zinc (II) iodide, zinc (II) trifluoromethanesulfonate, zinc (II) sulfate, magnesium sulfate, lithium perchlorate, copper (II) trifluoromethanesulfonate, copper (II) tetrafluoroborate and the like. Certain Lewis acids may have optically pure ligands attached to the electron acceptor atom, as set forth in Corey, E. J. Angewandte Chemie, International Edition (2002), 41(10), 1650-1667; Aspinall, H. C. Chemical Reviews (Washington, D.C., United States) (2002), 102(6), 1807-1850; Groger, H. Chemistry—A European Journal (2001), 7(24), 5246-5251; Davies, H. M. L. Chemtracts (2001), 14(11), 642-645; Wan, Y. Chemtracts (2001), 14(11), 610-615; Kim, Y. H. Accounts of Chemical Research (2001), 34(12), 955-962; Seebach, D. Angewandte Chemie, International Edition (2001), 40(1), 92-138; Blaser, H. U. Applied Catalysis, A: General (2001), 221(1-2), 119-143; Yet, L. Angewandte Chemie, International Edition (2001), 40(5), 875-877; Jorgensen, K. A. Angewandte Chemie, International Edition (2000), 39(20), 3558-3588; Dias, L. C. Current Organic Chemistry (2000), 4(3), 305-342; Spindler, F. Enantiomer (1999), 4(6), 557-568; Fodor, K. Enantiomer (1999), 4(6), 497-511; Shimizu, K. D.; Comprehensive Asymmetric Catalysis I-III (1999), 3, 1389-1399; Kagan, H. B. Comprehensive Asymmetric Catalysis I-III (1999), 1, 9-30; Mikami, K. Lewis Acid Reagents (1999), 93-136 and all references cited therein. Such Lewis acids maybe used by one of ordinary skill and knowledge in the art to produce optically pure compounds from achiral starting materials.

[0082] The term "acylating agent" refers to a molecule that can transfer an alkylcarbonyl, substituted alkylcarbonyl or aryl carbonyl group to another molecule. The definition of "acylating agent" includes but is not limited to ethyl acetate, vinyl acetate, vinyl propionate, vinyl butyrate, isopropenyl acetate, 1-ethoxyvinyl acetate, trichloroethyl butyrate, trifluoroethyl butyrate, trifluoroethyl laureate, S-ethyl thiooctanoate, biacetyl monooxime acetate, acetic anhydride, acetyl chloride, succinic anhydride, diketene, diallyl carbonate, carbonic acid but-3-enyl ester cyanomethyl ester, amino acid and the like.

[0083] The term "nucleophile" or "nucleophilic reagent" refers to a negatively charged or neutral molecule that has an unshared pair of electrons and as such would be obvious to one of ordinary skill and knowledge in the art. The definition of "nucleophile" includes but is not limited to: water, alkylhydroxy, alkoxy anion, arylhydroxy, aryloxy anion, alkylthiol, alkylthio anion, arylthiol, arylthio anion, ammonia, alkylamine, arylamine, alkylamine anion, arylamine anion, hydrazine, alkyl hydrazine, arylhydrazine, alkylcarbonyl hydrazine, arylcarbonyl hydrazine, hydrazine anion, alkyl hydrazine anion, arylhydrazine anion, alkylcarbonyl hydrazine anion, arylcarbonyl hydrazine anion, cyanide, azide, hydride, alkyl anion, aryl anion and the like.

[0084] The term "electrophile" or "electrophilic reagent" refers to a positively charged or neutral molecule that has an open valence shell and as such would be obvious to one of ordinary skill and knowledge in the art. The definition of "electrophile" includes but is not limited to: hydronium, acylium, lewis acids, such as for example, boron trifluoride and the like, halogens, such as for example Br_2 and the like, carbocations, such as for example tert-butyl cation and the like, diazomethane, trimethylsilyldiazomethane, alkyl halides, such as for example methyl iodide, benzyl bromide and the like, alkyl triflates, such as for example methyl triflate and the like, alkyl sulfonates, such as for example ethyl toluenesulfonate, butyl methanesulfonate and the like, acyl halides, such as for example acetyl chloride, benzoyl bromide and the like, acid anhydrides, such as for example acetic anhydride, succinic anhydride, maleic anhydride and the like, isocyanates, such as for example methyl isocyanate, phenylisocyanate and the like, chloroformates, such as for example methyl chloroformate, ethyl chloroformate, benzyl chloroformate and the like, sulfonyl halides, such as for example methanesulfonyl chloride, p-toluenesulfonyl chloride and the like, silyl halides, such as for example trimethylsilyl chloride, tertbutyldimethyl silyll chloride and the like, phosphoryl halide such as for example dimethyl chlorophosphate and the like, alpha-beta-unsaturated carbonyl compounds such as for example acrolein, methyl vinyl ketone, cinnamaldehyde and the like.

[0085] The term "oxidant" refers to any reagent that will increase the oxidation state of a carbon atom in the starting material by either adding an oxygen atom to this carbon or removing an electron from this carbon and as such would be obvious to one of ordinary skill and knowledge in the art. The definition of "oxidant" includes but is not limited to: osmium tetroxide, ruthenium tetroxide, ruthenium trichloride, potassium permanganate, meta-chloroperbenzoic acid, hydrogen peroxide, dimethyl dioxirane and the like.

[0086] The term "metal ligand" refers to a molecule that has an unshared pair of electrons and can coordinate to a metal atom and as such would be obvious to one of ordinary skill and knowledge in the art. The definition of "metal ligand" includes but is not limited to: water, alkoxy anion, alkylthio anion, ammonia, trialkylamine, triarylamine, trialkylphosphine, triarylphosphine, cyanide, azide and the like.

[0087] The term "reducing reagent" refers to any reagent that will decrease the oxidation state of a carbon atom in the starting material by either adding a hydrogen atom to this carbon or adding an electron to this carbon and as such would be obvious to one of ordinary skill and knowledge in the art.

The definition of "reducing reagent" includes but is not limited to: borane-dimethyl sulfide complex, 9-borabicyclo[3.3.1.]nonane (9-BBN), catechol borane, lithium borohydride, sodium borohydride, sodium borohydride-methanol complex, potassium borohydride, sodium hydroxyborohydride, lithium triethylborohydride, lithium n-butylborohydride, sodium cyanoborohydride, calcium (II) borohydride, lithium aluminum hydride, diisobutylaluminum hydride, n-butyl-diisobutylaluminum hydride, sodium bis-methoxyethoxyaluminum hydride, triethoxysilane, diethoxymethylsilane, lithium hydride, lithium, sodium, hydrogen Ni/B, and the like. Certain acidic and Lewis acidic reagents enhance the activity of reducing reagents. Examples of such acidic reagents include: acetic acid, methanesulfonic acid, hydrochloric acid, and the like. Examples of such Lewis acidic reagents include: trimethoxyborane, triethoxyborane, aluminum trichloride, lithium chloride, vanadium trichloride, dicyclopentadienyl titanium dichloride, cesium fluoride, potassium fluoride, zinc (II) chloride, zinc (II) bromide, zinc (II) iodide, and the like.

[0088] The term "coupling reagent" refers to any reagent that will activate the carbonyl of a carboxylic acid and facilitate the formation of an ester or amide bond. The definition of "coupling reagent" includes but is not limited to: acetyl chloride, ethyl chloroformate, dicyclohexylcarbodiimide (DCC), diisopropyl carbodiiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI), N-hydroxybenzotriazole (HOBT), N-hydroxysuccinimide (HOSu), 4-nitrophenol, pentafluorophenol, 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), O-benzotriazole-N,N,N'N'-tetramethyluronium hexafluorophosphate (HBTU), benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP), benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate, bromo-trispyrrolidino-phosphonium hexafluorophosphate, 2-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU), O—(N-succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU), tetramethylfluoroformamidinium hexafluorophosphate and the like.

[0089] The term "removable protecting group" or "protecting group" refers to any group which when bound to a functionality, such as the oxygen atom of a hydroxyl or carboxyl group or the nitrogen atom of an amino group, prevents reactions from occurring at these functional groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the functional group. The particular removable protecting group employed is not critical.

[0090] The definition of "hydroxyl protecting group" includes but is not limited to:

[0091] a) methyl, tert-butyl, allyl, propargyl, p-chlorophenyl, p-methoxyphenyl, p-nitrophenyl, 2,4-dinitrophenyl, 2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl, methoxymethyl, methylthiomethyl, (phenyldimethylsilyl)methoxymethyl, benzyloxymethyl, p-methoxy-benzyloxymethyl, p-nitrobenzyloxymethyl, o-nitrobenzyloxymethyl, (4-methoxyphenoxy)methyl, guaiacolmethyl, tert-butoxymethyl, 4-pentenyloxymethyl, tert-butyldimethylsiloxymethyl, thexyldimethylsiloxymethyl, tert-butyldiphenylsiloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl) ethoxymethyl, menthoxymethyl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-[2-(trimethylsilyl)ethoxy]ethyl, 1-methyl-1-ethoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 1-methyl-1-phenoxyethyl, 2,2,2-trichloroethyl, 1-dianisyl-2,2,2-trichloroethyl, 1,1,1,3,3,3-hexafluoro-2-phenylisopropyl, 2-trimethylsilylethyl, 2-(benzylthio)ethyl, 2-(phenylselenyl)ethyl, tetrahydropyranyl, 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl, 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydropyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl, 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl and the like;

[0092] b) benzyl, 2-nitrobenzyl, 2-trifluoromethylbenzyl, 4-methoxybenzyl, 4-nitrobenzyl, 4-chlorobenzyl, 4-bromobenzyl, 4-cyanobenzyl, 4-phenylbenzyl, 4-acylaminobenzyl, 4-azidobenzyl, 4-(methylsulfinyl)benzyl, 2,4-dimethoxybenzyl, 4-azido-3-chlorobenzyl, 3,4-dimethoxybenzyl, 2,6-dichlorobenzyl, 2,6-difluorobenzyl, 1-pyrenylmethyl, diphenylmethyl, 4,4'-dinitrobenzhydryl, 5-benzosuberyl, triphenylmethyl (Trityl), □-naphthyldiphenylmethyl, (4-Methoxyphenyl)-diphenyl-methyl, di-(p-methoxyphenyl)-phenylmethyl, tri-(p-methoxyphenyl)methyl, 4-(4'-bromophenacyloxy)-phenyldiphenylmethyl, 4,4',4"-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-tris(levulinoyloxyphenyl)methyl, 4,4'-dimethoxy-3"-[N-(imidazolylmethyl)]trityl, 4,4'-dimethoxy-3"-[N-(imidazolylethyl)carbamoyl]trityl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 4-(17-tetrabenzo[a,c,g,l]fluorenylmethyl)-4,4'-dimethoxytrityl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl and the like;

[0093] c) trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylhexylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, tri-p-xylylsilyl, triphenylsilyl, diphenylmethylsilyl, di-tert-butylmethylsilyl, tris(trimethylsilyl)silyl, (2-hydroxystyryl)dimethylsilyl, (2-hydroxystyryl)diisopropylsilyl, tert-butylmethoxyphenylsilyl, tert-butoxydiphenylsilyl and the like;

[0094] d) —C(O)R_{20}, where R_{20} is selected from alkyl, substituted alkyl, aryl and more specifically R_{20} is hydrogen, methyl, ethyl, tert-butyl, adamantyl, crotyl, chloromethyl, dichloromethyl, trichloromethyl, trifluoromethyl, methoxymethyl, triphenylmethoxymethyl, phenoxymethyl, 4-chlorophenoxymethyl, phenylmethyl, diphenylmethyl, 4-methoxycrotyl, 3-phenylpropyl, 4-pentenyl, 4-oxopentyl, 4,4-(ethylenedithio)pentyl, 5-[3-bis(4-methoxyphenyl)hydroxymethylphenoxy]-4-oxopentyl, phenyl, 4-methylphenyl, 4-nitrophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methoxyphenyl, 4-phenylphenyl, 2,4,6-trimethylphenyl, □-naphthyl, benzoyl and the like;

[0095] e) —C(O)OR_{20}, where R_{20} is selected from alkyl, substituted alkyl, aryl and more specifically R_{20} is methyl, methoxymethyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloromethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 2-(trimethylsilyl) ethyl, 2-(phenylsulfonyl)ethyl, isobutyl, tert-Butyl, vinyl, allyl, 4-nitrophenyl, benzyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 2-(methylthiomethoxy)ethyl, 2-dansenylethyl, 2-(4-nitrophenyl)ethyl, 2-(2,4-dinitrophenyl)ethyl, 2-cyano-1-phenylethyl, thiobenzyl, 4-ethoxy-1-naphthyl and the like.

[0096] The definition of "amino protecting group" includes but is not limited to:

[0097] a) 2-methylthioethyl, 2-methylsulfonylethyl, 2-(p-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 1-methyl-1-(triphenylphosphonio)ethyl, 1,1-dimethyl-2-

cyanoethyl, 2-dansylethyl, 2-(4-nitrophenyl)ethyl, 4-phenylacetoxybenzyl, 4-azidobenzyl, 4-azidomethoxybenzyl, m-chloro-p-acyloxybenzyl, p-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl, m-nitrophenyl, 3.5-dimethoxybenzyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, o-nitrobenzyl, □-methylnitropiperonyl, 3,4-dimethoxy-6-nitrobenzyl, N-benzenesulfenyl, N-o-nitrobenzenesulfenyl, N-2,4-dinitrobenzenesulfenyl, N-pentachlorobenzenesulfenyl. N^2-nitro-4-methoxybenzenesulfenyl, N-triphenylmethylsulfenyl, N-1-(2,2,2-trifluoro-1,1-diphenyl)ethylsulfenyl, N-3-nitro-2-pyridinesulfenyl, N-p-toluenesulfonyl, N-benzenesulfonyl, N-2,3,6-trimethyl-4-methoxybenzenesulfonyl, N-2,4,6-trimethoxybenzene-sulfonyl, N-2,6-dimethyl-4-methoxybenzenesulfonyl, N-pentamethylbenzenesulfonyl, N-2,3,5,6-tetramethyl-4-methoxybenzenesulfonyl and the like;

[0098] b) —C(O)OR_{20}, where R_{20} is selected from alkyl, substituted alkyl, aryl and more specifically R_{20}=methyl, ethyl, 9-fluorenylmethyl, 9-(2-sulfo)fluorenylmethyl. 9-(2,7-dibromo)fluorenylmethyl, 17-tetrabenzo[a,c,g,i]fluorenylmethyl. 2-chloro-3-indenylmethyl, benz[f]inden-3-ylmethyl, 2,7-di-t-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothloxanthyl)]methyl, 1,1-dioxobenzo[b]thiophene-2-ylmethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 2-chloroethyl, 1.1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-tert-butylphenyl)-1-methylethyl, 2-(2'-pyridyl) ethyl, 2-(4'-pyridyl)ethyl, 2,2-bis(4'-nitrophenyl)ethyl, N-(2-pivaloylamino)-1,1-dimethylethyl, 2-[(2-nitrophenyl) dithio]-1-phenylethyl, tert-butyl, 1-adamantyl, 2-adamantyl, Vinyl, allyl, 1-Isopropylallyl, cinnamyl. 4-nitrocinnamyl, 3-(3'-pyridyl)prop-2-enyl, 8-quinolyl, N-Hydroxypiperidinyl, alkyldithio, benzyl, p-methoxybenzyl, p-nitrobenzyl, p-bromobenzyl. p-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl, tert-amyl, S-benzyl thiocarbamate, butynyl, p-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, p-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, o-(N,N'-dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(N,N'-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-Iodoethyl, isobornyl, isobutyl, isonicotinyl, p-(p'-methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(p-phenylazophenyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-4'-pyridylethyl, phenyl, p-(phenylazo)benzyl, 2,4,6-trimethylphenyl, 4-(trimethylammonium)benzyl, 2,4,6-trimethylbenzyl and the like.

[0099] The definition of "carboxyl protecting group" includes but is not limited to:

[0100] 2-N-(morpholino)ethyl, choline, methyl, methoxyethyl, 9-fluorenylmethyl, methoxymethyl, methylthiomethyl, tetrahydropyranyl, tetrahydrofuranyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, benzyloxymethyl, pivaloyloxymethyl, phenylacetoxymethyl, triisopropylsilylmethyl, cyanomethyl, acetol, p-bromophenacyl, α-methylphenacyl, p-methoxyphenacyl, desyl, carboxamidomethyl, p-azobenzenecarboxamido-methyl, N-phthalimidomethyl, (methoxyethoxy)ethyl, 2,2,2-trichloroethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 4-chlorobutyl, 5-chloropentyl, 2-(trimethylsilyl)ethyl, 2-methylthioethyl, 1,3-dithianyl-2-methyl, 2-(p-nitrophenylsulfenyl)ethyl, 2-(p-toluenesulfonyl)ethyl, 2-(2-pyridyl) ethyl, 2-(p-methoxyphenyl)ethyl, 2-(diphenylphosphino)ethyl, 1-methyl-1-phenylethyl, 2-(4-acetyl-2-nitrophenyl)ethyl, 2-cyanoethyl, heptyl, tert-butyl, 3-methyl-3-pentyl, dicyclopropylmethyl, 2,4-dimethyl-3-pentyl, cyclopentyl, cyclohexyl, allyl, methallyl, 2-methylbut-3-en-2-yl, 3-methylbut-2-(prenyl), 3-buten-1-yl, 4-(trimethylsilyl)-2-buten-1-yl, cinnamyl, □-methylcinnamyl, propargyl, phenyl, 2,6-dimethylphenyl, 2,6-diisopropylphenyl, 2,6-di-tert-butyl-4-methylphenyl, 2,6-di-tert-butyl-4-methoxyphenyl, p-(methylthio)phenyl, pentafluorophenyl, benzyl, triphenylmethyl, diphenylmethyl, bis(o-nitrophenyl)methyl, 9-anthrylmethyl, 2-(9,10-dioxo)anthrylmethyl. 5-dibenzosuberyl, 1-pyrenylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl, 2,4,6-trimethylbenzyl, p-bromobenzyl, o-nitrobenzyl, p-nitrobenzyl, p-methoxybenzyl, 2.6-dimethoxybenzyl, 4-(methylsulfinyl) benzyl, 4-sulfobenzyl, 4-azidomethoxybenzyl, 4-{a/-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl]amino}benzyl, piperonyl, 4-picolyl, trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, isopropyldimethylsilyl, phenyldimethylsilyl, di-tert-butylmethylsilyl, triisopropylsilyl and the like.

[0101] The term "amino acid" refers to any of the naturally occurring amino acids, as well as synthetic analogs and derivatives thereof. Alpha-Amino acids comprise a Carbon atom to which is bonded an amino group, a carboxy group, a hydrogen atom, and a distinctive group referred to as a "side chain." The side chains of naturally occurring amino acids are well known in the art and include, for example, hydrogen (e.g., as in glycine), alkyl (e.g., as in alanine, valine, leucine, isoleucine, proline), substituted alkyl (e.g., as in threonine, serine, methionine, cysteine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, and lysine), arylalkyl (e.g., as in phenylalanine), substituted arylalkyl (e.g., as in tyrosine), heteroarylalkyl (e.g., as in tryptophan, histidine) and the like. One of skill in the art will appreciate that the term "amino acid" can also include beta-, gamma-, delta-, omega-amino acids, and the like. Unnatural amino acids are also known in the art, as set forth in, Natchus, M. G. Organic Synthesis: Theory and Applications (2001), 5, 89-196; Ager, D. J. Current Opinion in Drug Discovery & Development (2001), 4(6), 800; Reginato, G. Recent Research Developments in Organic Chemistry (2000), 4(Pt. 1), 351-359; Dougherty, D. A. Current Opinion in Chemical Biology (2000), 4(6), 645-652; Lesley, S. A. Drugs and the Pharmaceutical Sciences (2000), 101 (Peptide and Protein Drug Analysis), 191-205; Pojitkov, A. E. Journal of Molecular Catalysis B: Enzymatic (2000), 10(1-3), 47-55; Ager, D. J. Speciality Chemicals (1999), 19(1), 10-12, and all references cited therein. Stereoisomers (e.g., D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as alpha, alpha-disubstituted amino acids and other unconventional amino acids may also be suitable components for compounds of the present invention. Examples of unconventional amino acids include: 4-hydroxyproline, 3-methylhistidine, 5-hydroxylysine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline).

[0102] The term "N-protected amino acid" refers to any amino acid which has a protecting group bound to the nitrogen of the amino functionality. This protecting group prevents reactions from occurring at the amino functional group and

can be removed by conventional chemical or enzymatic steps to reestablish the amino functional group. The particular protecting group employed is not critical.

[0103] The term "O-protected amino acid" refers to any amino acid which has a protecting group bound to the oxygen of the carboxyl functionality. This protecting group prevents reactions from occurring at the carboxyl functional group and can be removed by conventional chemical or enzymatic steps to reestablish the carboxyl functional group. The particular protecting group employed is not critical.

[0104] The term "prodrug" refers to an agent that is converted into the parent drug in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A prodrug may be converted into the parent drug by various mechanisms, including enzymatic processes and metabolic hydrolysis. See Harper, "Drug Latentiation" in Jucker, ed. Progress in Drug Research 4:221-294 (1962); Morozowich et al., "Application of Physical Organic Principles to Prodrug Design" in E. B. Roche ed. Design of Biopharmaceutical Properties through Prodrugs and Analogs, APHA Acad. Pharm. Sci. (1977); Bioreversible Carriers in Drug in Drug Design, Theory and Application, E. B. Roche, ed., APHA Acad. Pharm. Sci. (1987); Design of Prodrugs, H. Bundgaard, Elsevier (1985); Wang et al. "Prodrug approaches to the improved delivery of peptide drug" in Curr. Pharm. Design. 5(4):265-287 (1999); Pauletti et al. (1997) Improvement in peptide bioavailability: Peptidomimetics and Prodrug Strategies, Adv. Drug. Delivery Rev. 27:235-256; Mizen et al. (1998) "The Use of Esters as Prodrugs for Oral Delivery of beta.-Lactam antibiotics," Pharm. Biotech. 11,:345-365; Gaignault et al. (1996) "Designing Prodrugs and Bioprecursors I. Carrier Prodrugs," Pract. Med. Chem. 671-696; Asgharnejad, "Improving Oral Drug Transport", in Transport Processes in Pharmaceutical Systems, G. L. Amidon, P. I. Lee and E. M. Topp, Eds., Marcell Dekker, p. 185-218 (2000); Balant et al., "Prodrugs for the improvement of drug absorption via different routes of administration", Eur. J. Drug Metab. Pharmacokinet., 15(2): 143-53 (1990); Balimane and Sinko, "Involvement of multiple transporters in the oral absorption of nucleoside analogues", Adv. Drug Delivery Rev., 39(1-3): 183-209 (1999); Browne, "Fosphenyloin (Cerebyx)", Clin. Neuropharmacol. 20(1): 1-12 (1997); Bundgaard, "Bioreversible derivatization of drugs—principle and applicability to improve the therapeutic effects of drugs", Arch. Pharm. Chemi 86(1): 1-39 (1979); Bundgaard H. "Improved drug delivery by the prodrug approach", Controlled Drug Delivery 17: 179-96 (1987); Bundgaard H. "Prodrugs as a means to improve the delivery of peptide drugs", Adv. Drug Delivery Rev. 8(1): 1-38 (1992); Fleisher et al. "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Adv. Drug Delivery Rev. 19(2): 115-130 (1996); Fleisher et al. "Design of prodrugs for improved gastrointestinal absorption by intestinal enzyme targeting", Methods Enzymol. 112 (Drug Enzyme Targeting, Pt. A): 360-81, (1985); Farquhar D, et al., "Biologically Reversible Phosphate-Protective Groups", J. Pharm. Sci., 72(3): 324-325 (1983); Freeman S, et al., "Bioreversible Protection for the Phospho Group: Chemical Stability and Bioactivation of Di(4-acetoxy-benzyl) Methylphosphonate with Carboxyesterase," J. Chem. Soc., Chem. Commun., 875-877 (1991); Friis and Bundgaard, "Prodrugs of phosphates and phosphonates: Novel lipophilic alpha-acyloxyalkyl ester derivatives of phosphate- or phosphonate containing drugs masking the negative charges of these groups", Eur. J. Pharm. Sci. 4: 49-59 (1996); Gangwar et al., "Pro-drug, molecular structure and percutaneous delivery", Des. Biopharm. Prop. Prodrugs Analogs, [Symp.] Meeting Date 1976, 409-21. (1977); Nathwani and Wood, "Penicillins: a current review of their clinical pharmacology and therapeutic use", Drugs 45(6): 866-94 (1993); Sinhababu and Thakker, "Prodrugs of anticancer agents", Adv. Drug Delivery Rev. 19(2): 241-273 (1996); Stella et al., "Prodrugs. Do they have advantages in clinical practice?", Drugs 29(5): 455-73 (1985); Tan et al. "Development and optimization of anti-HIV nucleoside analogs and prodrugs: A review of their cellular pharmacology, structure-activity relationships and pharmacokinetics", Adv. Drug Delivery Rev. 39(1-3): 117-151 (1999); Taylor, "Improved passive oral drug delivery via prodrugs", Adv. Drug Delivery Rev., 19(2): 131-148 (1996); Valentino and Borchardt, "Prodrug strategies to enhance the intestinal absorption of peptides", Drug Discovery Today 2(4): 148-155 (1997); Wiebe and Knaus, "Concepts for the design of anti-HIV nucleoside prodrugs for treating cephalic HIV infection", Adv. Drug Delivery Rev.: 39(1-3):63-80 (1999); Waller et al., "Prodrugs", Br. J. Clin. Pharmac. 28: 497-507 (1989).

[0105] All references to reagents ordinarily containing hydrogens, hydrides, or protons may include partially or fully deuterated versions (containing deuterium, deuteride, or deuteronium) as required to effect transformation to the improved drug substances outlined herein.

[0106] The term "halogen," "halide," or "halo" includes fluorine, chlorine, bromine, and iodine.

[0107] The terms "alkyl" and "substituted alkyl" are interchangeable and include substituted, optionally substituted and unsubstituted C_1-C_{10} straight chain saturated aliphatic hydrocarbon groups, substituted, optionally substituted and unsubstituted C_2-C_{10} straight chain unsaturated aliphatic hydrocarbon groups, substituted, optionally substituted and unsubstituted C_4-C_{10} branched saturated aliphatic hydrocarbon groups, substituted and unsubstituted C_4-C_{10} branched unsaturated aliphatic hydrocarbon groups, substituted, optionally substituted and unsubstituted C_3-C_8 cyclic saturated aliphatic hydrocarbon groups, substituted, optionally substituted and unsubstituted C_5-C_8 cyclic unsaturated aliphatic hydrocarbon groups having the specified number of Carbon atoms. For example, the definition of "alkyl" shall include but is not limited to: methyl (Me), trideuteromethyl (—CD_3), ethyl (Et), propyl (Pr), butyl (Bu), pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, ethenyl, propenyl, butenyl, penentyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, undecenyl, isopropyl (i-Pr), isobutyl (i-Bu), tert-butyl (t-Bu), sec-butyl (s-Bu), isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, methylcyclopropyl, ethylcyclohexenyl, butenylcyclopentyl, adamantyl, norbornyl and the like. Alkyl substituents are independently selected from the group consisting of hydrogen, deuterium, halogen, —OH, —SH, —NH_2, —CN, —NO_2, =O, =CH_2, trihalomethyl, carbamoyl, arylC_{0-10}alkyl, heteroarylC_{0-10}alkyl, C_{1-10}alkyloxy, arylC_{0-10}alkyloxy, C_{1-10}alkylthio, arylC_{0-10}alkylthio, C_{1-10}alkylamino, arylC_{0-10}alkylamino, N-aryl-N—C_{0-10}alkylamino, C_{1-10}alkylcarbonyl, arylC_{0-10}alkylcarbonyl, C_{1-10}alkylcarboxy, arylC_{0-10}alkylcarboxy, C_{1-10}alkylcarbonylamino, arylC_{0-10}alkylcarbonylamino, tetrahydrofuryl, morpholinyl,

piperazinyl, hydroxypyronyl, —C_{0-10}alkylCOOR$_{21}$ and —C_{0-10}alkylCONR$_{22}$R$_{23}$ wherein R$_{21}$, R$_{22}$ and R$_{23}$ are independently selected from the group consisting of hydrogen, deuterium, alkyl, aryl, or R$_{22}$ and R$_{23}$ are taken together with the nitrogen to which they are attached forming a saturated cyclic or unsaturated cyclic system containing 3 to 8 carbon atoms with at least one substituent as defined herein.

[0108] All references to "alkyl" groups or any groups ordinarily containing C—H bonds may include partially or fully deuterated versions as required to effect the improvements outlined herein.

[0109] The term "alkyloxy" (e.g. methoxy, ethoxy, propyloxy, allyloxy, cyclohexyloxy) represents a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms attached through an oxygen bridge. The term "alkyloxyalkyl" represents an alkyloxy group attached through an alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms.

[0110] The term "alkylthio" (e.g. methylthio, ethylthio, propylthio, cyclohexenylthio and the like) represents a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms attached through a sulfur bridge. The term "alkylthioalkyl" represents an alkylthio group attached through an alkyl or substituted alkyl group as defined above having the indicated number of carbon atoms.

[0111] The term "alkylamino" (e.g. methylamino, diethylamino, butylamino, N-propyl-N-hexylamino, (2-cyclopentyl)propylamino, hexenylamino, and the like) represents one or two substituted or unsubstituted alkyl groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The substituted or unsubstituted alkyl groups maybe taken together with the nitrogen to which they are attached forming a saturated cyclic or unsaturated cyclic system containing 3 to 10 carbon atoms with at least one substituent as defined above. The term "alkylaminoalkyl" represents an alkylamino group attached through a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms.

[0112] The term "alkylhydrazino" (e.g. methylhydrazino, diethylhydrazino, butylhydrazino, (2-cyclopentyl)propylhydrazino, cyclohexanehydrazino, and the like) represents one or two substituted or unsubstituted alkyl groups as defined above having the indicated number of carbon atoms attached through a nitrogen atom of a hydrazine bridge. The substituted or unsubstituted alkyl groups maybe taken together with the nitrogen to which they are attached forming a saturated cyclic or unsaturated cyclic system containing 3 to 10 carbon atoms with at least one substituent as defined above. The term "alkylhydrazinoalkyl" represents an alkylhydrazino group attached through a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms.

[0113] The term "alkylcarbonyl" (e.g. cyclooctylcarbonyl, pentylcarbonyl, 3-hexenylcarbonyl and the like) represents a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms attached through a carbonyl group. The term "alkylcarbonylalkyl" represents an alkylcarbonyl group attached through a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms.

[0114] The term "alkylcarboxy" (e.g. heptylcarboxy, cyclopropylcarboxy, 3-pentenylcarboxy and the like) represents an alkylcarbonyl group as defined above wherein the carbonyl is in turn attached through an oxygen. The term "alkylcarboxyalkyl" represents an alkylcarboxy group attached through an alkyl group as defined above having the indicated number of carbon atoms.

[0115] The term "alkylcarbonylamino" (e.g. hexylcarbonylamino, cyclopentylcarbonyl-aminomethyl, methylcarbonylaminophenyl and the like) represents an alkylcarbonyl group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group. The nitrogen group may itself be substituted with a substituted or unsubstituted alkyl or aryl group. The term "alkylcarbonylaminoalkyl" represents an alkylcarbonylamino group attached through a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms.

[0116] The term "alkylcarbonylhydrazino" (e.g. ethylcarbonylhydrazino, tert-butylcarbonylhydrazino and the like) represents an alkylcarbonyl group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of a hydrazino group.

[0117] The term "aryl" represents an unsubstituted, mono-, di- or trisubstituted monocyclic, polycyclic, biaryl aromatic groups covalently attached at any ring position capable of forming a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art (e.g., 3-phenyl, 4-naphtyl and the like). The aryl substituents are independently selected from the group consisting of halogen, —OH, —SH, —CN, —NO_2, trihalomethyl, hydroxypyronyl, C_{1-10}alkyl, arylC_{0-10}alkyl, C_{0-10}alkyloxyC_{0-10}alkyl, arylC_{0-10}alkyloxyC_{0-10}alkyl, C_{0-10}alkylthioC_{0-10}alkyl, arylC_{0-10}alkylthioC_{0-10}alkyl, C_{0-10}alkylaminoC_{0-10}alkyl, arylC_{0-10}alkylaminoC_{0-10}alkyl, N-aryl-N—C_{0-10}alkylaminoC_{0-10}alkyl, C_{0-10}alkylcarbonylC_{0-10}alkyl, arylC_{0-10}alkylcarbonylC_{0-10}alkyl, C_{1-10}alkylcarboxyC_{0-10}alkyl, arylC_{0-10}alkylcarboxyC_{0-10}alkyl, C_{1-10}alkylcarbonylaminoC_{0-10}alkyl, arylC_{0-10}alkylcarbonylaminoC_{0-10}alkyl, —C_{0-10}alkylCOOR$_{21}$, and —C_{0-10}alkylCONR$_{22}$R$_{23}$ wherein R$_{21}$, R$_{22}$ and R$_{23}$ are independently selected from hydrogen, C_1-C_{10}alkyl, arylC_0-C_{10}alkyl, or R$_{22}$ and R$_{23}$ are taken together with the nitrogen to which they are attached forming a saturated cyclic or unsaturated cyclic system containing 3 to 8 carbon atoms with at least one substituent as defined above.

[0118] The definition of "aryl" includes but is not limited to phenyl, biphenyl, naphthyl, dihydronaphthyl, tetrahydronaphthyl, indenyl, indanyl, azulenyl, anthryl, phenanthryl, fluorenyl, pyrenyl and the like.

[0119] The term "arylalkyl" (e.g. (4-hydroxyphenyl)ethyl, (2-aminonaphthyl)hexenyl and the like) represents an aryl group as defined above attached through a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms.

[0120] The term "arylcarbonyl" (e.g. 2-thiophenylcarbonyl, 3-methoxyanthrylcarbonyl and the like) represents an aryl group as defined above attached through a carbonyl group.

[0121] The term "arylalkylcarbonyl" (e.g. (2,3-dimethoxyphenyl)propylcarbonyl, (2-chloronaphthyl)pentenyl-carbonyl and the like) represents an arylalkyl group as defined above wherein the alkyl group is in turn attached through a carbonyl.

[0122] The term "aryloxy" (e.g. phenoxy, naphthoxy, 3-methylphenoxy, and the like) represents an aryl or substituted aryl group as defined above having the indicated number of carbon atoms attached through an oxygen bridge. The term "aryloxyalkyl" represents an aryloxy group attached

through a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms.

[0123] The term "arylthio" (e.g. phenylthio, naphthylthio, 3-bromophenylthio, and the like) represents an aryl or substituted aryl group as defined above having the indicated number of carbon atoms attached through a sulfur bridge. The term "arylthioalkyl" represents an arylthio group attached through a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms.

[0124] The term "arylamino" (e.g. phenylamino, diphenylamino, naphthylamino, N-phenyl-N-naphthylamino, o-methylphenylamino, p-methoxyphenylamino, and the like) represents one or two aryl groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The term "arylaminoalkyl" represents an arylamino group attached through a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms. The term "arylalkylamino" represents an aryl group attached through an alkylamino group as defined above having the indicated number of carbon atoms. The term "N-aryl-N-alkylamino" (e.g. N-phenyl-N-methylamino, N-naphthyl-N-butylamino, and the like) represents one aryl and one a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms independently attached through an amine bridge.

[0125] The term "arylhydrazino" (e.g. phenylhydrazino, naphthylhydrazino, 4-methoxyphenylhydrazino, and the like) represents one or two aryl groups as defined above having the indicated number of carbon atoms attached through a hydrazine bridge. The term "arylhydrazinoalkyl" represents an arylhydrazino group attached through a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms. The term "arylalkylhydrazino" represents an aryl group attached through an alkylhydrazino group as defined above having the indicated number of carbon atoms. The term "N-aryl-N-alkylhydrazino" (e.g. N-phenyl-N-methylhydrazino, N-naphthyl-N-butylhydrazino, and the like) represents one aryl and one a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms independently attached through an amine atom of a hydrazine bridge.

[0126] The term "arylcarboxy" (e.g. phenylcarboxy, naphthylcarboxy, 3-fluorophenylcarboxy and the like) represents an arylcarbonyl group as defined above wherein the carbonyl is in turn attached through an oxygen bridge. The term "arylcarboxyalkyl" represents an arylcarboxy group attached through a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms.

[0127] The term "arylcarbonylamino" (e.g. phenylcarbonylamino, naphthylcarbonylamino, 2-methylphenylcarbonylamino and the like) represents an arylcarbonyl group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group. The nitrogen group may itself be substituted with an a substituted or unsubstituted alkyl or aryl group. The term "arylcarbonylaminoalkyl" represents an arylcarbonylamino group attached through a substituted or unsubstituted alkyl group as defined above having the indicated number of carbon atoms. The nitrogen group may itself be substituted with a substituted or unsubstituted alkyl or aryl group.

[0128] The term "arylcarbonylhydrazino" (e.g. phenylcarbonylhydrazino, naphthylcarbonylhydrazino, and the like) represents an arylcarbonyl group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of a hydrazino group.

[0129] The terms "heteroaryl", "heterocycle," or "heterocyclic" refers to a monovalent unsaturated group having a single ring or multiple condensed rings, from 1 to 8 Carbon atoms and from 1 to 4 hetero atoms selected from nitrogen, sulfur or oxygen within the ring. For the purposes of this application, the terms "heteroaryl," "heterocycle," or "heterocyclic" do not include carbohydrate rings (i.e. mono- or oligosaccharides).

[0130] Unless otherwise constrained by the definition for the "heteroaryl" substituent, such heterocyclic groups can be optionally substituted with 1 to 3 substituents selected from the group consisting of: halogen, —OH, —SH, —CN, —NO_2, trihalomethyl, hydroxypyronyl, $C_{1\text{-}10}$alkyl, aryl$C_{0\text{-}10}$alkyl, $C_{0\text{-}10}$alkyloxy$C_{0\text{-}10}$alkyl, aryl$C_{0\text{-}10}$alkyloxy$C_{0\text{-}10}$alkyl, $C_{0\text{-}10}$alkylthio$C_{0\text{-}10}$alkyl, aryl$C_{0\text{-}10}$alkylthio$C_{0\text{-}10}$alkyl, $C_{0\text{-}10}$alkylamino$C_{0\text{-}10}$alkyl, aryl$C_{0\text{-}10}$alkylamino$C_{0\text{-}10}$alkyl, N-aryl-N—$C_{0\text{-}10}$alkylamino$C_{0\text{-}10}$alkyl, $C_{1\text{-}10}$alkylcarbonyl$C_{0\text{-}10}$alkyl, aryl$C_{0\text{-}10}$alkylcarbonyl$C_{0\text{-}10}$alkyl, $C_{1\text{-}10}$alkylcarboxy$C_{0\text{-}10}$alkyl, aryl$C_{0\text{-}10}$alkylcarboxy$C_{0\text{-}10}$alkyl, $C_{1\text{-}10}$alkylcarbonylamino$C_{0\text{-}10}$alkyl, aryl$C_{0\text{-}10}$alkylcarbonylamino$C_{0\text{-}10}$-alkyl, —$C_{0\text{-}10}$alkyl$COOR_{21}$, and —$C_{0\text{-}10}$alkyl$CONR_{22}R_{23}$ wherein R_{21}, R_{22} and R_{23} are independently selected from hydrogen, C_1-C_{10}alkyl, arylC_0-C_{10}alkyl, or R_{22} and R_{23} are taken together with the nitrogen to which they are attached forming a saturated cyclic or unsaturated cyclic system containing 3 to 8 carbon atoms with at least one substituent as defined above.

[0131] The definition of "heteroaryl" includes but is not limited to thienyl, benzothienyl, isobenzothienyl, 2,3-dihydrobenzothienyl, furyl, pyranyl, benzofuranyl, isobenzofuranyl, 2,3-dihydrobenzofuranyl, pyrrolyl, maleimidyl (or pyrrolyl-2,5-dione), 3-pyrrolinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, indolizinyl, indazolyl, phthalimidyl (or isoindoly-1,3-dione), imidazolyl, 2H-imidazolinyl, benzimidazolyl, pyridyl, pyrazinyl, pyradazinyl, pyrimidinyl, triazinyl, quinolyl, isoquinolyl, 4H-quinolizinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromanyl, benzodioxolyl, piperonyl, purinyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, benzthiazolyl, oxazolyl, isoxazolyl, benzoxazolyl, oxadiazolyl, thiadiazolyl and the like.

[0132] The term "saturated heterocyclic" represents an unsubstituted, mono-, di- or trisubstituted monocyclic, polycyclic saturated heterocyclic group covalently attached at any ring position capable of forming a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art (e.g., 1-piperidinyl, 4-piperazinyl and the like).

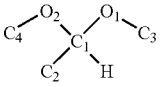
[0133] The saturated heterocyclic substituents are independently selected from the group consisting of halo, —OH, —SH, —CN, —NO_2, trihalomethyl, hydroxypyronyl, $C_{1\text{-}10}$alkyl, aryl$C_{0\text{-}10}$alkyl, $C_{0\text{-}10}$alkyloxy$C_{0\text{-}10}$alkyl, aryl$C_{0\text{-}10}$alkyloxy$C_{0\text{-}10}$alkyl, $C_{0\text{-}10}$alkylthio$C_{0\text{-}10}$alkyl, aryl$C_{0\text{-}10}$alkylthio$C_{0\text{-}10}$alkyl, $C_{0\text{-}10}$alkylamino$C_{0\text{-}10}$alkyl, aryl$C_{0\text{-}10}$alkylamino$C_{0\text{-}10}$alkyl, N-aryl-N—$C_{0\text{-}10}$alkylamino$C_{0\text{-}10}$alkyl, $C_{1\text{-}10}$alkylcarbonyl$C_{0\text{-}10}$alkyl, aryl$C_{0\text{-}10}$alkylcarbonyl$C_{0\text{-}10}$alkyl, $C_{1\text{-}10}$alkylcarboxy$C_{0\text{-}10}$alkyl, aryl$C_{0\text{-}10}$alkylcarboxy$C_{0\text{-}10}$alkyl, $C_{1\text{-}10}$alkylcarbonylamino$C_{0\text{-}10}$alkyl, aryl$C_{0\text{-}10}$alkylcarbonylamino$C_{0\text{-}10}$alkyl, —$C_{0\text{-}10}$alkyl$COOR_{21}$, and —$C_{0\text{-}10}$alkyl$CONR_{22}R_{23}$ wherein R_{21},

R_{22} and R_{23} are independently selected from hydrogen, C_1-C_{10}alkyl, arylC_0-C_{10}alkyl, or R_{22} and R_{23} are taken together with the nitrogen to which they are attached forming a saturated cyclic or unsaturated cyclic system containing 3 to 8 carbon atoms with at least one substituent as defined above.

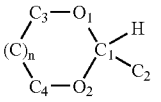
[0134] The definition of saturated heterocyclic includes but is not limited to pyrrolidinyl, pyrazolidinyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithienyl, thiomorpholinyl, piperazinyl, quinuclidinyl and the like.

[0135] The term "alpha-beta-unsaturated carbonyl" refers to a molecule that has a carbonyl group directly attached to a double or triple bonded carbon and which would be obvious to one of ordinary skill and knowledge in the art. The definition of alpha-beta-unsaturated carbonyl includes but is not limited to acrolein, methyl vinyl ketone, and the like.

[0136] The term "acetal" refers to a molecule that contains a carbon atom Cl that is directly attached to a hydrogen atom (Hi), a substituted carbon atom (C_2-) and two oxygen atoms (O_1 and O_2). These oxygen atoms are in turn attached to other substituted carbon atoms (C_3 and C_4), which would be obvious to one of ordinary skill and knowledge in the art. The definition of acetal includes but is not limited to 1,1-dimethoxypropane, 1,1-bis-allyloxybutane and the like.

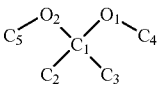


[0137] The term "cyclic acetal" refers to an acetal as defined above where C_3 and C_4, together with the Oxygen atoms to which they are attached, combine thru an alkyl bridge to form a 5- to 10-membered ring, which would be obvious to one of ordinary skill and knowledge in the art. The definition of cyclic acetal includes but is not limited to 2-methyl-[1,3]dioxolane, 2-ethyl-[1,3]dioxane, 2-phenyl-[1,3]dioxane, 2 2-phenyl-hexahydro-pyrano[3,2-d][1,3]dioxine and the like.

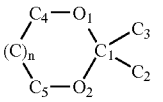


n = 1 to 5

[0138] The term "ketal" refers to a molecule that contains a carbon atom C_1 that is directly attached to two substituted carbon atom (C_2 and C_3) and two oxygen atoms (O_1 and O_2). These oxygen atoms are in turn attached to other substituted carbon atoms (C_4 and C_5), which would be obvious to one of ordinary skill and knowledge in the art. The definition of acetal includes but is not limited to 2,2-dimethoxy-butane, 3,3-diethoxy-pentane and the like.



[0139] The term "cyclic ketal" refers to a ketal as defined above where C_4 and C_5, together with the oxygen atoms to which they are attached, combine thru an alkyl bridge to form a 5- to 10-membered ring, which would be obvious to one of ordinary skill and knowledge in the art. The definition of cyclic acetal includes but is not limited to 2,2,4,5-tetramethyl-[1,3]dioxolane, 2,2-diethyl-[1,3]dioxepane, 2,2-dimethyl-hexahydro-pyrano[3,2-d][1,3]dioxine and the like.



n = 1 to 5

[0140] A "C-carboxy" group refers to a —C(═O)OR groups where R is as defined herein. An "acetyl" group refers to a —C(═O)CH_3, group. A "trihalomethanesulfonyl" group refers to a $X_3CS(═O)_2$— group where X is a halogen. A "cyano" group refers to a —CN group. An "isocyanato" group refers to a —NCO group. A "thiocyanato" group refers to a —CNS group. An "isothiocyanato" group refers to a —NCS group. A "sulfinyl" group refers to a —S(═O)—R group, with R as defined herein. A "S-sulfonamido" group refers to a —S(═O)$_2$NR, group, with R as defined herein. A "N-sulfonamido" group refers to a RS(═O)$_2$NH— group with R as defined herein. A "trihalomethanesulfonamido" group refers to a $X_3CS(═O)_2NR$— group with X and R as defined herein. An "O-carbamyl" group refers to a —OC(═O)—NR, group-with R as defined herein. An "N-carbamyl" group refers to a ROC(═O)NH— group, with R as defined herein. An "O-thiocarbamyl" group refers to a —OC(═S)—NR, group with R as defined herein. An "N-thiocarbamyl" group refers to an ROC(═S)NH— group, with R as defined herein. A "C-amido" group refers to a —C(═O)—NR_2 group with R as defined herein. An "N-amido" group refers to a RC(═O)NH— group, with R as defined herein. The term "perhaloalkyl" refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

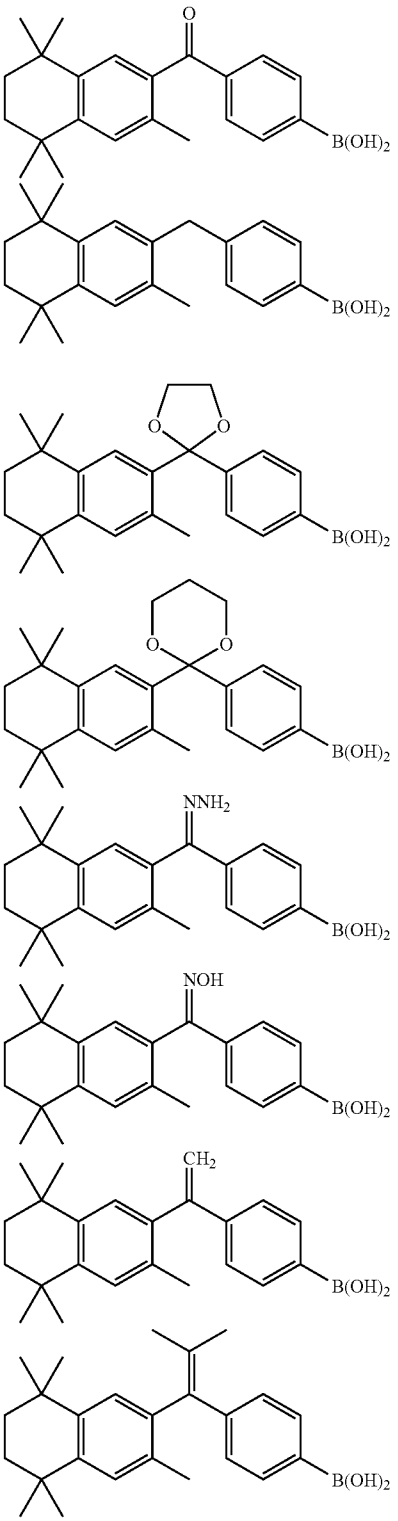
[0141] The term "pharmaceutical composition" refers to a mixture of a compound disclosed herein with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to, oral, injection, aerosol, parenteral, and topical administration. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0142] The term "carrier" defines a chemical compound that facilitates the incorporation of a compound into cells or tissues. For example dimethyl sulfoxide (DMSO) is a commonly utilized carrier as it facilitates the uptake of many organic compounds into the cells or tissues of an organism.

[0143] The term "diluent" defines chemical compounds diluted in water that will dissolve the compound of interest as well as stabilize the biologically active form of the compound. Salts dissolved in buffered solutions are utilized as diluents in the art. One commonly used buffered solution is phosphate buffered saline because it mimics the salt conditions of human blood. Since buffer salts can control the pH of

a solution at low concentrations, a buffered diluent rarely modifies the biological activity of a compound.

[0144] Invention compounds according to structural formula A include



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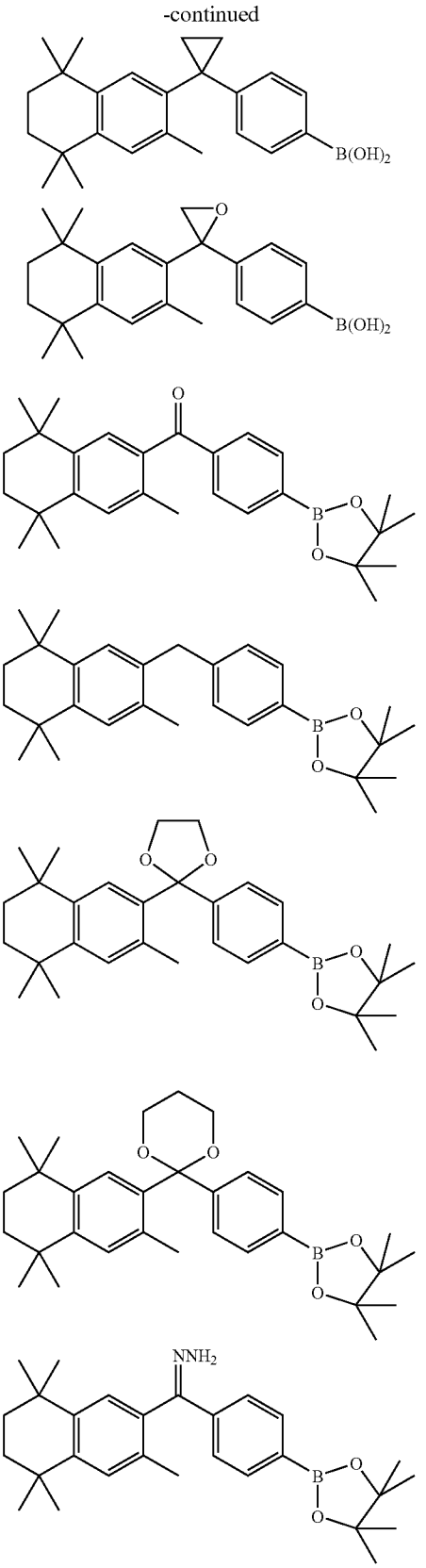

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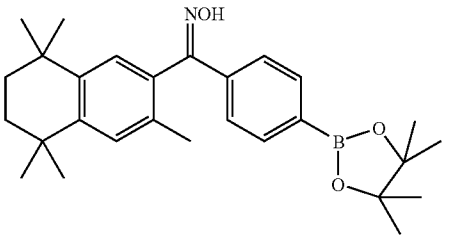

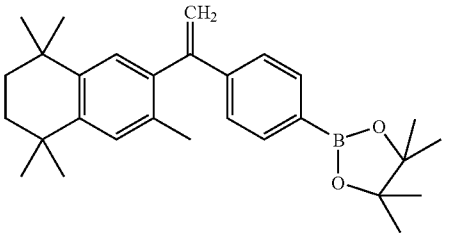

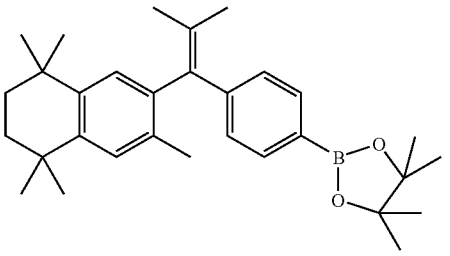

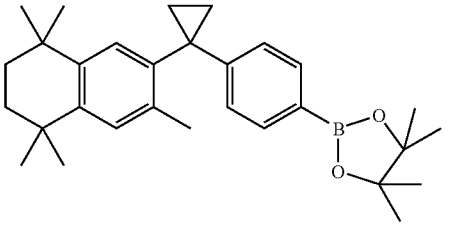

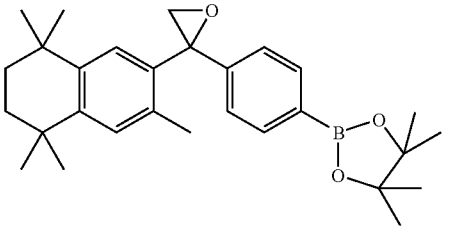

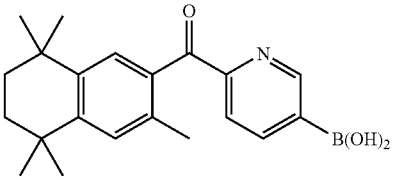

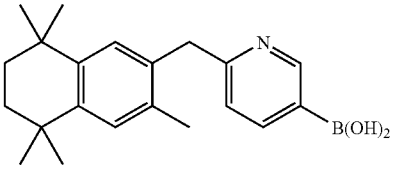

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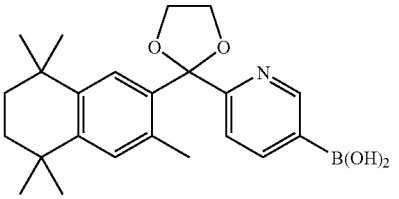

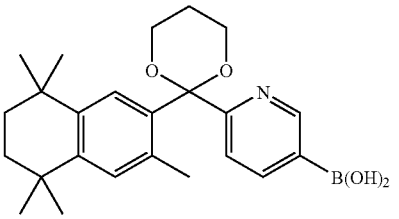

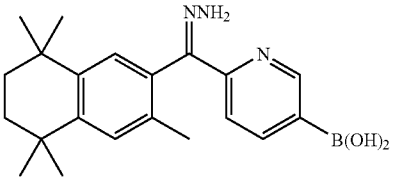

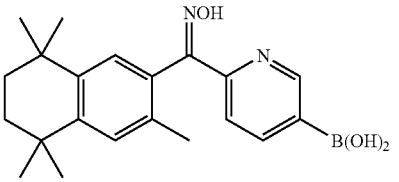

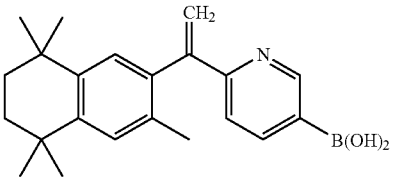

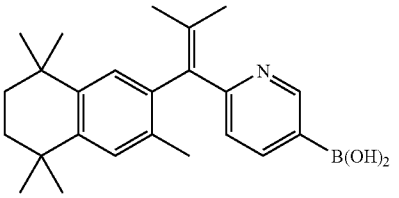

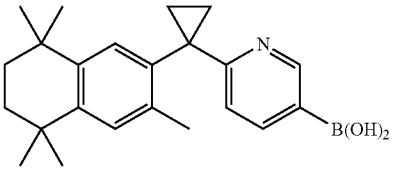

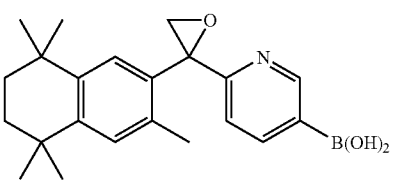

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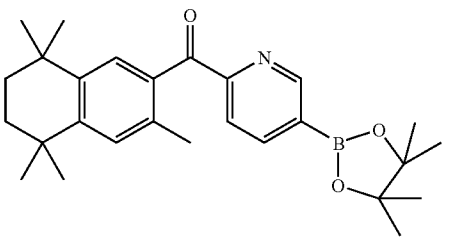

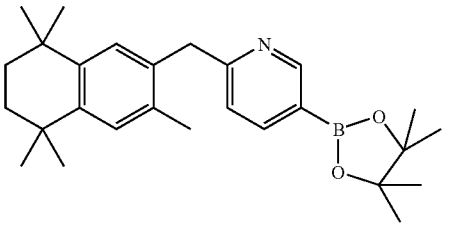

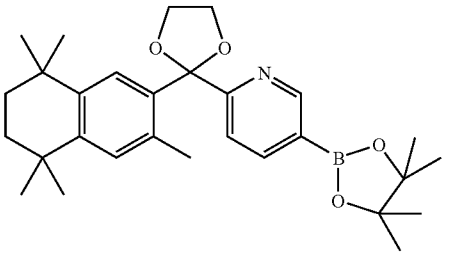

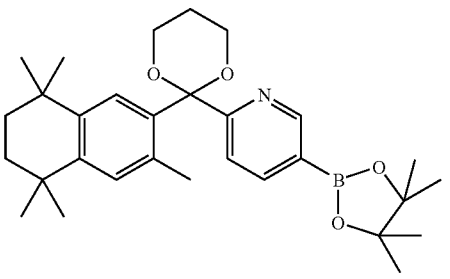

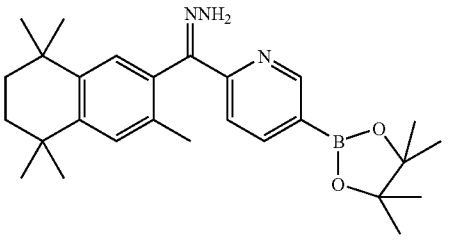

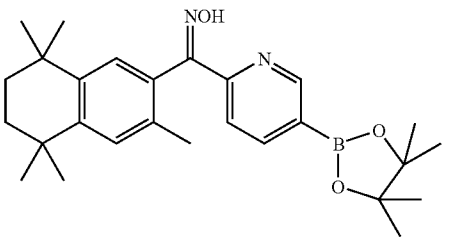

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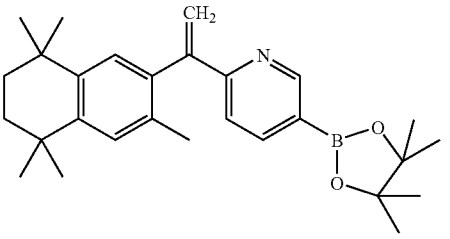
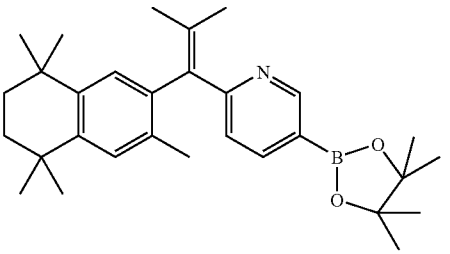
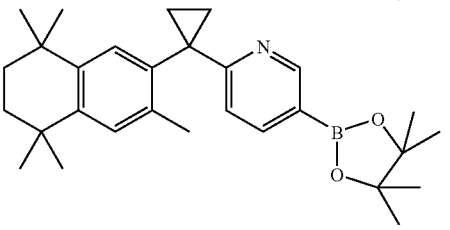
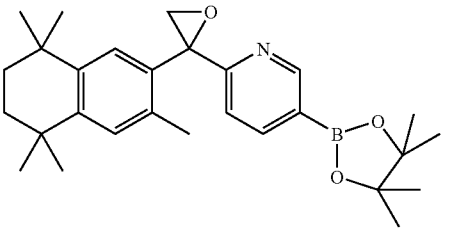








and pharmaceutically acceptable salts, solvates, and prodrugs thereof.

[0145] In another embodiment of the invention, there are provided pharmaceutical compositions comprising at least one of the compounds of the invention, as well as pharmaceutically acceptable pro-drugs and salts of such compounds, in a pharmaceutically acceptable vehicle, for enteral, parenteral, topical or ocular administration.

[0146] In another embodiment of the invention, there are provided pharmaceutical compositions comprising an effective regulating amount of at least one of the compounds of the invention in combination with a pharmaceutically acceptable carrier, for control of cellular processes, cellular differentiation, cellular proliferation or apoptosis.

[0147] In another embodiment of the invention, there are provided pharmaceutical compositions comprising in a pharmaceutically acceptable vehicle suitable for enteral, parenteral, or topical administration, one or more compounds of the invention for treating a mammalian subject wherein said wherein said compound exerts its therapeutic effects via the in vivo modulation of lipid metabolism, lipid homeostasis, hyperlipidemia, skin-related processes, autoimmune diseases, fatty acid metabolism, malignant cell development, premalignant lesions, programmed cell death, endocrinological processes, or AP-1 metabolism.

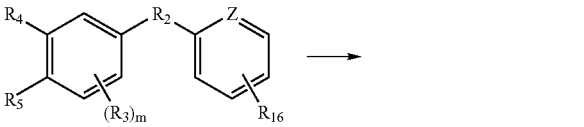
[0148] In another embodiment of the invention, there are provided pharmaceutical compositions comprising at least one of the compounds of the invention, in a pharmaceutically acceptable vehicle, for the treatment of carcinomas. Examples of carcinomas include mammary cancer, prostate cancer, kidney cancer, Karposi's sarcoma, colon cancer, cervical cancer, lung cancer, cutaneous T-cell lymphoma, cancer of the head and neck, cancers of the aerodigestive pathway, skin cancer, bladder cancer, sarcomas, leukoplakias, acute promyelocytic leukemia, and the like.

[0149] In another embodiment of the invention, there are provided pharmaceutical compositions comprising at least one the compounds of the invention in combination with other chemotherapeutic agents, in a pharmaceutically acceptable vehicle, for the treatment of carcinomas. Examples of chemotherapeutic agents contemplated for use in the practice of this particular invention include Busulfan, Carboplatin, Cisplatin, Cyclophosphamide, Cytosine arabinoside, Etoposide, 5-Fluorouracil, Melphalan, Methotrexate, Mitoxantrone, Taxol, Gemzar, Irinotican, Interferon, Fareston, Arzoxifene, Evista, Tamoxifen, and the like.

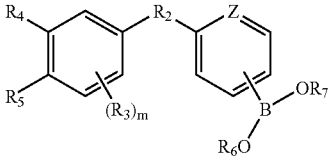
[0150] In another embodiment of the invention, there are provided pharmaceutical compositions comprising at least one the compounds of the invention in combination with one or more antiestrogenic agents, in a pharmaceutically acceptable vehicle, for the treatment of mammary carcinoma. Examples of antiestrogenic agents contemplated for use in the practice of this particular invention include Fareston, Arzoxifene, Evista, Tamoxifen, and the like.

[0151] In another embodiment of the invention, there are provided cosmeceutical compositions comprising at least one the compounds of the invention, in a cosmetically acceptable vehicle, for dermal indications.

[0152] In another embodiment, the present invention provides a process for preparing a compound of formula D. Such a process can be performed, for example, by contacting a compound of formula C with a Boron contain compound under conditions suitable to form compound of formula D, as set forth below:

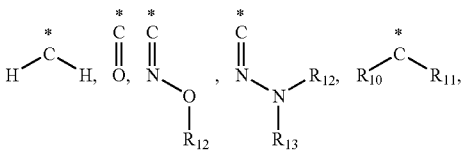


C



D

[0153] In the scheme shown above, Z is typically —CH or nitrogen, R_2 is typically



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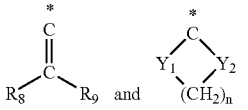


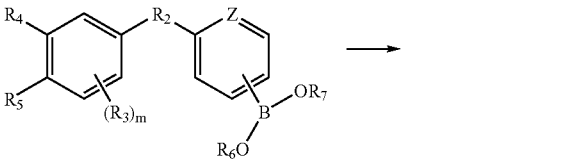
[0154] wherein R_3 is alkyl, alkyloxy, or halogen; R_4 is alkyl, aryl, heteroaryl, or adamantyl; R_5 is alkyl, alkyloxy, alkylthio, aryl, or heteroaryl; or R_4 and R_5 may be linked together to form a substituted or unsubstituted 5- or 6-membered cycloalkyl or cycloalkenyl ring, where said substituents are selected from the group consisting of —OH, =O, halogen, alkyl, and where 1 or 2 of the carbon atoms on said 5- or 6-membered cycloalkyl or cycloalkenyl ring may be optionally replaced by W where W is selected from the group consisting of O, S, N, NH, alkylamino, or arylamino; R_6 and R_7 are selected from the group consisting of alkyl, aryl and heteroaryl; R_6 and R_7 may be linked together to form a substituted or unsubstituted 5- or 6-membered cycloalkyl or cycloalkenyl ring, where said substituents are described as herein. R_5, R_9, R_{10} and R_{11} are independently selected from the group consisting of hydrogen, halogen and alkyl, R_{12} and R_{13} are independently selected from the group consisting of hydrogen, alkyl, aryl, and heteroaryl, Y_1 and Y_2 are independently O, S, NH, or CH_2, or Y_1 is O, S or NH, and Y_2 is CH_2, with the proviso that Y_1 and Y_2 cannot both be O, S, or NH if n is 0 or 1, R_{16} is halogen, alkyl sulfonate, or aryl sulfonate; m and n are independently 0, 1, 2 or 3, and * represents the point of attachment of R_2 to the molecules of formula C and D.

[0155] Solvents contemplated for use in the practice of this particular invention process are typically ethereal solvents, such as for example, diethyl ether, dioxane, tetrahydrofuran, and the like, aromatic solvents, such as for example, toluene, benzene, and the like, and alcoholic solvents, such as for example, tert-butanol and the like, or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about 0° C. up to about 500° C., for 0.5 to 240 hours, at a pH in the range of about 7 up to about 12, and at a pressure in the range of about 1 mBar up to about 350 Bar.

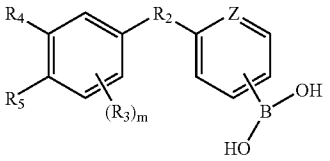
[0156] Compound C is typically contacted with a boron containing compound in the presence of a mixture of a palladium catalyst and a base. Palladium catalysts contemplated for use in the practice of this particular invention process include palladium (II) species such as for example palladium (II) acetate, tris(dibenzylideneacetone)-dipalladium, palladium (II) acetylacetonate, palladium (II) bromide, palladium (II) chloride, palladium (II) hexafluoroacetylacetonate, palladium (II) sulfate, palladium (II) trifluoroacetate, dichloro [1,1'-bis(diphenylphosphino)-ferrocene]palladium (II) dichloromethane adduct ($PdCl_2$(dppf)) and the like. Bases contemplated for use in the practice of this particular invention process include potassium acetate, sodium acetate, sodium tert-butoxide, potassium tert-butoxide, cesium carbonate, potassium carbonate, sodium carbonate, potassium phosphate tribasic (K_3PO_4), and the like. Boron containing compounds contemplated for use in the practice of this particular invention include optionally substituted [2,2']-bi-[1,3,2]-dioxaborolanes, optionally substituted [2,2']-bi-[1,3,2]-dioxaborinanes, diboron pinacol ester, 2,2'-bi-1,3,2-benzodioxaborole, bis(neopentyl glycolato)diboron, bis(diethyl-L-tartrate glycolato)diboron, bis(diethyl-L-tartrateglycolato)diboron, bis(diethyl-D-tartrate glycolato) diboron, bis(diisopropyl-D-tartrateglycolato)diboron, bis(di-

isopropyl-L-tartrateglycolato)diboron, bis(m,n,n',n'-tetramethyl-D-tartramideglycolato)diboron, bis(m,n,n',n'-tetramethyl-L-tartramideglycolato)diboron, bis(hexyleneglycolato)diboron, bis(m,n,n',n'-tetramethyl-D-tartaramideglycolato)diboron, bis(m,n,n',n'-tetramethyl-L-tartaramideglycolato)diboron, bis[(−)-pinanediolato]diboron, catecholborane, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, (+)-pinaneborane, 4,4,6-trimethyl-1

[0157] In another embodiment, the present invention provides a process for preparing a compound of formula E. Such a process can be performed, for example, by contacting a compound of formula D under conditions suitable to form compound of formula E, as set forth below:

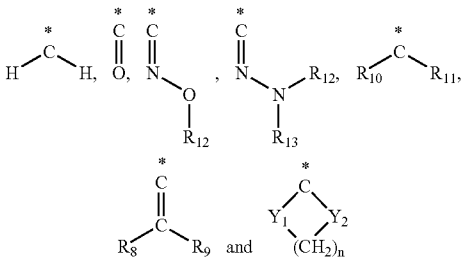


D



E

[0158] In the scheme shown above, Z is typically —CH or nitrogen, R_2 is typically



wherein R_3 is alkyl, alkyloxy, or halogen; R_4 is alkyl, aryl, heteroaryl, or adamantyl; R_5 is alkyl, alkyloxy, alkylthio, aryl, or heteroaryl; or R_4 and R_5 may be linked together to form a substituted or unsubstituted 5- or 6-membered cycloalkyl or cycloalkenyl ring, where said substituents are selected from the group consisting of —OH, =O, halogen, alkyl, and where 1 or 2 of the carbon atoms on said 5- or 6-membered cycloalkyl or cycloalkenyl ring may be optionally replaced by W where W is selected from the group consisting of O, S, N, NH, alkylamino, or arylamino; R_8, R_5, R_{10} and R_{11} are independently selected from the group consisting of hydrogen, halogen and alkyl, R_{12} and R_{13} are independently selected from the group consisting of hydrogen, alkyl, aryl, and heteroaryl, Y_1 and Y_2 are independently O, S, NH, or CH_2, or Y_1 is O, S or NH, and Y_2 is CH_2, with the proviso that Y_1 and Y_2 cannot both be O, S, or NH if n is 0 or 1; m and n are independently 0, 1, 2 or 3, and * represents the point of attachment of R_2 to the molecules of formula D and E.

[0159] Solvents contemplated for use in the practice of this particular invention process are typically diethyl ether, acetonitrile, acetone, dioxane, tetrahydrofuran, toluene, benzene, dichloromethane, water, and the like or any suitable mixtures thereof. The process is typically carried out at a temperature in the range of about 0° C. up to about 500° C., for 0.5 to 240 hours, at a pH in the range of about 0.1 up to about 7, and at a pressure in the range of about 1 mBar up to about 350 Bar.

[0160] Compound D is typically contacted with a mixture of an additive and a boron containing compound, where the additive contemplated for use in the practice of this particular invention include an acid, a Lewis acid, trifluoroacetic acid, acetic acid, hydrochloric acid, ammonium acetate, sodium periodate, and the like, and the boron containing compound contemplated for use in the practice of this particular invention include an alkyl boronic acid, aryl boronic acid, heteroaryl boronic acid, polymer supported boronic acid, polystyrene boronic acid, and the like.

[0161] Certain pharmaceutically acceptable salts of the invention are prepared by treating the novel compounds of the invention with an appropriate amount of pharmaceutically acceptable base. Representative pharmaceutically acceptable bases are ammonium hydroxide, sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, magnesium hydroxide, ferrous hydroxide, zinc hydroxide, copper hydroxide, aluminum hydroxide, ferric hydroxide, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, lysine, arginine, histidine, and the like. The reaction is conducted in water, alone or in combination with an inert, water-miscible organic solvent, at a temperature of from about 0° C. to about 100° C., preferably at room temperature. The molar ratio of compounds of structural formula A to base used is chosen to provide the ratio desired for any particular salts. For preparing, for example, the ammonium salts of the starting material, compounds of formula A can be treated with approximately one equivalent of the pharmaceutically acceptable base to yield a neutral salt. When calcium salts are prepared, approximately one-half a molar equivalent of base is used to yield a neutral salt, while for aluminum salts, approximately one-third a molar equivalent of base will be used.

[0162] The compounds of the invention according to formula A, including the pharmacologically acceptable prodrugs or salts thereof, are useful to elicit, modulate and/or regulate selective gene expression by cellular receptors and provide control over cellular growth, proliferation and differentiation processes regulated by certain hormones or vitamins such as for example all-trans-retinoic acid, 13-cis-retinoic acid, 9-cis-retinoic acid, vitamin D, thyroid hormone and the like. As noted above, the compounds of the invention are thus useful in the treatment of conditions and/or diseases that are regulated by the aforementioned entities. Examples of such conditions include for example cancer, mammary cancer, prostate cancer, kidney cancer, Karposi's sarcoma, colon cancer, cervical cancer, lung cancer, cutaneous T-cell lymphoma, cancer of the head and neck, cancers of the aerodigestive pathway, skin cancer, bladder cancer, sarcomas, leukoplakias, acute promyelocytic leukemia, acne, psoriasis, aging, wrinkling, diabetes, hyperglycemia, bone calcification, thyroid conditions, and the like

[0163] The compounds of the invention may be conveniently formulated into pharmaceutical compositions composed of one or more of the compounds together with a

pharmaceutically acceptable carrier as described in Remington's Pharmaceutical Sciences, latest edition, by E. W. Martin (Mack Publ. Co., Easton Pa.).

[0164] The compounds of the invention may be administered orally, parenterally (e.g., intravenously), by intramuscular injection, by intraperitoneal injection, topically, transdermally, or the like, although oral or topical administration is typically preferred. The amount of active compound administered will, of course, be dependent on the subject being treated, the subject's weight, the manner of administration and the judgment of the prescribing physician. The dosage will be in the range of about 2 microgram per kilogram per day to 4 milligram per kilogram per day.

[0165] Depending on the intended mode of administration, the pharmaceutical compositions may be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, lotions, creams, gels and the like, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include, as noted above, an effective amount of the selected drug in combination with a pharmaceutically acceptable carrier and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents and the like.

[0166] For solid compositions, conventional non-toxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmaceutically administrable-compositions can, for example, be prepared by dissolving, dispersing, etc., an active compound as described herein and optional pharmaceutical adjuvants in an excipient, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, referenced above.

[0167] For oral administration, fine powders or granules may contain diluting, dispersing, and/or surface active agents, and may be presented in water or in a syrup, in capsules or sachets in the dry state, or in a non-aqueous solution or suspension wherein suspending agents may be included, in tablets wherein binders and lubricants may be included, or in a suspension in water or a syrup. Wherever required, flavoring, preserving, suspending, thickening, or emulsifying agents may also be included. Tablets and granules are preferred oral administration forms, and these may be coated.

[0168] Parenteral administration, if used, is generally characterized by injection. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, as emulsions, or as sustained release delivery system.

EXAMPLES

[0169] Used herein, the following abbreviations have the following meanings: Me refers to methyl (CH_3—), Et refers to ethyl (CH_3CH_2—), i-Pr refers to isopropyl ((CH_3)$_2CH_2$—), t-Bu or tert-butyl refers to tertiary butyl ((CH_3)$_3CH$—), Ph refers to phenyl, Bn refers to benzyl ($PhCH_2$—), Bz refers to benzoyl (PhCO—), MOM refers to methoxymethyl, Ac refers to acetyl, TMS refers to trimethylsilyl, TBS refers to ter-butyldimethylsilyl, Ms refers to methanesulfonyl (CH_3SO_2—), Ts refers to p-toluenesulfonyl (p-CH_3PhSO_2—), Tf refers to trifluoromethanesulfonyl (CF_3SO_2—), TfO refers to trifluoromethanesulfonate (CF_3SO_3—), DMF refers to N,N-dimethylformamide, DCM refers to dichloromethane (CH_2Cl_2), THF refers to tetrahydrofuran, EtOAc refers to ethyl acetate, Et_2O refers to diethyl ether, MeCN refers to acetonitrile (CH_3CN), NMP refers to 1-N-methyl-2-pyrrolidinone, DMA refers to N,N-dimethylacetamide, DMSO refers to dimethylsulfoxide, DCC refers to 1,3-dicyclohexyldicarbodiimide, EDCI refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, Boc refers to tert-butylcarbonyl, Fmoc refers to 9-fluorenylmethoxycarbonyl, TBAF refers to tetrabutylammonium fluoride, TBAI refers to tetrabutylammonium iodide, TMEDA refers to N,N,N,N-tetramethylethylene diamine, Dess-Martin periodinane or Dess Martin reagent refers to 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one, DMAP refers to 4-N,N-dimethylaminopyridine, (i-Pr)$_2$NEt or DIEA or Hunig's base refers to N,N-diethylisopropylamine, DBU refers to 1,8-Diazabicyclo [5.4.0]undec-7-ene, $(DHQ)_2AQN$ refers to dihydroquinine anthraquinone-1,4-diyl diether, $(DHQ)_2PHAL$ refers to dihydroquinine phthalazine-1,4-diyl diether, $(DHQ)_2PYR$ refers to dihydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQD)_2AQN$ refers to dihydroquinidine anthraquinone-1,4-diyl diether, $(DHQD)_2PHAL$ refers to dihydroquinidine phthalazine-1,4-diyl diether, $(DHQD)_2PYR$ refers to dihydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether, LDA refers to lithium diisopropylamide, LiTMP refers to lithium 2,2,6,6-tetramethylpiperidinamide, n-BuLi refers to n-butyllithium, t-BuLi refers to tert-butyl lithium, IBA refers to 1-hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide, OsO_4 refers to osmium tetroxide, m-CPBA refers to meta-chloroperbenzoic acid, DMD refers to dimethyl dioxirane, PDC refers to pyridinium dichromate, NMO refers to N-methyl morpholine-N-oxide, NaHMDS refers to sodium hexamethyldisilazide, LiHMDS refers to lithium hexamethyldisilazide, HMPA refers to hexamethylphosphoramide, TMSCl refers to trimethylsilyl chloride, TMSCN refers to trimethylsilyl cyanide, TBSCl refers to tert-butyldimethylsilyl chloride, TFA refers to trifluoroacetic acid, TFAA refers to trifluoroacetic anhydride, AcOH refers to acetic acid, Ac_2O refers to acetic anhydride, AcCl refers to acetyl chloride, TsOH refers to p-toluenesulfonic acid, TsCl refers to p-toluenesulfonyl chloride, MBHA refers to 4-methylbenzhydrylamine, BHA refers to benzhydrylamine, $ZnCl_2$ refers to zinc (II) dichloride, BF_3 refers to boron trifluoride, $Y(OTf)_2$ refers to yttrium (III) trifluoromethanesulfonate, $Cu(BF_4)_2$ refers to copper (II) tetrafluoroborate, LAH refers to lithium aluminum hydride ($LiAlH_4$), $NaHCO_3$ refers to sodium bicarbonate, K_2CO_3 refers to potassium carbonate, NaOH refers to sodium hydroxide, KOH refers to potassium hydroxide, LiOH refers to lithium hydroxide, HCl refers to hydrochloric acid, H_2SO_4 refers to sulfuric acid, $MgSO_4$ refers to magnesium sulfate, and Na_2SO_4 refers to sodium sulfate. ^{1}H-NMR refers to proton nuclear magnetic resonance, ^{13}C NMR-refers to carbon 13 nuclear magnetic resonance, NOE refers to nuclear overhauser effect, NOESY refers to nuclear overhauser and exchange spectroscopy, COSY refers to homonuclear correlation spectroscopy, HMQC refers to proton detected hetero-

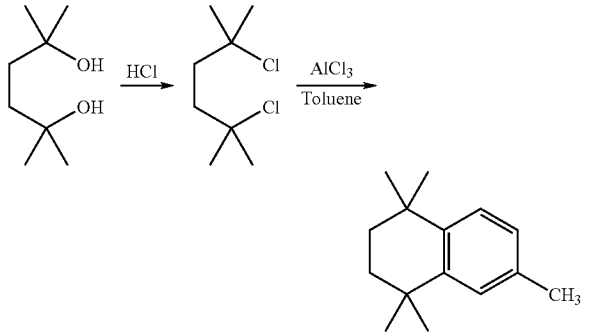
nuclear multiplet-quantum coherence, HMBC refers to heteronuclear multiple-bond connectivity, s refers to singlet, br s refers to broad singlet, d refers to doublet, br d refers to broad doublet, t refers to triplet, q refers to quartet, dd refers to double doublet, m refers to multiplet, ppm refers to parts per million, IR refers to infrared spectrometry, MS refers to mass spectrometry, HRMS refers to high resolution mass spectrometry, EI refers to electron impact, FAB refers to fast atom bombardment, CI refers to chemical ionization, HPLC refers to high pressure liquid chromatography, TLC refer to thin layer chromatography, R_f refers to, R_t refers to retention time, GC refers to gas chromatography, min is minutes, h is hours, rt or RT is room temperature, g is grams, mg is milligrams, L is liters, mL is milliliters, mol is moles and mmol is millimoles.

[0170] For all of the following examples, standard work-up and purification methods can be utilized and will be obvious to those skilled in the art. Synthetic methodologies that make up the invention are shown in Schemes 1-4. These Schemes are intended to describe the applicable chemistry through the use of specific examples and are not indicative of the scope of the invention.

Example 1

1,1,4,4,6-pentamethyl-1,2,3,4-tetrahydronaphthalene

[0171]



[0172] To 2,5-dimethyl-2,5-hexanediol (10 g, 68.5 mmol) in a 500 mL flask was added reagent grade concentrated HCl (150 mL) and the solution was stirred at ambient temperature for 1 h. Water (100 mL) and CH_2Cl_2 (100 mL) were then added slowly and the layers were separated. The aqueous layer was washed with additional CH_2Cl_2 (100 mL). The combined organic layers were dried over $MgSO_4$ and filtered thru silica gel pad. The solvent was removed to yield 10.9 g (87%) of 2,5-dichloro-2,5-dimethylhexane. The dichloride was dissolved in 150 mL of CH_2Cl_2 and 9.6 mL of toluene (90 mmol) was added. $AlCl_3$ (390 mg, 2.9 mol) was added in portions over 5 min at ambient temperature. HCl is evolved and the solution turns dark red. The reaction was placed in an ice-bath and quenched with deionized water (120 mL). Hexane (150 μL) was added and the organic layer was removed. The aqueous layer was washed with additional hexane (150 mL). The combined organic layers were washed with water (200 mL) and brine (100 mL) and dried over $MgSO_4$. The solvent was removed in vacuo to give 1,1,4,4,6-pentamethyl-1,2,3,4-tetrahydronaphthalene as a colorless oil that crystallized after storage at −20° C.

[0173] Yield: 12 g (91%); low melting white solid; R_f=0.7 in 100% hexane.

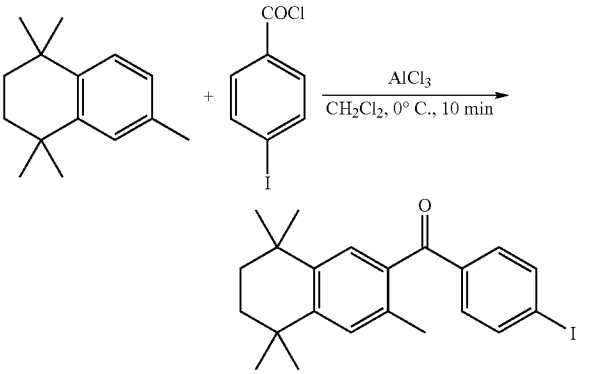
[0174] ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.32 (s, 12H), 1.7 (s, 4H), 2.34 (s, 3H), 6.85 (dd, 1H), 7.14 (d, 1H), 7.22 (d, 1H)

[0175] ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 21.54, 32.26, 32.32, 34.29, 34.51, 35.57, 35.63, 126.64, 126.75, 127.21, 134.93, 142.00, 144.83.

Example 2

(4-iodophenyl)-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)-methanone

[0176]



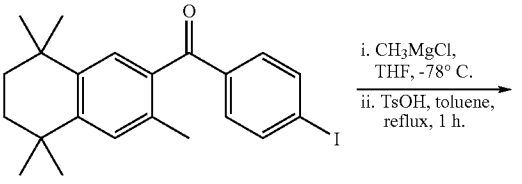
[0177] 1,1,4,4,6-pentamethyl-1,2,3,4-tetrahydronaphthalene (2.02 g, 10 mmol) and 4-iodobenzoyl chloride (2.66 g, 10 mmol) were dissolved in 20 mL of CH_2Cl_2 and cooled to 0° C. using an ice-water-NaCl bath. Anhydrous $AlCl_3$ (4.0 g, 30 mmol) was added in portions at over 5 min. The reaction mixture was allowed to stir at 0° C. for 5 min. The reaction was quenched by slow addition of ice at 0° C. The mixture was diluted with water and 150 mL of EtOAc was added and the layers were separated. The aqueous layer was washed with additional EtOAc (150 mL). The combined organic layers were washed with water (200 mL) and brine (50 μL) and dried over Na_2SO_4. The filtrate was concentrated in vacuum to yield a white solid and that was recrystallized from CH_3OH (10 mg/mL) to afford the product as white crystalline solid.

[0178] Yield: 3.04 g (71%). ^{1}H-NMR ($CDCl_3$,) δ ppm: 1.2 (s, 6H), 1.3 (s, 6H), 1.7 (s, 4H), 2.3 (s, 3H), 7.19 (s, 1H), 7.22 (s, 1H), 7.56 (d, 2H), 7.82 (d, 2H).

Example 3

6-[1-(4-Iodo-phenyl)-vinyl]-1,1,4,4,7-pentamethyl-1,2,3,4-tetrahydro-naphthalene

[0179]



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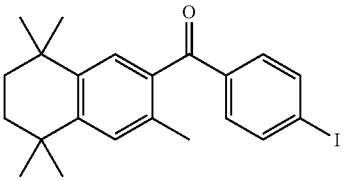


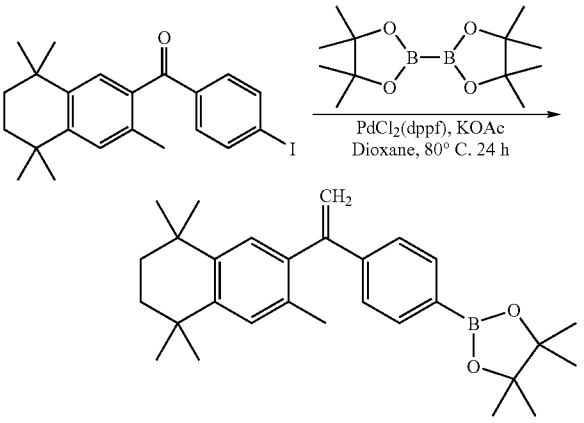
[0180] A solution of (4-iodophenyl)-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-methanone (2.95 g, 6.82 mmol) in 30 mL of dry THF was cooled to −78° C. under an atmosphere of nitrogen. A 3.0 M solution of CH_3MgCl in THF (3.6 mL, 10.5 mmol) was added dropwise at −78° C. and the mixture warmed to ambient temperature. The reaction was heated to reflux for 10 min, cooled to ambient temperature and quenched with CH_3OH-EtOAc. Reaction mixture was extracted with EtOAc (100 mL) and dried (Na_2SO_4). The solvent was removed in vacuum, toluene (50 mL) and p-toluenesulfonic acid monohydrate (1.32 g) were added and the mixture was heated to reflux, allowing the distillate to condense in a Dean-Stark trap pre-filled with toluene. The reaction was complete after 1 h and the reaction cooled and was extracted with water and EtOAc. The organic layer was washed with $NaHCO_3$ and brine and dried over Na_2SO_4 and filtered thru a pad of silica gel. The solvent was removed in vacuum to give the product as a pale yellow foam.

[0181] Yield: 2.9 g (99%); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.28 (s, 6H), 1.30 (s, 6H), 1.66 (s, 4H), 1.96 (s, 3H), 5.22 (s, 1H), 5.7 (s, 1H), 7.0 (s, 1H), 7.06 (s, 1H), 7.12 (d, 2H), 7.4 (d, 2H).

Example 4

4,4,5,5-Tetramethyl-2-{4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-phenyl}-[1,3,2]dioxaborolane

[0182]



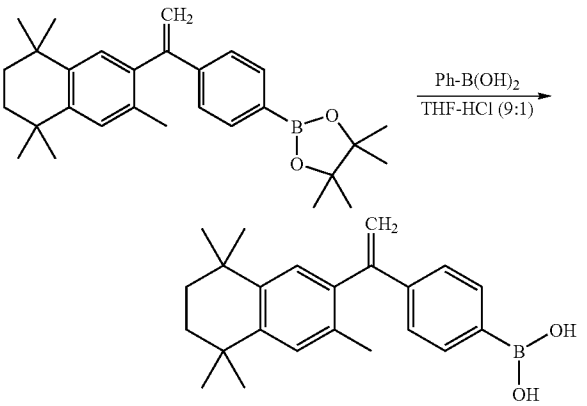
[0183] Anhydrous 1,4-dioxane (2 mL) was added to a solid mixture of 6-[1-(4-Iodo-phenyl)-vinyl]-1,1,4,4,7-pentamethyl-1,2,3,4-tetrahydro-naphthalene (107 mg, 0.25 mmol), dichloro[1,1'-bis(diphenylphosphino) ferrocene]palladium (II) dichloromethane adduct ($PdCl_2$(dppf)), 6.0 mg, 0.0075 mmol), diboron pinacol ester (70 mg, 0.275 mmol), and potassium acetate (74 mg, 0.75 mmol) under nitrogen, and the reaction was placed in a pre-heated oil bath at 80° C. for 24 h. The reaction was diluted with benzene (50 mL), washed with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4 and passed through a short bed of silica gel. Removal of the solvent afforded the product as a white solid.

[0184] Yield: 100 mg (99%). ^{1}H-NMR ($CDCl_3$) δ ppm: 1.28 (s, 6H), 1.32 (s, 6H), 1.35 (s, 12H), 1.7 (s, 4H), 1.96 (s, 3H), 5.22 (s, 1H), 5.76 (s, 1H), 7.02 (s, 1H), 7.1 (s, 1H), 7.26 (d, 2H), 7.7 (d, 2H)

Example 5

4-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-phenylboronic acid

[0185]



[0186] A mixture of 4,4,5,5-tetramethyl-2-{4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-phenyl}-[1,3,2]dioxaborolane (22 mg, 0.05 mmol) and phenylboronic acid (34 mg, 0.255 mmol) was taken up in 1 mL of a 9:1 solution of THF and 1N HCl. The mixture was stirred at ambient temperature for 15 h, was subsequently diluted with water (5 mL) and the pH was adjusted to 10 with 1N NaOH. The aqueous layer was extracted with EtOAc (30 mL), washed with water (10 mL), brine (2.0 mL) and the organic layer was dried over Na_2SO_4. The solvent was removed and the crude residue was purified by column chromatography using 10% EtOAc-DCM to give the product as a white solid.

[0187] Yield: 10 mg (57%). ^{1}H-NMR ($CDCl_3$) δ ppm: 1.26 (2s, 12H), 1.72 (s, 4H), 2.0 (s, 3H), 5.36 (s, 1H), 5.82 (s, 1H), 7.06 (s, 1H), 7.16 (s, 1H), 7.4 (d, 2H), 8.16 (d, 2H). Mass: 349.2 [M+H]+, 371.2 [M+Na]+.

Example 6

A375 Tumor Cell Proliferation Assay

[0188] A375 cells (5,000 per well in 90% RPMI-1640 plus 10% Fetal Bovine Serum [FBS]) were pre-incubated in a black clear bottom 96-well plate in an atmosphere of 5% CO2 at 37° C. for 24 hours. Stock solutions of compounds in DMSO were diluted using a buffer and dilutions were added to each well. The final concentration DMSO in each well did not exceed 0.5%. The final assay pH was 7.4. The cells were incubated in RPMI-1640 with each compound for an additional 72 to 168 hours. Alamar Blue was added and the plate was incubated for an additional 12 hours. Fluorescence intensity was measured using a Gemini plate reader with excitation

at 530 nm and emission at 590 nm. A decrease of 50 percent or more (≧50%) in fluorescence intensity relative to vehicle treated controls is an indication of significant anti-cancer activity.

Reference Data

[0189]

Compound	IC_{50} (μM)	TGI (M)	LC_{50} (μM)
Doxorubicin	0.19	0.30	8.00
Mitomycin	4.20	8.00	10.0

[0190] IC_{50} (50% Inhibitory Concentration): Test compound concentration where the increase in number or mass of cells from $time_0$ to 72 to 168 hours is reduced 50% relative to the corresponding vehicle controls.

[0191] TGI (Total Growth Inhibition): Test compound concentration where the increase in number or mass of cells after 72 to 168 hours is reduced to equal that at time t=0.

[0192] LC_{50} (50% Lethal Concentration): Test compound concentration where the number or mass of cells after 72 to 168 hours is reduced 50% relative to that at time t=0.

Example 7

SW-480 Tumor Cell Proliferation Assay

[0193] SW-480 cells (4×103/well in 90% EMEM medium plus 2 mM glutamine, 1 mM pyruvate, 0.1 mM non-essential amino acids and 10% Fetal Bovine Serum [FBS]), are pre-incubated in 96-well plates in an atmosphere of 5% CO_2 at 37° C. for 24 hours. Test compounds and/or vehicle is then added to each well with a final concentration of 0.5% DMSO, pH 7.4 in EMEM for an additional 72 hours. After a further 6-hour incubation in the presence of Alamar Blue, fluorescence intensity is measured using a Gemini plate reader with excitation at 530 nm and emission at 590 nm. The EC_{50} (50% Effective Concentration) of test compounds where the increase in number or mass of cells from time t=0 to t=72 hours is reduced 50% relative to the corresponding vehicle controls were measured.

Example 8

SKMES Tumor Cell Proliferation Assay

[0194] SKMES cells (8×10^3/well in 90% RPMI-1640 medium plus 2 mM glutamine, 10 mM HEPES and 10% Fetal Bovine Serum [FBS]), are pre-incubated in 96-well plates in an atmosphere of 5% CO_2 at 37° C. for 24 hours. Test compounds and/or vehicle is then added to each well with a final concentration of 0.5% DMSO, pH 7.4 in RPMI-1640 for an additional 72 hours. After a further 150 minutes incubation in the presence of Alamar Blue, fluorescence intensity is measured using a Gemini plate reader with excitation at 530 nm and emission at 590 μm. The EC_{50} (50% Effective Concentration) of test compounds where the increase in number or mass of cells from time t=0 to t=72 hours is reduced 50% relative to the corresponding vehicle controls were measured.

Example 9

Radioactive Ligand Binding Assay

[0195] [^{3}H]-9-cis-retinoic acid (29 Ci/mmol) and MicroSpin G-25 Columns were purchased from Amersham Biosciences (Piscataway, N.J.). Unlabeled 9-cis retinoic acid was purchased from Affinity BioReagents (Golden, Colo.). The retinoic acid receptor subtype RXRγ was purchased from BIOMOL (Plymouth Meeting, Pa.). Stock solution of 9-cis-retinoic acid, was prepared as either 5 mM ethanol or DMSO stock solutions, and serial dilutions were carried out in 1:1 DMSO-ethanol. The assay buffer consisted of the following for receptor assay: 8% glycerol, 120 mM KCl, 8 mM Tris, 5 mM CHAPS, 4 mM DTT, and 0.24 mM PMSF, pH 7.4, at room temperature.

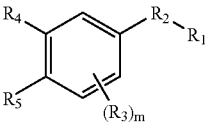
[0196] The receptor binding assay was performed with a final volume of 250 μL containing from 10 to 20 μg of protein, plus 10 DM [^{3}H]-9-cis-retinoic acid, RXRγ and varying concentrations of competing ligand (0-10-5 M). Incubations were carried out at 4° C. for 18 h. Equilibrium under these conditions of buffer and temperature was achieved by 4 h. Non-specific binding was defined as that binding remaining in the presence of 1000 nM unlabeled 9-cis-retinoic acid. The receptor-ligand complex was separated from unincorporated [^{3}H]-9-cis-retinoic acid by applying the binding reaction solution to pre-spun MicroSpin G-25 Column and centrifuged at 735 G for 2 minutes in a microcentrifuge. The amount of receptor-ligand complex was determined by liquid scintillation counting of the purified receptor-ligand complex. After correcting for non-specific binding, the IC_{50} value was determined. The IC_{50} value is defined as the concentration of competing ligand required to decrease specific binding by 50%; the IC_{50} value was determined graphically from a log-logit plot of the data. K_d value for 9-cis-retinoic acid using a modified Cheng-Prussof equation as described by Motulsky.

[0197] Although the invention has been described with reference to the above examples, it will be understood that modifications and variations are encompassed within the spirit and scope of the invention. Accordingly, the invention is limited only by the following claims.

What is claimed is:

1. A compound having the structural formula A

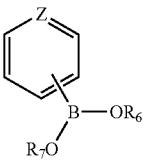
A



wherein:

a. R_1 is

A_1

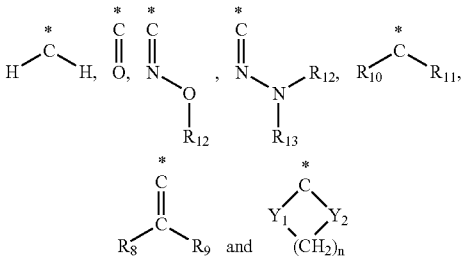


wherein:

i) Z is selected from the group consisting of CH, and nitrogen;

ii) R_6 and R_7 are selected from the group consisting of hydrogen, alkyl, aryl and heteroaryl; R_6 and R_7 may be linked together to form a substituted or unsubstituted 5- or 6-membered cycloalkyl or cycloalkenyl ring, where said substituents are described as herein.

b. R_2 is selected from the group consisting of



wherein:

i) R_8, R_9, R_{10} and R_{11} are independently selected from the group consisting of hydrogen, halogen and alkyl;

ii) R_{10} and R_{11} are independently selected from the group consisting of hydrogen, alkyl, and aryl;

iii) Y_1 and Y_2 are independently O, S, NH, or CH_2, or Y_1 is O, S or NH, and Y_2 is CH_2, with the proviso that Y_1 and Y_2 cannot both be O, S, or NH if n is 0 or 1; and

iv)* represents the point of attachment of the R_2 to the molecule of formula A;

c. R_3 substituents are independently selected from the group consisting of alkyl, alkyloxy, and halogen;

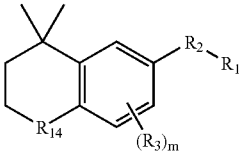
d. R_4 is selected from the group consisting of alkyl, aryl, heteroaryl, and adamantyl; R_5 is selected from the group consisting of alkyl, alkyloxy, alkylthio, aryl, and heteroaryl; or R_4 and R_5 may be linked together to form a substituted or unsubstituted 5- or 6-membered cycloalkyl or cycloalkenyl ring, where said substituents are selected from the group consisting of —OH, =O, halogen, alkyl, and where 1 or 2 of the carbon atoms on said 5- or 6-membered cycloalkyl or cycloalkenyl ring may be optionally replaced by W where W is selected from the group consisting of O, S, N, NH, alkylamino, and arylamino;

e. m and n are independently 0, 1, 2 or 3,

and pharmaceutically acceptable salts, solvates, and prodrugs thereof.

2. Compounds according to claim **1**, having a structure selected from the group consisting of compounds having formulae B_1, B_2, B_3, B_4, B_5, B_6, B_7, B_8, B_9, and B_{10}

B_1



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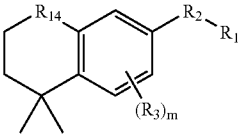
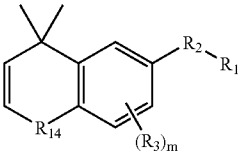
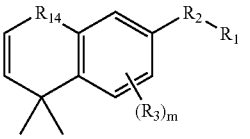
B_2



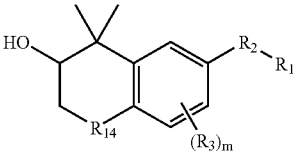
B_3



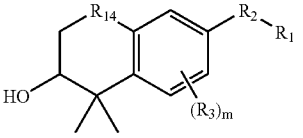
B_4



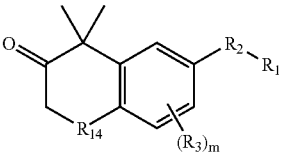
B_5



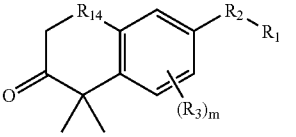
B_6



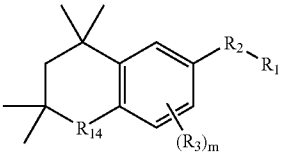
B_7



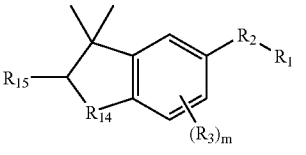
B_8



B_9

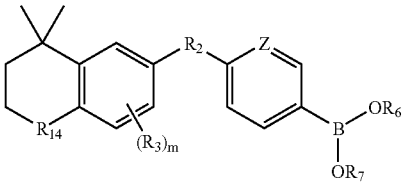


B_{10}



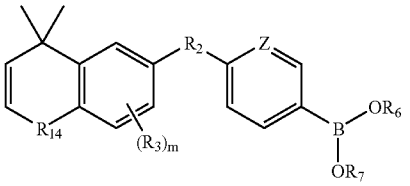
wherein R_1, R_2, R_3 and m are as defined in claim **1**, R_{14} is selected from the group consisting of O, S, $(CH_3)_2C$ and CH_2, and R_{15} is hydrogen or methyl.

3. Compounds according to claim **1**, having the structural formula



wherein R_2, R_6, R_7, Z and m are as defined in claim **1**, and R_{14} is selected from the group consisting of O, S, $(CH_3)_2C$ and CH_2.

4. Compounds according to claim **1**, having the structural formula

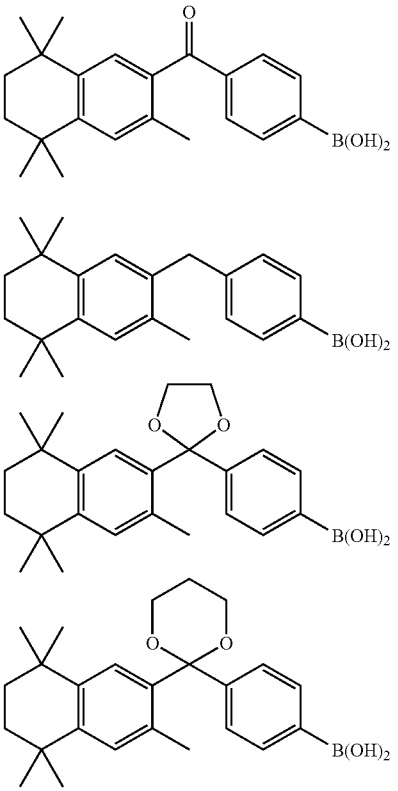


wherein R_2, R_6, R_7, Z and m are as defined in claim **1**, and R_{14} is selected from the group consisting of O, S, $(CH_3)_2C$ and CH_2.

5. Compounds according to claim **1**, wherein m is 0.

6. Compounds according to claim **1**, wherein m is 1.

7. A compound selected from a group consisting of



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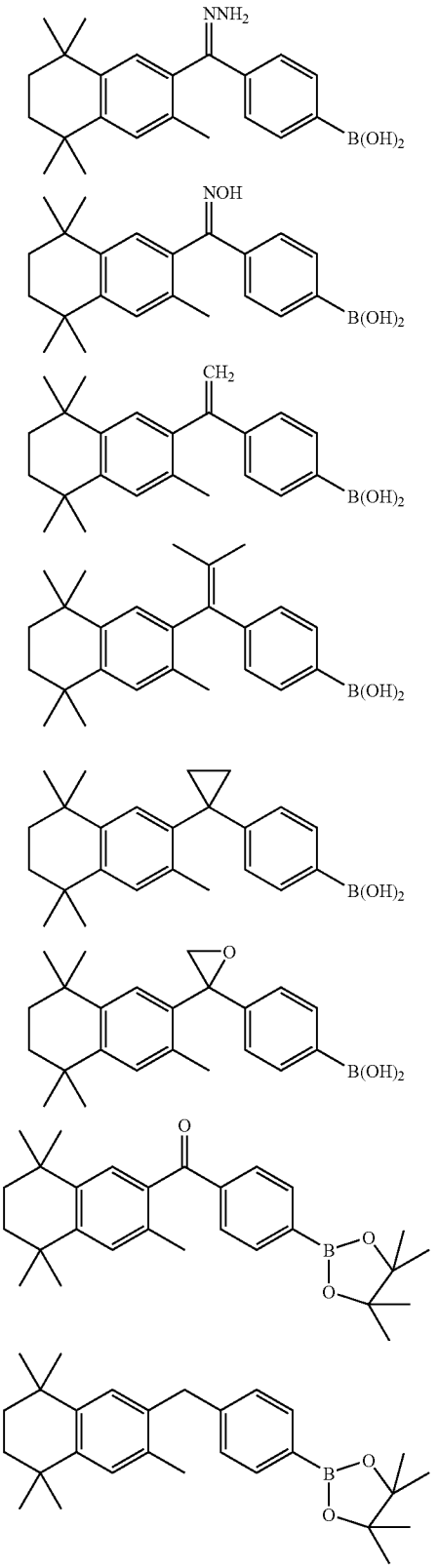

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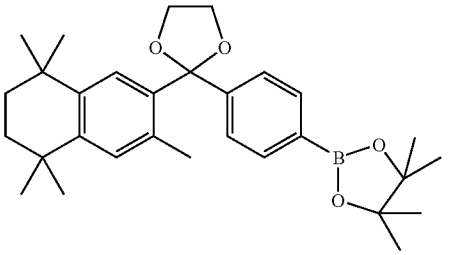

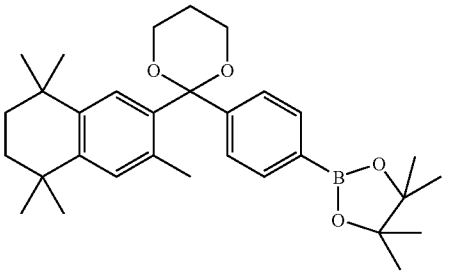

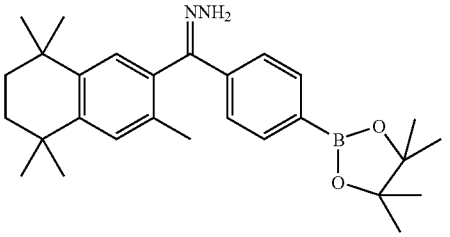

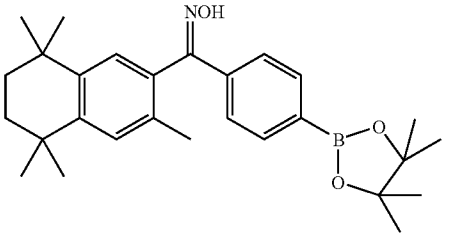

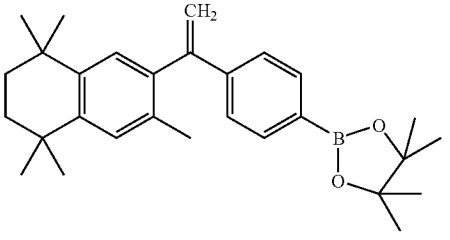

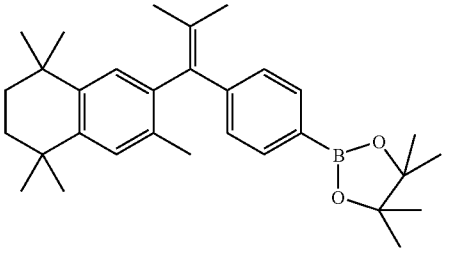

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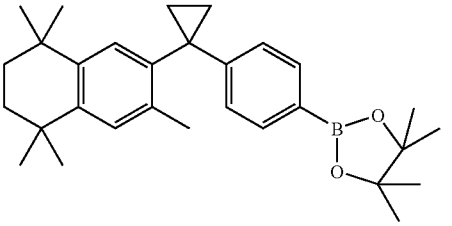

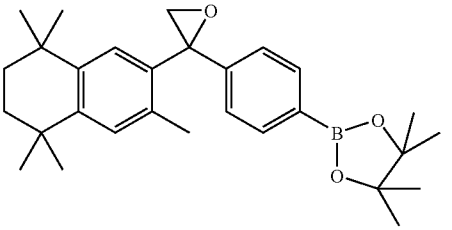

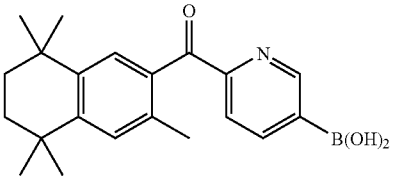

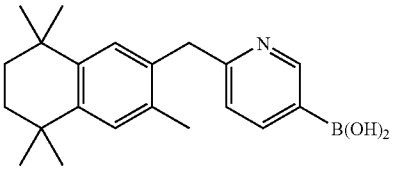

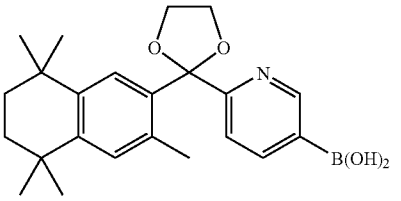

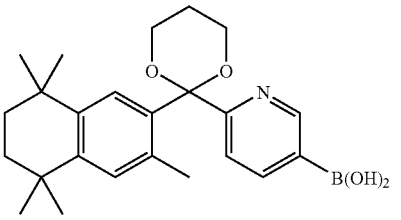

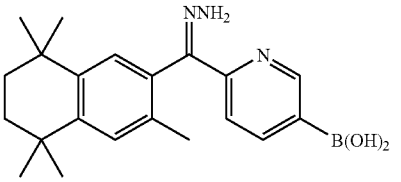

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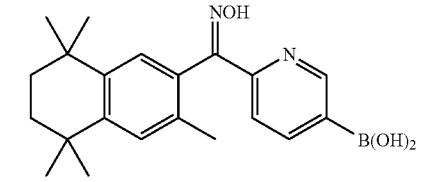

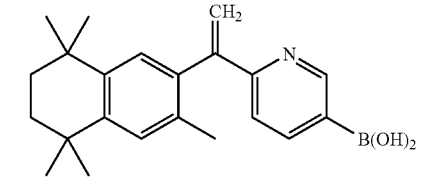

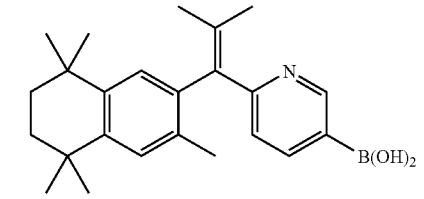

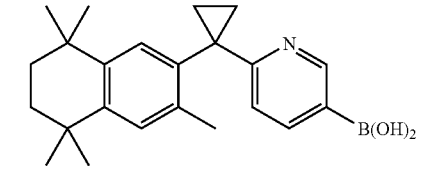

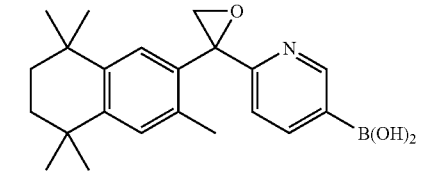

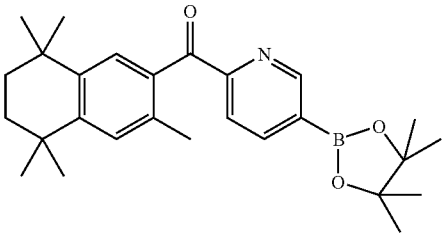

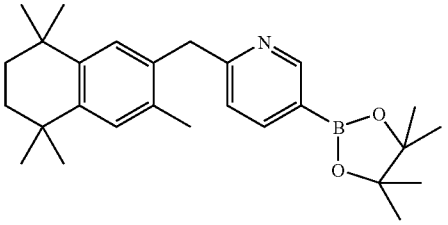

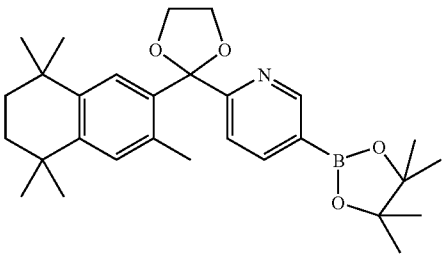

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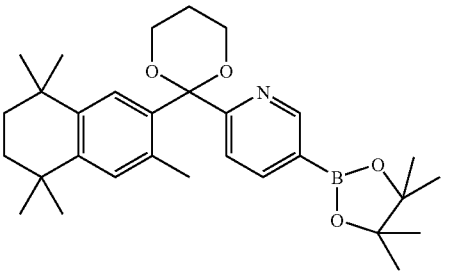

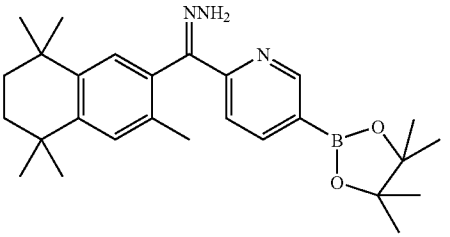

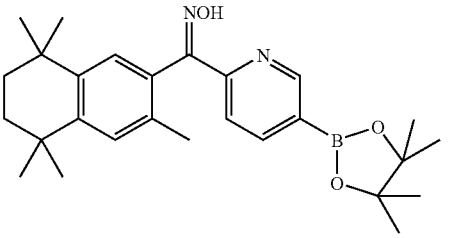

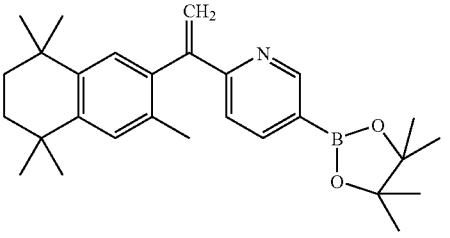

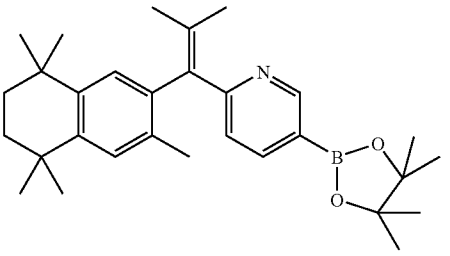

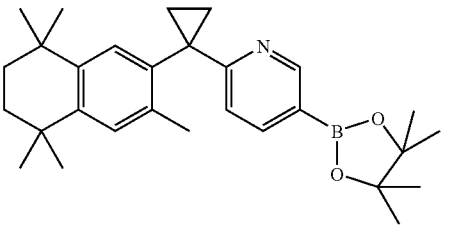

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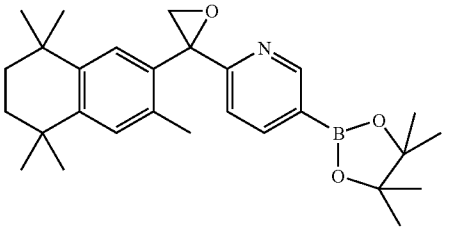


and pharmaceutically acceptable salts, solvates, and prodrugs thereof.

8. A pharmaceutical composition comprising an effective regulating amount of at least one compound according to claim **1** in combination with a pharmaceutically acceptable carrier, for control of cellular processes, cellular differentiation, cellular proliferation or apoptosis.

9. A pharmaceutical composition comprising at least one compound according to claim **1**, in a pharmaceutically acceptable vehicle, for enteral, parenteral, topical or ocular administration.

10. A pharmaceutical composition comprising at least one compound according to claim **1**, in a pharmaceutically acceptable vehicle, for the treatment of cancer.

11. A pharmaceutical composition comprising at least one compound according to claim **1**, in a pharmaceutically acceptable vehicle, for the treatment of cutaneous T-cell lymphoma, squamous cell carcinoma of the head and neck, lung cancer, mammary cancer, colon cancer, skin cancer, cervical cancer, prostate cancer, kidney cancer, cancers of the aerodigestive pathway, bladder cancer, sarcomas, and/or leukemia.

12. A pharmaceutical composition comprising at least one compound according to claim **1** in combination with other chemotherapeutic agents, in a pharmaceutically acceptable vehicle, for the treatment of cancer.

13. A pharmaceutical composition comprising at least one compound according to claim **1** in combination with at least one other chemotherapeutic agent selected from the group comprising Busulfan, Carboplatin, Cisplatin, Cyclophosphamide, Cytosine arabinoside, Etoposide, 5-Fluorouracil, Melphalan, Methotrexate, Mitoxantrone, Taxol, Gemzar, Irinotican, Interferon, Fareston, Arzoxifene, Evista, and Tamoxifen, in a pharmaceutically acceptable vehicle, for the treatment of cancer.

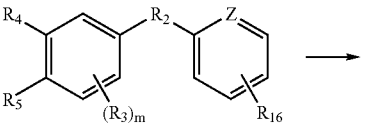
14. A pharmaceutical composition comprising at least one compound according to claim **1** in combination with at least one antiestrogenic agent, in a pharmaceutically acceptable vehicle, for the treatment of cancer.

15. A pharmaceutical composition comprising at least one compound according to claim **1** in combination with at least one other chemotherapeutic selected from the group consisting of Fareston, Arzoxifene, Evista, and Tamoxifen, in a pharmaceutically acceptable vehicle, for the treatment of mammary cancer.

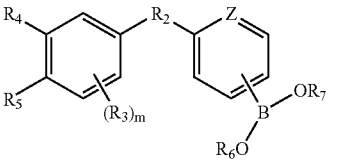
16. A cosmeceutical composition comprising at least one compound according to claim **1**, in a cosmetically acceptable vehicle, for dermal indications.

17. A cosmeceutical composition comprising at least one compound according to claim **1**, in a cosmetically acceptable vehicle, for the treatment of acne and/or psoriasis.

18. A process for preparing compound of formula D comprising contacting compound of formula C with a Boron containing compound under conditions to produce compound of formula D, where:



C

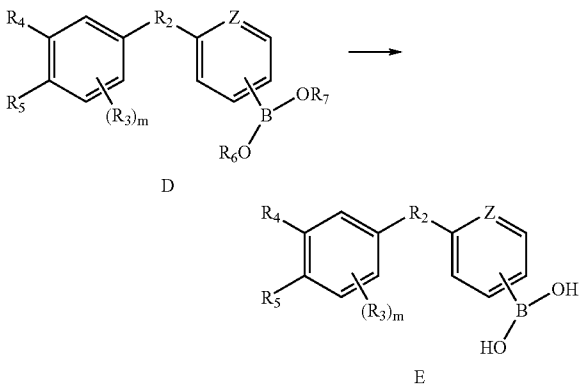


D

R_2, R_3, R_4, R_5, Z and m are defined as in claim **1**, R_6 and R_7 are selected from a group consisting of alkyl, aryl, and heteroaryl, and R_{16} is selected from a group consisting of halogen, alkyl sulfonate, and aryl sulfonate.

19. A process according to claim **18**, where the reaction is carried out in a solvent or a mixture of solvents selected from the group consisting of diethyl ether, dioxane, tetrahydrofuran, toluene, benzene, water and tert-butanol, at a temperature in the range of about 0° C. up to about 500° C., for 0.5 to 240 hours, at a pH in the range of about 7 up to about 12, and at a pressure in the range of about 1 mBar up to about 350 Bar, and in the presence of a mixture of a palladium catalyst, a base and a boron containing compound, where the palladium catalyst is selected from the consisting of a palladium (II) species, palladium (II) acetate, tris(dibenzylideneacetone)-dipalladium, palladium (II) acetylacetonate, palladium (II) bromide, palladium (II) chloride, palladium (II) hexafluoroacetylacetonate, palladium (II) sulfate, palladium (II) trifluoroacetate, and dichloro [1,1'-bis(diphenylphosphino)-ferrocene]palladium (II) dichloromethane adduct ($PdCl_2$(dppf)), the base is selected from the group consisting of potassium acetate, sodium acetate, sodium tert-butoxide, potassium tert-butoxide, cesium carbonate, potassium carbonate, sodium carbonate, and potassium phosphate tribasic (K_3PO_4), and the boron containing compound is selected from the group consisting of optionally substituted [2,2']-bi-[1,3,2]-dioxaborolane, optionally substituted [2,2']-bi-[1,3,2]-dioxaborinane, diboron pinacol ester, 2,2'-bi-1,3,2-benzodioxaborole, bis(neopentyl glycolato)diboron, bis(diethyl-L-tartrate glycolato)diboron, bis(diethyl-L-tartrateglycolato)diboron, bis(diethyl-D-tartrate glycolato) diboron, bis(diisopropyl-D-tartrateglycolato)diboron, bis(diisopropyl-L-tartrateglycolato)diboron, bis(m,n,n',n'-tetramethyl-D-tartramideglycolato)diboron, bis(m,n,n',n'-tetramethyl-L-tartramideglycolato)diboron, bis(hexyleneglycolato) diboron, bis(m,n,n',n'-tetramethyl-D-tartaramideglycolato) diboron, bis(m,n,n',n'-tetramethyl-L-tartaramideglycolato) diboron, bis[(−)-pinanediolato]diboron, catecholborane, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane, (+)-pinaneborane, and 4,4,6-trimethyl-1,3,2-dioxaborinane.

20. A process for preparing compound of formula E comprising contacting compound of formula D under conditions to produce compound of formula E, where:



D

E

R_2, R_3, R_4, R_5, Z and m are defined as in claim **1**.

21. A process according to claim **20**, where the reaction is carried out in a solvent or a mixture of solvents selected from the group consisting of acetonitrile, acetone, dioxane, diethyl ether, tetrahydrofuran, toluene, benzene, dichloromethane, and water, at a temperature in the range of about 0° C. up to about 500° C., for 0.5 to 240 hours, at a pH in the range of about 0.1 up to about 7, and at a pressure in the range of about 1 mBar up to about 350 Bar, and in the presence of a mixture of an additive and a boron containing compound, where the additive is selected from the group consisting of an acid, a Lewis acid, trifluoroacetic acid, acetic acid, hydrochloric acid, ammonium acetate, sodium periodate, and the boron containing compound is selected from the group consisting of alkyl boronic acid, aryl boronic acid, heteroaryl boronic acid, polymer supported boronic acid, and polystyrene boronic acid.

22. A process according to claim **18** where compound of formula E is one of the compounds described in claim **7**.

23. A process according to claim **20** where compound of formula E is one of the compounds described in claim **7**.

24. A pharmaceutical composition comprising in a pharmaceutically acceptable vehicle suitable for enteral, parenteral, or topical administration, one or more compounds according to claim **1** for treating a mammalian subject wherein said wherein said compound exerts its therapeutic effects via the in vivo modulation of lipid metabolism, lipid homeostasis, hyperlipidemia, skin-related processes, autoimmune diseases, fatty acid metabolism, malignant cell development, premalignant lesions, programmed cell death, endocrinological processes, or AP-1 metabolism.

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