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(54) Title: COMPOUNDS, COMPOSITIONS, AND METHODS EMPLOYING SAME

(57) Abstract: Compounds and pharmaceutical compositions containing the same are provided, which are useful in therapeutic treatment or prevention of various diseases.

WO 2004/006858 A2

COMPOUNDS, COMPOSITIONS, AND METHODS EMPLOYING SAME

CROSS REFERENCE TO RELATED U.S. APPLICATION

This application claims the benefit of U.S. Provisional Application Serial No. 60/396,266, filed on July 15, 2002 and U.S. Provisional Application Serial No. 60/396,773, filed July 16, 2002, the contents of both of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD OF THE INVENTION

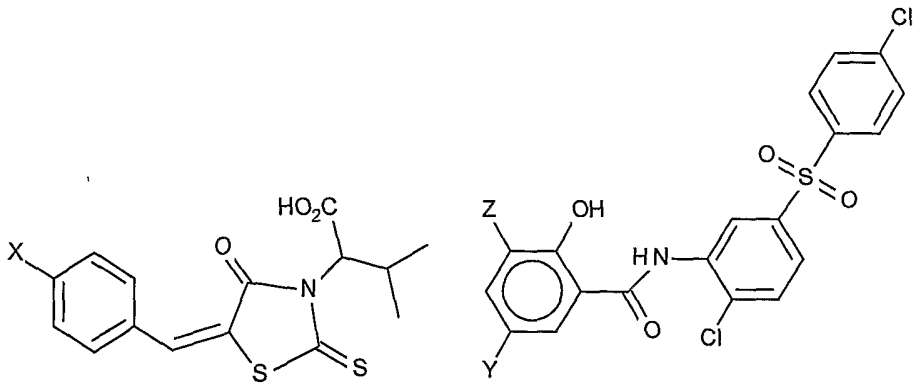
The invention relates to compounds, pharmaceutical compositions and methods of employing such compounds and pharmaceutical compositions for purposes of therapeutic and/or prophylactic treatment of diseases and disorders.

TECHNICAL BACKGROUND OF THE INVENTION

Apoptosis, also known as programmed cell death, is an active process essential for normal development and functions of multicellular organisms. Typically, apoptosis involves isolated single cells and is characterized by DNA fragmentation, morphological changes of cells and nuclei including cell shrinkage, cell surface blebbing, exposure of phosphatidylserine on the cell surface, involution, contraction, chromatin condensation and fragmentation, and phagocytosis without cell infiltration or inflammation. *See* Honig and Rosenberg, *Am. J. Med.*, 108:317-330 (2000). Dysregulation of apoptosis can lead to various diseases and disorders. It is now well-known that reduced apoptosis may contribute to tumorigenesis and formation of cancer. Thus, induction of tumor cell apoptosis can be an effective approach in treating cancer. In addition, stimulation of endothelial cell apoptosis may prevent tumor blood supply and cause tumor regression.

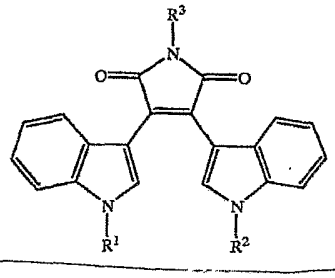
See Dimmeler and Zeiher, *Cir. Res.*, 87:434-439 (2000). Dysregulation of apoptosis is also an integral part of a wide range of autoimmune diseases and disorders. *See* Ravirajan *et al., Int. Rev. Immunol.*, 18:563-589 (1999). In addition, many neurological disorders involve apoptosis. During adulthood, there is little normal neuronal cell death. However, neurological diseases, particularly neurodegenerative diseases are often associated with excessive neural cell death. *See* Honig and Rosenberg, *Am. J. Med.*, 108:317-330 (2000). For example, Parkinson's disease is associated with the loss of substantia nigra pars compacta and sympathetic ganglia, while Alzheimer's disease is characterized with selective cell loss of entorhinal neurons, and hippocampal neurons, cortical neurons. *See* Honig and Rosenberg, *Am. J. Med.*, 108:317-330 (2000). Apoptosis also plays an important role in osteoporotic disorders including, but not limited to, postmenopausal osteoporosis, involutional osteoporosis, and glucocorticoid-induced osteoporosis. *See* Weinstein, *et al., Am. J. Med.*, 108:153-164 (2000). Apoptosis also has physiological significance in animal virus infection. *See* Kyama *et al., Microbes and Infection*, 2:1111-1117 (2000).

Degterev, Alexei, et al, "Identification of small-molecule inhibitors of interaction between the Bak BH3 domain and Bcl-x_L," *Nat. Cell Biol.*, 3:173-182 (2001), disclose apoptosis promoting compounds of the formulas:



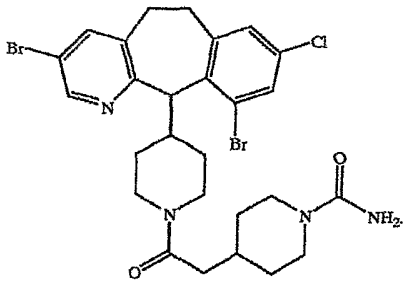
wherein X can be Br, Cl, or H, Y is Cl, or I, and Z is Br, or I. The compounds were shown via binding assay tests, to promote displacement of BH3 from a Bcl-X_L fusion protein. The compounds were also shown to have apoptotic cytotoxicity when applied to Jurkat T lymphoma cells. The apoptotic cytotoxicity of the compounds quantitatively paralleled their *in vitro* Bcl-X_L binding activities.

U.S. Patent No. 6,284,783 discloses a method of inducing apoptosis in target cells of a subject by administering, to the subject a pharmaceutically effective amount of at least one compound of the formula: I



wherein: R_1 is hydrogen, C_1-C_{12} alkyl, C_1-C_{12} substituted alkyl, C_3-C_7 heterocycle, or C_3-C_7 substituted heterocycle, R_2 and R_3 are independently H or C_1-C_{12} alkyl, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof, wherein following the administration of the compound of Formula I, the target cell is caused to undergo apoptosis.

U.S. Patent No. 6,316,462 discloses a method of treating cancer in a patient by inducing apoptosis with (1) a farnesyl protein transferase inhibiting amount of a fused-ring tricyclic benzocycloheptapyridine and (2) an additional Ras signaling pathway inhibitor. The farnesyl protein transferase inhibitor has a formula:

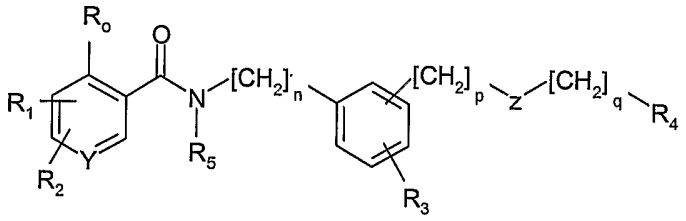


Despite of recent success in designing and identifying compounds that affect apoptosis, there is a continuing search for compounds capable of modulating apoptosis, and effective in treating diseases and disorders.

SUMMARY OF THE INVENTION

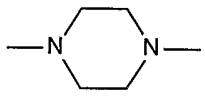
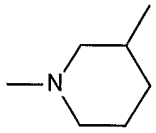
The present invention provides pro-apoptotic compounds, compositions and therapeutic treatment processes employing such pro-apoptotic compositions, comprising at least one compound of Formula 1, set forth below.

In particular, compounds of Formula 1 have the structure:



Formula 1

wherein Y is C or N;

Z is selected from the group consisting of a covalent bond, sulfur, i.e., -S-, oxygen, i.e., -O-, amino (e.g., primary, secondary, and tertiary amino), carbonyl, i.e., -CO-,  and  ;

R_0 is selected from the group consisting of hydroxy, lower (C_1-C_6) alkoxy (which can be unsubstituted or substituted, e.g., hydroxyalkoxy, haloalkoxy), nitro, amide (e.g., formamide, acetamide, sulfonamide, alkylsulfonamide, and aryl sulfonamide);

R_1 and R_2 are positioned at the 3, 4 and/or 5 position (the amide side chain defining the 1 position), and are independently selected from the group consisting of hydrogen, hydrophobic substituents such as halo (e.g., F, Cl, Br, I), nitro, alkyl, aryl, heterocycle, haloalkyl and the like, formamido, formamidoalkyl, and alkoxy substituents, or at the 3 and 4 positions together form a substituted or unsubstituted fused ring having 3, 4, 5, or 6 carbon atoms;

R_3 represents from one to four substituents independently selected from the group consisting of hydrogen, hydrophobic substituents such as halo, alkyl (preferably lower (C_1-C_6) alkyl, haloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, a heterocycle, a heterocycle(oxy), or heterocycle(alkyl), cyano, and nitro substituents. Preferably, R_3 is haloalkyl (preferably trihaloalkyl, e.g., trifluoromethyl) or haloalkoxy (preferably trihaloalkoxy, e.g., trifluoromethoxy);

R_4 represents a substituent selected from the group consisting of hydrogen, alkyl, aryl, alkaryl, cycloalkyl, alkoxy, aryloxy, aralkoxy, heterocycle, heterocycle(oxy), and heterocycle(alkyl) substituents;

R_5 represents hydrogen or lower alkyl (e.g., methyl);

n, p and q are the same or different integers selected from the group consisting of 0, 1, 2 or 3.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the present invention, or a therapeutically acceptable salt, ester, amide or hydrate thereof, in combination with a pharmaceutically acceptable carrier.

The present invention also provides a method of promoting apoptosis in a mammal in recognized need thereof comprising administering to the mammal, a pharmaceutical composition comprising a compound of the present invention or a pharmaceutically acceptable salt, ester, amide or hydrate thereof. Advantageously, the pharmaceutical composition is administered in an amount sufficient to promote apoptosis and/or to reduce the proliferation of abnormal cells, particularly tumor cells or proliferation of uncontrolled cells.

Another embodiment of the invention comprises the use of a compound of the present invention, or a pharmaceutically acceptable salt, ester or amide or hydrate thereof, in the manufacture of a medicament or pharmaceutical composition comprising the compound, or a therapeutically acceptable salt, ester or amide or hydrate thereof, for promoting apoptosis in a mammal in recognized need thereof.

In yet another embodiment of the present invention, a method is provided for treating or preventing cancer or neoplastic diseases comprising identifying a mammal, particularly human patient in need of such treatment and administering a compound

according to the present invention, or a pharmaceutically acceptable salt, ester, amide or hydrate thereof, or a pharmaceutical composition according to the present invention. Similarly, the compounds and compositions of the present invention can also be used in treating other diseases that benefit from promoting apoptosis, e.g., autoimmune diseases, viral infection, psoriasis, and the like, as discussed in detail below.

The foregoing and other advantages and features of the invention, and the manner in which the same are accomplished, will become more readily apparent upon consideration of the following detailed description of the invention taken in conjunction with the accompanying examples, which illustrate preferred and exemplary embodiments.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel compounds and pharmaceutical compositions which are useful in the treatment of diseases involving apoptosis impairment.

Unless specifically defined otherwise, chemical terms, and substituent names in particular, as used herein, have their normal meaning as understood in the art. The following terms are specifically defined for the sake of clarity.

The term "alkyl," as used herein, represents a group of one to twelve carbon atoms derived from a straight or branched chain saturated hydrocarbon attached to the parent molecular moiety through a carbon atom. The term "lower," as applied to an alkyl or alkyl-containing group herein, means that the alkyl group is formed of one to six carbon atoms derived from a straight or branched chain saturated hydrocarbon. An alkyl group may be unsubstituted, or substituted at one or more substitutable position by one or more groups independently selected from halo (e.g., F, Cl, Br, I), alkoxy, aryloxy, amino, hydroxy, carboxy (e.g., carboxylic acid and esters thereof), nitro, cyano, thiol, alkylthio, aryl, heteroaryl, heterocyclo and carbocyloalkyl, etc. The term "alkoxyalkyl" refers to an alkyl group substituted with an alkoxy group.

The term "alkoxy," as used herein, represents an alkyl group (substituted or unsubstituted) attached to the parent molecular moiety through an oxygen atom, and further includes the alkylenedioxy group, i.e., the group –O-loweralkyl-O- attached to a

parent aryl, cycloalkyl, or heterocycle moiety through both of the oxygen atoms. "Lower alkoxy" refer to such groups containing from one to six carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, trifluoromethoxy and the like.

The term "aryl," as used herein, represents a phenyl group or a bicycic or tricyclic fused ring system wherein one or more of the fused rings is a phenyl group. The aryl group can be optionally substituted with one, or a plurality of substituents independently selected from the group consisting of alkoxy, alkyl, arylalkoxy, aryloxy, halo (e.g., F, Cl, Br, I), haloalkoxy, haloalkyl, hydroxy, aralkyl, amino, alkylamino, a heterocycle, a heterocycle(oxy), or heterocycle(alkyl), carboxy (e.g., carboxylic acid and esters thereof), cyano, thiol, nitro substituents and the like.

The term "aralkyl," as used herein, represents one or more aryl groups attached to one or more carbon atoms of an alkyl group, and being attached to the parent molecular moiety through a carbon atom of the alkyl group.

The term "aryloxy," as used herein, represents an aryl group attached to the parent molecular moiety through an oxygen atom.

The term "aralkoxy," as used herein, represents at least one aryl group attached to one or more carbon atoms of an alkoxy group, attached to the parent molecular moiety through an oxygen atom.

The term "alkaryloxy," as used herein, represents an alkyl group attached to a carbon atom of an aryloxy group, attached to the parent molecular moiety through an oxygen atom.

The term "cycloalkyl," as used herein, represents a saturated or partially unsaturated ring system having three to twelve carbon atoms and one to three rings (e.g., monocyclic, bridged monocyclic, bicyclic, and spiro rings). Examples of cycloalkyl groups include cyclopropyl, cyclopentyl, bicyclo(3.1.1)heptyl, adamantyl, bicyclohexyl, bicyclooctyl, bicyclononyl, spirononyl and spirodecyl, and the like. The cycloalkyl groups of this invention can be optionally substituted with one, or a plurality of substituents independently selected from the group consisting of alkoxy, alkyl, arylalkoxy, aryloxy, halo, haloalkoxy, haloalkyl, hydroxy, aralkyl, amino, alkylamino, a heterocycle, a heterocycle(oxy), or heterocycle(alkyl), carboxy (e.g., carboxylic acid and esters thereof), cyano, thiol, nitro substituents and the like.

The term "alkanoyl" as used herein refers to an acyl radical derived from an alkanecarboxylic acid, particularly a lower alkanecarboxylic acid, and includes e.g., acetyl, propionyl, butyryl, valeryl, and 4-methylvaleryl.

The term "thiol" means –SH or a substituted thiol which results from substitution of the hydrogen with another suitable group such as alkyl, aryl, alkoxy, arylalkoxy, aryloxy, halo (e.g., F, Cl, Br, I), haloalkoxy, haloalkyl, hydroxy, aralkyl, amino, alkylamino, a heterocycle, a heterocycle(oxy), or heterocycle(alkyl), carboxy (e.g., carboxylic acid and esters thereof), cyano, nitro substituents and the like.

The term "amino" refers to unsubstituted amino ($-NH_2$), primary amino (i.e., mono-substituted amino), and secondary amino (i.e., di-substituted amino) groups. The optional substituents can be independently selected from the group consisting of alkyl (preferably lower alkyl), cycloalkyl, aryl, heteroaryl and heterocyclo, or two substituents in a secondary amino taken together with the nitrogen atom to which they are attached form a heterocyclic ring.

The term "alkylamino" as used herein, represents the group $N(R)_2$ wherein one or both R groups are the same or different substituted or unsubstituted alkyl group, the alkylamino group being attached to the parent moiety through the nitrogen atom.

The term "amide," as used herein, represents the group, R-C(O)-N(H or alkyl or aryl)-, attached to the parent molecular moiety through the nitrogen atom, wherein R is substituent such as H, lower alkyl, and aryl. The term "formamide," or "formamido," as used herein, represents —NHCHO attached to the parent moiety through the nitrogen atom.

The term "formamidoalkyl" as used herein, represents HCONH-(alkyl)-, or HCONH-(lower alkyl)-, attached to the parent moiety through a carbon atom of the alkyl group.

The term "sulfonamide," as used herein represents the group $–SO_2NH-$ attached to the parent moiety through the nitrogen atom, wherein the H on the nitrogen atom can be substituted with e.g., lower alkyl or aryl.

The term "alkylsulfonamide," as used herein, represents (alkyl)-SO_2N(H or lower alkyl or aryl)-, or (lower alkyl)-SO_2N(H or lower alkyl or aryl)-, attached to the parent moiety through the nitrogen atom of the sulfonamide group.

The term "arylsulfonamide," as used herein, represents (aryl)-SO_2N(H or lower alkyl or aryl)-, attached to the parent moiety through the nitrogen atom of the sulfonamide group.

The term "halo," as used herein, represents F, Cl, Br, or I.

The term "cyano" as used herein, represents the group CN, attached to the parent moiety through the carbon atom.

The term "nitro" as used herein, represents the group NO_2 attached to the parent moiety through the nitrogen atom.

The term "haloalkyl" as used herein, represents an alkyl group substituted with one or more halogens (e.g., F, Cl, Br, and I), attached to the parent moiety through a carbon atom of the halogen. "Lower haloalkyl" means the halo-substituted alkyl group has 1-6 carbon atoms.

The term "heterocycle," as used herein, represents a saturated or partially unsaturated monocyclic or a bicycic or tricyclic fused ring system having three to twelve carbon atoms and containing one, two or three heteroatoms independently selected from the group consisting of oxygen, nitrogen, and sulfur. The heterocycle group can be optionally substituted with one, or a plurality of substituents independently selected from the group consisting of alkoxy, alkyl, arylalkoxy, aryloxy, halo, haloalkoxy, haloalkyl, hydroxy, aralkyl, amino, alkylamino, a heterocycle, a heterocycle(oxy), or heterocycle(alkyl), cyano, nitro substituents and the like.

The term "heterocycle(oxy)," as used herein, represents an heterocycle group attached to the parent molecular moiety through an oxygen atom.

The term "heterocycle(alkyl)," as used herein, represents an heterocycle group attached to an alkyl group, attached to the parent molecular moiety through a carbon atom of the alkyl group.

The term "hydrophobic substituent" as used herein represents a substituent such as halo, alkyl, lower alkyl, haloalkyl, halo-lower-alkyl, di- or tri-haloalkyl, di- or tri-halo-lower-alkyl, aryl, haloalkyl, or the like which has a substituent hydrophobic parameter such that it increases (renders more hydrophobic) the overall water/octanol partition coefficient of the substituted parent molecule as compared to the unsubstituted parent

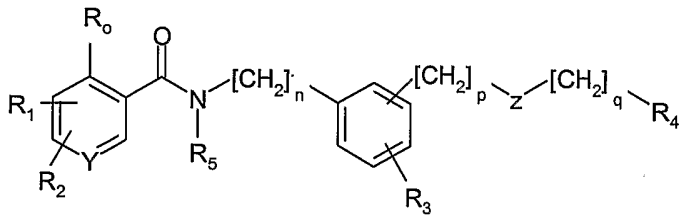
molecule. The meaning of hydrophobic substituent, substituent hydrophobic parameter, and water/octanol partition coefficient are well known to the skilled artisan.

The term, "EC_{50} cytotoxic response" as used herein, means a concentration of the active compound sufficient to achieve 50% cell death. The EC_{50} cytotoxic response is considered to be pro-apoptotic when a positive apoptotic response can be observed upon examination of the cells under a test protocol designed to discriminate between cells with intact or damaged plasma membranes. One such protocol involves dual annexin V-FITC and propidium iodide (PI) staining. Flipping of phosphatidylserine to the outer leaflet of the plasma membrane is a characteristic of all apoptotic cells. AnnexinV is a serum protein that binds to phosphatidylserine in the presence of the divalent cations (calcium). PI is a DNA stain that is excluded from live cells and is used to discriminate between cells with intact or damaged plasma membranes.

The term "standard incubating conditions" as used herein, means an environment defined by a temperature of 37 degrees Celsius within a humidified chamber containing 5% CO_2.

The present invention provides pro-apoptotic compounds, compositions and therapeutic treatment processes employing such pro-apoptotic compositions, comprising at least one compound of Formula 1, set forth below.

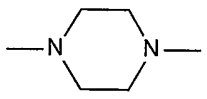
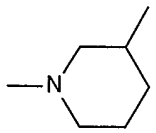
In particular, compounds of Formula 1 have the structure:



Formula 1

wherein Y is C or N;

Z is selected from the group consisting of a covalent bond, sulfur, i.e., -S-, oxygen, i.e., -O-, amino (e.g., primary, secondary, and tertiary amino), carbonyl, i.e.,

-CO-,  and  ;

R_0 is selected from the group consisting of hydroxy, lower (C_1-C_6) alkoxy (which can be unsubstituted or substituted, e.g., hydroxyalkoxy, haloalkoxy), nitro, amide (e.g., formamide, acetamide), sulfonamide, alkylsulfonamide, and aryl sulfonamide;

R_1 and R_2 are positioned at the 3, 4 and/or 5 position (the amide side chain defining the 1 position), and are independently selected from the group consisting of hydrogen, hydrophobic substituents such as halo (e.g., F, Cl, Br, I), nitro, alkyl, aryl, heterocycle, haloalkyl and the like, formamido, formamidoalkyl, and alkoxy substituents, or at the 3 and 4 positions together form a substituted or unsubstituted fused ring having 3, 4, 5, or 6 carbon atoms;

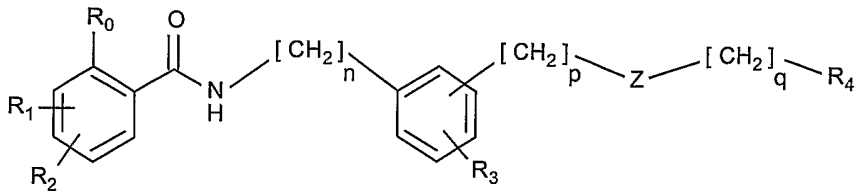
R_3 represents from one to four substituents independently selected from the group consisting of hydrogen, hydrophobic substituents such as halo, alkyl (preferably lower (C_1-C_6) alkyl, haloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, a heterocycle, a heterocycle(oxy), or heterocycle(alkyl), cyano, and nitro substituents. Preferably, R_3 is haloalkyl (preferably trihaloalkyl, e.g., trifluoromethyl) or haloalkoxy (preferably trihaloalkoxy, e.g., trifluoromethoxy);

R_4 represents a substituent selected from the group consisting of haloalkyl, alkyl, aryl, alkaryl, cycloalkyl, alkoxy, aryloxy, aralkoxy, heterocycle, heterocycle(oxy), and heterocycle(alkyl) substituents;

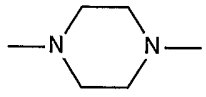
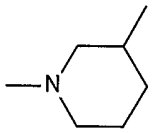
R_5 represents hydrogen or lower alkyl (e.g., methyl);

n, p and q are the same or different integers selected from the group consisting of 0, 1, 2 or 3.

In one preferred embodiment, the pro-apoptotic compounds have the following formula:



Formula 2

wherein Z is selected from the group consisting of a covalent bond, sulfur, i.e., -S-, oxygen, i.e., -O-, amino (e.g., primary, secondary, and tertiary amino), carbonyl, i.e., -CO-,  and  ;

R_0 is selected from the group consisting of hydroxy, lower (C_1-C_6) alkoxy (which can be unsubstituted or substituted, e.g., hydroxyalkoxy, haloalkoxy), nitro, amide (e.g., formamide, acetamide, sulfonamide, alkylsulfonamide, and aryl sulfonamide);

R_1 and R_2 are positioned at the 3, 4 and/or 5 position (the amide side chain defining the 1 position), and are independently selected from the group consisting of hydrogen, hydrophobic substituents such as halo (e.g., F, Cl, Br, I), nitro, alkyl, aryl, heterocycle, haloalkyl and the like, formamido, formamidoalkyl, and alkoxy substituents, or at the 3 and 4 positions together form a substituted or unsubstituted fused ring;

R_3 represents from one to four substituents independently selected from the group consisting of hydrogen, hydrophobic substituents such as halo, alkyl (preferably lower (C_1-C_6) alkyl, haloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, a heterocycle, a heterocycle(oxy), or heterocycle(alkyl), cyano, and nitro substituents. Preferably, R_3 is haloalkyl (preferably trihaloalkyl, e.g., trifluoromethyl) or haloalkoxy (preferably trihaloalkoxy, e.g., trifluoromethoxy);

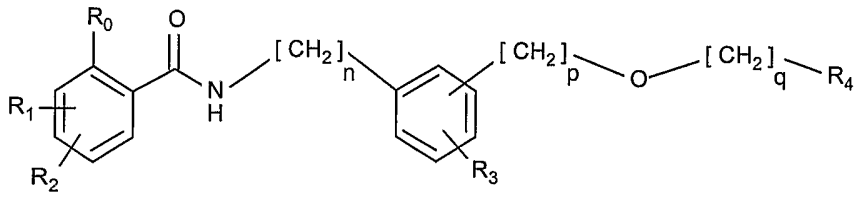
R_4 represents a substituent selected from the group consisting of haloalkyl, alkyl, aryl, alkaryl, cycloalkyl, alkoxy, aryloxy, aralkoxy, heterocycle, heterocycle(oxy), and heterocycle(alkyl) substituents. In preferred embodiments, R_4 represents haloalkyl, e.g., halo-substituted lower alkyl (preferably trihalo lower alkyl, e.g., trifluoromethyl);

alkoxyalkoxy (including halo-substituted alkoxyalkoxy); R_8 as defined below; and R_8-Ak- or (R_8R9)-Ak-, wherein Ak is lower alkyl with a straight or branched chain, R_8 and R_9 are independently selected from (1) cycloalkyl, (2) aryl such as benzene and naphthalene, (3) aryloxy, (4) a saturated or partially unsaturated or aromatic moncyclic 3, 4, 5, 6, or 7-membered heterocycle containing one or more N, O, or S, or (5) a saturated or partially unsaturated or aromatic biocyclic 8 to 12-membered heterocycle containing one or more N, O, or S, wherein the rings of the cycloalkyl, aryloxy, aryl and heterocyle may be substituted by one or more identical or different substituents selected from lower alkyl, halo, haloalkyl (e.g., halo-substituted lower alkyl, preferably trihalo lower alkyl, e.g., trifluoromethyl), alkoxy, alkoxyalkoxy, (C_1-C_6)-alkyl-O-C(O)-, (C_1-C_6)-alkyl-O-C(O)-(C_1-C_3)-alkyl-, (C_1-C_6)-alkyl-O-C(O)-(C_1-C_3)-alkene-, alkylsulfonyl (e.g., lower alkyl-SO_2-), halo-substituted lower alkoxy (preferably trihalo lower alkoxy, e.g., trifluoromethoxy), and halo-aryl-;

R_5 represents hydrogen or lower alkyl (e.g., methyl);

n, p and q are the same or different integers selected from the group consisting of 0, 1, 2 or 3.

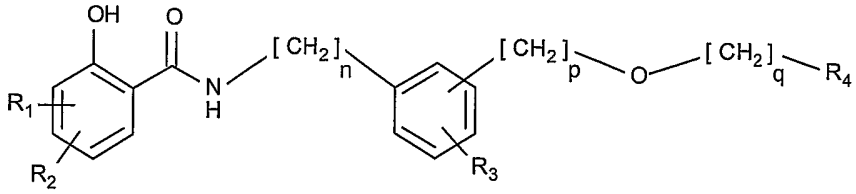
In one preferred embodiment, the pro-apoptotic compositions of Formula 2, and therapeutic treatment processes employing same, comprise a compound of Formula 2a, set forth below:



Formula 2a

wherein R_0, R_1, R_2, R_3, R_4, n, p, and q have the same meanings as set forth above.

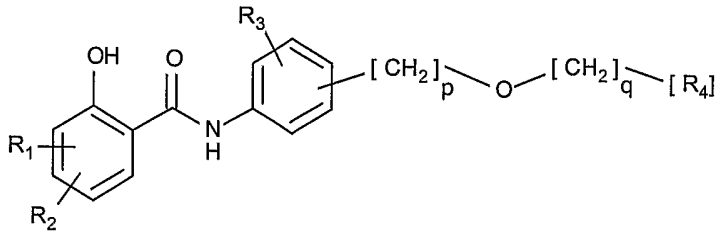
In another preferred embodiment, the pro-apoptotic compositions of Formula 2, and therapeutic treatment processes employing same, comprise a compound of Formula 1b, set forth below:



Formula 2b

wherein R_1, R_2, R_3, R_4, n, p, and q have the same meanings as set forth above.

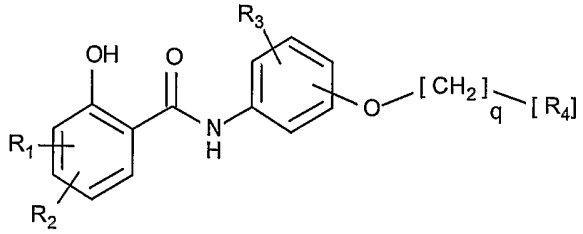
In another preferred embodiment, the pro-apoptotic compositions of Formula 2, and therapeutic treatment processes employing same, comprise a compound of Formula 2c, set forth below;



Formula 2c

wherein R_1, R_2, R_3, R_4, p, and q have the same meanings as set forth above.

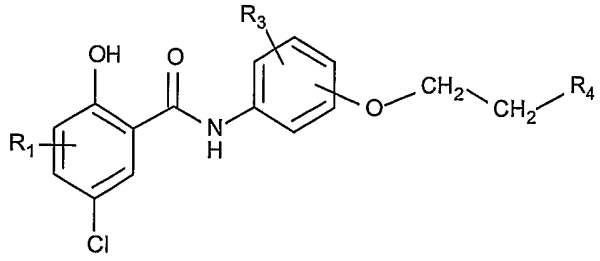
In another preferred embodiment, the pro-apoptotic compositions of Formula 2, and therapeutic treatment processes employing same, comprise a compound of Formula 2d, set forth below:



Formula 2d

wherein R_1, R_2, R_3, R_4, and q have the same meanings as set forth above.

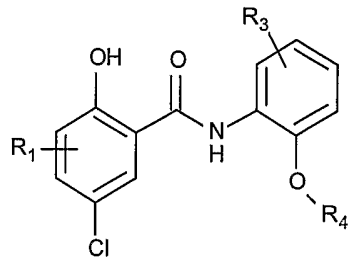
In yet another preferred embodiment, the pro-apoptotic compositions of Formula 2, and therapeutic treatment processes employing same, comprise a compound of Formula 2e, set forth below:



Formula 2e

wherein R_1, R_3, and R_4, have the same meanings as set forth above.

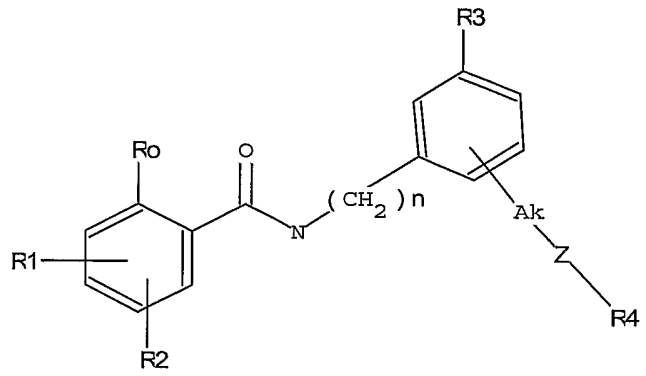
In yet another preferred embodiment, the pro-apoptotic compositions of Formula 2, and therapeutic treatment processes employing same, comprise a compound of Formula 2f, set forth below:



Formula 2f

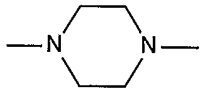
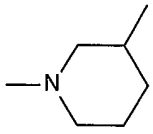
wherein R_1, R_3, and R_4, have the same meanings as set forth above. In a more preferred embodiment R_3 represents halo, haloalkyl, cyano or nitro. Even more preferably, R_3 trihalomethyl, halo or nitro. It is also preferred that R_3 is positioned para to $-O-R_4$.

In another preferred embodiment, the pro-apoptotic compositions of Formula 2, and therapeutic treatment processes employing same, comprise a compound of Formula 2g, set forth below:



Formula 2g

wherein

Z is oxygen, amino, sulfur,  or  ;

n is an integer of 0, 1, 2, or 3;

Ak is lower alkyl;

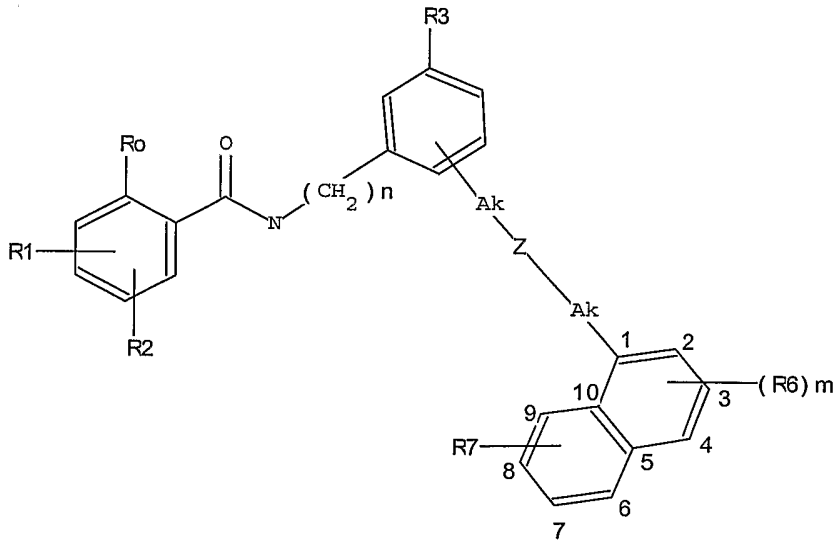
R_0 is hydroxy, lower (C_1-C_6) alkoxy, hydroxyalkoxy (e.g. hydroxymethoxy, hydroxyethoxy), nitro;

R_1 and R_2 are independently selected from hydrogen, halo, nitro, alkoxy, aryl, heterocycle, halo-substituted lower alkyl (preferably trihalo lower alkyl, e.g., trifluoromethyl), wherein R_1 and R_2 are not both hydrogen at the same time;

R_3 is halo, halo-substituted lower alkyl (preferably trihalo lower alkyl, e.g., trifluoromethyl), or haloalkoxy (preferably halo-substituted C_1-C_6 alkoxy, e.g., trihalo-substituted methoxy); and

R_4 represents haloalkyl, e.g., halo-substituted lower alkyl (preferably trihalo lower alkyl, e.g., trifluoromethyl); alkoxyalkoxy (including halo-substituted alkoxyalkoxy); R_8 as defined below; and R_8-Ak- or (R_8R9)-Ak-, wherein Ak is lower alkyl with a straight or branched chain, R_8 and R_9 are independently selected from (1) cycloalkyl, (2) aryl such as benzene and naphthalene, (3) aryloxy, (4) a saturated or partially unsaturated or aromatic moncyclic 3, 4, 5, 6, or 7-membered heterocycle containing one or more N, O, or S, or (5) a saturated or partially unsaturated or aromatic biocyclic 8 to 12-membered heterocycle containing one or more N, O, or S, wherein the rings of the cycloalkyl, aryloxy, aryl and heterocyle may be substituted by one or more identical or different substituents selected from lower alkyl, halo, haloalkyl (e.g., halo-substituted lower alkyl, preferably trihalo lower alkyl, e.g., trifluoromethyl), alkoxy, alkoxyalkoxy, (C_1-C_6)-alkyl-O-C(O)-, (C_1-C_6)-alkyl-O-C(O)-(C_1-C_3)-alkyl-, (C_1-C_6)-alkyl-O-C(O)-(C_1-C_3)-alkene-, alkylsulfonyl (e.g., lower alkyl-SO_2-), halo-substituted lower alkoxy (preferably trihalo lower alkoxy, e.g., trifluoromethoxy), and halo-aryl-.

In a specific embodiment, the compounds of present invention have a formula:



Formula 2h

wherein

Z is oxygen, amino or sulfur;

n is an integer of 0, 1, 2, or 3;

Ak is lower alkyl;

R_0 is hydroxy, lower (C_1-C_6) alkoxy, hydroxyalkoxy, nitro, amide, sulfonamide, alkylsulfonamide, or aryl sulfonamide;

R_1 is hydrogen, halo, nitro, alkoxy, alkyl, aryl, heterocycle, haloalkyl, or amide;

R_2 is halo;

R_3 is halo, haloalkyl, or haloalkoxy;

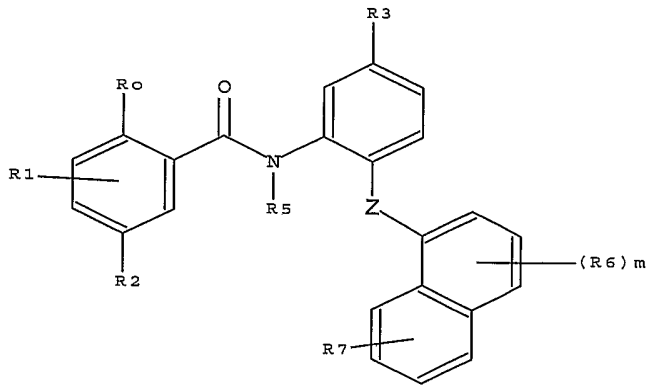
R_5 is hydrogen or lower alkyl, preferably hydrogen;

R_6 is independently selected from F, Cl, Br, and I;

R_7 is hydrogen, halo, lower alkyl, alkoxy, or haloalkyl; and

m is 1, 2, or 3, wherein all R_6 groups are positioned para, meta, or ortho to the group –Z-, i.e., at positions 2, 3, and/or 4. In specifically preferred embodiment, m is 1, R_6 is positioned para to –Z-, i.e., at position 4.

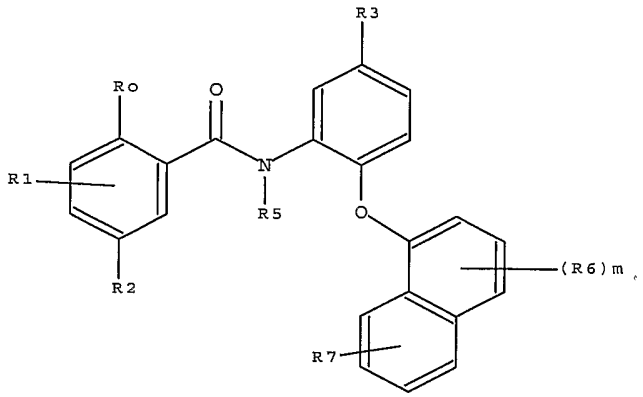
In another preferred embodiment, the pro-apoptotic compositions of Formula 2, and therapeutic treatment processes employing same, comprise a compound of Formula 2h, set forth below:



Formula 2i

wherein Z is oxygen or amino; R_0 is hydroxy, lower (C_1-C_6) alkoxy, hydroxyalkoxy, nitro, amide, sulfonamide, alkylsulfonamide, or aryl sulfonamide; R_1 is hydrogen, halo, nitro, alkoxy, alkyl, aryl, heterocycle, haloalkyl, or amide; R_2 is halo; R_3 is halo, haloalkyl, or haloalkoxy; R_5 is hydrogen or lower alkyl, preferably hydrogen; R_6 is independently selected from F, Cl, Br, and I; R_7 is hydrogen, halo, lower alkyl, alkoxy, or haloalkyl; and m is 1, 2, or 3, wherein all R_6 groups are positioned para, meta, or ortho to the group –Z-. In specifically preferred embodiment, m is 1, R_6 is positioned para to –Z-.

In another preferred embodiment, the pro-apoptotic compositions of Formula 2, and therapeutic treatment processes employing same, comprise a compound of Formula 2j, set forth below:

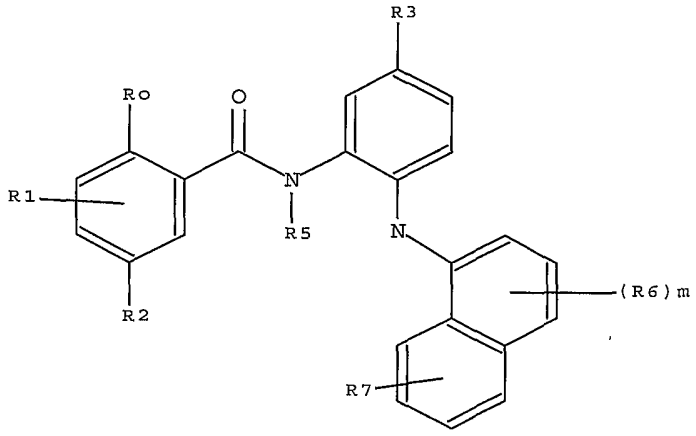


Formula 2j

wherein R_0 is hydroxy, lower (C_1-C_6) alkoxy, hydroxyalkoxy, nitro, amide, sulfonamide, alkylsulfonamide, or aryl sulfonamide; R_1 is hydrogen, halo, nitro, alkoxy, alkyl, aryl, heterocycle, haloalkyl, or amide; R_2 is halo; R_3 is halo, halo-substituted lower alkyl

(preferably trihalo lower alkyl, e.g., trifluoromethyl), or haloalkoxy (preferably halo-substituted C_1-C_6 alkoxy, e.g., trihalo-substituted methoxy); R_5 is hydrogen or lower alkyl, preferably hydrogen; R_6 is independently selected from F, Cl, Br, and I; R_7 is hydrogen, halo, lower alkyl, alkoxy, or haloalkyl; and m is 1, 2, or 3, wherein all R_6 groups are positioned para, meta, or ortho to the group –O-. In specifically preferred embodiment, m is 1, R_6 is positioned para to –O-.

In another preferred embodiment, the pro-apoptotic compositions of Formula 2, and therapeutic treatment processes employing same, comprise a compound of Formula 2k, set forth below:



Formula 2k

wherein R_0 is hydroxy, lower (C_1-C_6) alkoxy, hydroxyalkoxy, nitro, amide, sulfonamide, alkylsulfonamide, or aryl sulfonamide; R_1 is hydrogen, halo, nitro, alkoxy, alkyl, aryl, heterocycle, haloalkyl, or amide; R_2 is halo; R_3 is halo, halo-substituted lower alkyl (preferably trihalo lower alkyl, e.g., trifluoromethyl), or haloalkoxy (preferably halo-substituted C_1-C_6 alkoxy, e.g., trihalo-substituted methoxy); R_5 is hydrogen or lower alkyl, preferably hydrogen; R_6 is independently selected from F, Cl, Br, and I; R_7 is hydrogen, halo, lower alkyl, alkoxy, or haloalkyl; and m is 1, 2, or 3, wherein all R_6 groups are positioned para, meta, or ortho to the group –NH-. In specifically preferred embodiment, m is 1, R_6 is positioned para to –NH-.

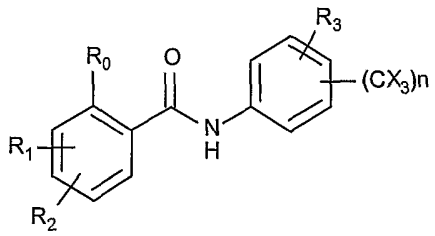
In particularly preferred embodiments according to each and every embodiment and aspect of the invention as set forth above, Z is advantageously oxygen.

In additional particularly preferred embodiments according to each and every embodiment and aspect of the invention as set forth above, at least one of R_1 and R_2 is halo, more preferably, chloro, and more preferably a chloro substituent positioned para to R_0 (in formulas 1 and 1a) or to the hydroxy group (in Formulas 2b, 2c, 2d, 2e, and 2f).

In additional particularly preferred embodiments according to each and every embodiment and aspect of the invention as set forth above, in Formulas 2b, 2c, 2d, 2e, and 2f, R_3 represents an alkyhalo, halo, nitro or cyano substituent; and it is independently and concurrently preferred that R_3 is positioned para to the group containing R_4; and it is independently and concurrently preferred that p is zero.

In additional particularly preferred embodiments according to each and every embodiment and aspect of the invention as set forth above, at least one of R_1, R_2, R_3, R_4, is or comprises trihalomethyl, more preferably, trifluoromethyl.

In another aspect, compounds are provided according to Formula 3:



Formula 3

wherein R_0 is selected from the group consisting of hydroxy, lower (C_1-C_6) alkoxy (which can be unsubstituted or substituted, e.g., hydroxyalkoxy, haloalkoxy, preferably hydroxymethoxy), acetylamide, sulfonamide, alkylsulfonamide, and aryl sulfonamide;

R_1 and R_2 are positioned at the 3, 4 and/or 5 position (the amide side chain defining the 1 position), and are independently selected from the group consisting of hydrogen, hydrophobic substituents such as halo (e.g., F, Cl, Br, I), nitro, alkyl, aryl, heterocycle, haloalkyl and the like, formamido, formamidoalkyl, and alkoxy substituents, or at the 3 and 4 positions together form a substituted or unsubstituted fused ring having 3, 4, 5, or 6 carbon atoms;

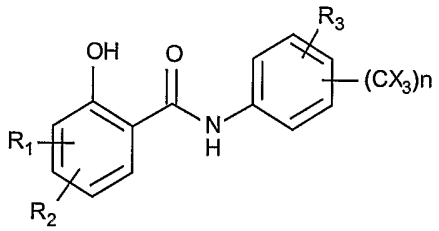
R_3 represents from one to four substituents independently selected from the group consisting of hydrogen, hydrophobic substituents such as halo, alkyl (preferably lower (C_1-C_6) alkyl, haloalkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, a heterocycle, a

heterocycle(oxy), or heterocycle(alkyl), cyano, and nitro substituents. Preferably, R_3 is haloalkyl (preferably trihaloalkyl, e.g., trifluoromethyl) or haloalkoxy (preferably trihaloalkoxy, e.g., trifluoromethoxy);

X represents halo (e.g., F, Cl, Br, I); and

n is an integer selected from the group consisting of 1, 2, or 3.

In one preferred embodiment, the pro-apoptotic compounds have the formula 3a, shown below:



Formula 3a

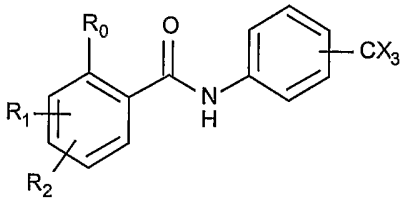
wherein R_1 and R_2 are independently selected from the group consisting of hydrogen, hydrophobic substituents such as halo, alkyl, aryl, haloalkyl and the like, formamido, formamidoalkyl, and alkoxy substituents, positioned at the 3,4 and/or 5 position (the amide side chain defining the 1 position) ;

R_3 represents hydrogen, halo, alkyl, cycloalkyl, aryl, or aralkyl;

X represents halo;

and n is an integer selected from the group consisting of 1, 2, or 3.

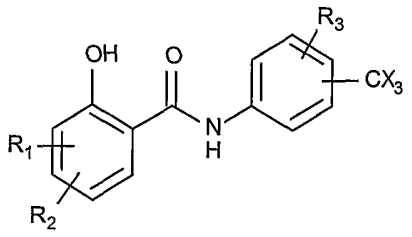
In another preferred embodiment, the pro-apoptotic compositions of Formula 3, and therapeutic treatment processes employing same, comprise a compound of Formula 3b, set forth below:



Formula 3b

wherein R_0, R_1, R_2, and X are as defined above.

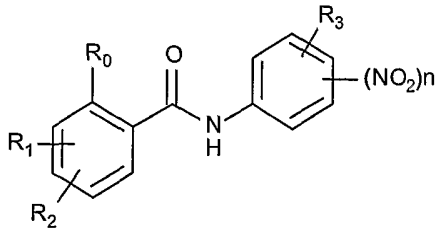
In another preferred embodiment, the pro-apoptotic compositions of Formula 3, and therapeutic treatment processes employing same, comprise a compound of Formula 3c, set forth below:



Formula 3c

wherein R_1, R_2, R_3, X and n are as defined above.

According to another aspect, the present invention provides pro-apoptotic compounds, compositions and therapeutic treatment processes employing such pro-apoptotic compositions, comprising at least one compound of Formula 4, set forth below.



Formula 4

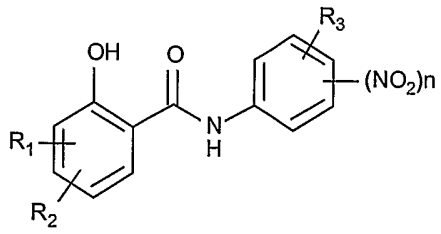
wherein R_0 is selected from the group consisting of hydroxy, lower (C_1-C_6) alkoxy (which can be unsubstituted or substituted, e.g., hydroxyalkoxy, haloalkoxy, preferably hydroxymethoxy), acetylamide, sulfonamide, alkylsulfonamide, and aryl sulfonamide;

R_1 and R_2 are independently selected from the group consisting of hydrogen, hydrophobic substituents such as halo, alkyl, aryl, haloalkyl and the like, formamido, formamidoalkyl, and alkoxy substituents, positioned at the 3,4 and/or 5 position (the amide side chain defining the 1 position) ;

R_3 represents hydrogen halo, alkyl, cycloalkyl, aryl, or aralkyl.

and n is an integer selected from the group consisting of 1, 2, or 3.

In one preferred embodiment, the pro-apoptotic compounds have the formula 4a, shown below:



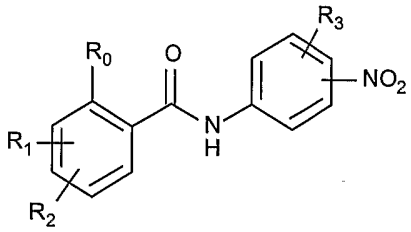
Formula 4a

wherein R_1 and R_2 are independently selected from the group consisting of hydrogen, hydrophobic substituents such as halo, alkyl, aryl, haloalkyl and the like, formamido, formamidoalkyl, and alkoxy substituents, positioned at the 3,4 and/or 5 position (the amide side chain defining the 1 position);

R_3 represents hydrogen, halo, alkyl, cycloalkyl, aryl, or aralkyl.

and n is an integer selected from the group consisting of 1, 2, or 3.

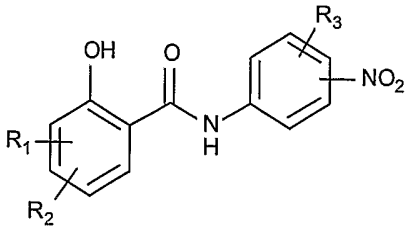
In another preferred embodiment, the pro-apoptotic compositions of Formula 4, and therapeutic treatment processes employing same, comprise a compound of Formula 4b, set forth below:



Formula 4b

wherein R_0, R_1, R_2, R_3, and n are as defined above.

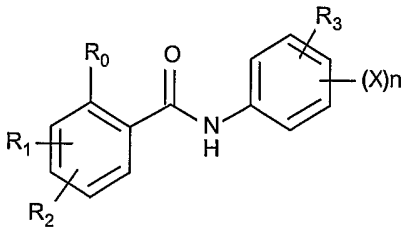
In another preferred embodiment, the pro-apoptotic compositions of Formula 4, and therapeutic treatment processes employing same, comprise a compound of Formula 4c, set forth below:



Formula 4c

wherein R_1, R_2, R_3, and n are as defined above.

According to another aspect, the present invention provides pro-apoptotic compounds, compositions and therapeutic treatment processes employing such pro-apoptotic compositions, comprising at least one compound of Formula 5, set forth below.



Formula 5

wherein R_0 is selected from the group consisting of hydroxy, lower (C_1-C_6) alkoxy (which can be unsubstituted or substituted, e.g., hydroxyalkoxy, haloalkoxy, preferably hydroxymethoxy), acetylamide, sulfonamide, alkylsulfonamide, and aryl sulfonamide;

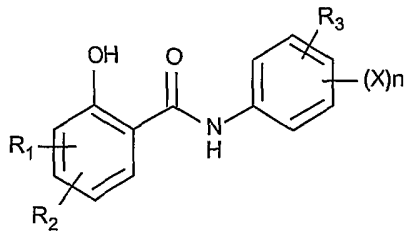
R_1 and R_2 are independently selected from the group consisting of hydrogen, hydrophobic substituents such as halo, alkyl, aryl, haloalkyl and the like, formamido, formamidoalkyl, and alkoxy substituents, positioned at the 3,4 and/or 5 position (the amide side chain defining the 1 position);

R_3 represents hydrogen halo, alkyl, cycloalkyl, aryl, or aralkyl;

X represents halo;

and n is an integer selected from the group consisting of 1, 2, or 3.

In one preferred embodiment, the pro-apoptotic compounds have the formula 5a, shown below:



Formula 5a

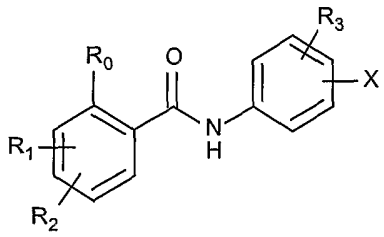
wherein R_1 and R_2 are independently selected from the group consisting of hydrogen, hydrophobic substituents such as halo, alkyl, aryl, haloalkyl and the like, formamido, formamidoalkyl, and alkoxy substituents, positioned at the 3,4 and/or 5 position (the amide side chain defining the 1 position);

R_3 represents hydrogen, halo, alkyl, cycloalkyl, aryl, or aralkyl;

X represents halo;

and n is an integer selected from the group consisting of 1, 2, or 3.

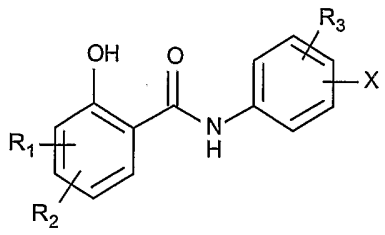
In another preferred embodiment, the pro-apoptotic compositions of Formula 5, and therapeutic treatment processes employing same, comprise a compound of Formula 3b, set forth below:



Formula 5b

wherein R_0, R_1, R_2, R_3, X, and n are as defined above.

In another preferred embodiment, the pro-apoptotic compositions of Formula 5, and therapeutic treatment processes employing same, comprise a compound of Formula 5c, set forth below:

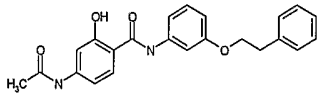
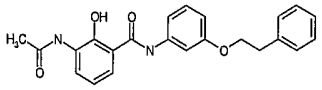
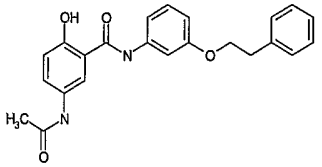
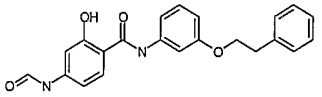
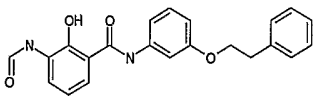
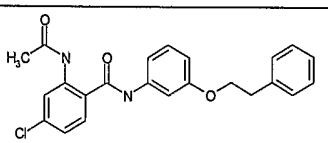


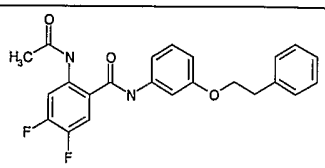
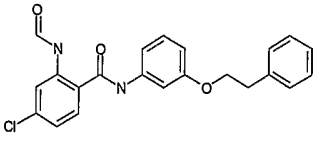
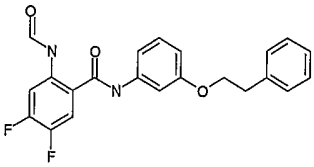
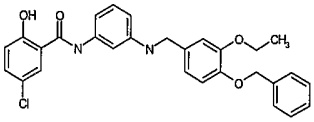
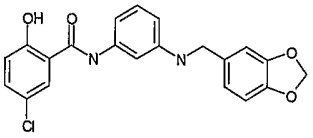
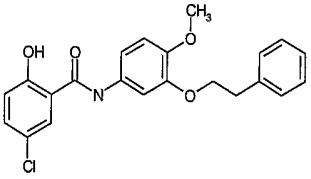
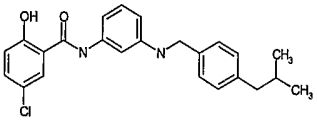
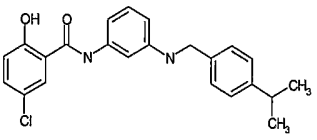
Formula 5c

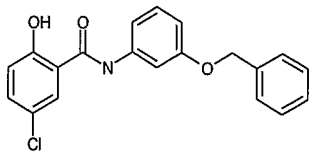
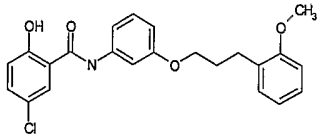
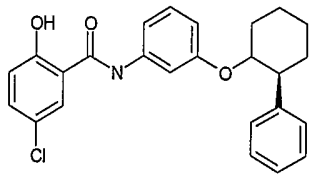
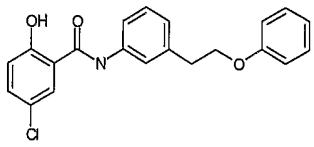
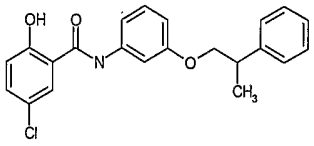
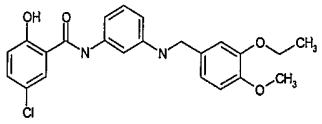
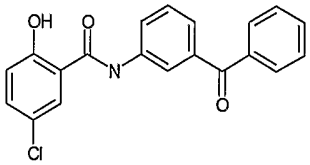
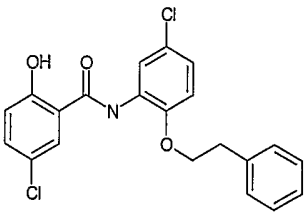
wherein R_1, R_2, R_3, X, and n are as defined above.

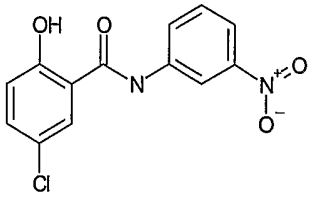
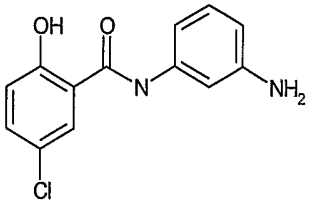
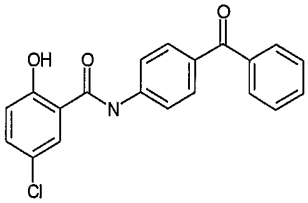
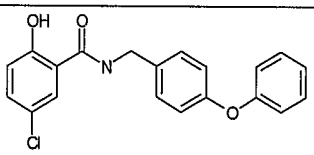
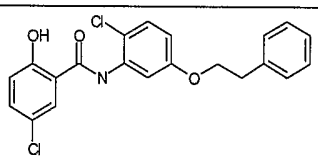
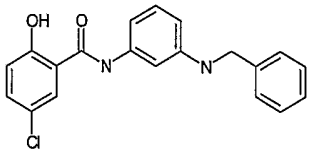
The structures of some representative compounds are provided in Table 1 below:

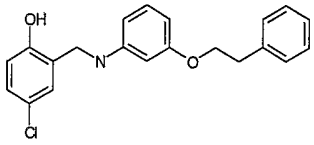
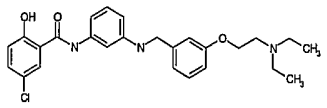
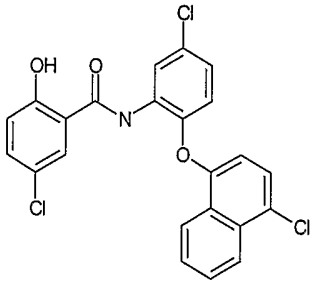
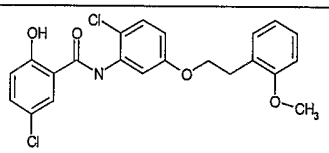
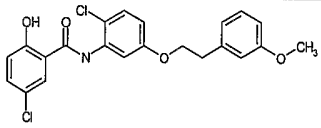
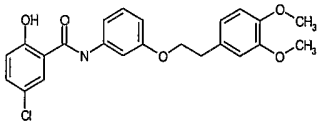
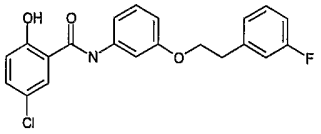
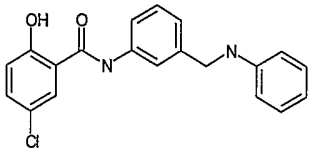
Table 1

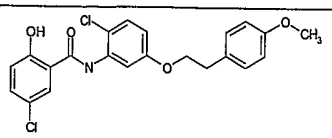
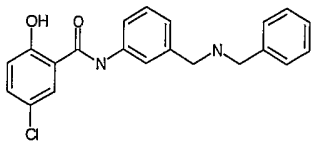
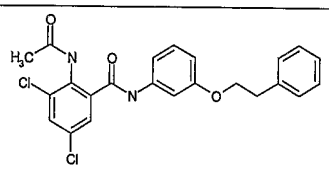
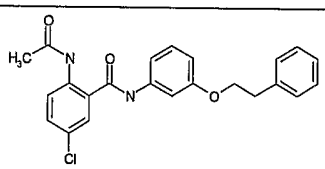
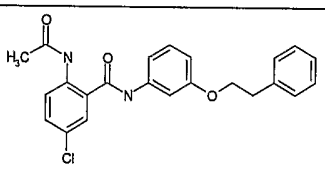
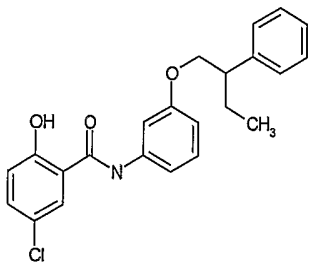
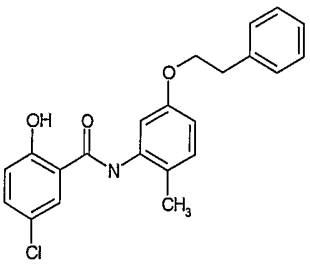
Compound No.	Structure
1	
2	
3	
4	
5	
6	

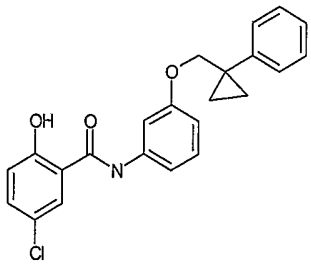
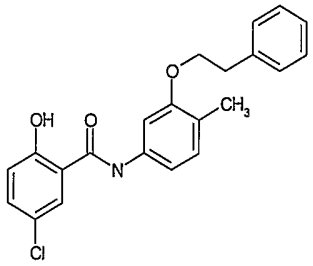
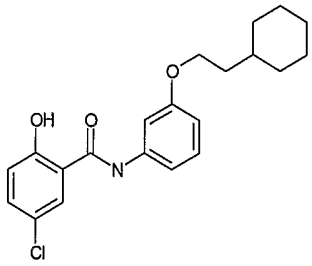
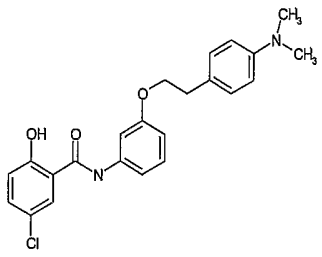
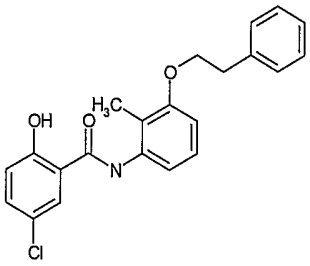
7	
8	
9	
10	
11	
12	
13	
14	

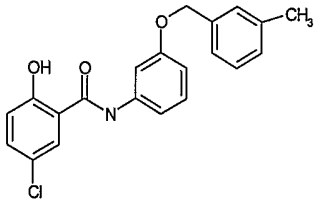
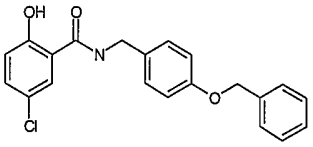
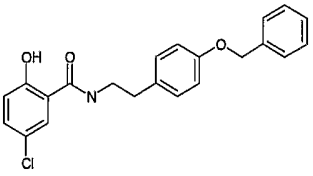
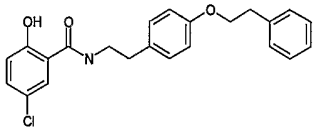
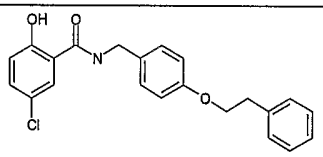
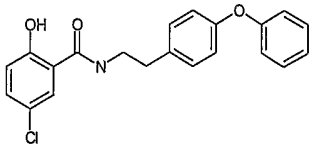
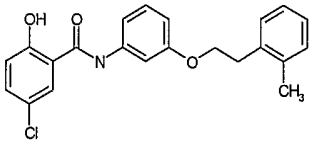
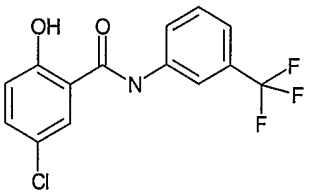
15	
16	
17	
18	
19	
20	
21	
22	

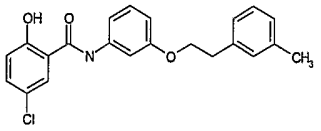
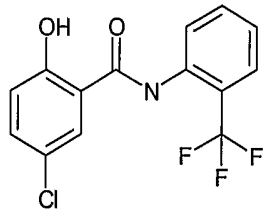
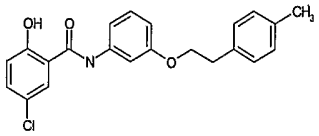
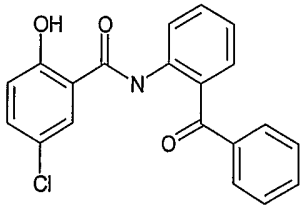
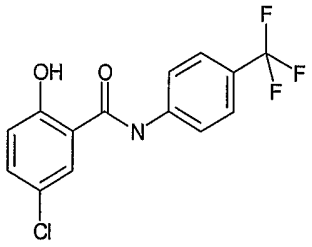
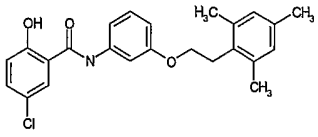
23	
24	
25	
26	
27	
28	

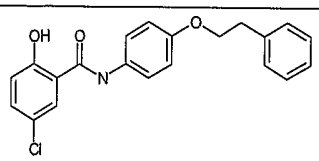
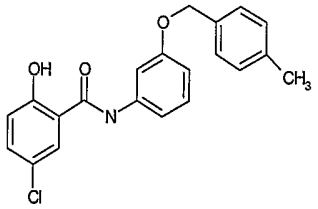
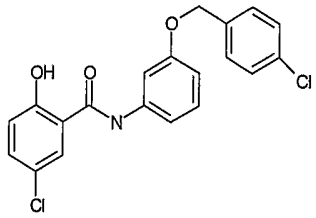
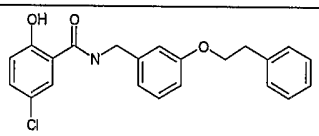
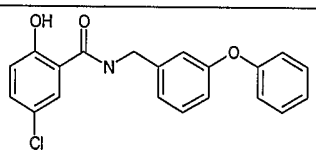
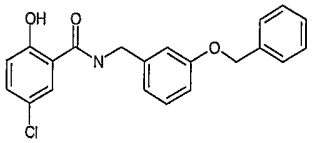
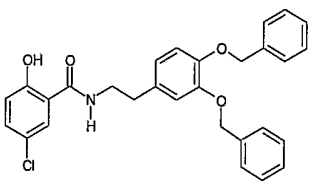
29	
30	
31	
32	
33	
34	
35	
36	

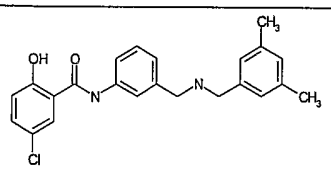
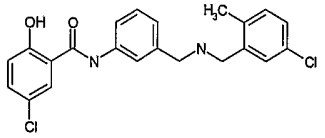
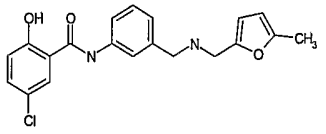
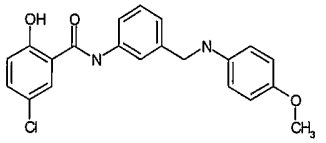
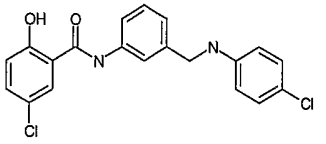
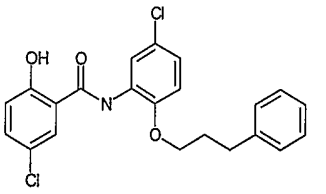
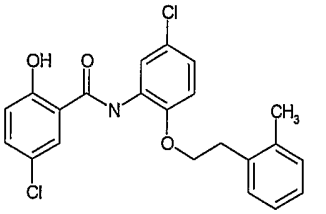
37	
38	
39	
40	
41	
42	
43	

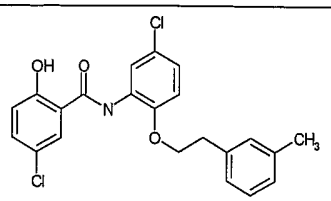
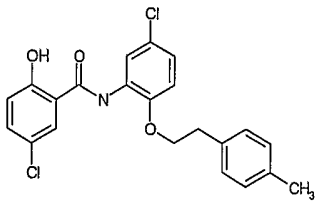
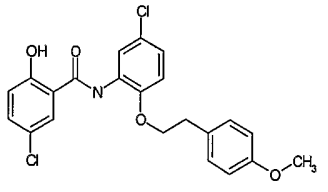
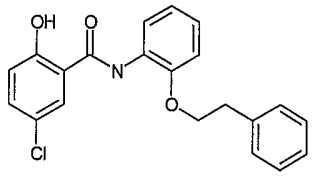
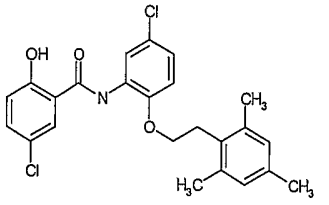
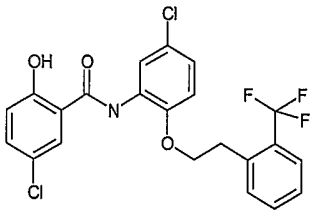
44	
45	
46	
47	
48	

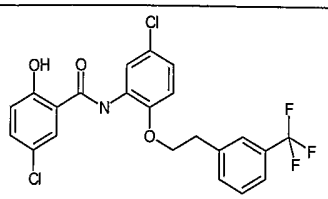
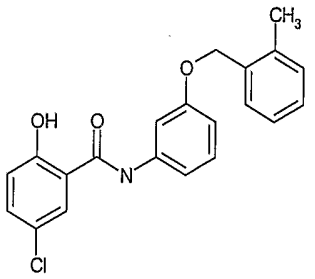
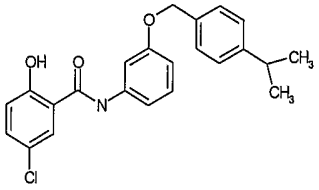
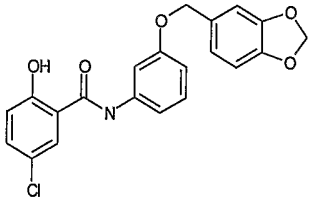
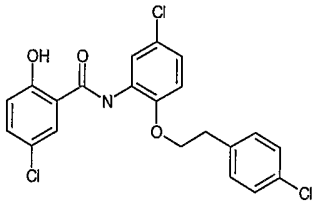
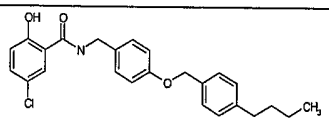
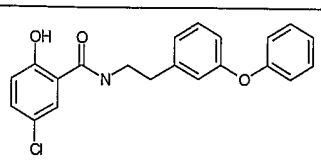
49	
50	
51	
52	
53	
54	
55	
56	

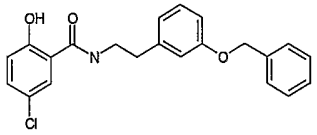
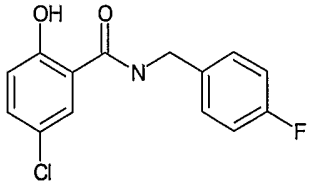
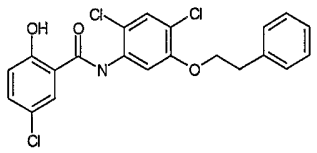
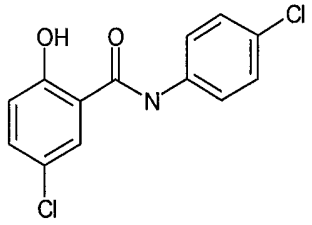
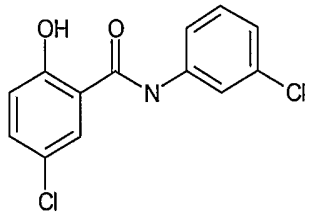
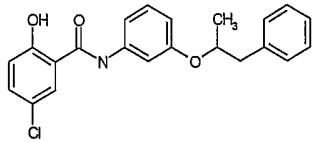
57	
58	
59	
60	
61	
62	

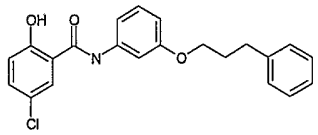
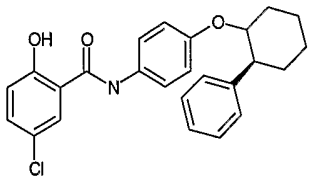
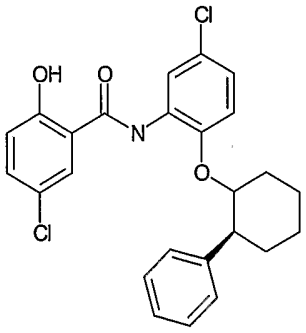
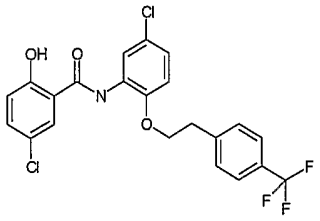
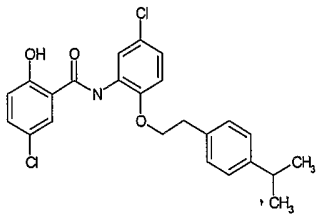
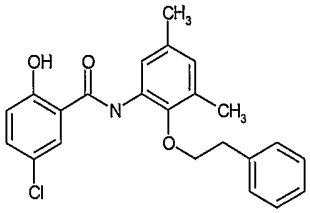
63	
64	
65	
66	
67	
68	
69	

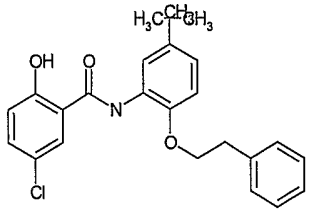
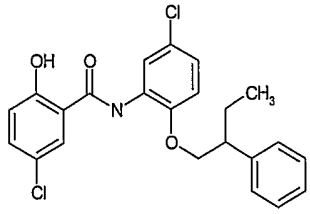
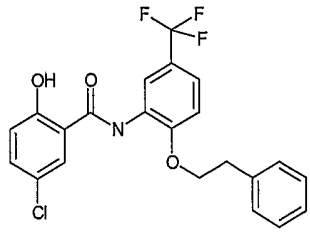
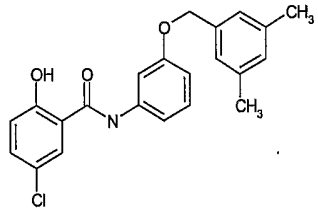
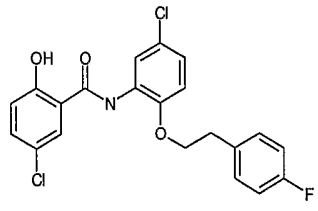
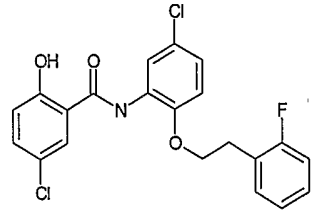
70	
71	
72	
73	
74	
75	
76	

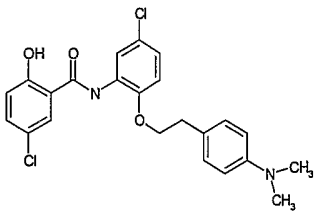
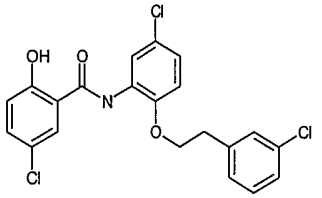
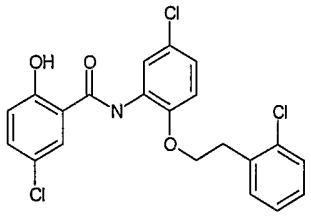
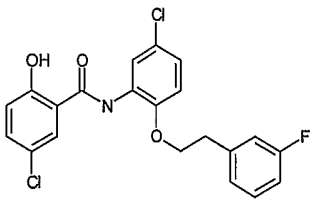
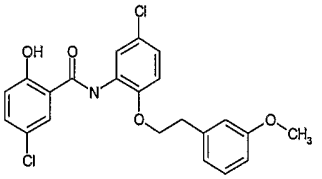
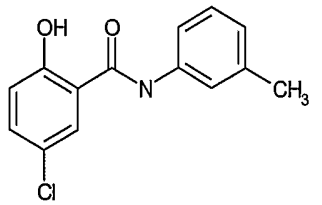
77	
78	
79	
80	
81	
82	

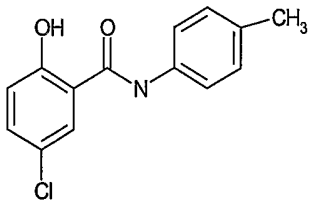
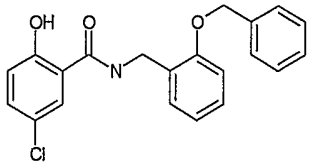
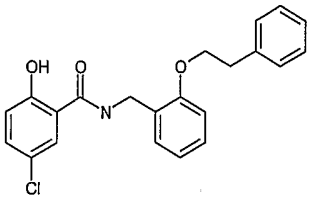
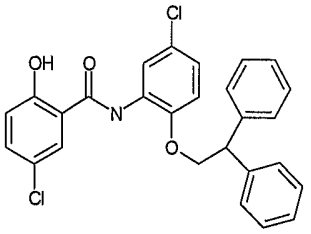
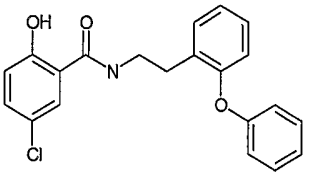
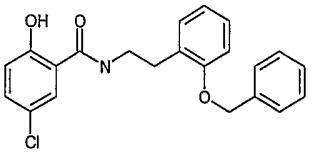
83	
84	
85	
86	
87	
88	
89	

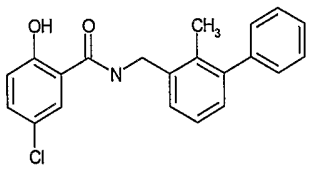
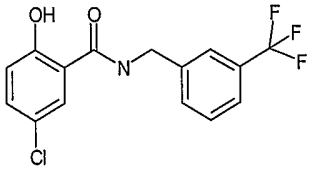
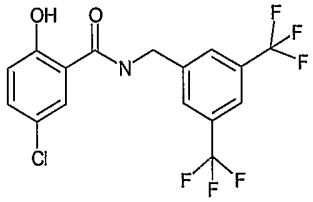
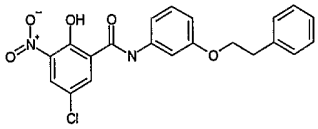
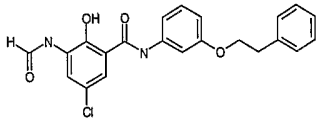
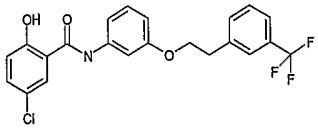
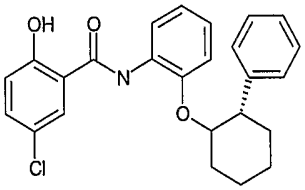
90	
91	
92	
93	
94	
95	

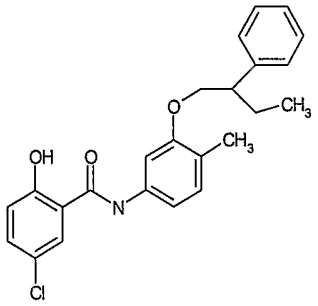
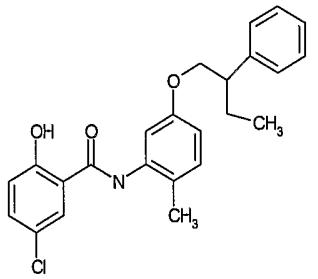
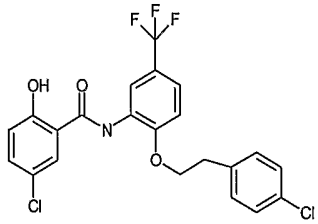
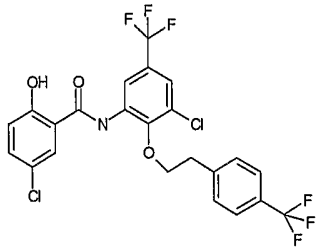
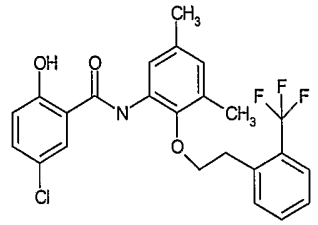
96	
97	
98	
99	
100	
101	

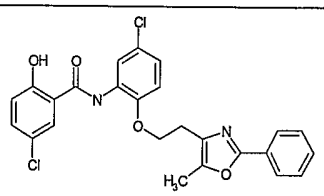
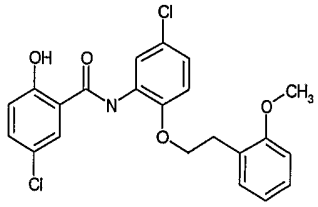
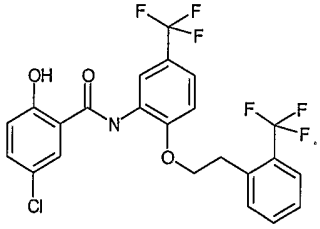
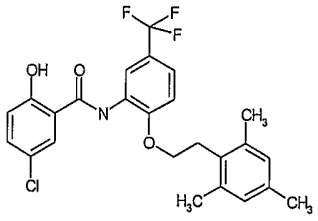
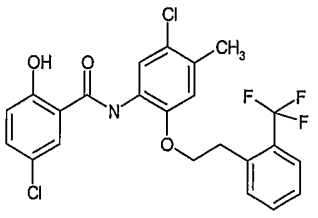
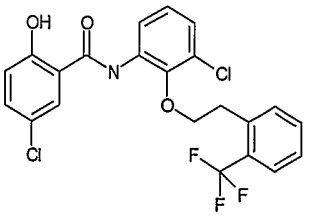
102	
103	
104	
105	
106	
107	

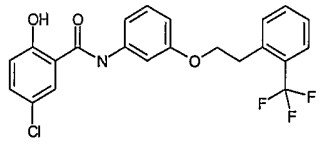
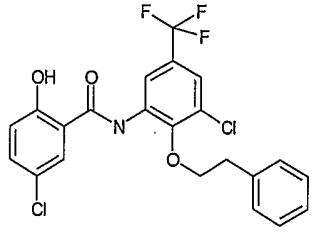
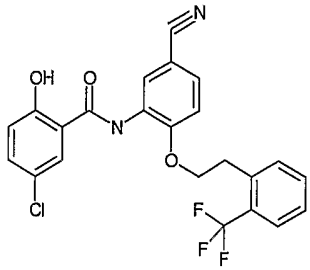
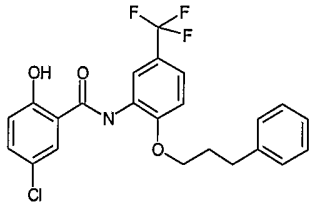
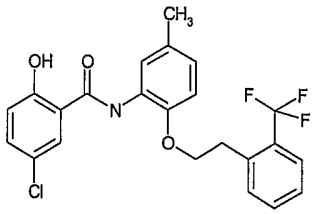
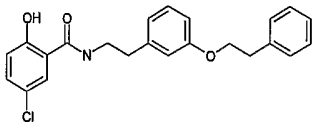
108	
109	
110	
111	
112	
113	

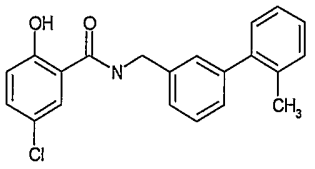
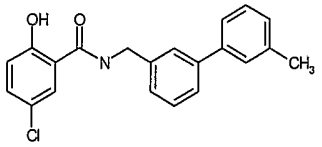
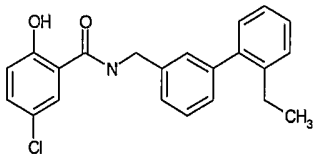
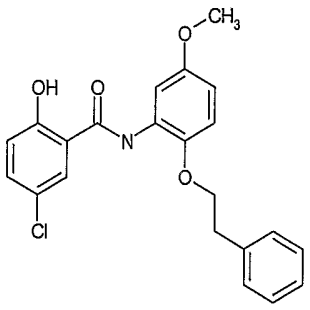
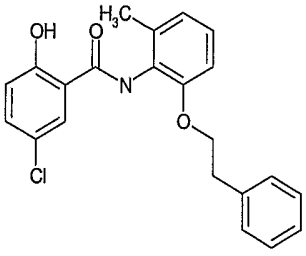
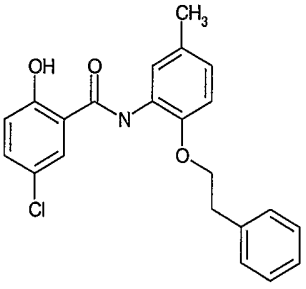
114	
115	
116	
117	
118	
119	

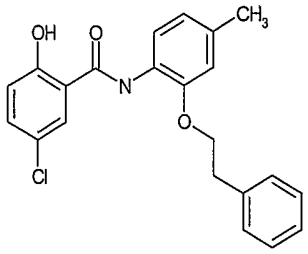
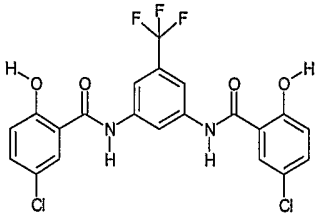
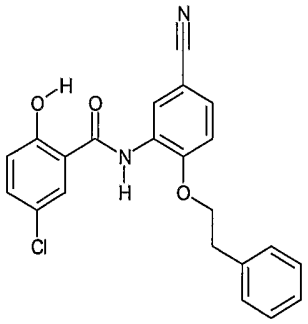
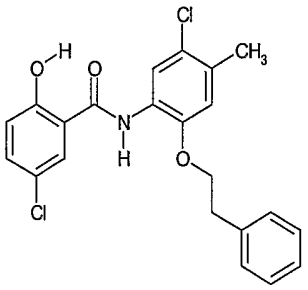
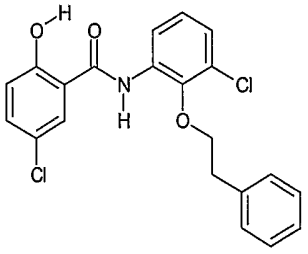
120	
121	
122	
123	
124	
125	
126	

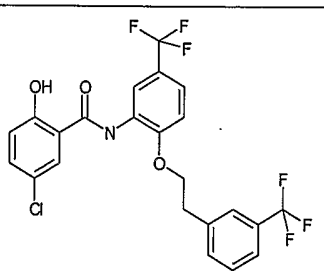
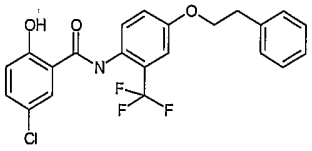
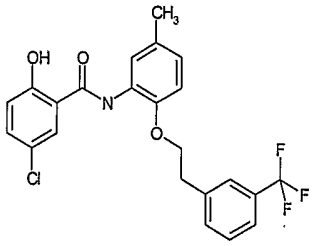
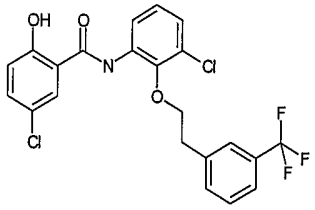
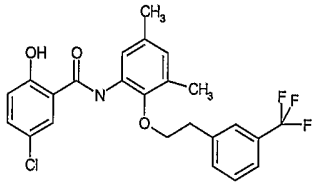
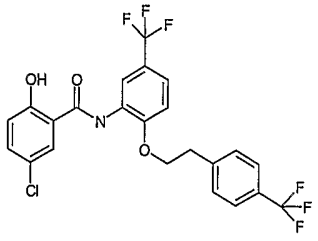
127	
128	
129	
130	
131	

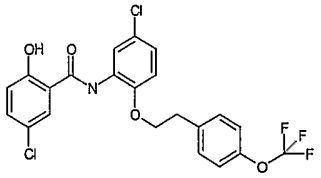
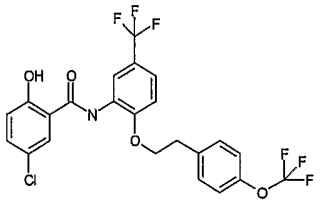
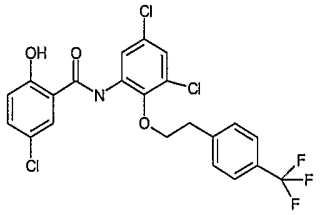
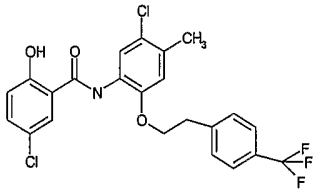
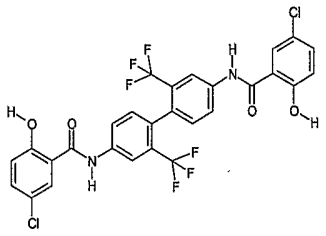
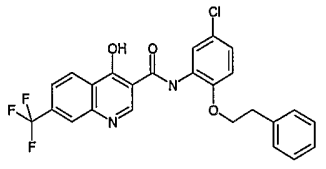
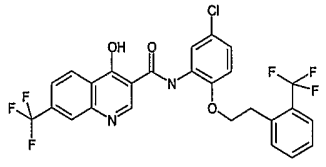
132	
133	
134	
135	
136	
137	

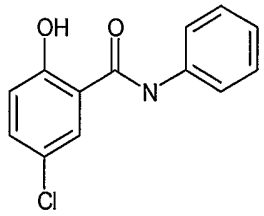
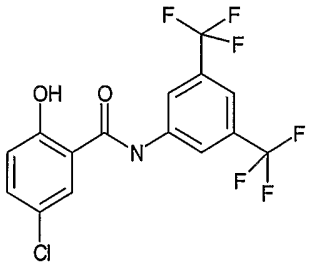
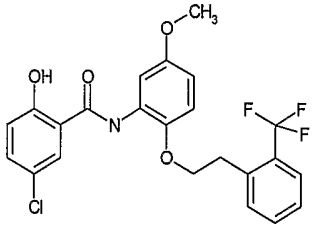
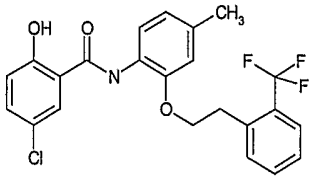
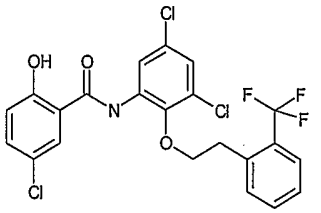
138	
138	
140	
141	
142	
143	

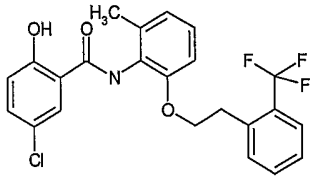
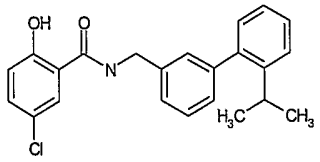
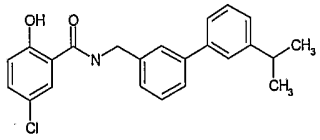
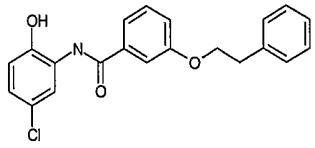
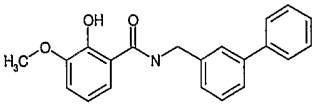
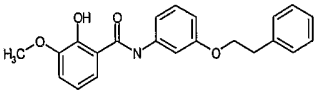
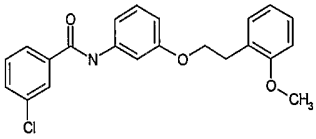
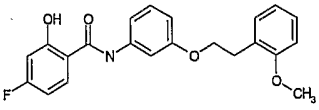
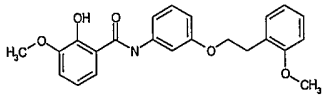
144	
145	
146	
147	
148	
149	

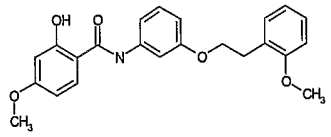
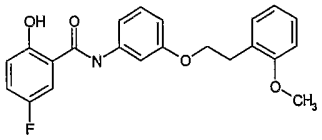
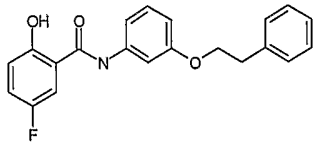
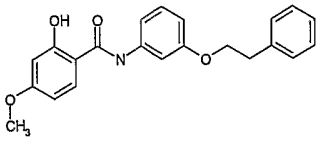
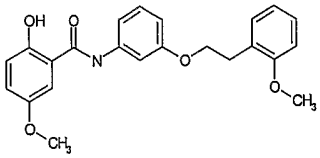
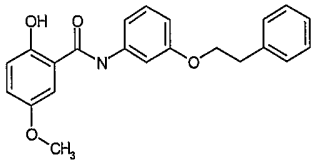
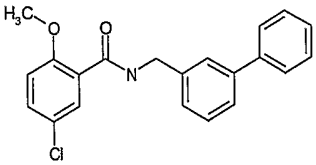
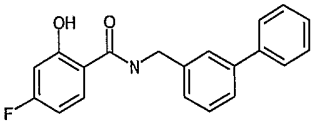
150	
151	
152	
153	
154	

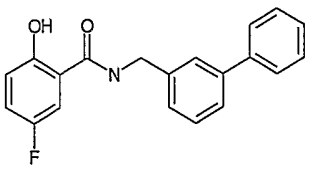
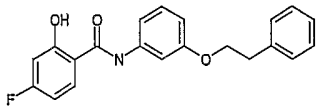
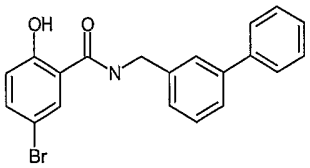
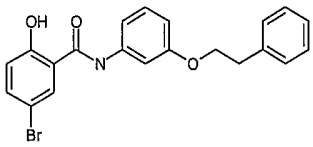
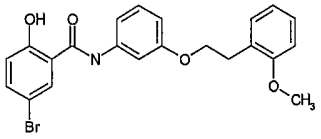
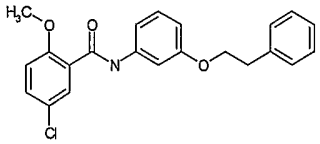
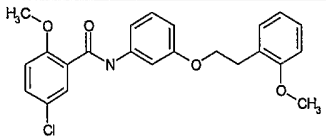
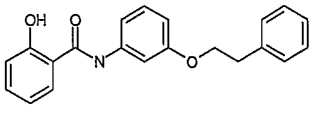
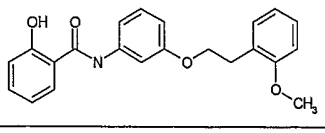
155	
156	
157	
158	
159	
160	

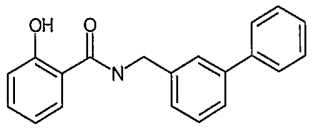
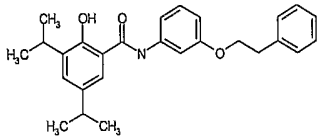
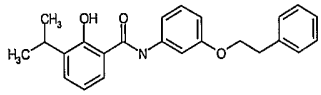
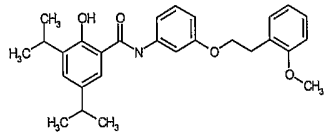
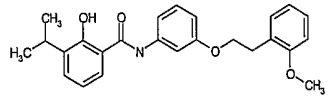
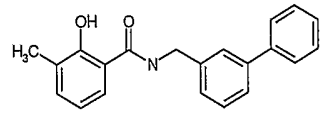
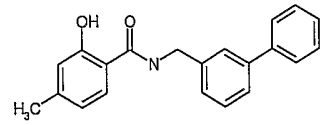
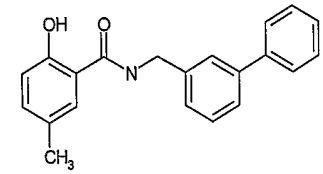
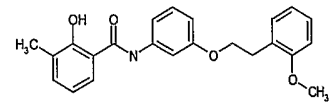
161	
162	
163	
164	
165	
166	
167	

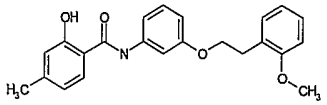
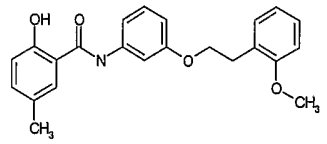
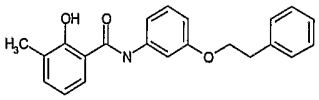
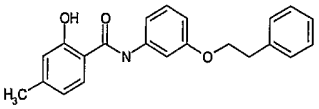
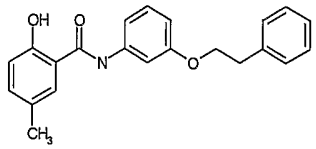
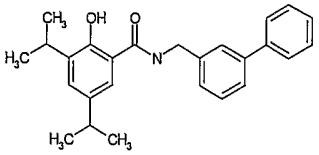
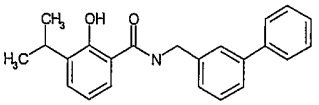
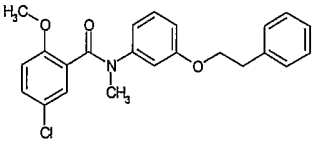
168	
169	
170	
171	
172	

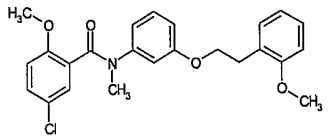
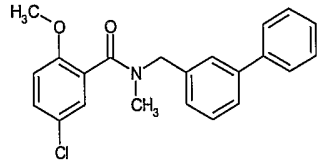
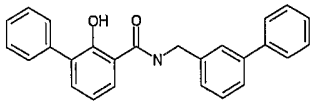
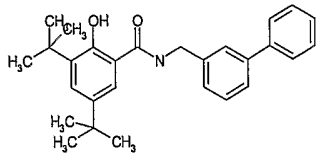
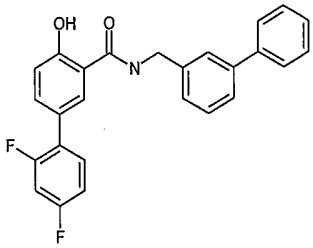
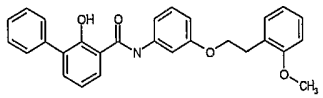
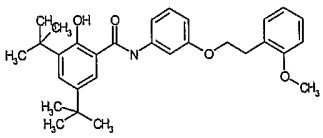
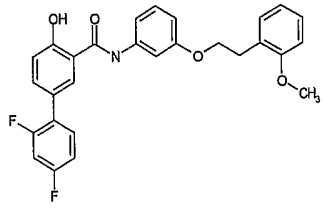
173	
174	
175	
176	
177	
178	
179	
180	
181	

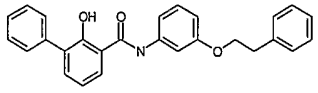
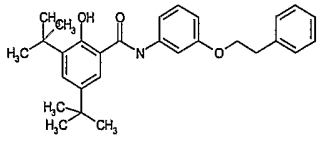
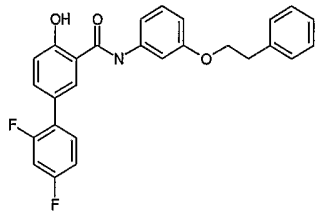
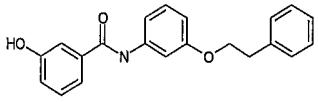
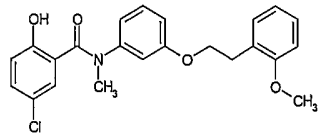
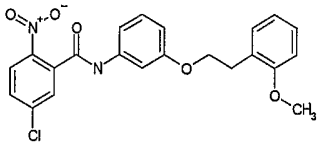
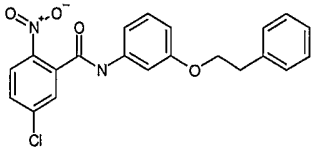
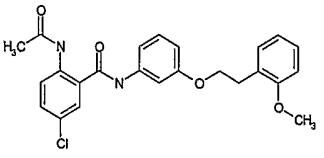
182	
183	
184	
185	
186	
187	
188	
189	

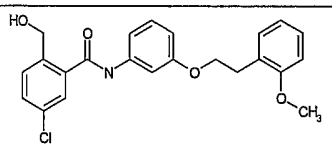
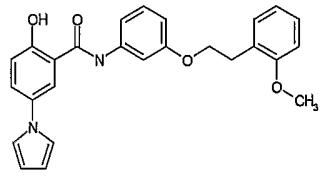
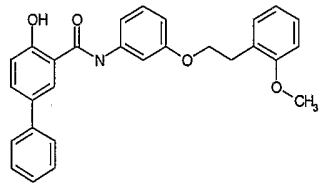
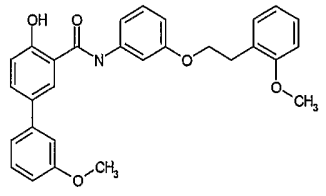
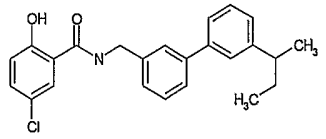
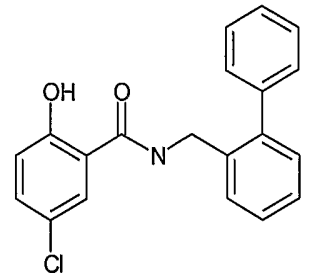
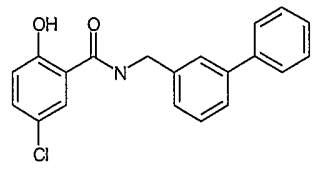
190	
191	
192	
193	
194	
195	
196	
197	
198	

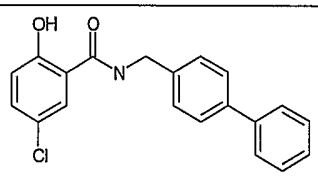
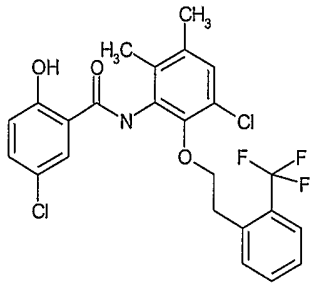
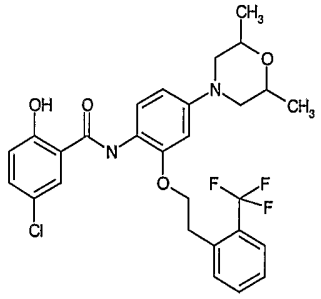
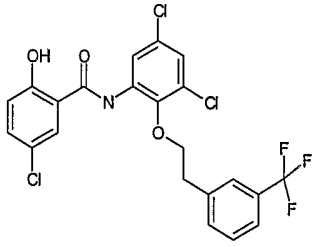
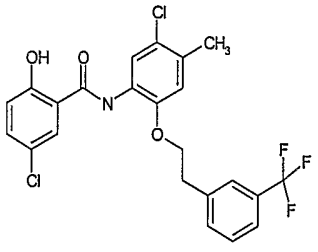
199	
200	
201	
202	
203	
204	
205	
206	
207	

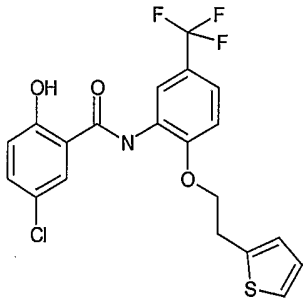
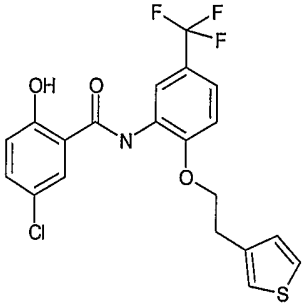
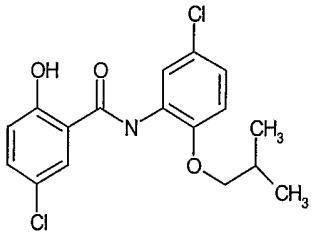
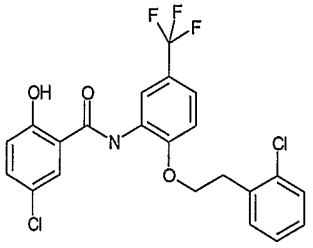
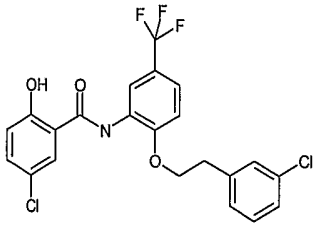
208	
209	
210	
211	
212	
213	
214	
215	

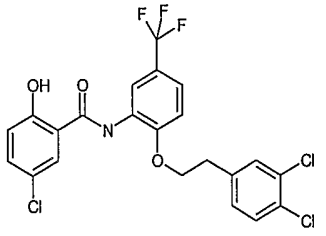
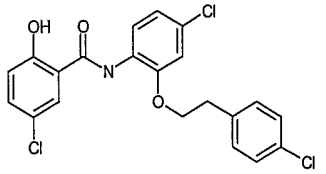
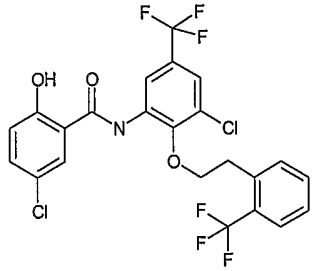
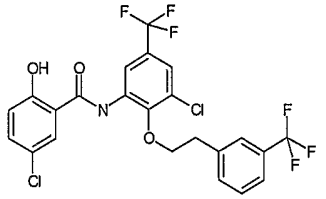
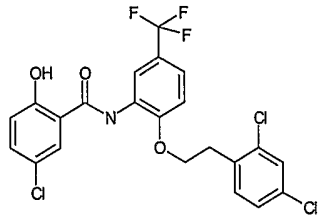
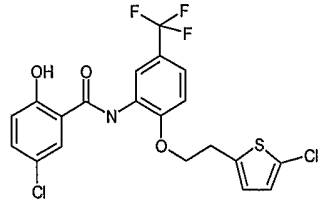
216	
217	
218	
219	
220	
221	
222	
223	

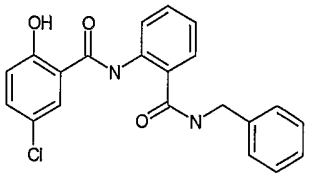
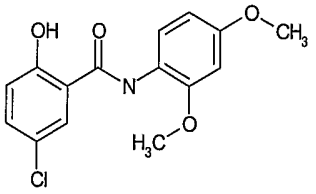
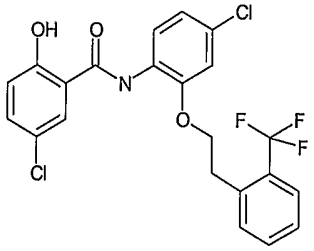
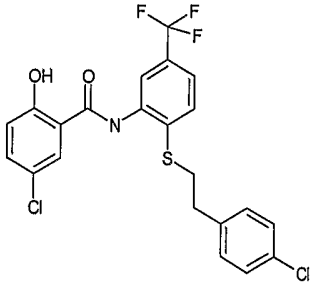
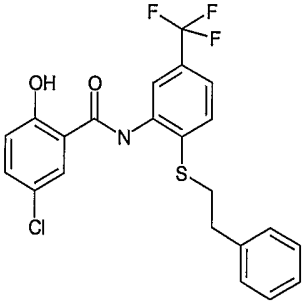
224	
225	
226	
227	
228	
229	
230	
231	

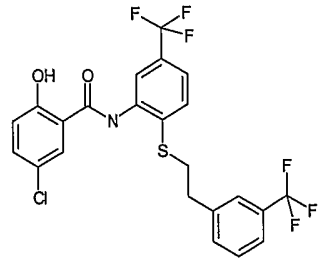
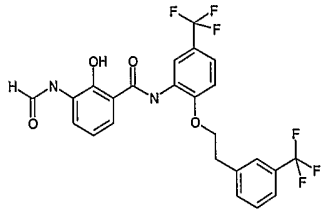
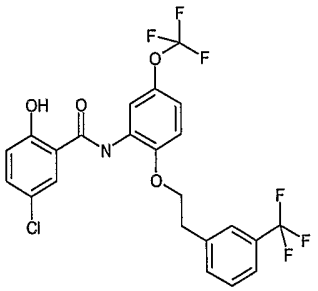
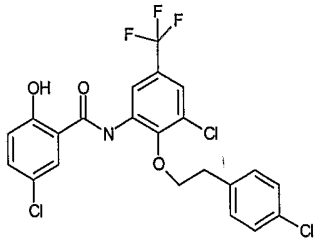
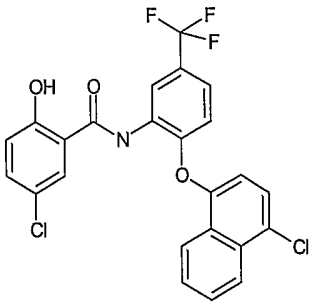
232	
233	
234	
235	
236	
237	
238	

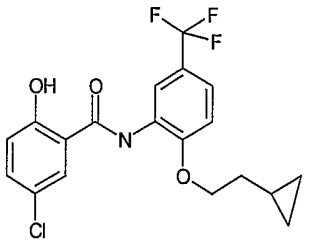
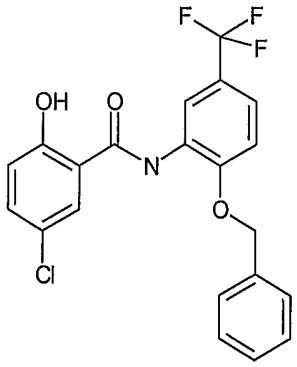
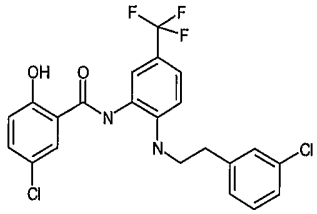
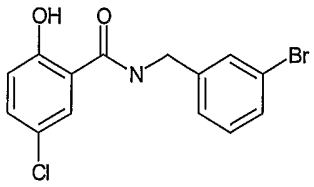
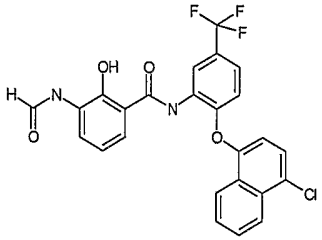
239	
240	
241	
242	
243	

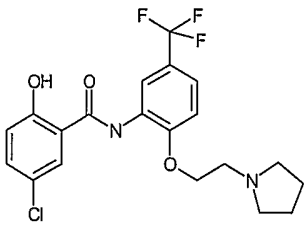
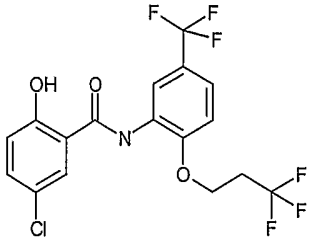
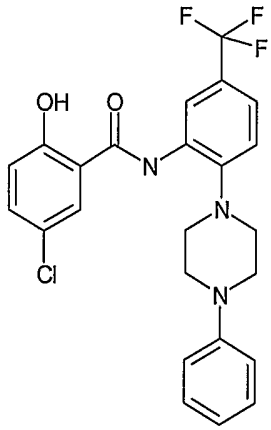
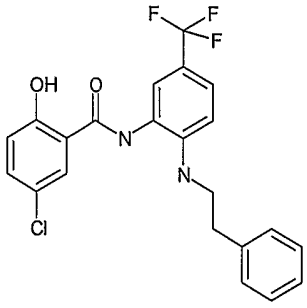
244	
245	
246	
247	
248	

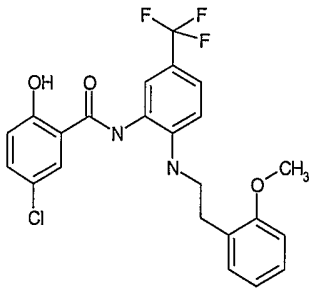
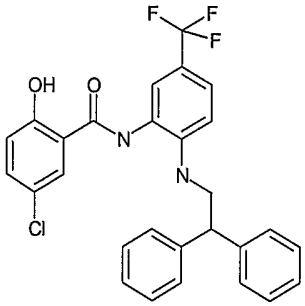
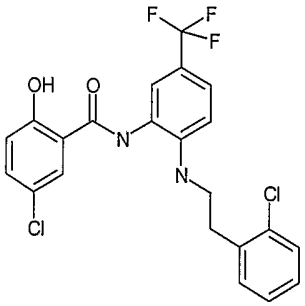
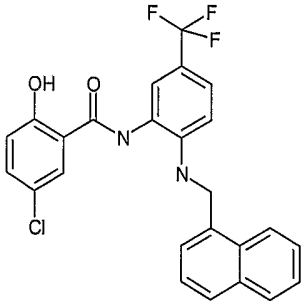
249	
250	
251	
252	
253	
254	

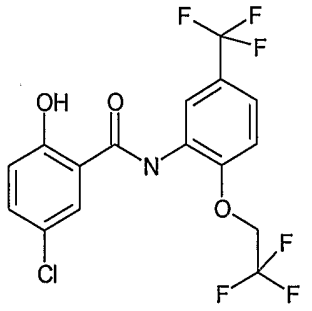
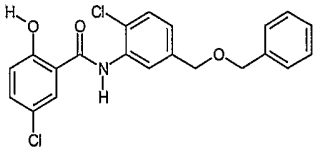
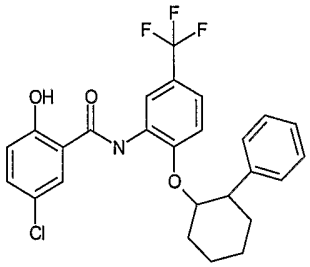
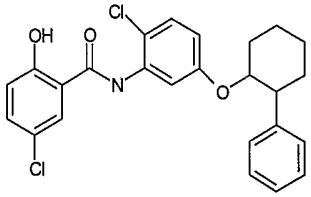
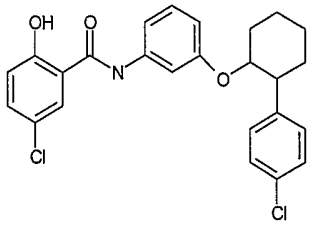
255	
256	
257	
258	
259	

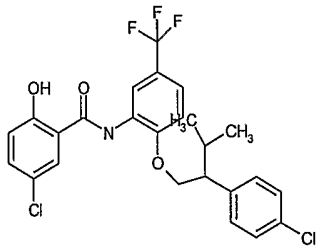
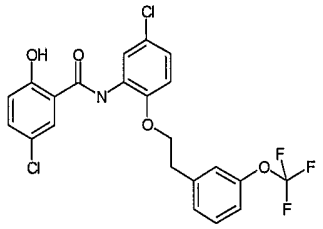
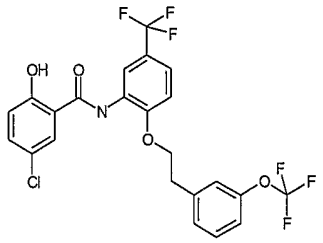
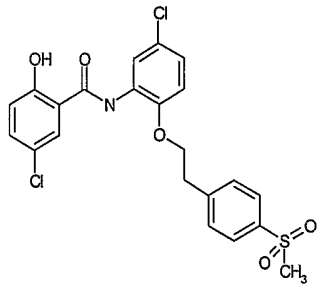
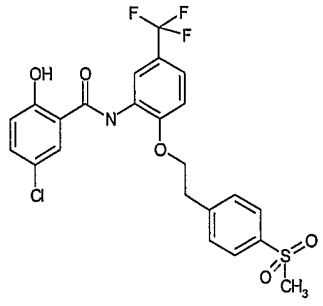
260	
261	
262	
263	
264	

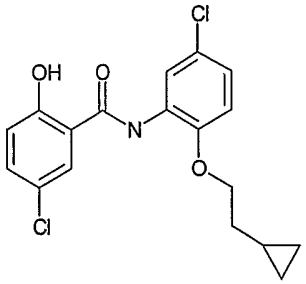
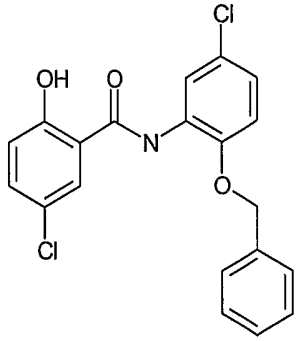
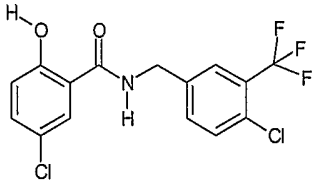
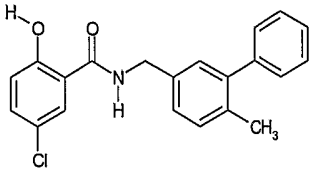
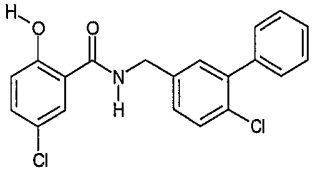
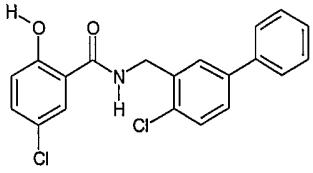
265	
266	
267	
268	
269	

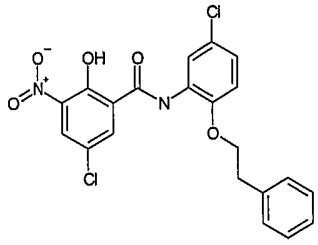
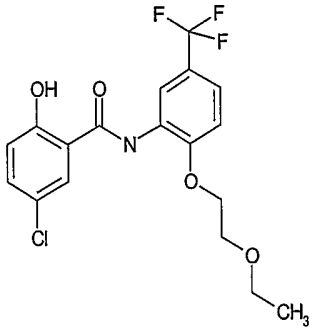
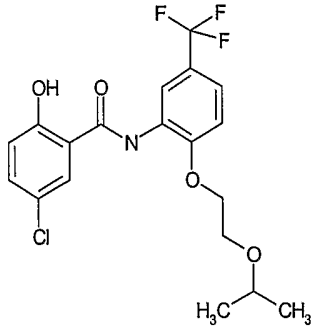
270	
271	
272	
273	

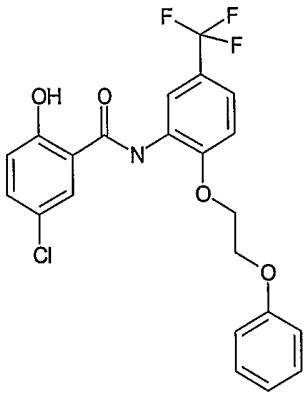
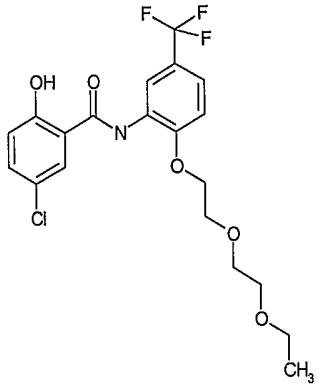
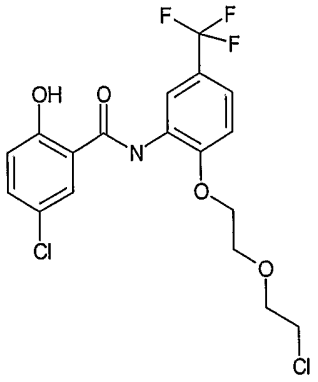
274	
275	
276	
277	

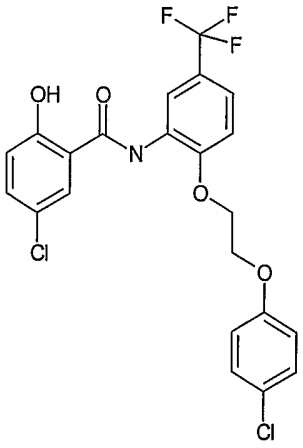
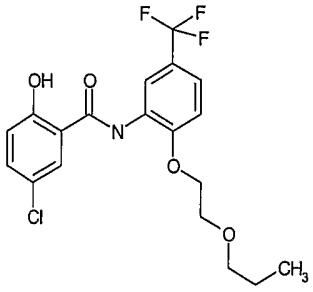
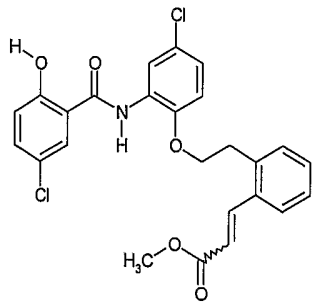
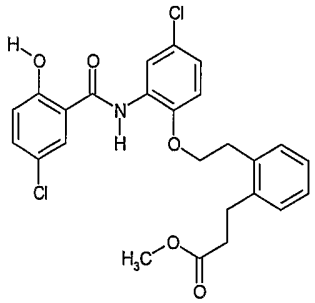
278	
279	
280	
281	
282	

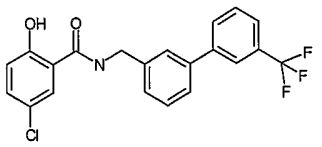
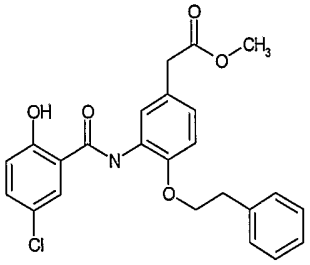
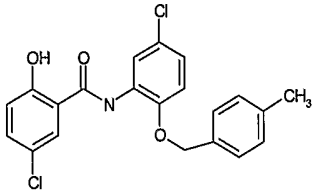
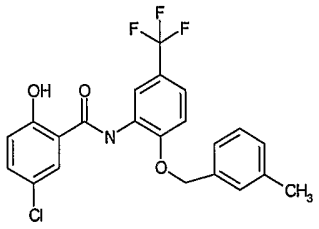
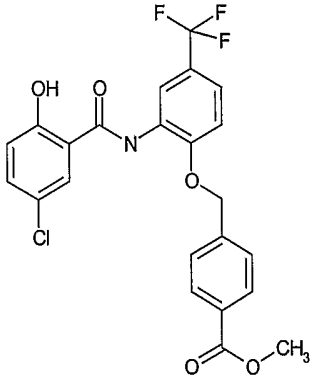
283	
284	
285	
286	
287	

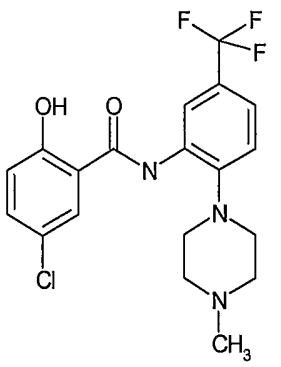
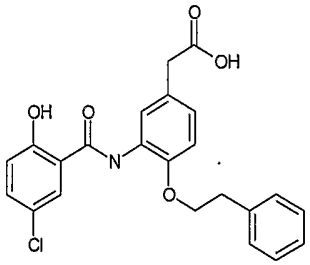
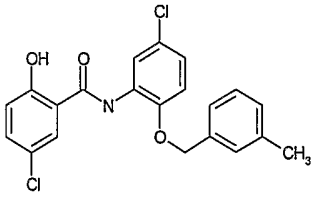
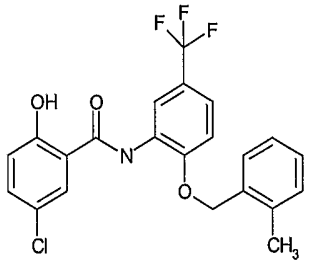
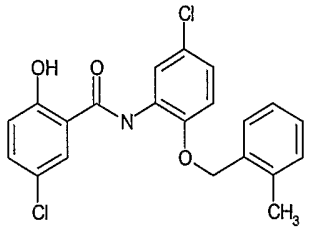
288	
289	
290	
291	
292	
293	

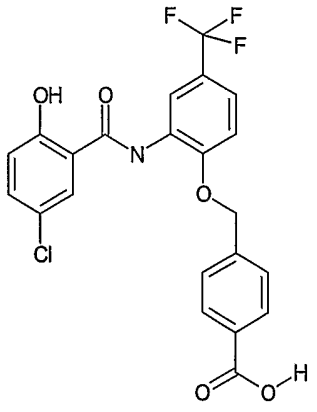
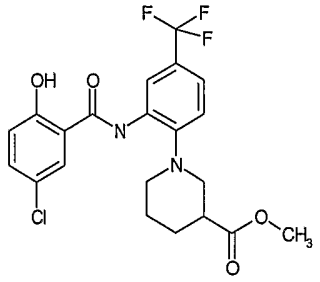
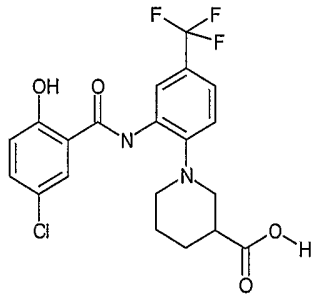
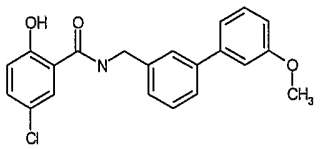
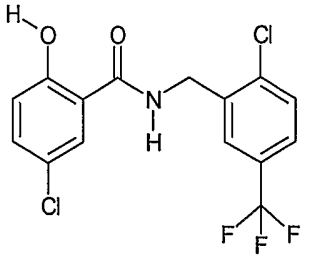
294	
295	
296	

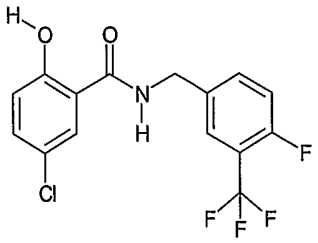
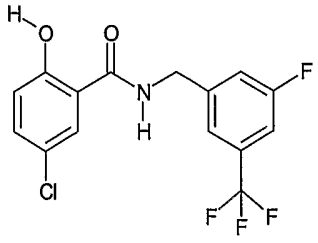
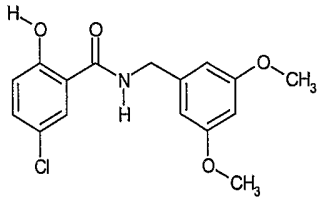
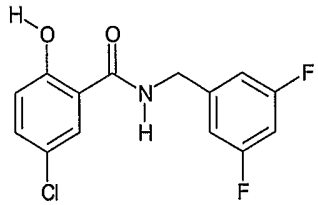
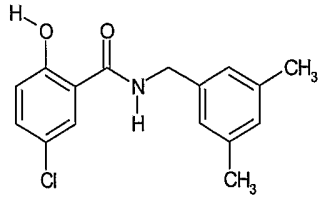
297	
298	
299	

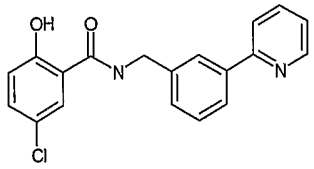
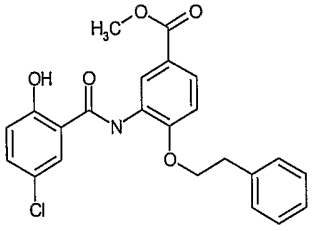
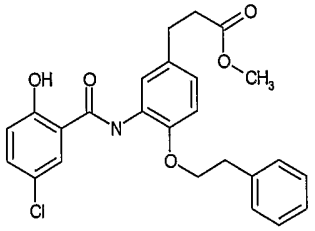
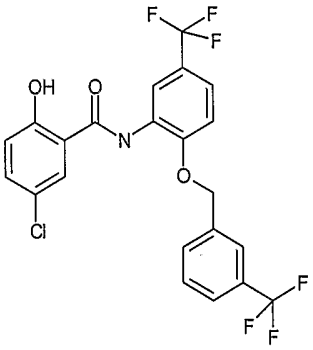
300	
301	
302	
303	

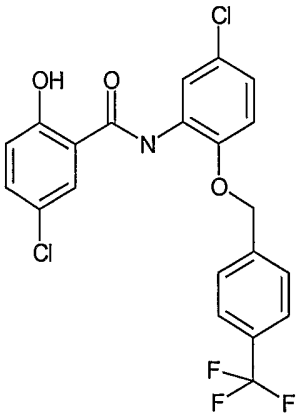
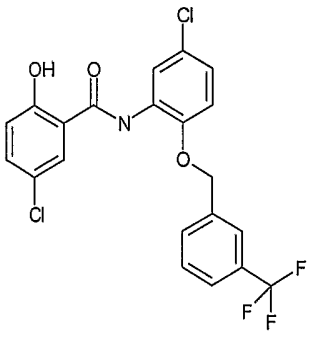
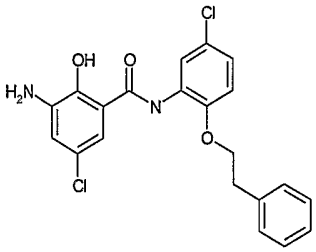
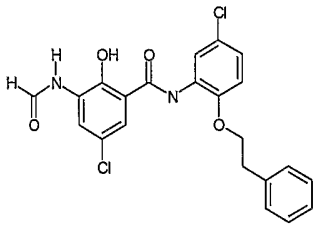
304	
305	
306	
307	
308	

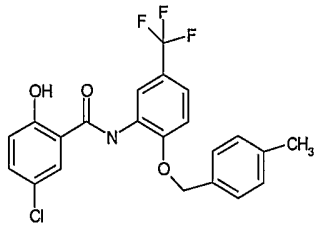
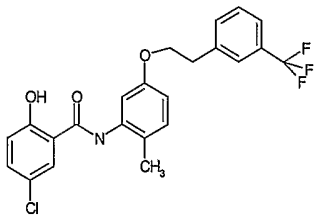
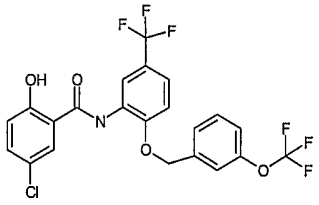
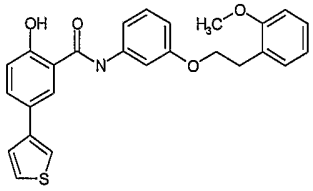
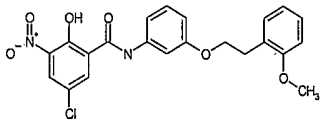
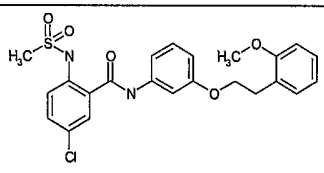
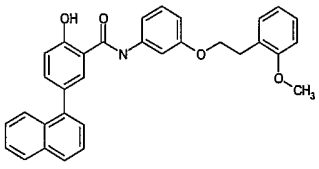
309	
310	
311	
312	
313	

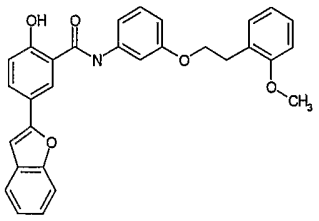
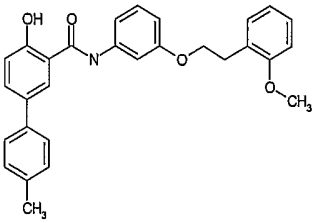
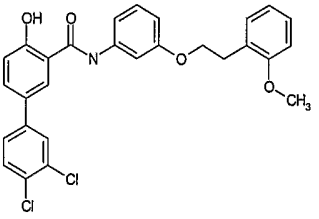
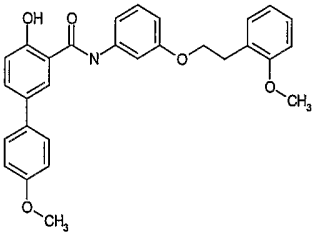
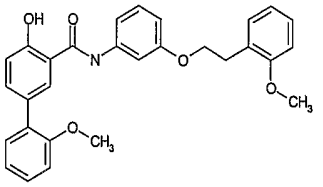
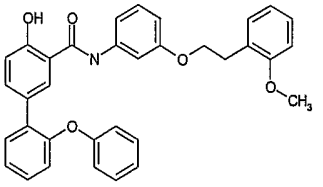
314	
315	
316	
317	
318	

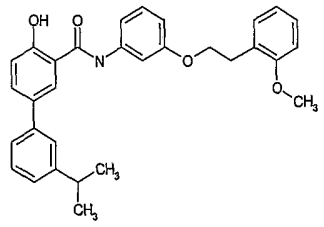
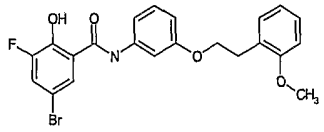
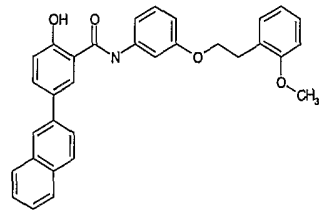
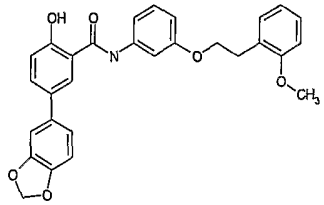
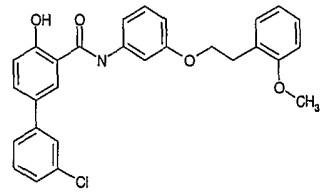
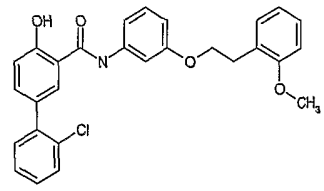
319	
320	
321	
322	
323	

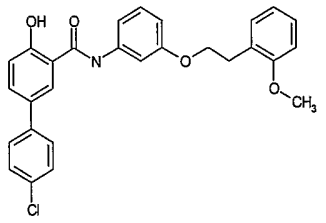
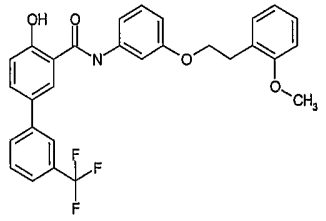
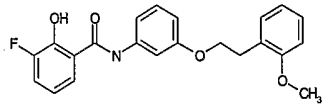
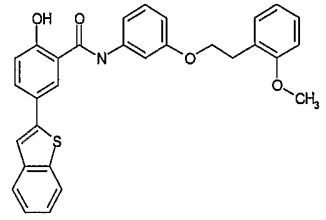
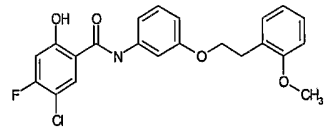
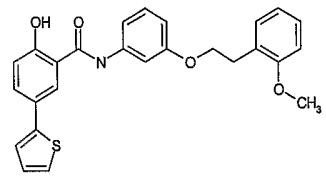
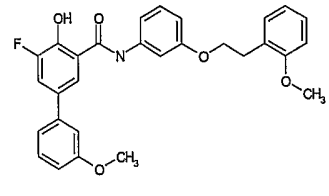
324	
325	
326	
327	

328	
329	
330	
331	

332	
333	
334	
335	
336	
337	
338	

339	
340	
341	
342	
343	
344	

345	
346	
347	
348	
349	
350	

351	
352	
353	
354	
355	
356	
357	

Pharmaceutically Acceptable Compositions, Formulations, and Salts, Esters, and Amides

The term "pharmaceutically acceptable" as applied to compositions, formulations, salts, esters, amides or hydrates of the invention and/or used in methods of the invention refers to compositions, formulations, salts, esters, amides, or hydrates which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic, or a like negative response that exceeds a reasonable risk/therapeutic benefit ratio. More simply, "pharmaceutically acceptable" compositions, formulations, salts, esters, amides, hydrates are compositions, formulations, salts, esters, amides, hydrates suitable for administration to a patient. Accordingly, the present invention also extends to pharmaceutically acceptable compositions, formulations, salts, and esters containing the pro-apoptotic compounds of the present invention.

In particular, pharmaceutically acceptable salts are generally known in the art, and in the case of the present invention, include relatively non-toxic, organic or inorganic salts of the compounds of the present invention. Examples of such salts include, but are not limited to, acid addition salts such as hydrochloride salts, sulfate salts, bisulfate salts, borate salts, nitrate salts, acetate salts, phosphate salts, hydrobromide salts, laurylsulfonate salts, glucoheptonate salts, oxalate salts, oleate salts, laurate salts, stearate salts, palmitate salts, valerate salts, benzoate salts, naththylate salts, mesylate salts, tosylate salts, citrate salts, lactate salts, maleate salts, succinate salts, tartrate salts, fumarate salts, and the like. *See, e.g.,* Berge, *et al., J. Pharm. Sci.*, 66:1-19 (1977). In addition, pharmaceutically acceptable salts also include basic salts such as alkali metal salts, alkaline earth salts, and ammonium salts. For example, pharmaceutically acceptable basic salts include salts of aluminum, calcium, lithium, magnesium, potassium, sodium, zinc, and the like. In addition, organic salts may also be used including, e.g., salts of lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), procaine and tris. The basic nitrogen-containing groups in the compounds of the present invention can be quaternized with various organic agents including, e.g., alkyl halides (such as lower alkyl halide including methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), long chain halides (e.g., decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides),

aralkyl halides (e.g., benzyl and phenethyl bromides), dialkyl sulfates (e.g., dimethyl, diethyl, dibutyl and diamyl sulfates).

The pharmaceutically acceptable salts of the compounds of the present invention also can exist in the form of solvates, e.g., with water, methanol, ethanol, dimethylformamide, ethyl acetate, and the like, and mixtures thereof.

Pharmaceutically acceptable esters can be made by reacting a hydroxyl group in the compounds of the present invention with a pharmaceutically acceptable organic acid, or by reacting a carboxylic acid group in the compounds with a pharmaceutically acceptable alcohol such as methanol, ethanol, propanol, etc. For example, when R_0 in the formulas provided above is hydroxyl or hydroxyl alkoxy, the hydroxyl group may be reacted with an acid to form an ester bond thereby forming an acid salt. The organic acids used to form acid addition salts described above can all be useful. Pharmaceutically acceptable amides can be prepared by reacting an amino functional group of the compounds of the above formulas with a pharmaceutically acceptable organic acid, as will be apparent to skilled artisans.

For oral delivery, the active compounds can be incorporated into a formulation that includes pharmaceutically acceptable carriers such as binders (e.g., gelatin, cellulose, gum tragacanth), excipients (e.g., starch, lactose), lubricants (e.g., magnesium stearate, silicon dioxide), disintegrating agents (e.g., alginate, Primogel, and corn starch), and sweetening or flavoring agents (e.g., glucose, sucrose, saccharin, methyl salicylate, and peppermint). The formulation can be orally delivered in the form of enclosed gelatin capsules or compressed tablets. Capsules and tablets can be prepared in any conventional techniques. The capsules and tablets can also be coated with various coatings known in the art to modify the flavors, tastes, colors, and shapes of the capsules and tablets. In addition, liquid carriers such as fatty oil can also be included in capsules.

Suitable oral formulations can also be in the form of suspension, syrup, chewing gum, wafer, elixir, and the like. If desired, conventional agents for modifying flavors, tastes, colors, and shapes of the special forms can also be included. In addition, for convenient administration by enteral feeding tube in patients unable to swallow, the active compounds can be dissolved in an acceptable lipophilic vegetable oil vehicle such as olive oil, corn oil and safflower oil.

The active compounds can also be administered parenterally in the form of solution or suspension, or in lyophilized form capable of conversion into a solution or suspension form before use. In such formulations, diluents or pharmaceutically acceptable carriers such as sterile water and physiological saline buffer can be used. Other conventional solvents, pH buffers, stabilizers, anti-bacterial agents, surfactants, and antioxidants can all be included. For example, useful components include sodium chloride, acetate, citrate or phosphate buffers, glycerin, dextrose, fixed oils, methyl parabens, polyethylene glycol, propylene glycol, sodium bisulfate, benzyl alcohol, ascorbic acid, and the like. The parenteral formulations can be stored in any conventional containers such as vials and ampoules.

Routes of topical administration include nasal, bucal, mucosal, rectal, or vaginal applications. For topical administration, the active compounds can be formulated into lotions, creams, ointments, gels, powders, pastes, sprays, suspensions, drops and aerosols. Thus, one or more thickening agents, humectants, and stabilizing agents can be included in the formulations. Examples of such agents include, but are not limited to, polyethylene glycol, sorbitol, xanthan gum, petrolatum, beeswax, or mineral oil, lanolin, squalene, and the like. A special form of topical administration is delivery by a transdermal patch. Methods for preparing transdermal patches are disclosed, e.g., in Brown, *et al., Annual Review of Medicine*, 39:221-229 (1988), which is incorporated herein by reference.

Subcutaneous implantation for sustained release of the active compounds may also be a suitable route of administration. This entails surgical procedures for implanting an active compound in any suitable formulation into a subcutaneous space, e.g., beneath the anterior abdominal wall. *See, e.g.,* Wilson *et al., J. Clin. Psych.* 45:242-247 (1984). Hydrogels can be used as a carrier for the sustained release of the active compounds. Hydrogels are generally known in the art. They are typically made by crosslinking high molecular weight biocompatible polymers into a network that swells in water to form a gel like material. Preferably, hydrogels is biodegradable or biosorbable. For purposes of this invention, hydrogels made of polyethylene glycols, collagen, or poly(glycolic-co-L-lactic acid) may be useful. *See, e.g.,* Phillips et al., *J. Pharmaceut. Sci.* 73:1718-1720 (1984).

The active compounds can also be conjugated, to a water soluble non-immunogenic non-peptidic high molecular weight polymer to form a polymer conjugate. For example, an active compound is covalently linked to polyethylene glycol to form a conjugate. Typically, such a conjugate exhibits improved solubility, stability, and reduced toxicity and immunogenicity. Thus, when administered to a patient, the active compound in the conjugate can have a longer half-life in the body, and exhibit better efficacy. *See generally,* Burnham, *Am. J. Hosp. Pharm.*, 15:210-218 (1994). PEGylated proteins are currently being used in protein replacement therapies and for other therapeutic uses. For example, PEGylated interferon (PEG-INTRON A®) is clinically used for treating Hepatitis C. PEGylated adenosine deaminase (ADAGEN®) is being used to treat severe combined immunodeficiency disease (SCIDS). PEGylated L-asparaginase (ONCAPSPAR®) is being used to treat acute lymphoblastic leukemia (ALL). It is preferred that the covalent linkage between the polymer and the active compound and/or the polymer itself is hydrolytically degradable under physiological conditions. Such conjugates known as "prodrugs" can readily release the active compound inside the body. In general, the term "prodrug," refers to compounds which are transformed, *in vivo*, to parent compounds of the active compound for example, by hydrolysis in blood. Controlled release of an active compound can also be achieved by incorporating the active ingredient into microcapsules, nanocapsules, or hydrogels generally known in the art.

Liposomes can also be used as pharmaceutically acceptable carriers for the active compounds of the present invention. Liposomes are micelles made of various lipids such as cholesterol, phospholipids, fatty acids, and derivatives thereof. Various modified lipids can also be used. Liposomes can reduce the toxicity of the active compounds, and increase their stability. Methods for preparing liposomal suspensions containing active ingredients therein are generally known in the art. *See, e.g.,* U.S. Patent No. 4,522,811; Prescott, Ed., *Methods in Cell Biology,* Volume XIV, Academic Press, New York, N.Y. (1976).

Therapeutic Pro-Apoptotic Treatments

As indicated previously, apoptosis, or 'programmed cell death', is an active process essential for normal development and functions of multi-cellular organisms. Apoptosis typically involves isolated single cells and is characterized by DNA fragmentation, morphological changes of cells and nuclei including cell shrinkage, cell surface blebbing, exposure of phosphatidylserine on the cell surface, involution, contraction, chromatin condensation and fragmentation, and phagocytosis without cell infiltration or inflammation. *See* Honig and Rosenberg, *Am. J. Med.*, 108:317-330 (2000). These characteristics are typically used as markers for assaying apoptosis and can be used in cell-based assays for identifying apoptosis. Many techniques have been developed in the art for detecting such apoptosis markers including, e.g., examining DNA ladders, detecting free DNA ends or breaks under TdT-mediated dUTP nick end labeling (TUNEL) or in situ end labeling (ISEL), determining chromatin clumping by bisbenzimide stain or acridine orange stain, observation under light or electron microscopy, immunochemistry analysis of apoptosis-specific proteins, Western blot analysis of caspase-3 cleavage, etc.

Dysregulation of apoptosis can lead to various diseases and disorders. It is now understood that reduced apoptosis may contribute to tumorigenesis and formation of cancer. Thus, induction of tumor cell apoptosis is now a commonly accepted effective approach in treating cancer. In addition, stimulation of endothelial cell apoptosis may prevent tumor blood supply and cause tumor regression. *See* Dimmeler and Zeiher, *Cir. Res.*, 87:434-439 (2000). Dysregulation of apoptosis is also an integral part of a wide range of autoimmune diseases and disorders. *See* Ravirajan *et al., Int. Rev. Immunol.*, 18:563-589 (1999). In addition, many neurological disorders involve apoptosis.

Apoptosis also plays an important role in osteoporotic disorders including, but not limited to, postmenopausal osteoporosis, involutional osteoporosis, and glucocorticoid-induced osteoporosis. *See* Weinstein, *et al., Am. J. Med.*, 108:153-164 (2000). Generally, under normal conditions, the balance between bone formation, bone resorption, bone cell proliferation and apoptosis maintains nearly constant bone mass. The imbalance of such processes leads to abnormal bone remodeling, and thus osteoporosis and other bone-related diseases. It has been suggested that treatment or

prevention of osteoporosis may be achieved by promotion of osteoclast apoptosis. *See* Weinstein, *et al., Am. J. Med.*, 108:153-164 (2000).

Apoptosis also has physiological significance in animal virus infection. *See* Kyama *et al., Microbes and Infection*, 2:1111-1117 (2000). Apoptosis of cells infected with viruses may slow the viral multiplication process, although animal viruses typically are able to escape apoptosis of the infected cells. However, it has been suggested that apoptosis of the infected cells triggers the phagocytosis of the dying cells by macrophages. This phagocytosis prevents the leakage of toxic substances that are mediators of dysregulated inflammatory reactions. As a result, dysregulated inflammatory reactions are prevented while specific immune responses against the viruses are initiated at the viral infection site. *See* Kyama *et al., Microbes and Infection*, 2:1111-1117 (2000).

Thus, the present invention provides a method of promoting apoptosis of mammalian cells, particularly human cells, comprising administering to the cells, a pharmaceutical composition comprising a compound of the present invention or a pharmaceutically acceptable salt, ester, amide or hydrate thereof. Advantageously, the pharmaceutical composition is administered in an amount sufficient to promote apoptosis and/or to reduce the proliferation of abnormal cells, particularly tumor cells or proliferation of uncontrolled cells.

Specifically, the present invention provides a method of promoting apoptosis in a mammal, particularly a human, in recognized need thereof comprising administering to the mammal, a pharmaceutical composition comprising a compound of the present invention or a pharmaceutically acceptable salt, ester, amide or hydrate thereof. Advantageously, the pharmaceutical composition is administered in an amount sufficient to promote apoptosis and/or to reduce the proliferation of abnormal cells, particularly tumor cells or proliferation of uncontrolled cells.

Another embodiment of the invention comprises the use of a compound of the present invention, or a pharmaceutically acceptable salt, ester or amide or hydrate thereof, in the manufacture of a medicament or pharmaceutical composition comprising the compound, or a therapeutically acceptable salt, ester or amide or hydrate thereof, for promoting apoptosis in a mammal in recognized need thereof.

In yet another embodiment of the present invention, a method is provided for treating or preventing cancer or neoplastic diseases comprising identifying a mammal, particularly human patient in need of such treatment and administering a compound according to the present invention, or a pharmaceutically acceptable salt, ester, amide or hydrate thereof, or a pharmaceutical composition according to the present invention. Similarly, the compounds and compositions of the present invention can also be used in treating other diseases which benefit from promoting apoptosis, e.g., autoimmune diseases, viral infection, psoriasis, and the like, as discussed in detail above.

In particularly preferred embodiments according to each and every embodiment and aspect of the invention as set forth above, the compound of the present invention, is selected to have a pro-apoptotic efficacy sufficient to achieve an EC_{50} cytotoxic response, at a concentration of about 50 μM (micromolar) or less, when applied for a period of 72 hours at standard incubating conditions, to a cell culture formed of cells selected from the group consisting of LNCaP, OVCAR-3, and SW480. More preferably, the compound has a pro-apoptotic EC_{50} efficacy under the above time and incubation conditions, and with respect to the specified cells, at a concentration of 25 μM or less, even more preferably at a concentration of 10 μM or less, and most preferably at a concentration of 5 μM or less.

Thus, the therapeutic treatment methods and compositions according to the present invention can be applicable to a variety of tumors, i.e., abnormal growth, whether cancerous (malignant) or noncancerous (benign), and whether primary tumors or secondary tumors. Such disorders include but are not limited to lung cancers such as bronchogenic carcinoma (e.g., squamous cell carcinoma, small cell carcinoma, large cell carcinoma, and adenocarcinoma), alveolar cell carcinoma, bronchial adenoma, chondromatous hamartoma (noncancerous), and sarcoma (cancerous); heart tumors such as myxoma, fibromas and rhabdomyomas; bone tumors such as osteochondromas, condromas, chondroblastomas, chondromyxoid fibromas, osteoid osteomas, giant cell tumors, chondrosarcoma, multiple myeloma, osteosarcoma, fibrosarcomas, malignant fibrous histiocytomas, Ewing's tumor (Ewing's sarcoma), and reticulum cell sarcoma; brain tumors such as gliomas (e.g., glioblastoma multiforme), anaplastic astrocytomas, astrocytomas, and oligodendrogliomas, medulloblastomas, chordoma, Schwannomas,

ependymomas, meningiomas, pituitary adenoma, pinealoma, osteomas, and hemangioblastomas, craniopharyngiomas, chordomas, germinomas, teratomas, dermoid cysts, and angiomas; various oral cancers; tumors in digestive system such as leiomyoma, epidermoid carcinoma, adenocarcinoma, leiomyosarcoma, stomach adenocarcinomas, intestinal lipomas, intestinal neurofibromas, intestinal fibromas, polyps in large intestine, familial polyposis such as Gardner's syndrome and Peutz-Jeghers syndrome, colorectal cancers (including colon cancer and rectal cancer); liver cancers such as hepatocellular adenomas, hemangioma, hepatocellular carcinoma, fibrolamellar carcinoma, cholangiocarcinoma, hepatoblastoma, and angiosarcoma; kidney tumors such as kidney adenocarcinoma, renal cell carcinoma, hypernephroma, and transitional cell carcinoma of the renal pelvis; bladder cancers; tumors in blood system including acute lymphocytic (lymphoblastic) leukemia, acute myeloid (myelocytic, myelogenous, myeloblastic, myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., Sézary syndrome and hairy cell leukemia), chronic myelocytic (myeloid, myelogenous, granulocytic) leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, mycosis fungoides, and myeloproliferative disorders (including myeloproliferative disorders are polycythemia vera, myelofibrosis, thrombocythemia, and chronic myelocytic leukemia); skin cancers such as basal cell carcinoma, squamous cell carcinoma, melanoma, Kaposi's sarcoma, and Paget's disease; head and neck cancers; eye-related cancers such as retinoblastoma and intraocular melanocarcinoma; male reproductive system cancers such as benign prostatic hyperplasia, prostate cancer, and testicular cancers (e.g., seminoma, teratoma, embryonal carcinoma, and choriocarcinoma); breast cancer; female reproductive system cancers such as uterus cancer (endometrial carcinoma), cervical cancer (cervical carcinoma), cancer of the ovaries (ovarian carcinoma), vulvar carcinoma, vaginal carcinoma, fallopian tube cancer, and hydatidiform mole; thyroid cancer (including papillary, follicular, anaplastic, or medullary cancer); pheochromocytomas (adrenal gland); noncancerous growths of the parathyroid glands; cancerous or noncancerous growths of the pancreas; etc.

Specifically, breast cancers, colon cancers, prostate cancers, lung cancers and skin cancers may be amenable to the treatment by the methods and compositions of the present invention. In addition, pre-malignant conditions may also be treated by the

methods of the present invention to prevent or stop the progression of such conditions towards malignancy, or cause regression of the premalignant conditions. Examples of pre-malignant conditions include hyperplasia, dysplasia, and metaplasia.

Thus, the term "treating cancer" as used herein, specifically refers to administering therapeutic agents to a patient diagnosed of cancer, i.e., having established cancer in the patient, to inhibit the further growth or spread of the malignant cells in the cancerous tissue, and/or to cause the death of the malignant cells. The term "treating cancer" also encompasses treating a patient having pre-malignant symptoms or physiological conditions, in order to mitigate or stop the progression of, or cause regression of, the pre-malignant conditions.

The methods and compositions of the present invention may also be useful in treating or preventing other diseases and disorders caused by abnormal cell proliferation (hyperproliferation or dysproliferation), e.g., keloid, liver cirrhosis, psoriasis, etc.

Additionally, the methods and compositions of the invention may be used in treating or preventing autoimmune diseases and disorders including, but not limited to, rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjogren's syndrome, Canale-Smith syndrome, psoriasis, scleroderma, dermatomyositis, polymyositis, Behcet's syndrome, skin-related autoimmue diseases such as bullus pemphigoid, IgA dermatosis, pemphigus vulgaris, pemphigus foliaceus, dermatitis herpetiformis, contact dermatitis, autoimmune allopecia, erythema nodosa, and epidermolysis bullous aquisita, drug-induced hemotologic autoimmune disorders, autoimmue thrombocytopenic purpura, autoimmune neutropenia, systemic sclerosis, multiple sclerosis, imflammatory demyelinating, diabetes mellitus, autoimmune polyglandular syndromes, vasculitides, Wegener's granulomatosis, Hashimoto's disease, multinodular goitre, Grave's disease, autoimmune encephalomyelitis (EAE), demyelinating diseases, etc.

The methods and compositions of the invention may also be used for treating or preventing osteoporotic disorders such as postmenopausal osteoporosis, involutional osteoporosis, and glucocorticoid-induced osteoporosis.

In addition, the methods and compositions of the present invention may also be useful in treating or preventing diseases or disorders associated with viral infection in animals, particularly humans. Such viral infection can be caused by viruses including,

but not limited to, hepatitis A, hepatitis B, hepatitis C, hepatitis E virus, hepatitis G virus, human foamy virus, human herpes viruses (e.g., human herpes virus 1, human herpes virus 2, human herpes virus 4/Epstein Barr virus, human herpes virus 5, human herpes virus 7), human papilloma virus, human parechovirus 2, human T-cell lymphotropic virus, Measles virus, Rubella virus, Semliki Forest virus, West Nile virus, Colorado tick fever virus, foot-and-mouth disease virus, Marburg virus, polyomavirus, TT virus, Lassa virus, lymphocytic choriomeningitis virus, vesicular stomatitis virus, influenza viruses, human parainfluenza viruses, respiratory syncytial virus, herpes simplex virus, herpes zoster virus, varicella virus, cytomegalovirus, variola virus, encephalitis, and various human retroviruses, etc.

As used herein, the term "HBV infection" generally encompasses infection of a human by any strain or serotype of hepatitis B virus, including acute hepatitis B infection and chronic hepatitis B infection. Thus, the treatment of HBV infection means the treatment of a person who is a carrier of any strain or serotype of hepatitis B virus or a person who is diagnosed of active hepatitis B to reduce the HBV viral load in the person or to alleviate one or more symptoms associated with HBV infection and/or hepatitis B, including, e.g., nausea and vomiting, loss of appetite, fatigue, muscle and joint aches, elevated transaminase blood levels, increased prothrombin time, jaundice (yellow discoloration of the eyes and body) and dark urine. A carrier of HBV may be identified by any methods known in the art. For example, a person can be identified as HBV carrier on the basis that the person is anti-HBV antibody positive (e.g., based on hepatitis B core antibody or hepatitis B surface antibody), or is HBV-positive (e.g., based on hepatitis B surface antigens (HBeAg or HbsAg) or HBV RNA or DNA) or has symptoms of hepatitis B infection or hepatitis B. That is, "treating HBV infection" should be understood as treating a patient who is at any one of the several stages of HBV infection progression. In addition, the term "treating HBV infection" will also encompass treating suspected infection by HBV after suspected past exposure to HBV by, e.g., contact with HBV-contaminated blood, blood transfusion, exchange of body fluids, "unsafe" sex with an infected person, accidental needle stick, receiving a tattoo or acupuncture with contaminated instruments, or transmission of the virus from a mother to a baby during pregnancy, delivery or shortly thereafter. The term "treating HBV infection" will also

encompass treating a person who is free of HBV infection but is believed to be at risk of infection by HBV.

The term "preventing hepatitis B" as used herein means preventing in a patient who has HBV infection or is suspected to have HBV infection or is at risk of HBV infection, from developing hepatitis B (which are characterized by more serious hepatitis-defining symptoms), cirrhosis, or hepatocellular carcinoma.

In another specific embodiment, the present invention provides methods for treating or preventing HCV infection and hepatitis C. As used herein, the term "HCV infection" generally encompasses infection of a human by any types or subtypes of hepatitis C virus, including acute hepatitis C infection and chronic hepatitis C infection. Thus, treating HCV infection means the treatment of a person who is a carrier of any types or subtypes of hepatitis C virus or a person who is diagnosed of active hepatitis C to reduce the HCV viral load in the person or to alleviate one or more symptoms associated with HCV infection and/or hepatitis C. A carrier of HCV may be identified by any methods known in the art. For example, a person can be identified as HCV carrier on the basis that the person is anti-HCV antibody positive, or is HCV-positive (e.g., based on HCV RNA or DNA) or has symptoms of hepatitis C infection or hepatitis C (e.g., elevated serum transaminases). That is, "treating HCV infection" should be understood as treating a patient who is at any one of the several stages of HCV infection progression. In addition, the term "treating HCV infection" will also encompass treating suspected infection by HCV after suspected past exposure to HCV by, e.g., contact with HCV-contaminated blood, blood transfusion, exchange of body fluids, "unsafe" sex with an infected person, accidental needle stick, receiving a tattoo or acupuncture with contaminated instruments, or transmission of the virus from a mother to a baby during pregnancy, delivery or shortly thereafter. The term "treating HCV infection" will also encompass treating a person who is free of HCV infection but is believed to be at risk of infection by HCV. The term of "preventing HCV" as used herein means preventing in a patient who has HCV infection or is suspected to have HCV infection or is at risk of HCV infection from developing hepatitis C (which is characterized by more serious hepatitis-defining symptoms), cirrhosis, or hepatocellular carcinoma.

Still further, the methods and compositions of the present invention may also be applied to treatment of benign proliferative conditions including, but not limited to, diabetic proliferative retinopathy, idiopathic fibrotic diseases such as fibrosing alveolitis, and vascular smooth muscle proliferation following balloon antioplasty that can lead to re-stenosis.

Combination Therapy

Pro-apototic compounds and compositions of the present invention can desirably be administered in combination with other pharmaceutically compatible therapeutic agents. For example, when used in the treatment of solid tumors, compounds of the present invention can be administered with chemotherapeutic agents such as alpha inteferon, COMP (cyclophosphamide, vincristine, methotrexate, and prednisone), etoposide, mBACOD (methortrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone), PRO-MACE/MOpp (prednisone, methotrexate (with leucovin rescue), doxorubicin, cyclophosphamide, taxol, etoposide/mechlorethamine, yincristine, prednisone, and procarbazine), vincristine, vinblastine, angioinhibins, TNP-470, pentosan polysulfate, platelet factor 4, angiostatin, LM-609, SU-101, CM-101, Techgalan, thalidomide, SP-PG, and the like.

By "pharmaceutically compatible" it is meant that the other therapeutic agent will not interact or react with the above composition, directly or indirectly, in such a way as to adversely affect the effect of the treatment, or to cause any significant adverse side reaction in the patient. The active compounds of this invention are administered at a therapeutically effective amount to achieve the desired therapeutic effect without causing any serious adverse effects in the patient treated.

Pro-apototic compounds and compositions of the present invention can also desirably be administered in combination with other therapeutic treatments including conventional surgery to remove a tumor, radiation and/or chemotherapy treatments wherein a compound or composition of the present invention can be administered to extend the dormancy of micrometastases and to stabilize and inhibit the growth of any residual primary tumor.

Dosage and Delivery

The active compounds of this invention are typically administered in combination with a pharmaceutically acceptable carrier through any appropriate routes such as parenteral, oral, or topical administration, in a therapeutically acceptable amount. The active compounds are further desirably administered in a therapeutically effective amount, i.e., in an amount sufficient to promote apoptosis and/or to reduce the proliferation of abnormal cells.

Generally, the toxicity profile and therapeutic efficacy of the therapeutic agents can be determined by standard pharmaceutical procedures in suitable cell models or animal models. As is known in the art, the LD_{50} represents the dose lethal to about 50% of a tested population. The ED_{50} is a parameter indicating the dose therapeutically effective in about 50% of a tested population. Both LD_{50} and ED_{50} can be determined in cell models and animal models. In addition, the IC_{50} may also be obtained in cell models and animal models, which stands for the circulating plasma concentration that is effective in achieving about 50% of the maximal inhibition of the symptoms of a disease or disorder. Such data may be used in designing a dosage range for clinical trials in humans. Typically, as will be apparent to skilled artisans, the dosage range for human use should be designed such that the range centers around the ED_{50} and/or IC_{50}, but remains significantly below the LD_{50} dosage level, as determined from cell or animal models.

Typically, the pro-apoptotic compounds and compositions of the invention can be effective at an amount of from about 0.05 mg to about 4000 mg per day, preferably from about 0.1 mg to about 2000 mg per day. However, the amount can vary with the body weight of the patient treated and the state of disease conditions. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at predetermined intervals of time. The EC_{50} values discussed previously can desirably be used to identify specific pro-apoptotic compounds and compositions that can be used within predetermined, desirable dosage ranges.

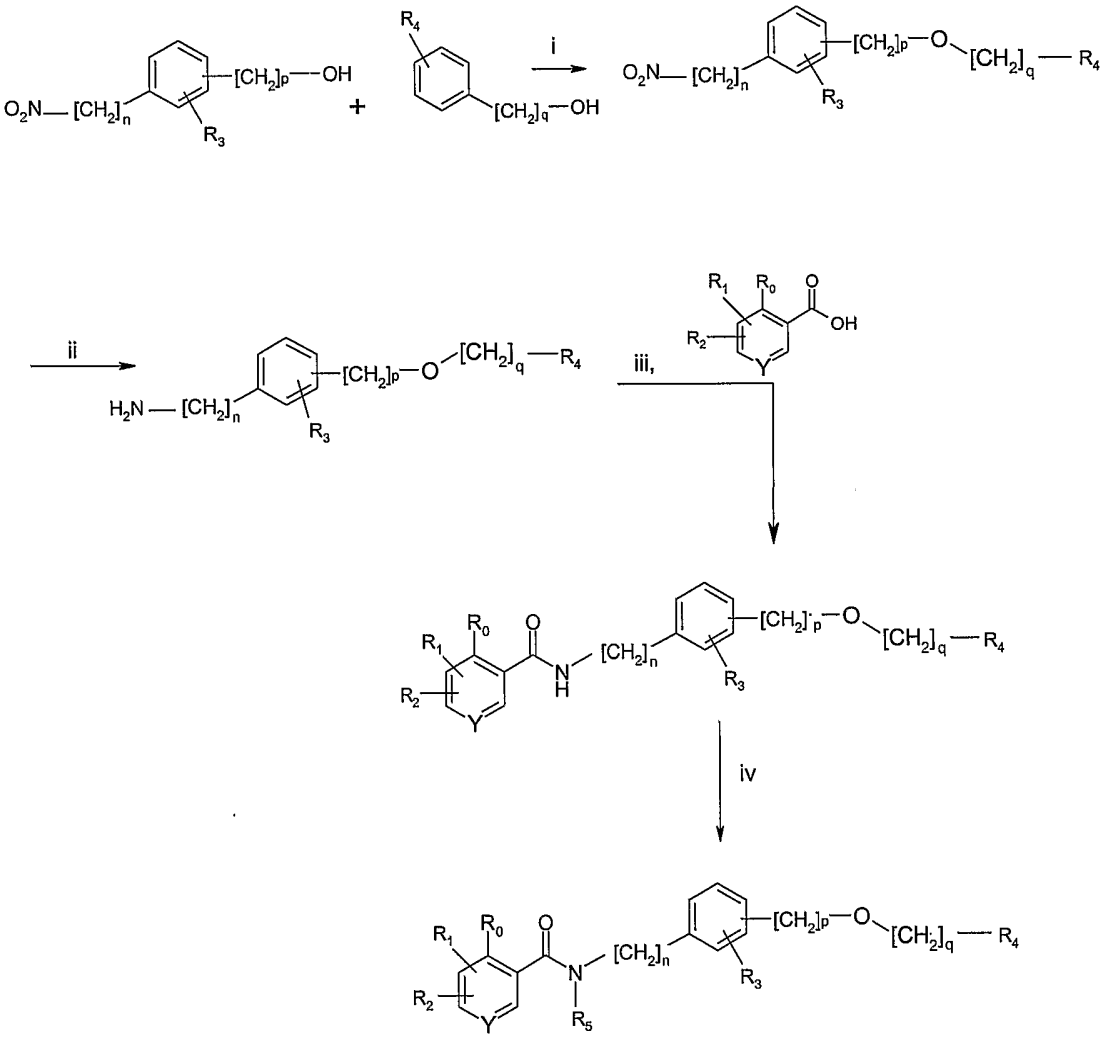
In the case of combination therapy, a therapeutically effective amount of another therapeutic compound can be administered in a separate pharmaceutical composition, or alternatively included in the pharmaceutical composition according to the present

invention. The pharmacology and toxicology of other therapeutic compositions are known in the art. *See e.g., Physicians Desk Reference*, Medical Economics, Montvale, NJ; and *The Merck Index*, Merck & Co., Rahway, NJ. The therapeutically effective amounts and suitable unit dosage ranges of such compounds used in art can be equally applicable in the present invention.

It should be understood that the dosage ranges set forth above are exemplary only and are not intended to limit the scope of this invention. The therapeutically effective amount for each active compound can vary with factors including but not limited to the activity of the compound used, stability of the active compound in the patient's body, the severity of the conditions to be alleviated, the total weight of the patient treated, the route of administration, the ease of absorption, distribution, and excretion of the active compound by the body, the age and sensitivity of the patient to be treated, and the like, as will be apparent to a skilled artisan. The amount of administration can also be adjusted as the various factors change over time.

Preparation of compounds and compositions according to the invention can be readily accomplished employing synthetic processes well known to those skilled in the art. Reference may be made to U.S. Patent No. 3,674,850 (which is incorporated herein by reference), which discloses preparation of various substituted salicylanilides, and to related patents and disclosures.

For example, compounds of Formula 1 can be made by the following scheme:

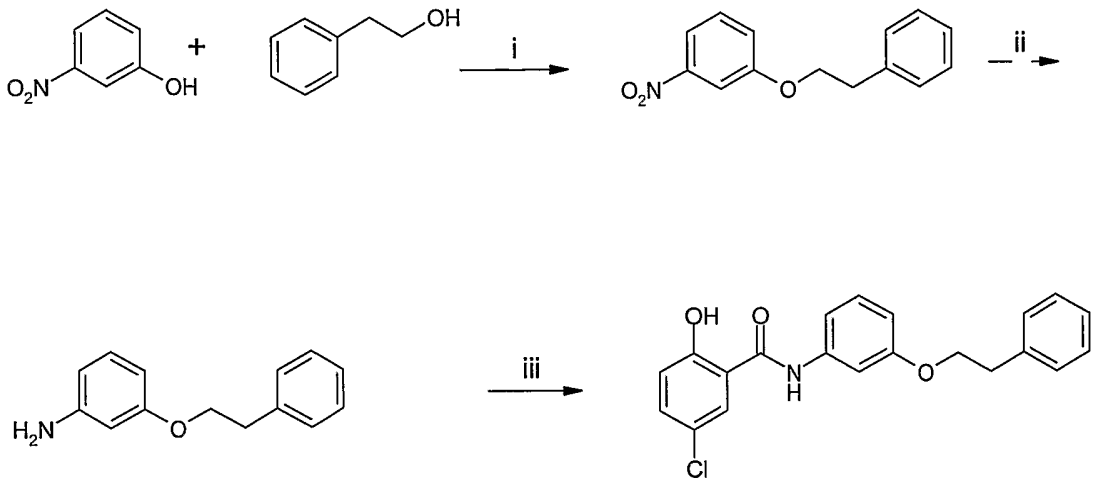


i) DEAD/PPh_3/THF/0-25°C ii) $SnCl_2.2H_2O$/EtOH/75°C or 5%Pt-C/$HCOONH_4$/CH_3OH
iii) Tetraethyl pyrophosphite/Toluene/135°C or CDI/DMP iv)R_5X/Base/DMF

In the above synthesis scheme, X is halo, and the various other substituents and symbols are as specified in Formula 1 above.

The following examples further illustrate various preferred aspects of the present invention. In the examples the methods and materials set forth below were used to evaluate compounds and compositions of the invention.

Example 1: Synthesis of 5-Chloro-2-hydroxy-N-(3-phenethyloxyphenyl)benzamide



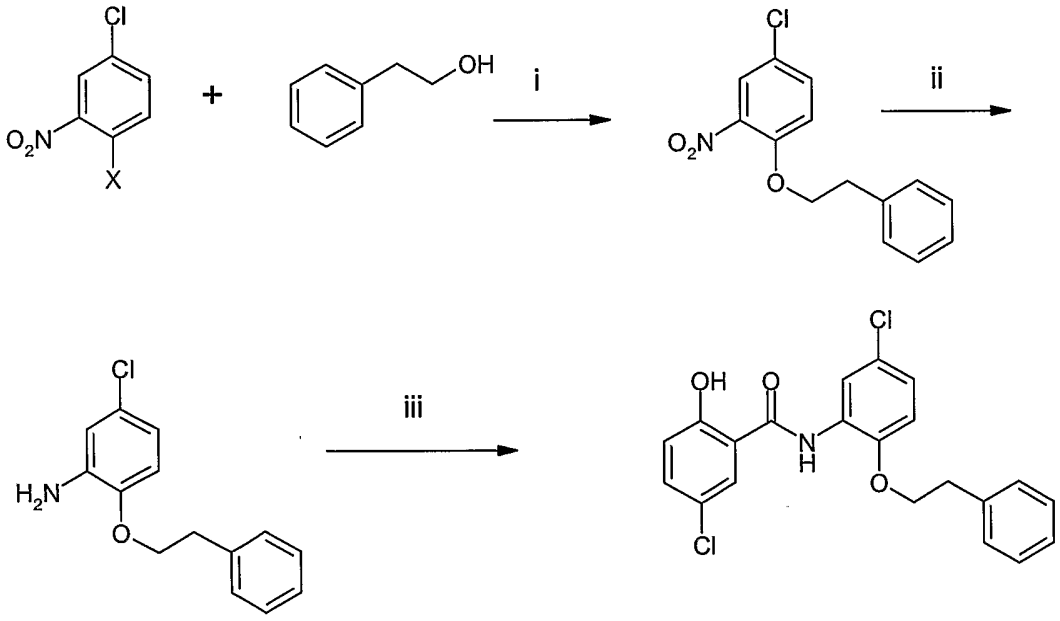
i) DEAD/PPh_3/THF/0-25°C ii) $SnCl_2.2H_2O$/EtOH/75°C iii) 5-Chlorosalicylic acid/Tetraethyl pyrophosphite/Toluene/135°C

To a solution of 3-nitrrophenol (1.5 g, 10.78 mmol) and triphenyl phosphine (4.24 g, 16.17 mmo) in anhydrous THF (30 mL) was added DEAD (2.25 g, 12.93 mmol) in THF (2.5 mL) and phenethyl alcohol (1.31 g, 10.78 mmol) in THF (2.5 mL) at 0°C simultaneously. The temperature of the reaction mixture was raised slowly to room temperature and stirring continued further at room temperature overnight. At the end of this period diluted with Ethyl acetate (100 mL) and washed with water (2 x 50 mL), dried (Na_2SO_4), filtered and the solvent was evaporated. The residu was chromatographed over silica gel using a mixture of ethyl acetate and hexane (2:8) to afford title product (1.80 g, 69%). ^{1}H NMR ($CDCl_3$) δ 3.12 (t, 2H), 4.22 (t, 2H), 7.10-7.49 (m, 7H), 7.70-7.90 (m, 2H).

A mixture of Step 1 product (1.80 g, 7.39 mmol) and stannous chloride dihydrate (4.16 g, 18.47 mmol) in ethanol was refluxed for 3 h. At the end of period solvent was evaporated, to the residue 2N NaOH (30 mL) was added and extracted with ethyl acetate (2 x 150 mL). The combined ethyl acetate layer was washed with water (2 x 75 mL), dried (Na2SO4), filtered and the solvent was evaporated to dryness to give the amine. The crude product was sufficiently pure enough to use for the next step and was used without any further purification. ^{1}H NMR ($CDCl_3$) δ 3.10 (t, 2H), 3.60 (bs, 2H), 4.20 (t, 2H), 6.18-6.40 (m, 3H), 7.10 (t, 1H), 7.20-7.39 (m, 5H)

A mixture of material from step 2 (0.102 g, 0.48 mmol), 5- chlorosalicylic acid (0.083 g, 0.48 mmol) and tetraethyl pyrophosphite (0.136g, 0.53 mmol) in toluene (5 mL) was refluxed for 6 h. The reaction mixture was cooled to 30oC and diluted with ethyl acetate (50 mL) and washed with 1N HCl (20 mL) followed by water (2 x 50 mL). The organic layer was dried (Na2SO4), filtered and the solvent was evaporated to dryness. The resultant crude material was chromatographed over silica gel using a mixture of ethyl acetate and hexane (2:8) to afford title product (0.092 g, 52 %). ^{1}H NMR ($CDCl_3$) δ 3.10 (t, 2H), 4.25 (t, 2H), 6.80 (d, 1H), 6.90-7.20 (m, 1H), 7.30-7.60 (m, 9H), 7.80 (bs, 1H), 11.92 (s, 1H)

Example 2: Synthesis of 5-Chloro-N-(5-chloro-2-phenethyloxyphenyl)-2-hydroxybenzamide



i) DEAD/PPh_3/THF/0-25°C ii) $SnCl_2.2H_2O$/EtOH/75°C iii) 5-Chlorosalicylic acid/Tetraethyl pyrophosphite/Toluene/135°C

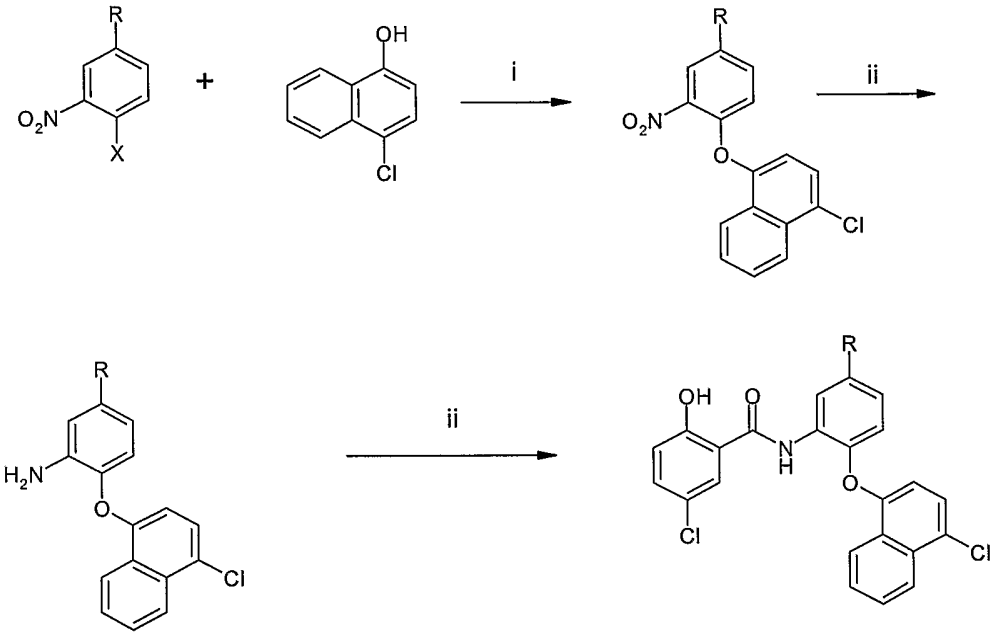
To a solution of 4-Chloro-3-nitrophenol (0.6 g, 3.457 mmol) and triphenyl phosphine (0.997 g, 3.802 mmol) in anhydrous THF (25 mL) was added DEAD (0.662 g, 3.802 mmol) in THF (2.5 mL) and phenethyl alcohol (0.464 g, 3.802 mmol) in THF (2.5 mL) at 0°C simultaneously. The temperature of the reaction mixture was raised slowly to room temperature and stirring continued further at room temperature overnight.

At the end of this period diluted with Ethyl acetate (100 mL) and washed with water (2 x 50 mL), dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was chromatographed over silica gel using a mixture of ethyl acetate and hexane (2:8) to afford title product (0.92 g, 95%). ^{1}H NMR ($CDCl_3$) δ 3.14 (t, 2H), 4.26 (t, 2H), 6.96 (d, 1H), 7.24-7.33 (m, 6H), 7.81 (d, 1H)

A mixture of Step 1 Product (0.3 g, 1.08 mmol) and stannous chloride dihydrate (0.974g, 4.32 mmol) in ethanol was refluxed for 3 h. At the end of period solvent was evaporated, to the residue 2N NaOH (20 mL) was added and extracted with ethyl acetate (2 x 75 mL). The combined ethy acetate layer was washed with water (2 x 75 mL), dried (Na_2SO_4), filtered and the solvent was evaporated to dryness. The crude product was sufficiently pure enough to use for the next step and was used without any further purification. ^{1}H NMR ($CDCl_3$) δ 3.11 (t, 2H), 3.77 (bs, 2H), 4.18 (t, 2H), 6.64-6.68 (m, 3H), 7.24-7.33 (m, 5H)

A mixture of material from step 2 (0.178 g, 0.718 mmol), 5- chlorosalicylic acid (0.124 g, 0.718 mmol) and tetraethyl pyrophosphite (0.204g, 0.790 mmol) in toluene (5 mL) was refluxed for 6 h. The reaction mixture was cooled to 30oC and diluted with ethyl acetate (50 mL) and washed with 1N HCl (20 mL) followed by water (2 x 50 mL). The organic layer was dried (Na_2SO_4), filtered and the solvent was evaporated to dryness. The resultant crude material was chromatographed over silica gel using a mixture of ethyl acetate and hexane (2:8) to afford title product (0.085 g, 29 %). ^{1}H NMR ($CDCl_3$) δ 3.17 (t, 2H), 4.37 (t, 2H), 6.85-7.41 (m, 10H), 8.35 (s, 1H), 8.40 (s, 1H), 11.82 (s,1H).

Example 3: 5-Chloro-N-[2-(4-chloronaphthalen-yloxy) –5-chlorophenyl]-2-hydroxybenzamide



i) Potassium tert-butoxide/THF/ 80°C ii) $HCOONH_4$/Pt-C/CH_3OH/70°C

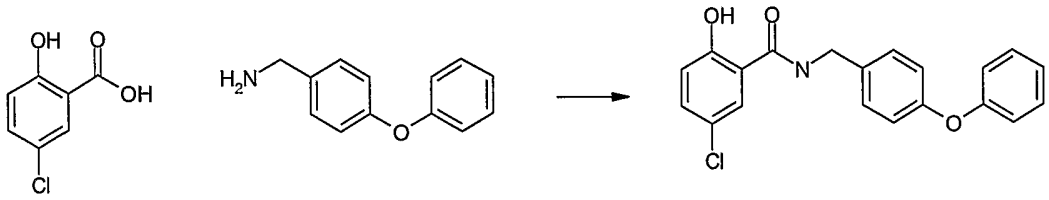
iii) 5-Chlorosalicylic acid/tetraethyl pyrophosphite/Toluene/ 130°C

A solution of 2,5-dichloronitrobenzene (5.0 g, 26.04 mmol), 4-chloronapphthol (5.11 g 28.64 mmol) in anhydrous THF (20 mL) was added 28.5 mL Potassium tert-butoxide (1M sol in THF) over 20 min period at 25°C. The dark reaction mixture was refluxed overnight . After cooling, the reaction mixture was diluted with Water (50 mL) and ethyl acetate (200 mL). The ethyl acetate layer was washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), filtered and solvent evaporated to dryness to give nitro compound in quantitative yield. ^1H NMR ($CDCl_3$) δ 6.87 (d, 1H), 6.93 (d, 1H), 7.40-6.69 (m, 4H), 8.00 (s, 1H), 8.13 (d, 1H), 8.30 (d, 1H)

A mixture of a step 1 material (3.8g, 11.37 mmol), ammonium formate (4.30 g, 68.23 mmol) and 5% Pt-C (1.0 g) in methanol was refluxed overnight. After cooling , the catalyst was removed by filtration through Celite and washed with methanol (2 x 25 mL). The filtrate was concentrated and the resulting solid was dissolved in dichloromethane (100 mL) an water (100 mL). The dichloromethane layer was washed with brine (100 mL), dried (Na_2SO_4), filtered and solvent was evaporated to dryness to afford amine (3.2 g, 93%). ^1H NMR ($CDCl_3$) δ 3.19 (bs, 2H), 6.53-6.85 (m, 4H), 7.60 (d, 1H), 7.61-7.66 (m, 2H), 8.25-8.33 (m, 2H).

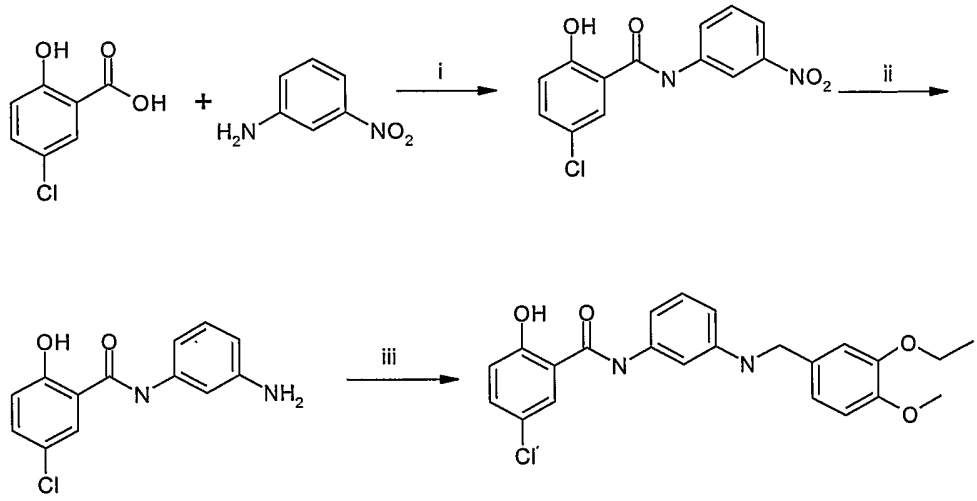
The title compound (5.4 g, 48%) was prepared from the step 2 material and 5-chlorosalicylic acid by procedure similar to that described for step 3 in Example 1. 1H NMR (d_6-DMSO) δ 6.78-7.00 (m, 4H), 7.21 (d, 1H), 7.53-7.79 (m, 3H), 8.04 (s, 1H), 8.26 (d, 2H), 8.75 (d, 1H), 11.14 (s, 1H), 11.24 (s, 1H)

Example 4: Synthesis of 5-Chloro-2-hydroxy-N-(4-phenoxybenzyl)benzamide



To a solution of 5-chlorocsalicyclic acid in anhydrous DMF (5 mL) was added CDI (0.167 g, 1.043 mmol), at 25°C under nitrogen atmosphere. The reaction mixture was stirred for another 2 h at 25°C. To the above reaction mixture 4-phenoxy benzylamine was added and stirring continued overnight. At the end of this period 2N HCl (20 mL) was added and extracted with ethyl acetate (2 x 20 mL). The combined ethyl acetate layer was washed with water (2 x 30 mL), dried (Na_2SO_4), filtered and solvent was evaporated. The resulting crude material was chromatographed over silica gel using mixture of ethyl acetate and hexanes (3:7) to give title product (0.121 g, 27 %). ^{1}H NMR ($CDCl_3$) δ 4.60 (d, 2H), 6.44 (bs, 1H), 6.90-7.37 (m, 12H), 12.21 (s, 1H).

Example 5: Synthesis of 5-Chloro-N-[3-(3-ethoxy-4-methoxybenzylamino)phenyl]-2-hydrxybenzamide



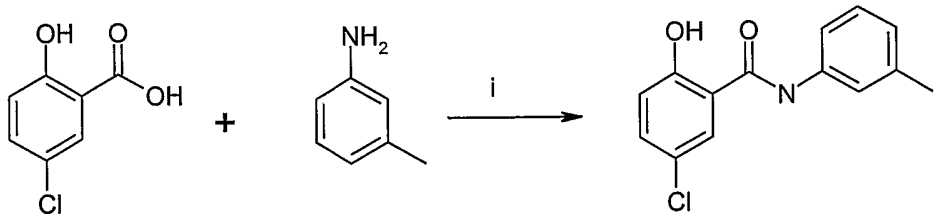
i) Tetraethyl pyrophosphite/Toluene/ 135° ii) 5% Pt-C/$HCOONH_4$/CH_3OH/ 70° iii) (a) 3-ethoxy-4-methoxy-benzaldehyde/CH_3OH/$NaBH_3CN$/RT

The Step 1 compound (1.6 g, 63%) was prepared by an analogous procedure described for step 3 in Example1 from 5-chlorosalicylic acid (1.5 g, 8.692 mmol) and 3-nitroaniline (1.44 g, 10.43 mmol). ^{1}H NMR ($CDCl_3$+d_6-DMSO) δ 6.97 (d, 1H), 7.35-7.57 (m, 3H), 7.98 (d, 1H), 8.15-8.24 (m, 1H), 8.67 (s, 1H), 10.55 (s, 1H), 11.91 (s, 1H)

The step 2 product (0.85 g, 95%) was prepared by a similar procedure described for step 2 in scheme 1 using product of step 1 (1.0 g, 3.416 mmol), $HCOONH_4$ (1.24 g, 17.683 mmol) and 5% Pt-C (110 mg). ^{1}H NMR ($CDCl_3$) δ 3.88 (bs, 2H), 6.49 (d, 1H), 6.92-7.35 (m, 5H), 8.05 (d, 1H), 9.80 (s, 1H), 12.00 (bs, 1H).

In Step 3, a mixture of the product of step 2 (0.08 g, 0.305 mmol) and 3-ethoxy-4-methoxybenzaldehyde (0.054 g, 0.305 mmol) in absolute ethanol (4 mL) was added 4 drops acetic acid and the mixture was refluxed for 6h. At the end of this period the reaction was cooled to 25°C and sodium cyanoborohydride was added. After stirring for further 2 h at 25°C, solvent was evaporated, water (20 mL) was added and extracted with ethyl acetate (75 mL). The ethyl acetate layer was dried (Na_2SO_4), filtered and solvent evaporated. The resulting crude product was chromatographed over silica gel using a mixture of ethyl acetate and hexanes (3:7) to give title product (0.098g, 75%). ^{1}H NMR ($CDCl_3$+d_6-DMSO) δ 1.49 (t, 3H), 3.88 (s, 3H), 4.11 (q, 2H), 4.29 (s, 2H), 4.63 (bs, 1H), 6.30-6.63 (m, 1H), 6.70-7.70 (m, 8H), 8.13 (s, 1H), 10.00 (s, 1H), 12.10 (s, 1H).

Example 6: Synthesis of 5-Chloro-2-hydroxy-N-(3-Methylphenyl)benzamide



i) Tetraethyl pyrophosphite/Toluene/130°C

A mixture of 5-Chlorosalicylic acid (0.338 g, 1.9 mmol), m-Toluidine (0.2 g, 1.9 mmol) and Tetraethyl pyrophosphite (0.53 g, 2.0 mmol) in dry toluene was refluxed 7 hrs under nitrogen atmosphere. It was diluted with ethyl acetate, washed with HCl (10%) and then with water (3 x 30 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated under vacuum. The resulting crude material was purified by column chromatography over SiO_2 using mixture of ethyl acetate and hexanes (2:8) to give title compound (0.134 g,) ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 2.38 (s, 3H), 6.89-7.03 (m, 2H), 7.19-7.59 (m, 4H), 8.08 (d, 1H), 9.92 (bs, 1H), 12.05 (s, 1H).

Using the methods described above and substituting the appropriate starting materials, other example compounds in Table 1 were similarly prepared and are summarized below in Table 2 and Table 3.

Table 2

Example#	^{1}H NMR ($CDCl_3$) δ
5	3.2 (t, 2H), 4.2 (t, 2H), 6.20-8.60 (m, 15H), 12.7(s, 1H)
11	4.24(d, 2H), 4.52 (bs, 1H), 5.94 (s,2H), 6.22-6.56 (m, 1H) 6.52-7.04 (m, 8H), 7.09 (s, 1H), 9.92 (s, 1H), 12.06 (s, 1H)
12	3.18 (t, 2H), 3.87 (s, 3H), 4.24 (t, 2H), 6.62-7.58 (m, 11H), 7.72 (s, 1H), 11.92 (s, 1H)
15	5.12 (s, 2H), 6.65-8.10 (m, 13H), 11.85 (s,1H)
16	($CDCl_3$+d_6-DMSO) 2.07 (m, 2H), 2.79 (t, 2H), 3.81 (s, 3H), 3.98(t, 2H),6.39-7.80 (m, 10H), 8.13 (s, 1H), 10.17 (s, 1H), 12.04 (s, 1H)
17	1.58-2.31 (m, 8H), 2.82-2.87 (m, 1H), 4.59 (bs, 1H), 6.61 (d, 1H), 6.96-7.66 (m, 12H), 11.87 (s, 1H)

18	($CDCl_3$+d_6-DMSO) 3.09 (t, 2H), 4.17 (t, 2H), 6.52-8.62 (m, 12H), 9.66 (bs, 1H), 12.00 (s, 1H)
19	1.43 (d, 3H), 3.86-4.85 (m, 3H), 6.55-7.90 (m, 12H), 11.86 (s, 1H)
22	3.17 (t, 2H), 4.37 (t, 2H), 6.84-7.42 (m, 9H), 8.32-8.40 (m, 2H), 11.82 (s, 1H)
26	4.60 (d, 2H), 6.44 (bs, 1H), 6.90-7.37 (m, 12H), 12.21 (s, 1H)
28	4.19 (bs, 1H), 4.36 (s, 2H), 6.50-7.71 (m, 13H), 11.94 (s, 1H)
31	($CDCl_3$+d_6-DMSO); 6.76-6.97 (m, 5H), 7.21-7.24 (m, 1H), 7.48-7.71 (m, 2H), 8.04 (d, 1H), 8.08-8.76 (m, 2H), 8.77 (s, 1H), 11.00 (s, 1H), 11.08 (s, 1H)
33	3.09 (t, 2H), 3.81 (s, 3H), 4.20 (t, 2H), 6.67-7.02 (m, 5H), 7.22-7.50 (m, 4H), 8.06 (d, 1H), 8.43 (s, 1H), 11.73 (s, 1H)
41	2.2 (s, 3H), 3.1 (t, 2H), 4.2 (t, 2H), 6.70-7.90 (m, 12H), 8.5 (s, 1H), 10.50 (s, 1H)
42	0.91 (t, 3H), 1.64-1.83 (m, 1H), 1.97-2.15 (m, 1H), 2.94-3.09 (m, 1H), 4.06-4.20 (m, 2H), 6.76 (dd, 1H), 7.02 (d, 1H), 7.09 (dd, 1H), 7.18-7.53 (m, 9H), 7.88 (bs, 1H), 11.88 (s, 1H)
44	0.98-1.09 (m, 4H), 4.08 (s, 2H), 6.73 (dd, 1H), 6.96-7.50 (m, 11H), 7.76 (bs, 1H), 11.86 (bs, 1H)
49	2.38 (s, 3H), 5.05 (s, 2H), 6.93-7.52 (m, 11H), 9.91 (bs, 1H), 12.00 (s, 1H)
50	4.51 (d, 2H), 5.10 (s, 2H), 6.35 (bs, 1H), 6.85-7.05 (m, 3H), 7.15-7.65 (m, 9H), 12.21(s, 1H)
53	3.08(t, 2H), 4.14(t, 2H), 4.53(d, 2H), 6.34 (bs, 1H), 6.86-6.94 (m, 5H), 7.22-7.33 (m, 7H), 12.22 (s, 1H)
54	2.90 (t, 2H), 3.69 (t, 2H), 6.21 (bs, 1H), 6.90-7.54 (m, 12H), 12.26 (s, 1H)
70	2.32 (s, 6H), 4.54 (d, 4H), 6.34 (bs, 1H), 6.93-6.96 (m, 6H), 7.26-7.29 (m, 5H), 12.25 (s, 1H)
74	($CDCl_3$+d_6-DMSO) 4.32 (d, 2H), 5.06 (bs, 1H), 6.53 (d, 2H), 6.73-7.34 (m, 5H), 7.55-7.69 (m, 3H), 8.12 (d, 1H), 10.23 (s, 1H), 12.03 (s, 1H)
95	1.30 (d, 3H), 2.85 (dd, 1H), 3.10 (dd, 1H) 4.61 (m, 1H), 6.65 (d, 1H), 6.92 (d, 1H), 6.95-7.41 (m, 8H), 7.74 (d, 1H), 8.10 (s, 1H), 10.23 (s, 1H), 12.02 (1H)
98	1.52-1.68 (m, 8H), 2.19-2.27 (m, 1H), 4.82 (s, 1H), 6.51-7.49 (m, 10H), 8.35 (s, 1H), 8.60 (s, 1H), 11.84(s, 1H)
124	3.10 (t, 2H), 4.20 (t, 2H), 6.76 (d, 1H), 7.06 (d, 1H), 7.25-7.33 (m, 8H), 7.95 (bs, 2H), 8.55(s, 1H), 8.59 (s, 1H), 12.71 (s, 1H)

179	3.13 (t, 2H), 3.85 (s, 3H), 4.18 (s, 2H), 6.74 (d, 1H), 6.86-6.93 (m, 2H), 7.08 (d, 1H), 7.21-7.54 (m, 6H), 7.69-7.74 (m, 2H), 7.84 (bs, 1H)
237	4.62 (d, 2H), 6.10 (bs, 1H), 6.87-6.90 (m, 2H), 7.26-7.48 (m, 10H), 12.10 (s, 1H)
238	4.69 (d, 2H), 6.49 (bs, 1H), 6.96 (d, 1H), 7.31-7.59 (m, 11H), 12.20 (s, 1H)
239	4.67 (d, 2H), 6.49 (bs, 1H), 7.32-7.61 (m, 11H), 12.20 (s, 1H)
241	1.25 (s, 3H), 1.28 (s, 3H), 2.41 (t, 2H), 3.37-3.41 (m, 4H), 3.78 –3.82 (m, 2H), 4.36 (t, 2H), 6.49-6.54 (m, 2H), 6.98 (d, 1H), 7.25-7.45 (m, 5H), 7.67 (d, 1H), 8.09(d, 1H), 8.16 (s, 1H), 12.06 (s, 1H)
244	3.43 (t, 2H), 4.41 (t, 2H), 6.96-7.43 (m, 8H), 8.52 9s, 1H), 8.69 (s, 1H), 11.78(s, 1H)
246	1.13 (d, 6H), 2.22-2.27 (m, 1H), 3.87 (d, 2H), 6.83-7.44 (m, 5H), 8.45 (d, 1H), 8.73 (bs, 1H), 11.88 (s, 1H)
247	3.35 (t, 2H), 4.47 (t, 2H), 6.99-7.44 (m, 9H), 8.43 (s, 1H), 8.65 (s, 1H), 11.73 (s, 1H)
248	3.19 (t, 2H), 4.43 (t, 2H), 6.98-7.43 (m, 9H), 8.42 (bs, 1H), 8.69 (s, 1H), 11.74 (s, 1H)
249	3.18 (t, 2H), 4.43 (t, 2H), 6.99-7.42 (m, 8H), 8.41 (bs, 1H), 8.69 (1H), 11.73 (bs, 1H)
250	3.17 (t, 2H), 4.25 (t, 2H), 6.90-7.33 (m, 7H), 7.57(s, 1H), 8.01 (d, 1H), 8.36 (d, 1H), 10.48 (bs, 1H), 11.30 (1H)
258	2.68 (t, 2H), 3.01(t, 2H), 6.58-7.00 (m, 8H), 7.21 (d, 1H), 8.23 (s, 1H), 8.66 (s, 1H), 11.06 (s, 1H)
259	2.89 (t, 2H), 3.26 (t, 2H), 6.91-7.42 (m, 9H), 7.66 (d, 1H), 8.72 (s, 1H), 9.16 (s, 1H), 11.77 (s, 1H)
264	6.79 (d, 1H), 6.99 (d, 1H), 7.07 (d, 1H), 7.28-7.35 (m, 3H), 7.57-7.72 (m, 3H), 8.03 (d, 1H), 8.34 (d, 1H), 8.75 (s, 1H), 8.85 (s, 1H), 11.63 (s, 1H)
265	0.19-0.21 (m, 2H), 0.58-0.60 (m, 2H), 0.78-0.92 (m, 1H), 1.82 (q, 2H), 4.25 (t, 2H), 6.98-7.04 (m, 3H), 7.38-7.45 (m , 3H), 8.72 (s, 1H), 11.81 (s, 1H)
266	5.25 (s, 2H), 6.96 (d, 1H), 7.10 (d, 1H), 7.30-7.47 (m, 9H), 8.75 (s, 1H), 11.82 (s, 1H)
267	2.92 (t, 2H), 3.43-3.49 (m, 2H), 4.10 (bs, 1H), 6.84-7.50 (m, 11H), 11.61 (s, 1H)
283	0.83 (d, 3H), 1.10 (d, 3H), 2.05-2.03 (m, 1H), 2.94 (m, 1H), 4.31 (t, 1H), 4.52-4.56 (m, 1H), 6.98-7.44 (m, 9H), 8.22 (s, 1H), 8.66 (s, 1H), 11.77 (s, 1H)
295	1.24 (t, 3H), 3.67 (q, 2H), 3.85 (t, 2H), 4.32 (t, 2H), 6.98-7.06 (m, 2H), 7.19-7.53(m, 3H), 8.73 (s, 1H),

	8.96 (s, 1H), 12.01(bs, 1H)
297	4.41 (t, 2H), 4.55(t, 2H), 6.92-7.41 (m, 10H), 8.74 (s, 1H), 8.81(s, 1H), 11.71 (s, 1H)
305	3.12 (t, 2H), 3.45 (s, 2H), 3.65 (s, 3H), 4.34 (t, 2H), 6.60-7.36 (m, 10H), 8.26 (s, 1H), 8.38 (s, 1H), 12.98 (bs, 1H)
309	2.35 (s, 3H), 4.40-2.43 (bs, 4H), 2.98-3.01 (bs, 4H), 7.01 (d, 1H), 7.32-7.43 (m, 4H), 7.59 (s, 1H), 8.74 (s, 1H), 9.45 (bs, 1H)
310	(d_6-DMSO) 3.14 (t, 2H), 3.49 (s, 2H), 4.24 (t, 2H), 7.02-7.60 (m, 9H), 7.99 (s, 1H), 8.33 (s, 1H), 10.85 (s, 1H), 11.90 (s, 1H), 12.20 (s, 1H)

Table 3

Example #	^{1}H NMR ($CDCl_3$) δ
9	3.10 (t, 2H), 4.20 (t, 2H), 6.80-7.10 (m, 3H), 7.20-7-60 (m, 8H), 8,10 (s, 1H), 8.20 (s, 1H)
15	5.12 (s, 2H), 6.65-8.10 (m, 13 H), 11.85 (s, 1H)
21	7.01 (d, 1H), 7.50 (d, 1H), 7.53-7.65 (m, 6H), 7.84 (d, 2H), 7.93-8.01 (m, 3H), 11.75 (s, 1H).
23	6.98 (d, 1H), 7.35-7.39 (m, 1H), 7.55 (t, 1H), 8.00 (d, 1H), 8.16 (d, 1H), 8.23 (d, 1H), 8.67 (s, 1H), 10.56 (bs, 1H), 11.91 (s, 1H).
24	3.88 (bs, 2H), 6.50 (dd, 1H), 6.94 (d, 2H), 7.12 (t, 1H), 7.22 (bs, 1H), 7.29-7.31 (m, 1H), 8.05 (d, 1H), 9.81 (bs, 1H), 12.01 (bs, 1H).
25	6.98 (d, 1H), 7.50 (t, 1H), 7.47-7.90 (m, 9H), 8.14 (d, 1H), 10.36 (s, 1H), 11.86 (s, 1H).
30	1.02-1.57 (m, 6H), 2.95-3.63 (m 6H), 4.30 (t, 2H), 4.36 (s, 2H), 6.27-6.55 (m, 1H), 6.66-7.67 (m, 10H), 8.08 (s, 1H), 10.01 (s, 1H)
39	2.30 (s, 3H), 3.10 (t, 2H), 4.20 (t, 2H), 6.7-7.5 (m, 11H), 7.80(s, 1H), 8.10 (s, 1H)
56	6.98 (d, 1H), 7.30-7.40 (m, 2H), 7.50 (t, 1H), 7.95-8.14 (m, 3H), 10.50 (bs, 1H), 11.93 (s, 1H).
58	7.00 (d, 1H), 7.39 (t, 1H), 7.62-7.73 (m, 3H), 8.14-8.19 (m, 3H), 11.65 (bs, 1H).
60	6.98 (d, 1H), 7.20 (t, 1H), 7.40-7.81 (m, 9H), 8.60 (d, 1H), 12.15 (s, 1H).
61	6.98 (d, 1H), 7.36 (dd, 1H), 7.61 (d, 2H), 7.90 (d, 2H), 8.13 (d, 1H), 10.51 (bs, 1H).
85	($CDCl_3$+d_6-DMSO) 1.26 (d, 6H), 2.85-3.01 (m, 1H),

	5.05 (s, 2H), 6.74-6.83 (m, 1H), 6.94 (d, 1H), 7.18-7.54 (m, 8H), 8.09 (d, 1H), 9.99 (bs, 1H), 12.00 (s, 1H)
93	6.97 (d, 1H), 7.30-7.36 (m, 3H), 7.69 (d, 2H), 8.10 (d, 1H), 10.32 (bs, 1H), 12.00 (bs, 1H).
94	6.93 (d, 1H), 7.07 (d, 1H), 7.23-7.31 (m, 2H), 7.54 (d, 1H), 7.80 (d, 1H), 8.05 (d, 1H), 10.32 (bs, 1H), 11.90 (bs, 1H).
100	1.14 (s, 6H), 2.80 (m, 1H), 3.14 (t, 2H), 4.32 (t, 2H), 6.70-7.43 (m, 10H), 8.45 (s, 1H), 11.98 (s, 1H)
114	2.34 (s, 3H), 6.93 (d, 1H), 7.17-7.56 (m, 5H), 8.10 (d, 1H), 10.04 (s, 1H), 12.13 (s, 1H).
123	3.11 (t, 2H), 4.21 (t, 2H), 6.73 (d, 1H), 7.11-7.42 (m, 8H), 8.30 (d, 1H), 8.59 (d, 1H), 9.57 (s, 1H), 12.20 (s, 1H)
138	3.24 (t, 2H), 4.53 (t, 2H), 6.98-7.55 (m, 10H), 8.45 (s, 1H), 8.60 (bs, 1H), 11.34 (s, 1H)
156	3.11 (t, 2H), 4.20 (t, 2H), 6.95-7.40 (m, 10H), 7.82 (d, 1H), 7.92 (s, 1H), 11.68 (s, 1H)
168	($CDCl_3$+d_6-DMSO) 6.94-7.68 (m, 7H), 8.12 (s, 1H), 10.16 (s, 1H), 12.04 (s, 1H)
169	($CDCl_3$+d_6-DMSO) 6.97 (d, 1H), 7.36-7.42 (m, 3H), 8.12 (d, 1H), 8.37 (s, 1H), 10.88 (s, 1H), 11.80 (s, 1H)
229	3.13 (t, 2H), 3.85 (s, 3H), 4.18 (t, 2H), 6.76-7.36 (m, 10H), 7.60 (d, 1H), 8.11(d, 1H)
230	3.11 (t, 2H), 4.21 (t, 2H), 7.01-7.34 (m, 11H), 7.59 (d, 1H), 8.12 (d, 1H)
245	3.25 (t, 2H), 4.43 (t, 2H), 6.97-7.42 (m, 8H), 8.44 (s, 1H), 8.69 (s, 1H), 11.79 (s, 1H)
254	3.32 (t, 2H), 4.32 (t, 2H), 6.75-7.37 (m, 6H), 7.82 (d, 1H), 8.85 (s, 1H), 10.83 (s, 1H), 11.10 (bs, 1H)
266	5.25 (s, 2H), 6.97 (d, 1H), 7.09 (d, 1H), 7.11-7.47 (m 9H), 8.75 (s, 1H), 11.82 (s, 1H)
278	4.55 (q, 2H), 6.98-7.03 (m, 2H), 7.40-7.44 (m, 3H), 8.65 (s, 1H), 8.78 (s, 1H), 11.55 (s, 1H)
285	3.24 (t, 2H), 4.44 (t, 2H), 6.98-7.43 (m, 9H), 8.42 (bs, 1H), 8.68 (s 1H), 11.73 (s, 1H)
294	3.18 (t, 2H), 4.39 (t, 2H), 6.86-7.31 (m, 7H), 8.27 (s, 1H), 8.52 (d, 1H), 8.59 (d, 1H), 10.05 (s, 1H), 11.60 (bs, 1H)
296	1.04 (d, 3H), 1.21 (d, 3H), 3.73 (m, 1H), 3.75 (t, 2H), 4.31 (t, 2H), 6.98-7.05 (m, 2H), 7.38-7.51 (m, 3H), 8.73 (s, 1H), 8.86 (s, 1H), 11.93 (s, 1H)

WST-1 Cell Proliferation and Viability Assay

Cell proliferation and cell viability was assessed using the tetrazolium salt WST-1 (Roche Applied Science, Indianapolis IN). The assay is based on the cleavage of WST-1 (light red) by mitochondrial dehydrogenase causing the formation of formazan (dark red), which can be measured on an optical density (O.D.) reader. LNCaP cell lines were plated in 96 well tissue culture plates (Corning Costar, NY) at a density of 5000 cells/ well in 150 μl complete media phenol-red free (RPMI-1640 [Invitrogen, Carlsbad CA] and 10% fetal calf serum). This plate is termed the assay plate. After the cells are plated, they are then incubated overnight at 37 degrees Celsius in a humidified chamber containing 5% CO_2 (incubator).

Compounds are added to the assay plate in 50μl of complete media and 0.4% DMSO (v:v) making the final DMSO concentration 0.1%. The assay plate is then returned to the incubator for 18-72 hours. WST-1 reagent is then added (20μl/well) and the plate is placed on an ELISA plate shaker for 30 minutes at room temperature. Plates are then transferred back to the incubator for an additional 3 hours. Plates are then read on a 96 well plate O.D. reader at A_{490}-A_{650}.

Propidium Iodide and Annexin V Flow Cytometer-Based Assay

Necrotic versus apoptotic killing of human cell lines by compounds was determined using dual annexin V-FITC and propidium iodide (PI) staining. Flipping of phosphatidylserine to the outer leaflet of the plasma membrane is a characteristic of all apoptotic cells. AnnexinV is a serum protein that binds to phosphatidylserine in the presence of the divalent cations (calcium). PI is a DNA stain that is excluded from live cells and is used to discriminate between cells with intact or damaged plasma membranes.

Cells were plated at varying densities in 6 well plates and treated with varying concentrations of compounds for 18-72 hours. Cells were grown in RPMI-1640 media supplemented with 10% FCS. DMSO concentrations did not exceed 0.1 % v:v in any assay. All cells in the wells were harvested and rinsed 1X with cold Hanks buffered saline solution (HBSS) containing calcium and magnesium (Invitrogen, Carlsbad CA). Carefully aspirate supernatant after the wash and resuspend in 100 μl Annexin V-FITC

(Annexin V/PI Apoptosis Detection Kit; R & D Systems TA4638; Minneapolis, MN) in binding buffer (10 mM HEPES pH 7.4, 150mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 1.8 mM $CaCl_2$ and 2% bovine serum albumin w:v). Incubate in dark for 15 minutes on ice. Prior to analyzing samples, the volume was adjusted to 500 µl with 1X Binding Buffer and 25 µl PI was added per sample. Staining was quantified on a flow cytometer (Becton-Dickenson, Franklin Lake, NJ).

The following results were found. In the following, "Estimated" data is based on actual data at different concentrations. Although not specifically tabulated, in most instances of active compounds below, positive indications of apoptotic cell death were observed based on one or both of the relevant tests, above.

Table 4

Compound No.	WST-1 EC_{50} (µM)	Estimated
1	500.00	
2	23.00	
3	500.00	
4	500.00	
5	5.00	
6	500.00	
7	30.00	Estimated
8	500.00	
9	500.00	
10	14.00	
11	40.00	
12	13.00	
13	18.00	
14	18.00	
15	12.00	
16	8.00	
17	2.00	

18	10.00	
19	7.00	
20	24.00	
21	9.00	
22	2.00	
23	4.00	
24	500.00	
25	20.00	Estimated
26	24.00	
27	4.00	
28	31.00	
29	30.00	Estimated
30	50.00	
31	2.00	
32	6.00	
33	3.00	
34	10.00	
35	10.00	
36	21.00	
37	3.00	
38		
39	500.00	
40	500.00	
41	500.00	
42	3.00	
43	3.00	
44	5.00	
45	4.00	
46	5.00	

47	4.00	
48	7.00	
49	500.00	
50	500.00	
51	500.00	
52	500.00	
53	23.00	
54	13.00	
55	15.00	
56	1.00	
57	15.00	
58	10.00	
59	10.00	
60	500.00	
61	1.00	
62	4.00	
63	20.00	
64	500.00	
65	17.00	
66	50.00	
67	50.00	
68	500.00	
69	14.00	
70	500.00	
71	500.00	
72	500.00	
73	500.00	
74	9.00	
75	1.00	

76	1.00	
77	1.00	
78	2.00	
79	2.00	
80	4.00	
81	1.00	
82	0.70	
83	0.80	
84	14.00	
85	6.00	
86	30.00	Estimated
87	0.90	
88	500.00	
89	500.00	
90	18.00	
91	500.00	
92	2.00	
93	4.00	
94	3.00	
95	6.00	
96	10.00	
97	3.00	
98	4.00	
99	1.00	
100	1.00	
101	4.00	
102	2.00	
103	2.00	
104	0.80	

105	8.00	
106	1.00	
107	2.00	
108	3.00	
109	1.00	
110	1.00	
111	1.00	
112	2.00	
113	8.00	
114	10.00	
115	500.00	
116	30.00	Estimated
117	2.00	
118	30.00	Estimated
119	20.00	Estimated
120	18.00	Estimated
121	30.00	Estimated
122	9.00	
123	30.00	Estimated
124	8.00	
125	6.00	
126	6.00	
127	2.00	
128	2.00	
129	0.80	
130	2.00	
131	2.00	
132	5.00	
133	3.00	

134	0.90	
135	0.80	
136	1.00	
137	5.00	
138	6.00	
138	1.00	
140	3.00	
141	1.00	
142	3.00	
143	14.00	
144	30.00	Estimated
145	17.00	
146	30.00	Estimated
147	6.00	
148	500.00	
149	4.00	
150	6.00	
151	30.00	Estimated
152	7.00	
153	1.00	
154	4.00	
155	0.40	
156	16.00	
157	2.00	
158	2.00	
159	2.00	
160	0.70	
161	1.00	
162	0.90	

163	2.00	
164	1.00	
165	500.00	
166	10.00	
167	6.00	
168	17.00	
169	2.00	
170	4.00	
171	5.00	
172	3.00	
173	11.00	
174	11.00	
175	14.00	
176	500.00	
177	500.00	
178	500.00	
179	500.00	
180	12.00	
181	500.00	
182	23.00	
183	19.00	
184	15.00	
185	32.00	
186	22.00	
187	30.00	
188	500.00	
189	30.00	
190	35.00	
191	15.00	

192	30.00	
193	7.00	
194	9.00	
195	500.00	
196	500.00	
197	26.00	
198	21.00	
199	47.00	Estimated
200	37.00	
201	33.00	
202	500.00	
203	33.00	
204	500.00	
205	43.00	
206	34.00	
207	33.00	
208	21.00	
209	17.00	
210	22.00	
211	22.00	
212	20.00	
213	500.00	
214	500.00	
215	45.00	Estimated
216	32.00	Estimated
217	500.00	
218	32.00	Estimated
219	32.00	
220	20.00	Estimated

221	17.00	
222	500.00	
223	8.00	
224	22.00	
225	500.00	
226	7.00	
227	22.00	Estimated
228	30.00	Estimated
229	30.00	Estimated
230	500.00	
231	500.00	
232	500.00	
233	10.00	
234	10.00	
235	6.00	
236	11.00	
237	30.00	Estimated
238	30.00	Estimated
239	500.00	
240	10.00	
241	3.00	
242	2.00	
243	1.00	
244	0.90	
245	0.90	
246	2.00	
247	0.90	
248	0.50	
249	0.90	

250	2.00	
251	2.00	
252	1.00	
253	1.00	
254	1.00	
255	30.00	Estimated
256	26.00	
257	500.00	
258	500.00	
259	1.00	
260	1.00	
261	6.00	
262	0.90	
263	2.00	
264	1.00	
265	0.90	
266	0.90	
267		
268	500.00	
269	8.00	
270	500.00	
271	0.90	
272	0.90	
273	500.00	
274	4.00	
275	3.00	
276	4.00	
277	3.00	
278	2.00	Estimated

279	6.00	
280	1.00	
281	3.00	
282	4.00	
283	0.90	
284	2.00	
285	0.90	
286	10.00	
287	3.10	
288	3.30	
289	3.30	
290	30.00	Estimated
291	30.00	Estimated
292	30.00	Estimated
293	30.00	Estimated
294	19.00	
295	1.00	
296	0.80	
297	0.90	
298	3.00	
299	1.00	
300	1.00	
301	0.67	
302	3.00	
303	3.30	
304	18.00	
305		
306	2.00	
307	1.80	

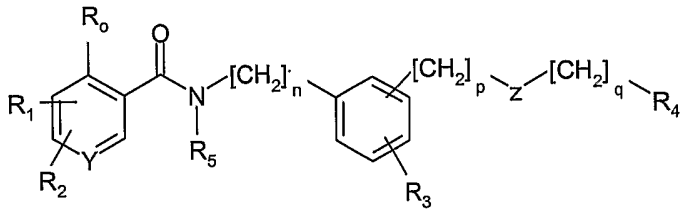
308	0.83	
309	17.40	
310	500.00	
311	3.00	
312	0.85	
313	3.00	
314	500.00	
315	1.20	
316	40.00	Estimated
317	30.00	Estimated
318	40.00	Estimated
319	17.70	
320	17.50	
321	500.00	
322	500.00	
323	30.00	Estimated
324	500.00	
325	3.30	
326	6.20	
327	2.10	
328	1.60	
329	2.20	
330	19.70	
331	12.40	
332	0.74	
333	2.60	
334	9.00	
335	13.00	
336	28.00	

337	19.00	
338	7.00	
339	8.00	
340	16.00	
341	9.00	
342	10.00	
343	17.00	
344	16.00	
345	9.00	
346	28.00	
347	6.00	
348	17.00	
349	10.00	
350	10.00	
351	11.00	
352	7.00	
353	25.00	Estimated
354	7.30	
355	15.00	
356	16.00	
357	500.00	

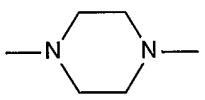
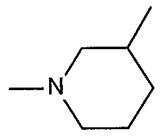
The invention has been described in considerable detail with reference to various preferred embodiments. However, numerous variations and modifications can be made without departing from the spirit and scope of the invention as described in the foregoing specification and defined in the following claims.

THAT WHICH IS CLAIMED:

1. Use of a compound or a pharmaceutically acceptable salt, ester, amide, hydrate or solvate thereof in the manufacture of a medicament useful in inducing cell apoptosis in mammals, wherein said compound has the formula:



wherein Y is C or N;

Z is selected from the group consisting of a covalent bond, oxygen, sulfur, amino, carbonyl,  and  ;

R_0 is selected from the group consisting of hydroxy, lower (C_1-C_6) alkoxy, hydroxyalkoxy, nitro, amide, sulfonamide, alkylsulfonamide, and aryl sulfonamide;

R_1 and R_2 are positioned at the 3, 4 and/or 5 position (the amide side chain defining the 1 position), and are independently selected from the group consisting of hydrogen, halo, nitro, alkoxy, alkyl, aryl, heterocycle, haloalkyl, amide; or R_1 and R_2 together forming a ring which has 3, 4, 5, or 6 carbon atoms and fused to the six memebered ring they substitute;

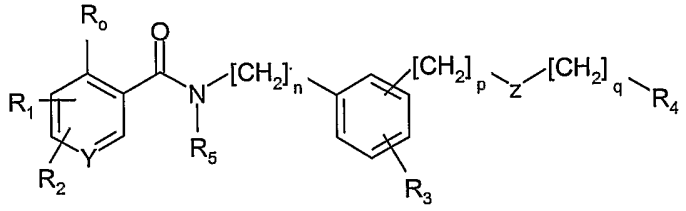
R_3 represents from one to four substituents independently selected from the group consisting of hydrogen, halo, lower alkyl, haloalkyl, aryl, aralkyl, alkoxy, haloalkoxy, aryloxy, aralkoxy, heterocycle, heterocycle(oxy), heterocycle(alkyl), cyano, and nitro;

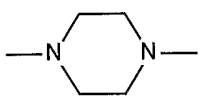
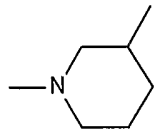
R_4 represents a substituent selected from the group consisting of alkyl, haloalkyl, aryl, alkaryl, cycloalkyl, alkoxy, aryloxy, aralkoxy, heterocycle, heterocycle(oxy), and heterocycle(alkyl);

R_5 represents hydrogen or lower alkyl; and

n, p and q are the same or different integers selected from the group consisting of 0, 1, 2 or 3.

2. The use of Claim 1, wherein the compound has the formula:



wherein Z is selected from the group consisting of oxygen, sulfur, amino, carbonyl,  and  ;

R_0 is selected from the group consisting of hydroxy, lower (C_1-C_6) alkoxy, hydroxy lower alkoxy, nitro, amide, sulfonamide, alkylsulfonamide, and aryl sulfonamide;

R_1 and R_2 are positioned at the 3, 4 and/or 5 position (the amide side chain defining the 1 position), and are independently selected from the group consisting of hydrogen, halo, nitro, alkoxy, alkyl, aryl, heterocycle, haloalkyl, amide;

R_3 represents from one to four substituents independently selected from the group consisting of hydrogen, halo, lower alkyl, haloalkyl, aryl, aralkyl, alkoxy, haloalkoxy, aryloxy, aralkoxy, heterocycle, heterocycle(oxy), heterocycle(alkyl), cyano, and nitro;

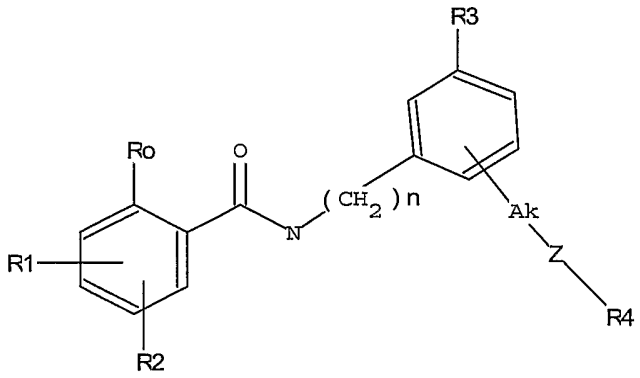
R_4 represents a substituent selected from the group consisting of alkyl, haloalkyl, aryl, alkaryl, cycloalkyl, alkoxy, aryloxy, aralkoxy, heterocycle, heterocycle(oxy), and heterocycle(alkyl); and

n, p and q are the same or different integers selected from the group consisting of 0, 1, 2 or 3,

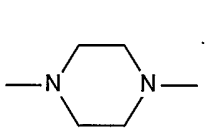
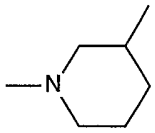
3. The use of Claim 2, wherein q is 0 and R_4 is haloalkyl, heterocyclo, or halo-substituted aryl.

4. The use of Claim 1, wherein Y is C; Z is oxygen or amino; R_0 is hydroxy or hydroxyalkoxy; R_3 is halo, haloalkyl, or haloalkoxy; R_4 is haloalkyl, heterocycle, or aryl with one or more halo or haloalkyl; and R_5 is hydrogen.

5. Use of a compound or a pharmaceutically acceptable salt, ester, amide, hydrate or solvate thereof in the manufacture of a medicament useful in inducing cell apoptosis in mammals, wherein said compound has the formula:



wherein

Z is oxygen, amino, sulfur,  or  ;

n is an integer of 0, 1, 2, or 3;

Ak is lower alkyl;

R_0 is hydroxy, lower (C_1-C_6) alkoxy, hydroxyalkoxy (e.g. hydroxymethoxy, hydroxyethoxy), nitro;

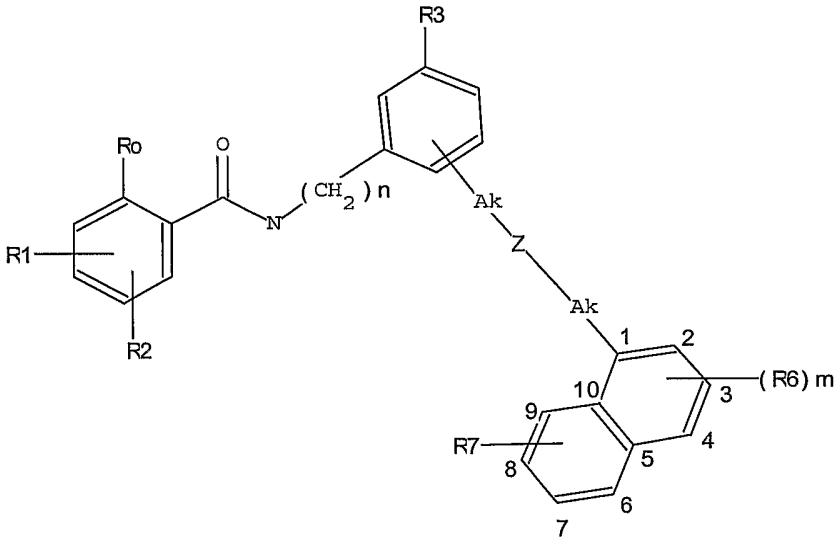
R_1 and R_2 are independently selected from hydrogen, halo, nitro, alkoxy, aryl, heterocycle, halo-substituted lower alkyl (preferably trihalo lower alkyl, e.g., trifluoromethyl), wherein R_1 and R_2 are not both hydrogen at the same time;

R_3 is halo, halo-substituted lower alkyl (preferably trihalo lower alkyl, e.g., trifluoromethyl), or haloalkoxy (preferably halo-substituted C_1-C_6 alkoxy, e.g., trihalo-substituted methoxy); and

R_4 represents haloalkyl, e.g., halo-substituted lower alkyl (preferably trihalo lower alkyl, e.g., trifluoromethyl); alkoxyalkoxy (including halo-substituted alkoxyalkoxy); R_8

as defined below; and R_8-Ak- or (R_8R9)-Ak-, wherein Ak is lower alkyl with a straight or branched chain, R_8 and R_9 are independently selected from (1) cycloalkyl, (2) aryl such as benzene and naphthalene, (3) aryloxy, (4) a saturated or partially unsaturated or aromatic moncyclic 3, 4, 5, 6, or 7-membered heterocycle containing one or more N, O, or S, or (5) a saturated or partially unsaturated or aromatic biocyclic 8 to 12-membered heterocycle containing one or more N, O, or S, wherein the rings of the cycloalkyl, aryloxy, aryl and heterocyle may be substituted by one or more identical or different substituents selected from lower alkyl, halo, haloalkyl (e.g., halo-substituted lower alkyl, preferably trihalo lower alkyl, e.g., trifluoromethyl), alkoxy, alkoxyalkoxy, (C_1-C_6)-alkyl-O-C(O)-, (C_1-C_6)-alkyl-O-C(O)-(C_1-C_3)-alkyl-, (C_1-C_6)-alkyl-O-C(O)-(C_1-C_3)-alkene-, alkylsulfonyl (e.g., lower alkyl-SO_2-), halo-substituted lower alkoxy (preferably trihalo lower alkoxy, e.g., trifluoromethoxy), and halo-aryl-.

6. The use of Claim 5, wherein said compound has the formula:



wherein

Z is oxygen, amino or sulfur;

n is an integer of 0, 1, 2, or 3;

Ak is lower alkyl;

R_0 is hydroxy, lower (C_1-C_6) alkoxy, hydroxyalkoxy, nitro, amide, sulfonamide, alkylsulfonamide, or aryl sulfonamide;

R_1 is hydrogen, halo, nitro, alkoxy, alkyl, aryl, heterocycle, haloalkyl, or amide;
R_2 is halo;

R_3 is halo, haloalkyl, or haloalkoxy;

R_5 is hydrogen or lower alkyl, preferably hydrogen;

R_6 is independently selected from F, Cl, Br, and I;

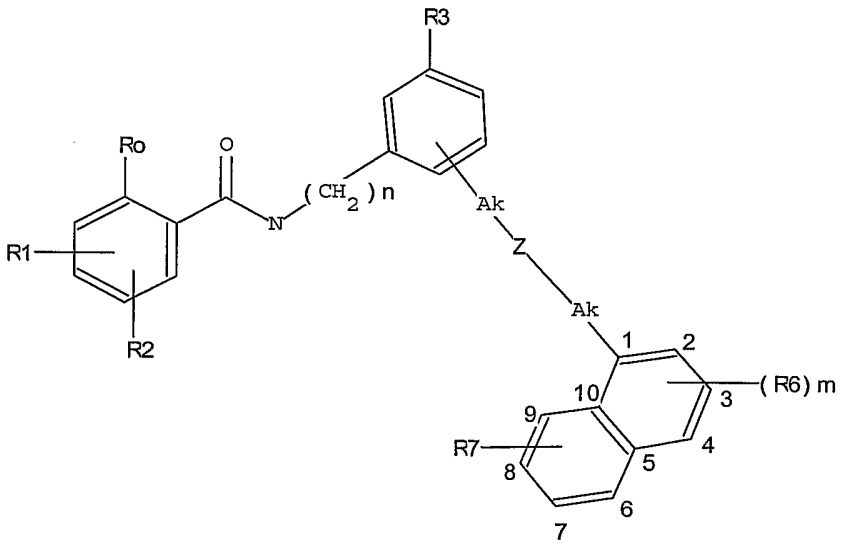
R_7 is hydrogen, halo, lower alkyl, alkoxy, or haloalkyl; and

m is 1, 2, or 3, wherein all R_6 groups are at positions 2, 3, and/or 4.

7. The use of Claim 6, wherein m is 1, R_6 is at position 4.

8. The use of any of Claims 2-7, wherein said medicament is useful in treating or preventing cancer.

9. A compound having the formula:



wherein

Z is oxygen, amino or sulfur;

n is an integer of 0, 1, 2, or 3;

Ak is lower alkyl;

R_0 is hydroxy, lower (C_1-C_6) alkoxy, hydroxyalkoxy, nitro, amide, sulfonamide, alkylsulfonamide, or aryl sulfonamide;

R_1 is hydrogen, halo, nitro, alkoxy, alkyl, aryl, heterocycle, haloalkyl, or amide;

R_2 is halo;

R_3 is halo, haloalkyl, or haloalkoxy;

R_5 is hydrogen or lower alkyl, preferably hydrogen;

R_6 is independently selected from F, Cl, Br, and I; and

R_7 is hydrogen, halo, lower alkyl, alkoxy, or haloalkyl; and

m is an integer or 1, 2, or 3, wherein all R_6 groups are at positions 2, 3, and/or 4.