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(54) Title: SYNTHESIS AND ANTICANCER ACTIVITY OF ARYL AND HETEROARYL-QUINOLIN DERIVATIVES

(57) Abstract: A class of compounds that are derivatives and analogues of aryl and heteroaryl-quinolin is disclosed. Also disclosed are synthesis and use of the aryl and heteroaryl -quinolin derivatives and analogues for anticancer activities.

SYNTHESIS AND ANTICANCER ACTIVITY OF ARYL AND HETEROARYL-QUINOLIN DERIVATIVES

REFERENCE TO RELATED APPLICATION

The present application claims the priority to U.S. Provisional Application Serial No. 61/364,760, filed July 15, 2010, which is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

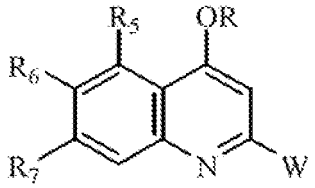
The present invention relates generally to derivatives and analogues of aryl and heteroaryl-quinolin, and more specifically to synthesis and use of aryl and heteroaryl -quinolin derivatives and analogues for anticancer activities.

BACKGROUND OF THE INVENTION

A series of substituted 2-phenylquinolin-4-ones (2-PQs) have been previously synthesized and identified as new anticancer agents. Through the process of structure-activity relationship (SAR) establishment, it was discovered that many of these compounds had potent cytotoxicity. In a recent *in vivo* evaluation of a series of 2-PQs with potent cytotoxicity, excellent antitumor activity was identified in 2-(2-fluorphenyl)-6,7-methylenedioxyquinolin-4-one (CHM-2133) and its phosphate derivative (CHM-2133-P) (FIG. 1). *See* WO2008/070176A1 and Yu-Hsun Chang et al. (2009) "Design and Synthesis of 2-(3-Benzo[b]thienyl)-6,7-methylenedioxyquinolin-4-one Analogues as Potent Antitumor Agents that Inhibit Tubulin Assembly" *J. Med. Chem.* 52, 4883–4891, each of which is herein incorporated by reference in its entirety. There is still a need for discovery of more potential anticancer compounds.

SUMMARY OF THE INVENTION

In one aspect, the invention relates to a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, prodrug, solvate, or metabolite thereof,

wherein

R is hydrogen, $P(=O)(OH)_2$, $P(=O)(O(C_1\text{-}C_{18})alkylene(C_6\text{-}C_{20})aryl)_2$, $P(=O)(OH)(OM)$, $P(=O)(OM)_2$, $P=O(O_2M)$, $S(=O)(OH)_2$, $S(=O)(O(C_1\text{-}C_{18})alkylene(C_6\text{-}C_{20})aryl)_2$, $S(=O)(OH)(OM)$, $S(=O)(OM)_2$;

M is a monovalent and divalent (ex: Mg, Ca) metal ion, or alkylammonium ion (ex: $N^{\oplus}R$);

W is (C_6-C_{20})aryl, (C_6-C_{20})heteroaryl, (C_1-C_{18})alkyl(C_6-C_{20})aryl, (C_1-C_{18})alkyl(C_6-C_{20})heteroaryl, hydroxy(C_6-C_{20})aryl, hydroxy(C_6-C_{20})heteroaryl, (C_1-C_{18})alkoxy(C_6-C_{20})aryl, (C_1-C_{18})alkoxy(C_6-C_{20})heteroaryl, (C_1-C_{18})alkylenedioxy(C_6-C_{20})aryl, (C_1-C_{18})alkylenedioxy(C_6-C_{20})heteroaryl, halo(C_6-C_{20})aryl, halo(C_6-C_{20})heteroaryl, (C_1-C_{18})alkylamino(C_6-C_{20})aryl, (C_1-C_{18})alkylamino(C_6-C_{20})heteroaryl, (C_1-C_{18})cycloalkylamino(C_6-C_{20})aryl, or (C_1-C_{18})cycloalkylamino(C_6-C_{20})heteroaryl, and their OR_8 substutes;

R_5 is (C_1-C_{18})alkoxy, hydrogen, hydroxyl, O-(C_1-C_{18})alkyl(C_6-C_{20})aryl, halo or OR_8, or R_5 and R_6 are (C_1-C_{18})dioxy provided that R_7 is hydrogen;

R_6 is hydroxyl, O-(C_1-C_{18})alkyl(C_6-C_{20})aryl, halo, OR_8, (C_1-C_{18})alkoxy, (C_1-C_{18})alkylamino, or (C_1-C_{18})cycloalkylamino, or R_6 and R_7 are (C_1-C_{18})dioxy provided that R_5 is hydrogen;

R_7 is hydrogen, halo or OR_8, hydroxyl, or O-(C_1-C_{18})alkyl(C_6-C_{20})aryl; and

R_8 is $P(=O)(OH)_2$, $P(=O)(O(C_1$-$C_{18})alkyl(C_6$-$C_{20})aryl)_2$, $P(=O)(OH)(OM)$, or $P(=O)(OM)_2$, $P=O(O_2M)$.

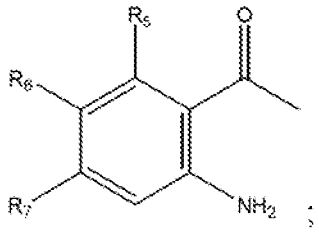
In one embodyment of the invention, the aforementioned class of the compound is restricted with the proviso that if R5 is hydroxyl, then R6 is not (C1)alkoxy and W is not 3-fluorophenyl.

In antoher embodiment of the invention, R5 is hydroxyl, R6 is (C1)alkoxy and W is 3-fluorophenyl.

In another aspect, the invention relates to a composition comprising a compound as aforementioned and a pharmaceutically acceptable carrier.

Further in another aspect, the invention relates to a method for treating a tumor disease comprising administering to a subject in need thereof an effective amount of a composition as aforementioned. The administering step may be performed *in vivo* or *in vitro*. In one embodiment, the subject is a mammal.

Yet in another aspect, the invention relates to a process for preparing a compound as aforementioned comprising reacting a compound of Formula II



;

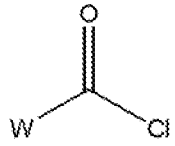
Formula II

wherein R_5 is (C_1-C_{18})alkoxy, hydrogen, hydroxyl, O-(C_1-C_{18})alkyl(C_6-C_{20})aryl, or OR_8 or R_5 and R_6 are (C_1-C_{18})dioxy provided that R_7 is hydrogen;

R_6 is hydroxyl, (C_1-C_{18})alkoxy, O-(C_1-C_{18})alkyl(C_6-C_{20})aryl, (C_1-C_{18})alkylamino, or (C_1-C_{18})cycloalkylamino or R_6 and R_7 are (C_1-C_{18})dioxy provided that R_5 is hydrogen;

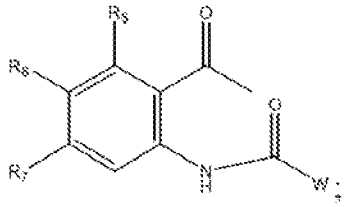
R_7 is hydrogen, hydroxyl, or O-(C_1-C_{18})alkyl(C_6-C_{20})aryl; and

R_8 is hydrogen; with a compound of Formula III



Formula III;

in the presence of a base; wherein W is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, benzo[d] [1,3]dioxol-4-yl, 2,3-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-benzyloxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3-benzyloxy-5-methoxyphenyl, 4-hydroxy-3-methoxyphenyl, 5-hydroxy-2-methoxyphenyl, 2,5-dihydroxyphenyl, benzo[b]thiophen-3-yl, benzo[b]thiophen-2-yl, benzo[b]furan-3-yl, naphtha-1-yl, naphtha-2-yl, quinolin-4-yl, quinolin-3-yl, quinolin-2-yl, quinolin-5-yl, or anthracen-1-yl to afford a compound of Formula IV



Formula IV

wherein

R is hydrogen;

W is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, benzo[d] [1,3]dioxol-4-yl, 2,3-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-benzyloxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3-benzyloxy-5-methoxyphenyl, 4-hydroxy-3-methoxyphenyl, 5-hydroxy-2-methoxyphenyl, 2,5-dihydroxyphenyl, benzo[b]thiophen-3-yl, benzo[b]thiophen-2-yl, benzo[b]furan-3-yl, naphtha-1-yl, naphtha-2-yl, quinolin-4-yl, quinolin-3-yl, quinolin-2-yl, quinolin-5-yl, or anthracen-1-yl;

R_5 is hydrogen, methoxy, hydroxyl, O-benzyl or OR_8, or R_5 and R_6 are methylenedioxy provided that R_7 is hydrogen;

R_6 is N,N-dimethylamino, hydroxyl, O-benzyl , methoxy, N-morpholino, or N-pyrrolindino, or R_6 and R_7 are methylenedioxy provided that R_5 is hydrogen;

R_7 is hydrogen, hydroxyl, or O-benzyl; and

R_8 is hydrogen; and

reacting a compound of Formula IV with a base to afford the compound of Formula I.

The process may further comprise dealkylating the compound of Formula I. The dealkylated or non-dealkylated compound of Formula I may further react with tetrabenzylpyrophosphate (Method A) or dibenzylphosphite (Method B) to afford the compound of Formula I, wherein R is $P(=O)(OCH_2Ph)_2$, which treated with alcohol provided monophosphate. The monophosphoric acid were obtained by catalytic hydrogenation of the monophosphate. The monophophoric acid may further react with a metal carbonate to afford the compound of Formula I, wherein R is $P(=O)(OH)(OM)$, or $P(=O)(OM)_2$, in which M is a monovalent metal ion.

These and other aspects will become apparent from the following description of the preferred embodiment taken in conjunction with the following drawings, although variations and modifications therein may be affected without departing from the spirit and scope of the novel concepts of the disclosure.

The accompanying drawings illustrate one or more embodiments of the invention and, together with the written description, serve to explain the principles of the invention. Wherever possible, the same reference numbers are used throughout the drawings to refer to the same or like elements of an embodiment.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the structures of substituted 2- phenylquinolin-4-ones (2-PQs), CHM-2133 and CHM-2133-P-Na.

FIG. 2 shows the structures of target compounds **16-21 and 37-45.**

FIGs. 3A-3C show differential activity patterns for compound ***3b*** against 60 human cancer cell lines. MG-MID: mean of log X values (X = GI_{50}, TGI, and LC_{50}). Delta: logarithm of the difference between the MG-MID and the log X of the most sensitive cell line. Range: logarithm of the difference between the log X of the most resistant cell line and the log X of the most sensitive cell line.

FIGs. 4A-4F show (A) Mean tumor volume-time profiles, (B) Mean tumor weight-time profiles and (C) Mean body weight-time profiles in Hep3B xenograft nude mice (n = 11) following iv dosing of doxorubicin at 5 mg/kg (qd) and compound **49** at 7.5, 15, and 30 mg/kg (bid) five days per week for four consecutive weeks; (D) Mean tumor volume-time profiles, (E) Mean tumor weight-time profiles and (F) Mean body weight-time profiles in Hep3B xenograft nude mice (n = 11)

following oral dosing of doxorubicin at 10 mg/kg (qd) and compound **49** at 7.5, 15, and 30 mg/kg (bid) five days per week for four consecutive weeks.

FIGs. 5A-5F show (A) Mean tumor volume-time profiles (B) Mean tumor weight-time profiles (C) Mean body weight-time profiles in Hep3B xenograft nude mice (n = 11) following oral dosing of doxorubicin at 5 mg/kg (qd) and **52** at 7.5, 15, and 30 mg/kg (qd) five days per week for four consecutive weeks; (D) Mean tumor volume-time profiles (E) Mean tumor weight-time profiles (F) Mean body weight-time profiles in Hep3B xenograft nude mice (n = 11) following intravenous dosing of doxorubicin at 10 mg/kg (qd) and **52** at 7.5, 15, and 30 mg/kg (qd) five days per week for four consecutive weeks.

FIGs. 6A-6C show (A) Mean tumor volume-time profiles (B) Mean tumor weight-time profiles (C) Mean body weight-time profiles in Hep3B xenograft nude mice (n = 6) following po dosing of doxorubicin at 10 mg/kg and 147 at 7.5, 15, and 30 mg/kg five days per week for four consecutive weeks.

FIGs. 7A-7C show (A) Mean tumor volume-time profiles (B) Mean tumor weight-time profiles (C) Mean body weight-time profiles in Hep3B xenograft nude mice (n = 6) following iv dosing of doxorubicin at 10 mg/kg and 147 at 7.5, 15, and 30 mg/kg five days per week for four consecutive weeks.

DETAILED DESCRIPTION OF THE INVENTION

One of ordinary skill in the art would readily appreciate that the pharmaceutical formulations and methods described herein can be prepared and practiced by applying known procedures in the pharmaceutical arts. These include, for example, unless otherwise indicated, conventional techniques of pharmaceutical sciences including pharmaceutical dosage form design, drug development, pharmacology, of organic chemistry, and polymer sciences. *See* generally, for example, Remington: The Science and Practice of Pharmacy, 21st edition, Lippincott, Williams & Wilkins, (2005).

DEFINITIONS

The terms used in this specification generally have their ordinary meanings in the art, within the context of the invention, and in the specific context where each term is used. Certain terms that are used to describe the invention are discussed below, or elsewhere in the specification, to provide additional guidance to the practitioner regarding the description of the invention. For convenience, certain terms may be highlighted, for example using italics and/or quotation marks. The use of highlighting has no influence on the scope and meaning of a term; the scope and meaning of a term is the same, in the same context, whether or not it is highlighted. It will be appreciated that same thing can be said in more than one way. Consequently, alternative language and synonyms may be used for any one or more of the terms discussed herein, nor is any special significance to be placed

upon whether or not a term is elaborated or discussed herein. Synonyms for certain terms are provided. A recital of one or more synonyms does not exclude the use of other synonyms. The use of examples anywhere in this specification including examples of any terms discussed herein is illustrative only, and in no way limits the scope and meaning of the invention or of any exemplified term. Likewise, the invention is not limited to various embodiments given in this specification.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. In the case of conflict, the present document, including definitions will control.

As used herein, "around", "about" or "approximately" shall generally mean within 20 percent, preferably within 10 percent, and more preferably within 5 percent of a given value or range. Numerical quantities given herein are approximate, meaning that the term "around", "about" or "approximately" can be inferred if not expressly stated.

The term "and/or" refers to any one of the items, any combination of the items, or all of the items with which this term is associated.

The singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. The claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely," "only," and the like in connection with the recitation of claim elements, or use of a "negative" limitation.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

The term "administration" refers to a method of placing a device to a desired site. The placing of a device can be by any pharmaceutically accepted means such as by swallowing, retaining it within the mouth until the drug has been dispensed, placing it within the buccal cavity, inserting, implanting, attaching, etc. These and other methods of administration are known in the art.

The term "anti-cancer agent" refers to an agent that either inhibits the growth of cancerous cells, or causes the death of cancerous cells. Known anti-cancer agents include, e.g., nucleotide and nucleoside analogs, adjunct antineoplastic agents, alkylating agents, etc. *See*, Physician's Desk Reference, 55th Edition, Medical Economics, Montvale, NJ, USA (2001).

The term "amino" refers to $-NH_2$. The amino group can be optionally substituted as defined herein for the term "substituted." The term "alkylamino" refers to $-NR_2$, wherein at least one R is alkyl and the second R is alkyl or hydrogen. The term "acylamino" refers to N(R)C(=O)R, wherein each R is independently hydrogen, alkyl, or aryl.

The term "alkyl" refers to a C_1–C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl, ethyl, 1–propyl, 2–propyl, 1–butyl, 2–methyl–1–propyl (iso–butyl, $–CH_2CH(CH_3)_2$), 2–butyl (sec–butyl, $–CH(CH_3)CH_2CH_3$), 2–methyl–2–propyl (tert–butyl, $–C(CH_3)_3$), 1–pentyl, 2–pentyl, 3–pentyl, 2–methyl–2–butyl, 3–methyl–2–butyl, 3–methyl–1–butyl, 2–methyl–1–butyl, 1–hexyl, 2–hexyl, 3–hexyl, 2–methyl–2–pentyl, 3–methyl–2–pentyl, 4–methyl–2–pentyl, 3–methyl–3–pentyl, 2–methyl–3–pentyl, 2,3–dimethyl–2–butyl, 3,3–dimethyl–2–butyl.

The alkyl can be a monovalent hydrocarbon radical, as described and exemplified above, or it can be a divalent hydrocarbon radical (i.e., alkylene).

The alkyl can optionally be substituted with one or more alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, acetamido, acetoxy, acetyl, benzamido, benzenesulfinyl, benzenesulfonamido, benzenesulfonyl, benzenesulfonylamino, benzoyl, benzoylamino, benzoyloxy, benzyl, benzyloxy, benzyloxycarbonyl, benzylthio, carbamoyl, carbamate, isocyannato, sulfamoyl, sulfinamoyl, sulfino, sulfo, sulfoamino, thiosulfo, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxy. The alkyl can optionally be interrupted with one or more non–peroxide oxy (–O–), thio (–S–), imino (–N(H)–), methylene dioxy ($–OCH_2O–$), carbonyl (–C(=O)–), carboxy (–C(=O)O–), carbonyldioxy (–OC(=O)O–), carboxylato (–OC(=O)–), imino (C=NH), sulfinyl (SO) or sulfonyl (SO_2). Additionally, the alkyl can optionally be at least partially unsaturated, thereby providing an alkenyl.

The term "alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical of 1–18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or different carbon atoms of a parent alkane. Typical alkylene radicals include, but are not limited to: methylene ($–CH_2–$) 1,2–ethylene ($–CH_2CH_2–$), 1,3–propylene ($–CH_2CH_2CH_2–$), 1,4–butylene ($–CH_2CH_2CH_2CH_2–$), and the like.

The alkylene can optionally be substituted with one or more alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, acetamido, acetoxy, acetyl, benzamido, benzenesulfinyl, benzenesulfonamido, benzenesulfonyl, benzenesulfonylamino, benzoyl, benzoylamino, benzoyloxy, benzyl, benzyloxy, benzyloxycarbonyl, benzylthio, carbamoyl, carbamate, isocyannato, sulfamoyl, sulfinamoyl, sulfino, sulfo, sulfoamino, thiosulfo, NR^xR^y and/or

$COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxy. Additionally, the alkylene can optionally be interrupted with one or more non–peroxide oxy (–O–), thio (–S–), imino (–N(H)–), methylene dioxy (–OCH_2O–), carbonyl (–C(=O)–), carboxy (–C(=O)O–), carbonyldioxy (–OC(=O)O–), carboxylato (–OC(=O)–), imine (C=NH), sulfinyl (SO) or sulfonyl (SO_2). Moreover, the alkylene can optionally be at least partially unsaturated, thereby providing an alkenylene.

The term "alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2–18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. Typical alkenylene radicals include, but are not limited to: 1,2–ethenylene (–CH=CH–).

The alkenylene can optionally be substituted with one or more alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, acetamido, acetoxy, acetyl, benzamido, benzenesulfinyl, benzenesulfonamido, benzenesulfonyl, benzenesulfonylamino, benzoyl, benzoylamino, benzoyloxy, benzyl, benzyloxy, benzyloxycarbonyl, benzylthio, carbamoyl, carbamate, isocyannato, sulfamoyl, sulfinamoyl, sulfino, sulfo, sulfoamino, thiosulfo, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl or hydroxy. Additionally, The alkenylene can optionally be interrupted with one or more non–peroxide oxy (–O–), thio (–S–), imino (–N(H)–), methylene dioxy (–OCH_2O–), carbonyl (–C(=O)–), carboxy (–C(=O)O–), carbonyldioxy (–OC(=O)O–), carboxylato (–OC(=O)–), imine (C=NH), sulfinyl (SO) or sulfonyl (SO_2).

The term "alkoxy" refers to the group alkyl–O–, where alkyl is defined herein. Preferred alkoxy groups include, e.g., methoxy, ethoxy, *n*–propoxy, *iso*–propoxy, *n*–butoxy, *tert*–butoxy, *sec*–butoxy, *n*–pentoxy, *n*–hexoxy, 1,2–dimethylbutoxy, and the like.

The alkoxy can optionally be substituted with one or more halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, acetamido, acetoxy, acetyl, benzamido, benzenesulfinyl, benzenesulfonamido, benzenesulfonyl, benzenesulfonylamino, benzoyl, benzoylamino, benzoyloxy, benzyl, benzyloxy, benzyloxycarbonyl, benzylthio, carbamoyl, carbamate, isocyannato, sulfamoyl, sulfinamoyl, sulfino, sulfo, sulfoamino, thiosulfo, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl, or hydroxy.

The term "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings, wherein at least one ring is aromatic (e.g., naphthyl, dihydrophenanthrenyl, fluorenyl, or anthryl). Preferred aryls include phenyl, naphthyl and the like. The aryl can optionally be a divalent radical, thereby providing an arylene.

The aryl can optionally be substituted with one or more alkyl, alkenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, acetamido, acetoxy, acetyl, benzamido, benzenesulfinyl, benzenesulfonamido, benzenesulfonyl, benzenesulfonylamino, benzoyl, benzoylamino, benzoyloxy, benzyl, benzyloxy, benzyloxycarbonyl, benzylthio, carbamoyl, carbamate, isocyannato, sulfamoyl, sulfinamoyl, sulfino, sulfo, sulfoamino, thiosulfo, NR^XR^Y and/or $COOR^X$, wherein each R^X and R^Y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl, or hydroxy.

The term "carbocycle" refers to a saturated, unsaturated or aromatic ring having 3 to 8 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 30 carbon atoms as a polycycle. Monocyclic carbocycles typically have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, e.g., arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl. The carbocycle can be optionally substituted as described above for alkyl groups.

The term "carboxyl" refers to –COOH.

All chiral, diastereomeric, racemic forms of a structure are intended, unless a particular stereochemistry or isomeric form is specifically indicated. Compounds used in the present invention can include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions, at any degree of enrichment. Both racemic and diastereomeric mixtures, as well as the individual optical isomers can be isolated or synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these are all within the scope of the invention.

The term "chemically feasible" refers to a bonding arrangement or a compound where the generally understood rules of organic structure are not violated; for example a structure within a definition of a claim that would contain in certain situations a pentavalent carbon atom that would not exist in nature would be understood to not be within the claim.

When a substituent is specified to be an atom or atoms of specified identity, "or a bond", a configuration is referred to when the substituent is "a bond" that the groups that are immediately adjacent to the specified substituent are directly connected to each other by a chemically feasible bonding configuration.

The phrase "compounds of the disclosure" refer to compounds of Formula I and pharmaceutically acceptable enantiomers, diastereomers, and salts thereof. Similarly, references to intermediates, are meant to embrace their salts where the context so permits.

The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

The cycloalkyl can optionally be substituted with one or more alkyl, alkenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, acetamido, acetoxy, acetyl, benzamido, benzenesulfinyl, benzenesulfonamido, benzenesulfonyl, benzenesulfonylamino, benzoyl, benzoylamino, benzoyloxy, benzyl, benzyloxy, benzyloxycarbonyl, benzylthio, carbamoyl, carbamate, isocyannato, sulfamoyl, sulfinamoyl, sulfino, sulfo, sulfoamino, thiosulfo, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl, or hydroxy.

The cycloalkyl can optionally be at least partially unsaturated, thereby providing a cycloalkenyl. Additionally, the cycloalkyl can optionally be a divalent radical, thereby providing a cycloalkylene.

The term "delivery" refers to the release of a drug from a device comprising that drug into an environment surrounding the device. The environment into which the drug so released may or may not be the ultimate site of activity for that drug. In some instances, the released drug may need to be transported to its ultimate site of activity.

The term "derivative or analogue" of a compound refers to a chemically modified compound wherein the chemical modification takes place at one or more functional groups of the compound and /or on an aromatic, alicyclic, or heterocyclic structures, when present. The derivative or analogue however is expected to retain the pharmacological activity of the compound from which it is derived.

The term "an effective amount" refers to an amount sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications, or

dosages. Determination of an effective amount for a given administration is well within the ordinary skill in the pharmaceutical arts.

The term "exchanged" is intended to indicate that in between two or more adjacent carbon atoms, and the hydrogen atoms to which they are attached (e.g., methyl (CH_3), methylene (CH_2), or methine (CH)), indicated in the expression using "interrupted" is inserted with a selection from the indicated group(s), provided that the each of the indicated atoms' normal valency is not exceeded, and that the interruption results in a stable compound. Such suitable indicated groups include, e.g., with one or more non–peroxide oxy (–O–), thio (–S–), imino (–N(H)–), methylene dioxy ($–OCH_2O–$), carbonyl (–C(=O)–), carboxy (–C(=O)O–), carbonyldioxy (–OC(=O)O–), carboxylato (–OC(=O)–), imino (C=NH), sulfinyl (SO) and sulfonyl (SO_2).

The term "halo" refers to fluoro, chloro, bromo, and iodo. Similarly, the term "halogen" refers to fluorine, chlorine, bromine, and iodine.

The term "haloalkyl" refers to alkyl as defined herein substituted by 1–4 halo groups as defined herein, which may be the same or different. Representative haloalkyl groups include, by way of example, trifluoromethyl, 3–fluorododecyl, 12,12,12–trifluorododecyl, 2–bromooctyl, 3–bromo–6–chloroheptyl, and the like.

The term "heteroaryl" is defined herein as a monocyclic, bicyclic, or tricyclic ring system containing one, two, or three aromatic rings and containing at least one nitrogen, oxygen, or sulfur atom in an aromatic ring, and which can be unsubstituted or substituted. The heteroaryl can optionally be a divalent radical, thereby providing a heteroarylene.

Examples of heteroaryl groups include, but are not limited to, 2*H*–pyrrolyl, 3*H*–indolyl, 4*H*–quinolizinyl, 4n*H*–carbazolyl, acridinyl, benzo[*b*]thienyl, benzothiazolyl, β–carbolinyl, carbazolyl, chromenyl, cinnaolinyl, dibenzo[b,d]furanyl, furazanyl, furyl, imidazolyl, imidizolyl, indazolyl, indolisinyl, indolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, naptho[2,3–*b*], oxazolyl, perimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, thiadiazolyl, thianthrenyl, thiazolyl, thienyl, triazolyl, and xanthenyl. In one embodiment the term "heteroaryl" denotes a monocyclic aromatic ring containing five or six ring atoms containing carbon and 1, 2, 3, or 4 heteroatoms independently selected from the group non–peroxide oxygen, sulfur, and N(Z) wherein Z is absent or is H, O, alkyl, phenyl, or benzyl. In another embodiment heteroaryl denotes an ortho–fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz–derivative or one derived by fusing a propylene, or tetramethylene diradical thereto.

The heteroaryl can optionally be substituted with one or more alkyl, alkenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, acetamido, acetoxy, acetyl, benzamido, benzenesulfinyl, benzenesulfonamido, benzenesulfonyl, benzenesulfonylamino, benzoyl, benzoylamino, benzoyloxy, benzyl, benzyloxy, benzyloxycarbonyl, benzylthio, carbamoyl, carbamate, isocyannato, sulfamoyl, sulfinamoyl, sulfino, sulfo, sulfoamino, thiosulfo, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl, or hydroxy.

The term "heterocycle" or "heterocyclyl" refers to a saturated or partially unsaturated ring system, containing at least one heteroatom selected from the group oxygen, nitrogen, and sulfur, and optionally substituted with alkyl, or $C(=O)OR^b$, wherein R^b is hydrogen or alkyl. Typically heterocycle is a monocyclic, bicyclic, or tricyclic group containing one or more heteroatoms selected from the group oxygen, nitrogen, and sulfur. A heterocycle group also can contain an oxo group (=O) attached to the ring. Non–limiting examples of heterocycle groups include 1,3–dihydrobenzofuran, 1,3–dioxolane, 1,4–dioxane, 1,4–dithiane, 2*H*–pyran, 2–pyrazoline, 4*H*–pyran, chromanyl, imidazolidinyl, imidazolinyl, indolinyl, isochromanyl, isoindolinyl, morpholine, piperazinyl, piperidine, piperidyl, pyrazolidine, pyrazolidinyl, pyrazolinyl, pyrrolidine, pyrroline, quinuclidine, and thiomorpholine. The heterocycle can optionally be a divalent radical, thereby providing a heterocyclene.

The heterocycle can optionally be substituted with one or more alkyl, alkenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, acetamido, acetoxy, acetyl, benzamido, benzenesulfinyl, benzenesulfonamido, benzenesulfonyl, benzenesulfonylamino, benzoyl, benzoylamino, benzoyloxy, benzyl, benzyloxy, benzyloxycarbonyl, benzylthio, carbamoyl, carbamate, isocyannato, sulfamoyl, sulfinamoyl, sulfino, sulfo, sulfoamino, thiosulfo, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H, alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl, or hydroxy.

Examples of nitrogen heterocycles and heteroaryls include, but are not limited to, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline,

piperidine, piperazine, indoline, morpholino, piperidinyl, tetrahydrofuranyl, and the like as well as N–alkoxy–nitrogen containing heterocycles.

The term "hydrate" refers to the complex where the solvent molecule is water.

The term "include," "for example," "such as," and the like are used illustratively and are not intended to limit the present invention.

The term "interrupted" indicates that another group is inserted between two adjacent carbon atoms (and the hydrogen atoms to which they are attached (e.g., methyl (CH_3), methylene (CH_2) or methine (CH))) of a particular carbon chain being referred to in the expression using the term "interrupted, provided that each of the indicated atoms' normal valency is not exceeded, and that the interruption results in a stable compound. Suitable groups that can interrupt a carbon chain include, e.g., with one or more non-peroxide oxy (-O-), thio (-S-), imino (-N(H)-), methylene dioxy (-OCH_2O-), carbonyl (-C(=O)-), carboxy (-C(=O)O-), carbonyldioxy (-OC(=O)O-), carboxylato (-OC(=O)-), imine (C=NH), sulfinyl (SO) and sulfonyl (SO_2). Alkyl groups can be interrupted by one ore more (e.g., 1, 2, 3, 4, 5, or about 6) of the aforementioned suitable groups. The site of interruption can also be between a carbon atom of an alkyl group and a carbon atom to which the alkyl group is attached.

As to any of the groups described herein, which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non–feasible. In addition, the compounds of this disclosed subject matter include all stereochemical isomers arising from the substitution of these compounds.

Selected substituents within the compounds described herein are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given claim. One of ordinary skill in the art of medicinal chemistry and organic chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

Recursive substituents are an intended aspect of the disclosed subject matter. One of ordinary skill in the art of medicinal and organic chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in a claim of the disclosed subject matter, the total number will be determined as set forth above.

The term "metabolite" refers to any compound of the formula (I) produced *in vivo* or *in vitro* from the parent drug, or its prodrugs. The term "molecular weight" refers to a weight-average molecular weight, as is well known in the art. The term "oxo" refers to =O.

The term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio. Several pharmaceutically acceptable ingredients are known in the art and official publications such as The United States Pharmacoepia describe the analytical criteria to assess the pharmaceutical acceptability of numerous ingredients of interest.

The term "pharmaceutically acceptable salts" refers to ionic compounds, wherein a parent non–ionic compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include conventional non–toxic salts and quaternary ammonium salts of the parent compound formed, for example, from non–toxic inorganic or organic acids. Non–toxic salts can include those derived from inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfamic, phosphoric, nitric and the like. Salts prepared from organic acids can include those such as acetic, 2–acetoxybenzoic, ascorbic, benzenesulfonic, benzoic, citric, ethanesulfonic, ethane disulfonic, formic, fumaric, gentisinic, glucaronic, gluconic, glutamic, glycolic, hydroxymaleic, isethionic, isonicotinic, lactic, maleic, malic, mesylate or methanesulfonic, oxalic, pamoic (1,1'–methylene–bis–(2–hydroxy–3–naphthoate)), pantothenic, phenylacetic, propionic, salicylic, sulfanilic, toluenesulfonic, stearic, succinic, tartaric, bitartaric, and the like. Certain compounds can form pharmaceutically acceptable salts with various amino acids. For a review on pharmaceutically acceptable salts, *see*, e.g., Berge et al., *J. Pharm. Sci.* 1977, *66*(1), 1–19, which is incorporated herein by reference.

The pharmaceutically acceptable salts of the compounds described herein can be synthesized from the parent compound, which contains a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of many suitable salts are found in Remington: The Science and Practice of Pharmacy, 21st edition, Lippincott, Williams & Wilkins, (2005).

It will be appreciated by those skilled in the art that compounds useful in the disclosed subject matter having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the presently disclosed subject matter encompasses any racemic, optically–active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the presently disclosed subject matter, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically–active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine anticancer activity using the standard tests described herein, or using other similar tests which are well known in the art.

One diastereomer of a compound disclosed herein may display superior activity compared with the other. When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Tucker et al., J. Med. Chem., 37, 2437 (1994). A chiral compound described herein may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g., Huffman et al., J. Org. Chem., 60:1590 (1995).

The terms "prevent," "preventative," "prevention," "protect," and "protection" refer to medical procedures that keep the malcondition from occurring in the first place. The terms mean that there is no or a lessened development of disease or disorder where none had previously occurred, or no further disorder or disease development if there had already been development of the disorder or disease.

The term "prodrug" refers to any pharmaceutically acceptable form of compound of the formula I, which, upon administration to a patient, provides a compound of the formula I. Pharmaceutically acceptable prodrugs refer to a compound that is metabolized, for example hydrolyzed or oxidized, in the host to form a compound of the formula I. Typical examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated to produce the active compound.

The prodrug may be prepared with the objective(s) of improved chemical stability, improved patient acceptance and compliance, improved bioavailability, prolonged duration of action, improved organ selectivity (including improved brain penetrance), improved formulation (e.g., increased hydrosolubility), and/or decreased side effects (e.g., toxicity). See e.g. T. Higuchi and V. Stella, "Prodrugs as Novel Delivery Systems", Vol. 14 of the A.C.S. Symposium Series; Bioreversible

Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, (1987). Prodrugs include, but are not limited to, compounds derived from compounds of formula I wherein hydroxy, amine or sulfhydryl groups, if present, are bonded to any group that, when administered to the subject, cleaves to form the free hydroxyl, amino or sulfhydryl group, respectively. Selected examples include, but are not limited to, biohydrolyzable amides and biohydrolyzable esters and biohydrolyzable carbamates, carbonates, acetate, formate and benzoate derivatives of alcohol and amine functional groups.

The prodrug can be readily prepared from the compounds of Formula (I) using methods known in the art. See, for example, Notari, R. E., "Theory and Practice of Prodrug Kinetics," *Methods in Enzymology*, 112:309 323 (1985); Bodor, N., "Novel Approaches in Prodrug Design," *Drugs of the Future*, 6(3):165 182 (1981); and Bundgaard, H., "Design of Prodrugs: Bioreversible-Derivatives for Various Functional Groups and Chemical Entities," in Design of Prodrugs (H. Bundgaard, ed.), Elsevier, N.Y. (1985); Burger's Medicinal Chemistry and Drug Chemistry, Fifth Ed., Vol. 1, pp. 172-178, 949-982 (1995).

The term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula I, or a salt or physiologically functional derivative thereof) and a solvent. Such solvents, for the purpose of the invention, should not interfere with the biological activity of the solute. Non-limiting examples of suitable solvents include, but are not limited to water, methanol, ethanol, and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Non-limiting examples of suitable pharmaceutically acceptable solvents include water, ethanol, and acetic acid.

The term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable.

The term "substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. Suitable indicated groups include, e.g., alkyl, alkenyl, alkylidenyl, alkenylidenyl, alkoxy, halo, haloalkyl, hydroxy, hydroxyalkyl, aryl, heteroaryl, heterocycle, cycloalkyl, alkanoyl, acyloxy, alkoxycarbonyl, amino, imino, alkylamino, acylamino, nitro, trifluoromethyl, trifluoromethoxy, carboxy, carboxyalkyl, keto, thioxo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, acetamido, acetoxy, acetyl, benzamido, benzenesulfinyl, benzenesulfonamido, benzenesulfonyl, benzenesulfonylamino, benzoyl, benzoylamino, benzoyloxy, benzyl, benzyloxy, benzyloxycarbonyl, benzylthio, carbamoyl, carbamate, isocyanato, sulfamoyl, sulfinamoyl, sulfino, sulfo, sulfoamino, thiosulfo, NR^xR^y and/or $COOR^x$, wherein each R^x and R^y are independently H,

alkyl, alkenyl, aryl, heteroaryl, heterocycle, cycloalkyl, or hydroxy. When a substituent is oxo (i.e., =O) or thioxo (i.e., =S) group, then two hydrogens on the atom are replaced. The term "sulfonyl" refers to $-SO_2-$.

The term "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule.

The term "therapeutically effective amount" is intended to include an amount of a compound described herein, or an amount of the combination of compounds described herein, e.g., to treat or prevent the disease or disorder, or to treat the symptoms of the disease or disorder, in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, Adv. Enzyme Regul., 22:27 (1984), occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased activity, or some other beneficial effect of the combination compared with the individual components.

The terms "therapy," and "therapeutic" refer to either "treatment" or "prevention," thus, agents that either treat damage or prevent damage are "therapeutic."

The terms "treating" or "treat" or "treatment" refer to obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse affect attributable to the disease. As used herein, the term "treatment," covers any treatment of a disease in a mammal, particularly in a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., causing regression of the disease.

In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group. For example, if X is described as selected from the group consisting of bromine, chlorine, and iodine, claims for X being bromine and claims for X being bromine and chlorine are fully described. Moreover, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any combination of individual members or subgroups of members of Markush groups. Thus, for example, if X is described as selected from the group consisting of bromine, chlorine, and iodine, and Y is described as selected

from the group consisting of methyl, ethyl, and propyl, claims for X being bromine and Y being methyl are fully described.

In various embodiments, the compound or set of compounds, such as are used in the inventive methods, can be any one of any of the combinations and/or sub-combinations of the above-listed embodiments.

Asymmetric carbon atoms may be present in the compounds described. All such isomers, including diastereomers and enantiomers, as well as the mixtures thereof are intended to be included in the scope of the recited compound. In certain cases, compounds can exist in tautomeric forms. All tautomeric forms are intended to be included in the scope. Likewise, when compounds contain an alkenyl or alkenylene group, there exists the possibility of cis- and trans-isomeric forms of the compounds. Both cis- and trans-isomers, as well as the mixtures of cis- and trans-isomers, are contemplated. Thus, reference herein to a compound includes all of the aforementioned isomeric forms unless the context clearly dictates otherwise.

Various forms are included in the embodiments, including polymorphs, solvates, hydrates, conformers, salts, and prodrug derivatives. A polymorph is a composition having the same chemical formula, but a different structure. A solvate is a composition formed by solvation (the combination of solvent molecules with molecules or ions of the solute). A hydrate is a compound formed by an incorporation of water. A conformer is a structure that is a conformational isomer. Conformational isomerism is the phenomenon of molecules with the same structural formula but different conformations (conformers) of atoms about a rotating bond. Salts of compounds can be prepared by methods known to those skilled in the art. For example, salts of compounds can be prepared by reacting the appropriate base or acid with a stoichiometric equivalent of the compound. A prodrug is a compound that undergoes biotransformation (chemical conversion) before exhibiting its pharmacological effects. For example, a prodrug can thus be viewed as a drug containing specialized protective groups used in a transient manner to alter or to eliminate undesirable properties in the parent molecule. Thus, reference herein to a compound includes all of the aforementioned forms unless the context clearly dictates otherwise.

Concentrations, amounts, etc., of various components are often presented in a range format throughout this disclosure. The description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the claimed invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as 1% to 8% should be considered to have specifically disclosed subranges such as 1% to 7%, 2% to 8%, 2% to 6%, 3% to 6%, 4% to 8%, 3% to 8% etc., as well as individual numbers

within that range, such as, 2%, 5%, 7% etc. This construction applies regardless of the breadth of the range and in all contexts throughout this disclosure.

In the claims provided herein, the steps specified to be taken in a claimed method or process may be carried out in any order without departing from the principles of the invention, except when a temporal or operational sequence is explicitly defined by claim language. Recitation in a claim to the effect that first a step is performed then several other steps are performed shall be taken to mean that the first step is performed before any of the other steps, but the other steps may be performed in any sequence unless a sequence is further specified within the other steps. For example, claim elements that recite "first A, then B, C, and D, and lastly E" shall be construed to mean step A must be first, step E must be last, but steps B, C, and D may be carried out in any sequence between steps A and E and the process of that sequence will still fall within the four corners of the claim.

Furthermore, in the claims provided herein, specified steps may be carried out concurrently unless explicit claim language requires that they be carried out separately or as parts of different processing operations. For example, a claimed step of doing X and a claimed step of doing Y may be conducted simultaneously within a single operation, and the resulting process will be covered by the claim. Thus, a step of doing X, a step of doing Y, and a step of doing Z may be conducted simultaneously within a single process step, or in two separate process steps, or in three separate process steps, and that process will still fall within the four corners of a claim that recites those three steps.

Similarly, except as explicitly required by claim language, a single substance or component may meet more than a single functional requirement, provided that the single substance fulfills the more than one functional requirement as specified by claim language.

The compounds described herein can be prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in Compendium of Organic Synthetic Methods (John Wiley & Sons, New York) Vol. 1, Ian T. Harrison and Shuyen Harrison (1971); Vol. 2, Ian T. Harrison and Shuyen Harrison (1974); Vol. 3, Louis S. Hegedus and Leroy Wade (1977); Vol. 4, Leroy G. Wade Jr., (1980); Vol. 5, Leroy G. Wade Jr. (1984); and Vol. 6, Michael B. Smith; as well as March, J., Advanced Organic Chemistry, 3rd Edition, John Wiley & Sons, New York (1985); Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes, Barry M. Trost, Editor–in–Chief, Pergamon Press, New York (1993); Advanced Organic Chemistry, Part B: Reactions and Synthesis, 4th Ed.; Carey and Sundberg; Kluwer Academic/Plenum Publishers: New York (2001); Advanced Organic Chemistry, Reactions, Mechanisms, and Structure, 2nd Edition, March, McGraw Hill (1977); Protecting Groups in Organic Synthesis, 2nd Edition,

Greene, T.W., and Wutz, P.G.M., John Wiley & Sons, New York (1991); and Comprehensive Organic Transformations, 2nd Edition, Larock, R.C., John Wiley & Sons, New York (1999). Exemplary methods of making the compounds described herein are described herein in the examples below.

Obviously, numerous modifications and variations of the presently disclosed subject matter are possible in light of the above teachings. It is therefore to be understood that within the scope of the claims, the disclosed subject matter may be practiced otherwise than as specifically described herein.

Specific ranges, values, and embodiments provided herein are for illustration purposes only and do not otherwise limit the scope of the disclosed subject matter, as defined by the claims.

It should be understood that the present disclosure encompasses all stereochemical isomeric forms, or mixtures thereof, which possess the ability to kill cancer cells and/or inhibit growth of cancer cells. Enantiomers of the present disclosure may be resolved by methods known to those skilled in the art, for example, by formation of diastereoisomeric salts which may be separated by crystallization, gas-liquid or liquid chromatography, or selective reaction of one enantiomer with an enantiomer-specific reagent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by a separation technique, then an additional step is required to form the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

Certain compounds of the present disclosure may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present disclosure includes each conformational isomer of these compounds and mixtures thereof.

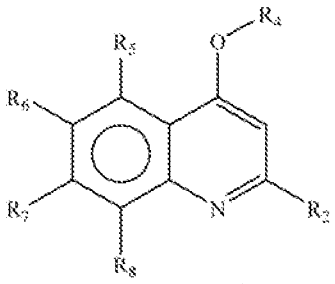
Certain compounds of the present disclosure may exist in zwitterionic form and the present disclosure includes each zwitterionic form of these compounds and mixtures thereof.

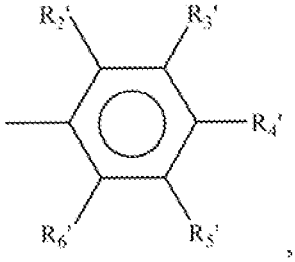
The starting materials useful to synthesize the compounds of the present disclosure are known to those skilled in the art and can be readily manufactured or are commercially available.

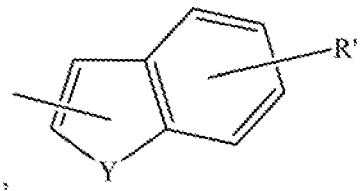
The following methods set forth below are provided for illustrative purposes and are not intended to limit the scope of the claimed disclosure. It will be recognized that it may be necessary to prepare such a compound in which a functional group is protected using a conventional protecting group then to remove the protecting group to provide a compound of the present disclosure. The details

concerning the use of protecting groups in accordance with the present disclosure are known to those skilled in the art.

The invention relates to synthesis of anticancer compounds of (fluorophenyl)quinolin-4-one derivatives of formula



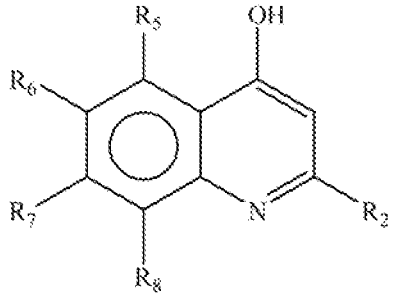




Where R2 =

And R4 = H or G

When R4 = H,



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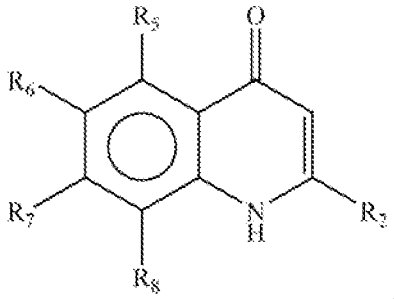


As mentioned above CHM-2133-P exhibited excellent antitumor activity, through both oral and intravenous administration, which is very likely related to its unique structure that was made up of the following three functional groups: Firstly, the phosphate group located on the 4-position of its quinoline ring. As stated in our previous report that pharmacokinetic study of CHM-2133-P confirmed its rapid bio-conversion into its active molecule CHM-2133 following administration. Alkaline phosphatase is known to over-expressed on the extracellular space of specific tumor cells such as ovarian and hepatoma cells, therefore the introduction of a phosphate group appears to be a reasonable strategy for target delivery.

Secondly, the methylenedioxy moiety bridges the 5- and 6-position of its quinoline ring, which could form an orthoquinone upon metabolism, and could be subsequently metabolized into more cytotoxic metabolites in hypoxia cells. Because severe hypoxia is a common situation of locally advanced solid tumor, the incorporation of methylenedioxy moiety to fight tumors becomes a meaningful approach.

Thirdly, the fluorine atom located on the 2-phenyl group. To certain medicines, the unordinary nature of fluorine was reported to impart a variety of properties including enhanced potency, improved duration of action and attenuation of biliary clearance.

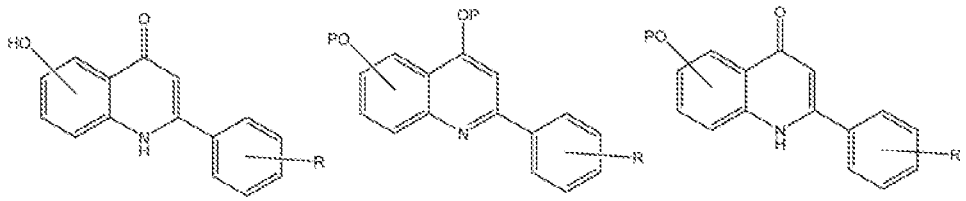
Meanwhile, established SAR indicated the existence of a group with lone pair electrons (for instance, OCH_3, NRR, Cl, F) at both the 6-position of quinoline ring and 3'-position of 2-phenyl group enhanced the cytotoxicity of 2-PQs. Bearing the structural characteristics of CHM-2133-P in mind, the inventor designed compounds **16-21**, **37-45** (FIG. 2) and their phosphates as target compounds based on the following principles: (1) The presence of a O-R group at 6-position of quinoline ring. (2) The presence of a fluorine atom at the 2-phenyl group. (3) Readiness to be metabolized into orthoquinone in vivo and (4) should be new 2-PQs that were not synthesized before. For illustration, methods of synthesizing target compounds **16-21**, **37-45** and evaluating their cytotoxicity are disclosed. Drug candidate compounds may be converted into water soluble, sodium salt of phosphate derivatives for improved hydrophilicity. All the synthesized phosphate derivatives may be evaluated for *in vivo* anticancer activity.

EXAMPLES

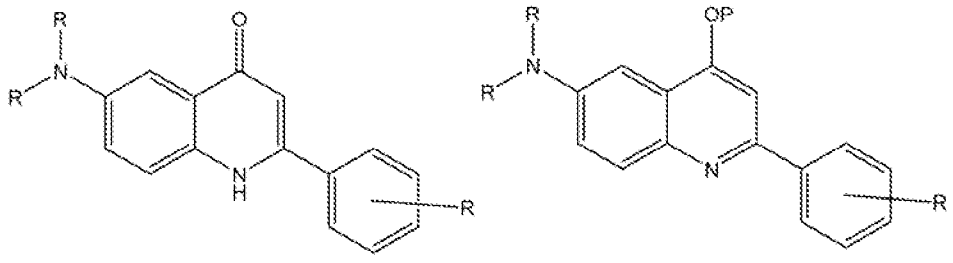
Without intent to limit the scope of the invention, exemplary instruments, apparatus, methods and their related results according to the embodiments of the present invention are given below. Note that titles or subtitles may be used in the examples for convenience of a reader, which in no way should limit the scope of the invention. Moreover, certain theories are proposed and disclosed herein; however, in no way they, whether they are right or wrong, should limit the scope of the invention so long as the invention is practiced according to the invention without regard for any particular theory or scheme of action.

General Strurctures of Compounds

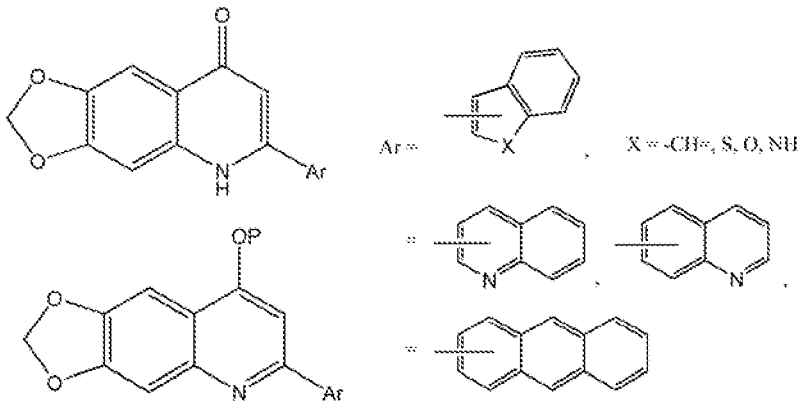
A-series (Scheme 1 ~ Scheme 5)



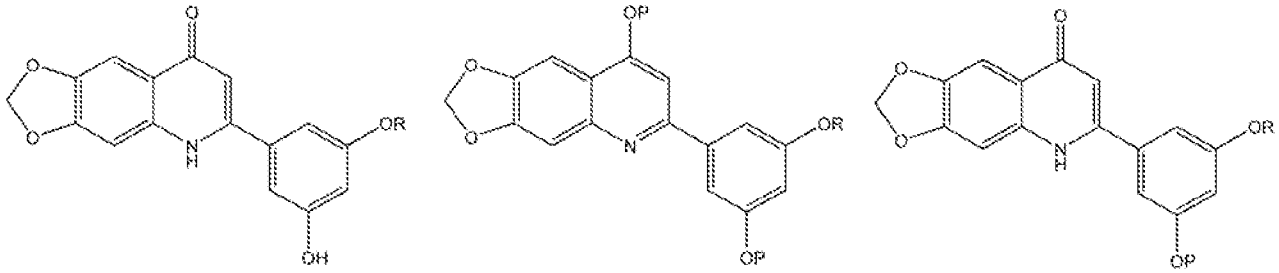
B-series (Scheme 6 ~ Scheme 10)



C-series (Scheme 11 and scheme 12)



D-series (Scheme 13)



I. A Series

Chemical synthesis

Scheme 1: Synthesis of Compounds 16–24. The synthesis of 5,6,7,2',3',4'-substituted 2-phenylquinolin-4-ones (**16**–**24**) was illustrated in Scheme 1. First, 3,4,5-substituted 1-amino-2-acetylbenzenes (**1**–**3**) were reacted separately with 2,3,4-substituted benzoyl chlorides (**4**–**6**) to yield the corresponding amides (**7**–**15**) that were subsequently cyclized in *t*-BuOH, in the presence of *t*-BuOK, to afford the desired compounds (**16**–**24**).

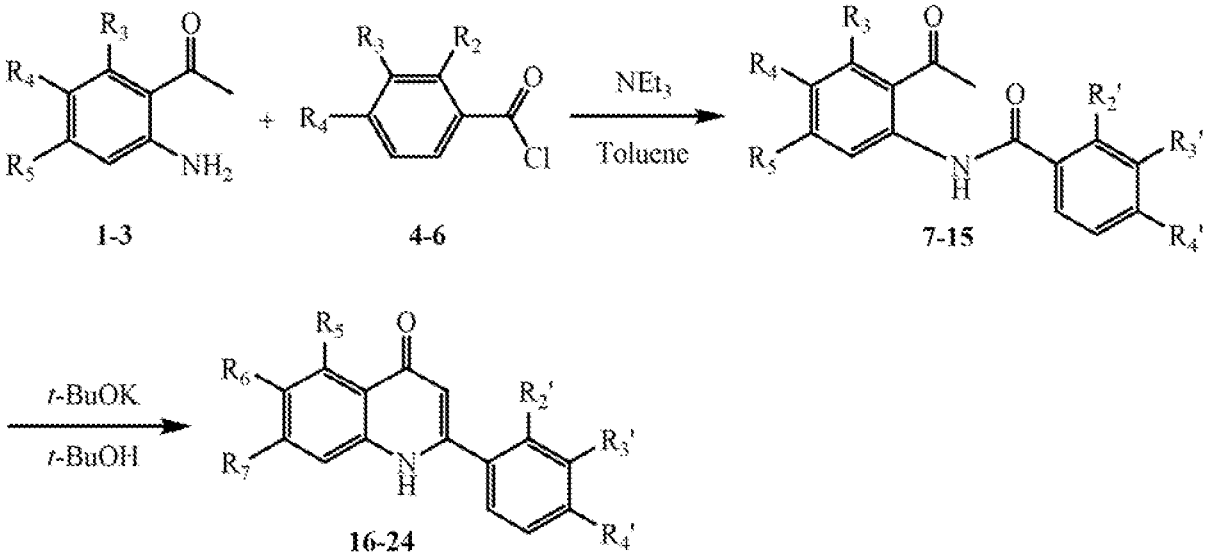
Scheme 2: Synthesis of Starting Compounds 1–3. The starting compounds **1**–**3** were not from commercial source, and were prepared according to Scheme 2. Following a published method,[8] 2,3-dimethoxybenzonitrile (**25**) was subjected to Grignard reaction by reacting with CH_3MgBr in ether to yield 2,3-dimethoxyacetophenone (**26**). Compound**26** was then nitrated with 70 % HNO_3 to give 2,3-dimethoxy-6-nitroacetophenone (**27**) which, without purification, was hydrogenated over Pd/C. The reaction product was purified by column chromatography to afford 6-amino-2,3-dimethoxyacetophenone (**1**) whose structure was confirmed by 2D-NMR spectra.

6-Amino-2,3-dimethoxyacetophenone (**2**) was also prepared according to published methods. The starting catechol (**28**) was acetylated, in microwave oven set at 300 Watt power, by reacting with mixture of acetic acid (**29**) and BF_3. Et_2O to yield 2,3-dihydroxyacetophenone (**30**) which was further reacted with diiodomethane in DMF, in the presence of K_2CO_3, to afford 2,3-methylenedioxyacetophenone (**31**). Subsequent nitration of compound **31** with 70 % HNO_3

afforded 2,3-methylenedioxy-6-nitroacetophenone (**32**). Without purification, compounds **32** was hydrogenated, and purified with column chromatography to provide 6-amino-2,3-methylenedioxyacetophenone (**2**).[10] Another published method was followed in preparation of 6-amino-3-methoxy-4-benzyloxyacetophenone (**3**). First, the benzylation of the starting acetovanillone (**33**) with benzylbromide (**34**) gave 4-benzyloxy-3-methoxyacetophenone (**35**) which was nitrated to yield 4-benzyloxy-3-methoxy-6-nitroacetophenone (**36**).[11] The so-obtained compound **36** was reduced with $SnCl_2$ to afford compound **3**.

Scheme 3: Synthesis of Compounds 37–45. Scheme 3 illustrated the preparation of designed compounds **37–45**. As shown, compounds **16–18** were selectively demethylated by treating with BCl_3 in CH_2Cl_2, to afford the corresponding 2-(fluorophenyl)-5-hydroxy-6-methoxyquinolin-4-ones (**37–39**) whose structures were confirmed by 2D-NMR spectra. Catalytic hydrogenation of compounds **19–21** yielded 2-(fluorophenyl)-5,6-dihydroxyquinolin-4-ones (**40–42**), and similarly, hydrogenation of 7-benzyloxy-2-(fluorophenyl)-6-methoxyquinolin-4-ones (**22–24**) gave 2-(fluorophenyl)-7-hydroxy-6-methoxyquinolin-4-ones (**43–45**).

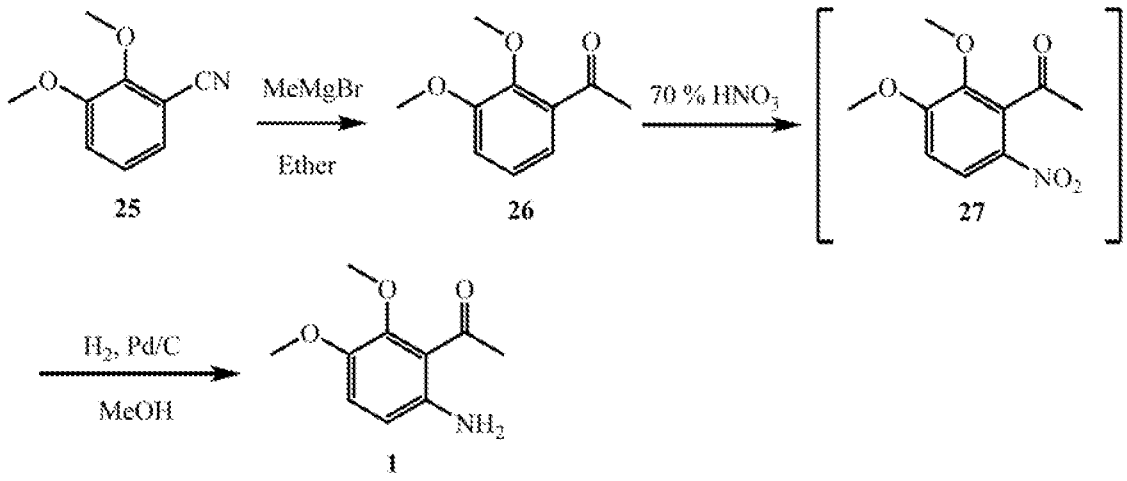
Schemes 4–5: Phosphorylation of Compound 38. The phosphorylation of 2-(3-fluorophenyl)-5-hydroxy-6-methoxyquinoline-4-one (**38**) was illustrated in Schemes 4 and 5. Compound **38** was first reacted with tetrabenzylpyrophosphate (**46**) in THF in the presence of NaH or dibenzylphosphite (**47**) to yield 2-(3-fluorophenyl)-6-methoxyquinoline-4,5-diyl bis(dibenzyl phosphate) (**48**). Compound **48** was then subjected to catalytic hydrogenation in MeOH to give its diphosphoric acid (**49**). Finally, compound **49** was converted into water soluble sodium salt (**50**) by treatment with $NaHCO_3$. In the process of purifying compound **48**, the coexistence of its dephosphorylated derivative was found. Presumably as illustrated in Scheme 5, the inductive effect by the nitrogen atom on the 1-position of quinoline ring facilitated the selective elimination of phosphate moiety on the 4-position of the same ring. Upon testing several conditions of reaction led to selective 4-phosphate elimination of compound **48**, it was found that stirring at room temperature of compound **48** dissolved in MeOH resulted in precipitation of its monophosphate derivative **51** whose structure was confirmed by the ^{1}H-NMR chemical shift of its proton on the 3-position (δ 6.27). Finally, using the same synthetic procedure for compound **50**, the hydrogenation of compound **51**, followed by treatment with $NaHCO_3$, resulted in desired water soluble, sodium salt of monophosphate derivative (**52**).



1, $R_3 = R_4 = OCH_3$, $R_5 = H$
2, R_3 , $R_4 = -OCH_2O-$, $R_5 = H$
3, $R_3 = H$, $R_4 = OCH_3$, $R_5 = OCH_2Ph$
4, $R_2 = F$, $R_3 = H$, $R_4 = H$
5, $R_2 = H$, $R_3 = F$, $R_4 = H$
6, $R_2 = H$, $R_3 = H$, $R_4 = F$
7, $R_3 = R_4 = OCH_3$, $R_5 = H$, $R_2' = F$, $R_3' = H$, $R_4' = H$
8, $R_3 = R_4 = OCH_3$, $R_5 = H$, $R_2' = H$, $R_3' = F$, $R_4' = H$
9, $R_3 = R_4 = OCH_3$, $R_5 = H$, $R_2' = H$, $R_3' = H$, $R_4' = F$
10, R_3 , $R_4 = -OCH_2O-$, $R_5 = H$, $R_2' = F$, $R_3' = H$, $R_4' = H$
11, R_3 , $R_4 = -OCH_2O-$, $R_5 = H$, $R_2' = H$, $R_3' = F$, $R_4' = H$
12, R_3 , $R_4 = -OCH_2O-$, $R_5 = H$, $R_2' = H$, $R_3' = H$, $R_4' = F$
13, $R_3 = H$, $R_4 = OCH_3$, $R_5 = OCH_2Ph$, $R_2' = F$, $R_3' = H$, $R_4' = H$
14, $R_3 = H$, $R_4 = OCH_3$, $R_5 = OCH_2Ph$, $R_2' = H$, $R_3' = F$, $R_4' = H$
15, $R_3 = H$, $R_4 = OCH_3$, $R_5 = OCH_2Ph$, $R_2' = H$, $R_3' = H$, $R_4' = F$
16, $R_5 = R_6 = OCH_3$, $R_7 = H$, $R_2' = F$, $R_3' = H$, $R_4' = H$
17, $R_5 = R_6 = OCH_3$, $R_7 = H$, $R_2' = H$, $R_3' = F$, $R_4' = H$
18, $R_5 = R_6 = OCH_3$, $R_7 = H$, $R_2' = H$, $R_3' = H$, $R_4' = F$
19, R_5 , $R_6 = -OCH_2O-$, $R_7 = H$, $R_2' = F$, $R_3' = H$, $R_4' = H$
20, R_5 , $R_6 = -OCH_2O-$, $R_7 = H$, $R_2' = H$, $R_3' = F$, $R_4' = H$
21, R_5 , $R_6 = -OCH_2O-$, $R_7 = H$, $R_2' = H$, $R_3' = H$, $R_4' = F$
22, $R_5 = H$, $R_6 = OCH_3$, $R_7 = OCH_2Ph$, $R_2' = F$, $R_3' = H$, $R_4' = H$
23, $R_5 = H$, $R_6 = OCH_3$, $R_7 = OCH_2Ph$, $R_2' = H$, $R_3' = F$, $R_4' = H$
24, $R_5 = H$, $R_6 = OCH_3$, $R_7 = OCH_2Ph$, $R_2' = H$, $R_3' = H$, $R_4' = F$

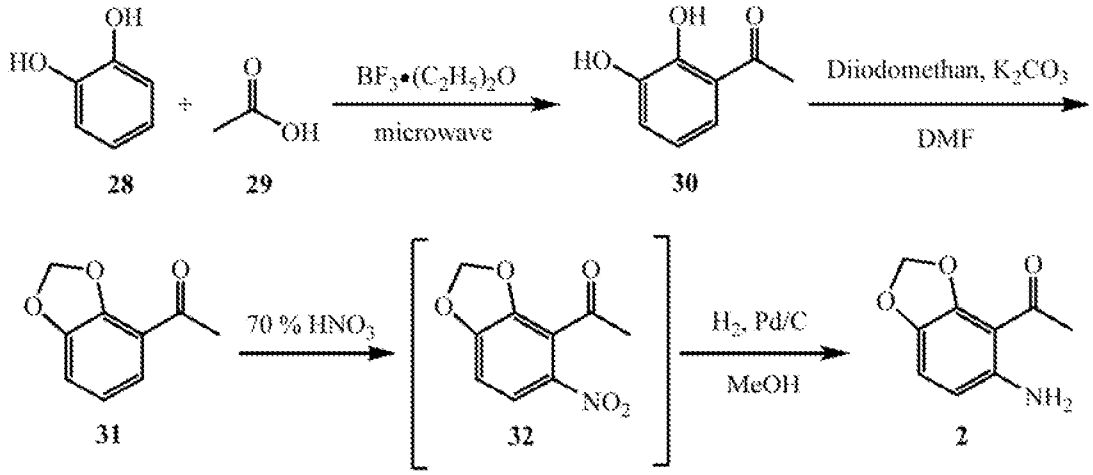
Scheme 1

A



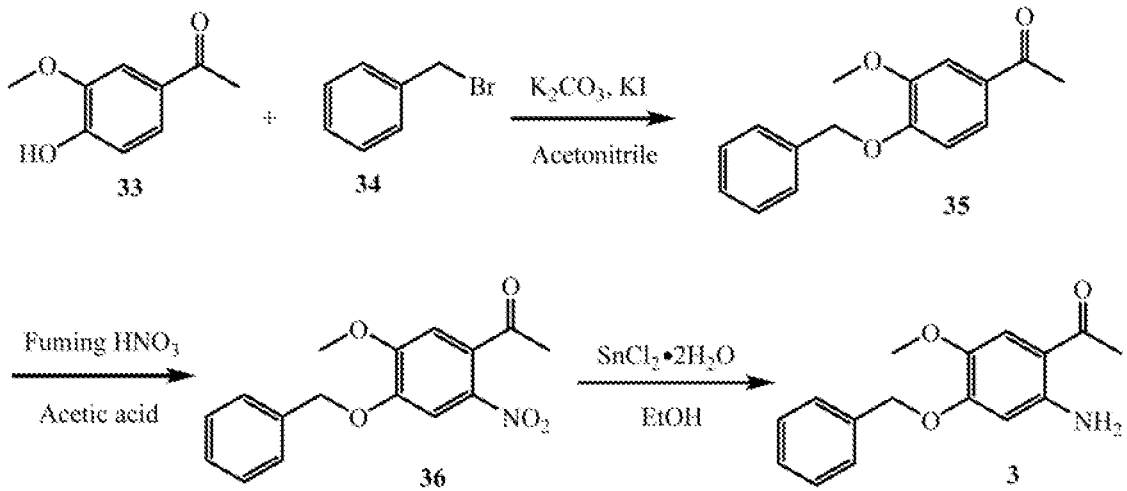
25 26 27 1

B



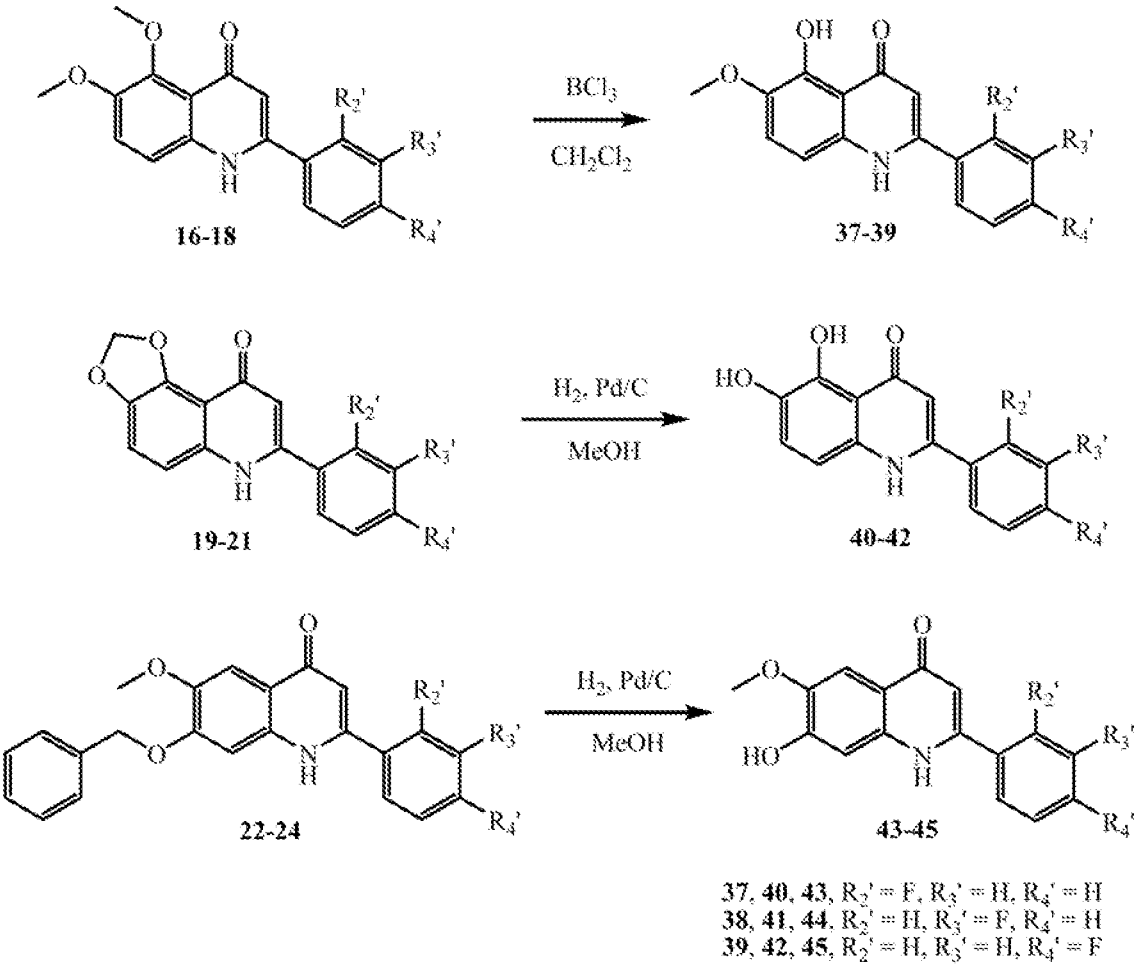
28 29 30 31 32 2

C

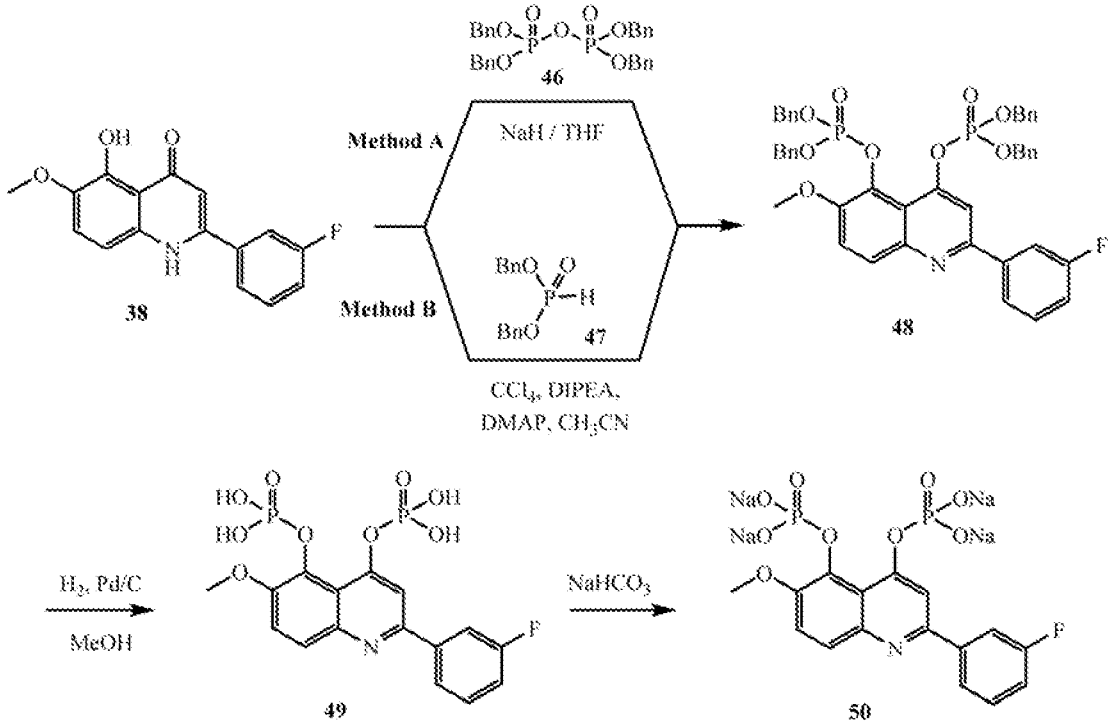


33 34 35 36 3

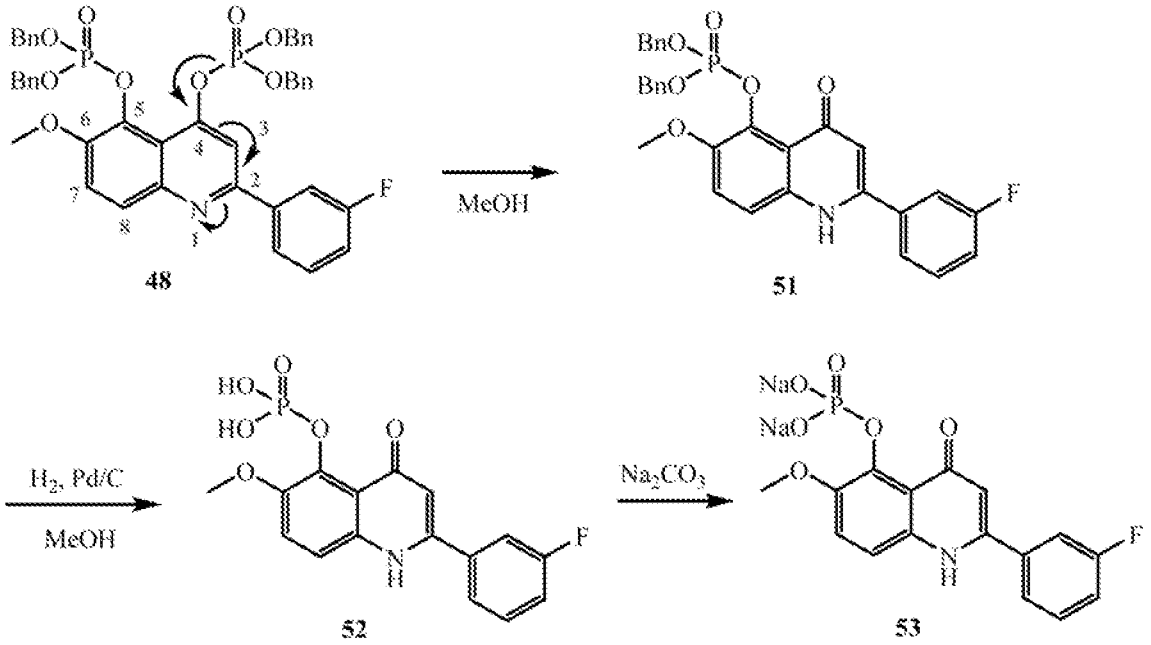
Scheme 2



Scheme 3



Scheme 4



Scheme 5

Examples

General Experimental Procedures. All of the reagents and solvents were obtained commercially and used without further purification. Reactions were monitored by thin-layer chromatography, using Merck plates with fluorescent indicator (TLC Silica gel 60 F_{254}). The following adsorbent was used for column chromatography: silica gel 60 (Merck, particle size 0.063-0.200 mm). Melting points were determined on a Yanaco MP-500D melting point apparatus and were uncorrected. IR spectra were recorded on Shimadzu IRPrestige-21 spectrophotometers as KBr pellets. NMR spectra were obtained on a Bruker Avance DPX-200 FT-NMR spectrometer in $CDCl_3$ or DMSO. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet and m, multiplet. EI-MS spectra were measured with an HP 5995 GC–MS instrument. ESI-MS spectra were measured with a Finnigan LCQ ion-trap mass spectrometer (TSQ Quantum, Thermo Finnigan Corporation, San Jose, CA). Elemental analyses (C, H, and N) were performed on a Perkin-Elmer 2400 Series II CHNS/O analyzer, and the results were within ±0.4% of the calculated values.

***N*-(2-Acetyl-3,4-dimethoxyphenyl)-2-fluorobenzamide (7).** To a solution of 2-fluorobenzoyl chloride (**4**), 0.48 g, 2.46 mmol) in 40 mL of dry toluene were added triethylamine (0.5 mL) and compound **1** (0.70 g, 4.43 mmol). The mixture was stirred at 55—60 °C for 30 min, and then poured into crushed ice, extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (Silica gel, EtOAc/*n*-hexane) to give **7** (0.5 g, 1.58 mmol) as a yellow solid. Yield: 64.1 %; mp 106–108 °C; MS (EI, 70 eV): *m/z* 317 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.45 (*s*, 3H), 3.76

(*s*, 3H), 3.81 (*s*, 3H), 7.14 (*d*, *J* = 2.6 Hz, 2H), 7.24–7.34 (*m*, 2H), 7.52–7.63 (*m*, 2H), 10.07 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 31.91, 56.52, 61.42, 114.52, 116.70, 121.43, 124.16, 125.06, 126.81, 130.52, 131.50, 133.35 (*d*, *J* = 8.0 Hz), 145.98, 150.47, 159.61 (*d*, *J* = 247.5 Hz), 163.19, 201.38; Anal. calcd for $C_{17}H_{16}FNO_4$: C, 64.35; H, 5.08; N, 4.41. Found: C, 64.31; H, 5.10; N, 4.43.

***N*-(2-Acetyl-3,4-dimethoxyphenyl)-3-fluorobenzamide (8)** was obtained from **1** and 3-fluorobenzoyl chloride (**5**). Yellow solid; Yield: 65.0 %; mp 98–99 °C; MS (EI, 70 eV): *m/z* 317 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.43 (*s*, 3H), 3.76 (*s*, 3H), 3.81 (*s*, 3H), 7.03–7.15 (*m*, 2H), 7.39–7.71 (*m*, 4H), 10.18 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 31.74, 56.45, 61.38, 114.30, 114.73 (*d*, *J* = 23 Hz), 119.04 (*d*, *J* = 21 Hz), 121.98, 124.13, 126.91, 131.12 (*d*, *J* = 7.5 Hz), 132.27, 136.89 (*d*, *J* = 6.5 Hz), 145.90, 150.65, 162.40 (*d*, *J* = 243 Hz), 164.67, 201.22; Anal. calcd for $C_{17}H_{16}FNO_4$: C, 64.35; H, 5.08; N, 4.41. Found: C, 64.34; H, 5.06; N, 4.44.

***N*-(2-Acetyl-3,4-dimethoxyphenyl)-4-fluorobenzamide (9)** was obtained from **1** and 4-fluorobenzoyl chloride (**6**). Yellow solid; Yield: 64.7 %; mp 146–147 °C; MS (EI, 70 eV): *m/z* 317 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.43 (*s*, 3H), 3.76 (*s*, 3H), 3.81 (*s*, 3H), 7.03–7.14 (*m*, 2H), 7.26–7.35 (*m*, 2H), 7.88–7.95 (*m*, 2H), 10.14 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 31.76, 56.48, 61.38, 114.33, 115.83 (*d*, *J* = 22 Hz), 121.91, 127.17, 130.65 (*d*, *J* = 9.0 Hz), 131.06, 132.21, 145.90, 150.53, 164.57 (*d*, *J* = 247 Hz), 164.94, 201.25; Anal. calcd for $C_{17}H_{16}FNO_4$: C, 64.35; H, 5.08; N, 4.41. Found: C, 64.36; H, 5.11; N, 4.40.

***N*-(2-Acetyl-3,4-methylenedioxyphenyl)-2-fluorobenzamide (10)** was obtained from **2** and **4**. Yellow solid; Yield: 90.0 %; mp 165–166 °C; MS (EI, 70 eV): *m/z* 301 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.53 (*s*, 3H), 6.13 (*s*, 2H), 7.12 (*d*, *J* = 8.6 Hz, 1H), 7.28–7.38 (*m*, 2H), 7.56–7.61 (*m*, 1H), 7.72–7.82 (*m*, 1H), 7.85 (*d*, *J* = 8.8 Hz, 1H), 11.50 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 32.53, 102.57, 111.92, 112.52, 114.74, 116.94 (*d*, *J* = 22.5 Hz), 123.55 (*d*, *J* = 12.5 Hz), 125.41, 130.98, 131.91, 134.04 (*d*, *J* = 8.5 Hz), 144.46, 149.00, 157.18, 162.22, 199.61; Anal. calcd for $C_{16}H_{12}FNO_4$: C, 63.79; H, 4.01; N, 4.65. Found: C, 63.75; H, 4.03; N, 4.67.

***N*-(2-Acetyl-3,4-methylenedioxyphenyl)-3-fluorobenzamide (11)** was obtained from **2** and **5**. Yellow solid; Yield: 95.0 %; mp 170–171 °C; MS (EI, 70 eV): *m/z* 301 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.56 (*s*, 3H), 6.14 (*s*, 2H), 7.13 (*d*, *J* = 8.4 Hz, 1H), 7.43 (*t*, *J* = 8.6 Hz, 1H), 7.52–7.68 (*m*, 2H), 7.72 (*d*, *J* = 8.6 Hz, 2H), 11.56 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 32.48, 102.61, 112.48, 112.62, 114.48 (*d*, *J* = 23 Hz), 114.89, 119.30 (*d*, *J* = 21.5 Hz), 123.56,

131.52 (*d*, *J* = 8.0 Hz), 131.96, 137.32, 144.61, 148.88, 162.61 (*d*, *J* = 243.5 Hz), 163.97, 199.88; Anal. calcd for $C_{16}H_{12}FNO_4$: C, 63.79; H, 4.01; N, 4.65. Found: C, 63.67; H, 4.00; N, 4.63.

***N*-(2-Acetyl-3,4-methylenedioxyphenyl)-4-fluorobenzamide (12)** was obtained from **2** and **6**. Yellow solid; Yield: 84.0 %; mp 185–186 °C; MS (EI, 70 eV): *m/z* 301 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.51 (*s*, 3H), 6.13 (*s*, 2H), 7.12 (*d*, *J* = 8.6 Hz, 1H), 7.20–7.40 (*m*, 2H), 7.77 (*d*, *J* = 8.6 Hz, 1H), 7.89–7.97 (*m*, 2H), 11.58 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 32.55, 102.55, 111.20, 112.61, 114.54, 116.26 (*d*, *J* = 22 Hz), 130.22 (*d*, *J* = 7.0 Hz), 131.47, 132.41, 144.36, 148.97, 162.22, 164.67 (*d*, *J* = 248 Hz), 200.04; Anal. calcd for $C_{16}H_{12}FNO_4$: C, 63.79; H, 4.01; N, 4.65. Found: C, 63.84; H, 3.98; N, 4.65.

***N*-(2-Acetyl-5-benzyloxy-4-methoxyphenyl)-2-fluorobenzamide (13)** was obtained from **3** and **4**. Yellow solid; Yield: 89.0 %; mp 142–143 °C; MS (EI, 70 eV): *m/z* 393 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.60 (*s*, 3H), 3.82 (*s*, 3H), 5.16 (*s*, 2H), 7.10–7.50 (*m*, 8H), 7.56–7.67 (*m*, 1H), 7.80–7.89 (*m*, 1H), 8.57 (*s*, 1H), 12.45 (*d*, *J* = 4.0 Hz,1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 29.08, 56.42, 70.41, 105.31, 115.28, 116.05, 117.08 (*d*, *J* = 22 Hz), 123.27 (*d*, *J* = 12.5 Hz), 125.60, 128.58, 128.95, 131.20, 134.45 (*d*, *J* = 8.5 Hz), 135.77, 136.50, 144.46, 152.98, 157.26, 162.35, 201.78; Anal. calcd for $C_{23}H_{20}FNO_4$: C, 70.22; H, 5.12; N, 3.56. Found: C, 70.18; H, 5.10; N, 3.55.

***N*-(2-Acetyl-5-benzyloxy-4-methoxyphenyl)-3-fluorobenzamide (14)** was obtained from **3** and **5**. Yellow solid; Yield: 86.6 %; mp 162–163 °C; MS (EI, 70 eV): *m/z* 393 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.62 (*s*, 3H), 3.81 (*s*, 3H), 5.15 (*s*, 2H), 7.26–7.52 (*m*, 7H), 7.54–7.78 (*m*, 3H), 8.51 (*s*, 1H), 12.70 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 29.10, 56.42, 70.40, 104.74, 114.45, 115.29, 115.83, 119.59 (*d*, *J* = 21.5 Hz), 123.36, 128.53, 128.95, 131.74 (*d*, *J* = 7.5 Hz), 136.28, 136.45, 137.30 (*d*, *J* = 6.5 Hz), 144.43, 153.26, 162.71 (*d*, *J* = 244 Hz), 163.91, 202.48; Anal. calcd for $C_{23}H_{20}FNO_4$: C, 70.22; H, 5.12; N, 3.56. Found: C, 70.20; H, 5.14; N, 3.52.

***N*-(2-Acetyl-5-benzyloxy-4-methoxyphenyl)-4-fluorobenzamide (15)** was obtained from **3** and **6**. Yellow solid; yield: 67.1 %; mp 168–169 °C; MS (EI, 70 eV): *m/z* 393 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.63 (*s*, 3H), 3.81 (*s*, 3H), 5.15 (*s*, 2H), 7.2–7.5 (*m*, 7H), 7.9–8.1 (*m*, 3H), 8.54 (*s*, 1H), 12.69 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 29.11, 56.47, 70.41, 104.73, 115.39, 115.83, 116.27, 116.72, 128.53, 128.94, 130.17 (*d*, *J* = 9.0 Hz), 132.54 (*d*, *J* = 9.5 Hz), 136.48, 136.58, 144.33, 153.33, 164.24, 166.82, 202.48; Anal. calcd for $C_{23}H_{20}FNO_4$: C, 70.22; H, 5.12; N, 3.56. Found: C, 70.24; H, 5.12; N, 3.59.

2-(2-Fluorophenyl)-5,6-dimethoxyquinolin-4-one (16). To a suspension of **7** (0.50 g, 1.58 mmol) in *t*-butyl alcohol (30 mL) was added potassium *t*-butoxide (1.0 g, 8.93 mmol). The mixture

was refluxed under argon for 20 h and evaporated. The residue was treated with a 10 % ammonium chloride solution (30 mL). The solid precipitate was collected and washed with *n*-hexane and Me_2CO. The crude product was recrystallized from MeOH afforded yellow needle of **16** (0.27 g, 0.9 mmol). Yield: 57.1 %; mp 215–217 °C; MS (EI, 70 eV): *m/z* 299 (M^+); IR (KBr): 1628 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.72 (*s*, 3H), 3.81 (*s*, 3H), 6.06 (*s*, 1H), 7.3–7.6 (*m*, 5H), 7.60–7.71 (*m*, 1H); Anal. calcd for $C_{17}H_{14}FNO_3$: C, 68.22; H, 4.71; N, 4.68. Found: C, 68.24; H, 4.67; N, 4.71.

2-(3-Fluorophenyl)-5,6-dimethoxyquinolin-4-one (17) was obtained from **8**. Yellow needle; yield: 53.1 %; mp 190–192 °C; MS (EI, 70 eV): *m/z* 299 (M^+); IR (KBr): 1599 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.73 (*s*, 3H), 3.81 (*s*, 3H), 6.35 (*s*, 1H), 7.28–7.40 (*m*, 1H), 7.46–7.60 (*m*, 3H), 7.64–7.76 (*m*, 2H); Anal. calcd for $C_{17}H_{14}FNO_3$: C, 68.22; H, 4.71; N, 4.68. Found: C, 68.17; H, 4.68; N, 4.66.

2-(4-Fluorophenyl)-5,6-dimethoxyquinolin-4-one (18) was obtained from **9**. White needle; yield: 54.6 %; mp 227–229 °C; MS (EI, 70 eV): *m/z* 299 (M^+); IR (KBr): 1607 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.72 (*s*, 3H), 3.80 (*s*, 3H), 6.26 (*s*, 1H), 7.31–7.40 (*m*, 2H), 7.44–7.54 (*m*, 2H), 7.83–7.90 (*m*, 2H); Anal. calcd for $C_{17}H_{14}FNO_3$: C, 68.22; H, 4.71; N, 4.68. Found: C, 68.16; H, 4.68; N, 4.65.

2-(2-Fluorophenyl)-5,6-methylenedioxyquinolin-4-one (19) was obtained from **10**. Yellow solid; yield: 47.6 %; mp 282–283 °C; MS (EI, 70 eV): *m/z* 283 (M^+); IR (KBr): 1605 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 5.92 (*s*, 1H), 6.11 (*s*, 2H), 7.09 (*d*, *J* = 8.8 Hz, 1H), 7.27–7.38 (*m*, 3H), 7.55–7.70 (*m*, 2H), 11.71 (*s*, 1H); Anal. calcd for $C_{16}H_{10}FNO_3$: C, 67.84; H, 3.56; N, 4.94. Found: C, 67.82; H, 3.53; N, 4.91.

2-(3-Fluorophenyl)-5,6-methylenedioxyquinolin-4-one (20) was obtained from **11**. White solid; yield: 44.9 %; mp 286–288 °C; MS (EI, 70 eV): *m/z* 283 (M^+); IR (KBr): 1609 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 6.11 (*s*, 2H), 6.19 (*s*, 1H), 7.19 –7.36 (*m*, 3H), 7.55–7.67 (*m*, 3H), 11.71 (*s*, 1H); Anal. calcd for $C_{16}H_{10}FNO_3$: C, 67.84; H, 3.56; N, 4.94. Found: C, 67.90; H, 3.52; N, 4.95.

2-(4-Fluorophenyl)-5,6-methylenedioxyquinolin-4-one (21) was obtained from **12**. White solid; yield: 45.9 %; mp 286–288 °C; MS (EI, 70 eV): *m/z* 283 (M^+); IR (KBr): 1613 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 6.10 (*s*, 3H), 7.17–7.31 (*m*, 2H), 7.32–7.41 (*m*, 2H), 7.78–7.85 (*m*, 2H), 11.46 (*s*, 1H); Anal. calcd for $C_{16}H_{10}FNO_3$: C, 67.84; H, 3.56; N, 4.94. Found: C, 67.88; H, 3.51; N, 4.97.

7-Benzyloxy-2-(2-fluorophenyl)-6-methoxyquinolin-4-one (22) was obtained from **13**. White solid; yield: 60.5 %; mp 132–134 °C; MS (EI, 70 eV): *m/z* 375 (M^+); ^{1}H-NMR (DMSO-d_6,

200 MHz): δ 3.82 (*s*, 3H), 5.16 (*s*, 2H), 6.21 (*s*, 1H), 7.20–7.80 (*m*, 11H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 56.02, 70.40, 101.86, 104.14, 108.80, 116.77 (*d*, *J* = 21.5 Hz), 118.86, 123.30 (*d*, *J* = 13 Hz), 125.43, 128.50, 128.97, 131.24, 132.56 (*d*, *J* = 8.0 Hz), 136.58, 137.08, 144.73, 147.73, 152.52, 159.64 (*d*, *J* = 247 Hz), 174.57; Anal. calcd for $C_{23}H_{18}FNO_3$: C, 73.59; H, 4.83; N, 3.73. Found: C, 73.55; H, 4.81; N, 3.71.

7-Benzyloxy-2-(3-fluorophenyl)-6-methoxyquinolin-4-one (23) was obtained from **14**. White solid; yield: 64.3 %; mp 154–155 °C; MS (EI, 70 eV): *m/z* 375 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.83 (*s*, 3H), 5.17 (*s*, 2H), 6.56 (*s*, 1H), 7.30–7.50 (*m*, 8H), 7.55–7.60 (*m*, 1H), 7.60–7.80 (*m*, 2H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 56.07, 70.45, 102.27, 103.72, 106.03, 114.71 (*d*, *J* = 23.5 Hz), 117.56 (*d*, *J* = 20.5 Hz), 118.44, 123.95, 128.56, 128.99, 131.50, 136.49, 137.41, 148.02, 148.44, 152.72, 165.13, 173.61; Anal. calcd for $C_{23}H_{18}FNO_3$: C, 73.59; H, 4.83; N, 3.73. Found: C, 73.61; H, 4.80; N, 3.72.

7-Benzyloxy-2-(4-fluorophenyl)-6-methoxyquinolin-4-one (24) was obtained from **15**. White solid; yield: 64.4 %; mp 248–249 °C; MS (EI, 70 eV): *m/z* 375 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.80 (*s*, 3H), 5.13 (*s*, 2H), 6.26 (*s*, 1H), 7.20–7.60 (*m*, 9H), 7.80–8.00 (*m*, 2H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 55.96, 70.36, 101.41, 104.51, 106.61, 116.30 (*d*, *J* = 21.5 Hz), 119.27, 128.56, 128.99, 130.05 (*d*, *J* = 8.0 Hz), 136.60, 147.39, 148.06, 152.19, 163.63 (*d*, *J* = 246.5 Hz), 176.10; Anal. calcd for $C_{23}H_{18}FNO_3$: C, 73.59; H, 4.83; N, 3.73. Found: C, 73.56; H, 4.83; N, 3.75.

2,3-Dimethoxyacetophenone (26). To a stirred solution of 2,3-dimethoxybenzonitrile (**25**)(5.0 g, 30 mmol) in Et_2O (12.5 mL) under N_2 atmosphere was added methylmagnesium bromide (37 % in Et_2O)(12.5 mL, 37 mmol). The mixture was stirred for 16 h, and then 50 % AcOH (20 mL) was added. After it was stirred for 30 min, the solution was poured into crushed ice, extracted with CH_2Cl_2, washed with 10 % Na_2CO_3 and then with water, dried over $MgSO_4$ and concentrated. The crude was purified by column chromatography (SiO_2, *n*-hexane: EtOAc = 4:1) to give **26**. Liquid; yield: 92.5 %; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.56 (*s*, 3H), 3.82 (*s*, 3H), 3.85 (*s*, 3H), 6.99–7.02 (*m*, 2H), 7.13–7.18 (*m*, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 31.18, 55.98, 61.29, 115.83, 120.80, 123.94, 133.62, 148.63, 153.04, 200.26; Anal. calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.60; H, 6.73.

6-Amino-2,3-dimethoxyacetophenone (1). Compound **26** (5.0 g, 27.8 mmol) was stirred at -5 ± 1 °C and 70 % HNO_3 (60 mL) was added dropwise. After it was stirred at -5 ± 1 °C for 10 min, the reaction mixture was poured into crushed ice, extracted with CH_2Cl_2. The extract was washed with 10 % Na_2CO_3 and then with water, dried over $MgSO_4$ and concentrated. The crud intermediate (**27**) was directly in the next step.

A solution of **27** (1.85 g, 8.22 mmol) in anhydrous MeOH (40 mL) was hydrogenated in the presence of 10 % Pd/C (0.5 g) at 25 ± 2 °C for 2 h. The Pd/C was filtered off and the filtrate was evaporated. The residue was purified by column chromatography (SiO_2, *n*-hexane: EtOAc = 25:1) to give **1**. Liquid; yield: 43.7 %; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.41 (*s*, 3H), 3.66 (*s*, 3H), 3.74 (*s*, 3H), 5.88 (*s*, 2H), 6.41 (*d*, *J* = 9.0 Hz,1H), 6.98 (*d*, *J* = 9.0 Hz,1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 33.09, 57.58, 61.14, 111.82, 116.82, 121.15, 142.62, 144.22, 149.87, 201.88; Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.51; H, 6.74; N, 7.22.

2,3-Dihydroxyacetophenone (30). To a solution of 1,2-dihydroxybenzene (**28**)(2.0 g, 18.2 mmol) in AcOH (1.3g, 21.7 mmol) was added boron trifluoride diethyl ether (98 % in Et_2O, 2 mL). The mixture was reacted under microwave irradiation (300 W) for 1.5 min and then cooled to 25 °C. The reaction mixture was dissolved in dichoromethane (10 mL) and H_2O (about 20 mL).The organic lay was washed with 10 % $NaHCO_3$ and then with water, dried over $MgSO_4$ and concentrated. The crude was purified by column chromatography (SiO_2, CH_2Cl_2) to give **30**. Yellow solid; yield: 10.4 %; mp 76–77 °C; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.58 (*s*, 3H), 5.79 (*s*, 1H), 6.79 (*t*, *J* = 8.0 Hz, 1H), 7.10 (*d*, *J* = 8.0 Hz, 1H), 7.26 (*d*, *J* = 8.0 Hz,1H), 12.45 (*s*, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 26.73, 118.79, 119.52, 120.39, 121.44, 145.40, 149.50, 205.08; Anal. calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.10; H, 5.33.

2,3-Methylenedioxyacetophenone (31). To a suspension of K_2CO_3 (1.24 g, 9.0 mmol) in DMF (10 mL) was added diiodomethane (2.4 g, 9.0 mmol). The mixture was heated to 100–110 °C and added a solution of **15** (1.0 g, 6.6 mmol) in DMF (5 mL) dropwise. The reaction mixture was stirred at 110 °C for 1 h and poured into crushed ice, extracted with CH_2Cl_2. The extract was washed with brine, dried over $MgSO_4$ and evaporated. The crude was purified by column chromatography (SiO_2, *n*-hexane: EtOAc = 4:1) to give **31**. White solid; yield: 61.0 %; mp 89–91 °C; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.58 (*s*, 3H), 6.07 (*s*, 2H), 6.87 (*q*, *J* = 7.8 Hz, 1H), 6.95 (*dd*, *J* = 8.0, 1.5 Hz, 1H), 7.35 (*dd*, *J* = 8.0, 1.5 Hz,1H); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 30.29, 101.58, 112.51, 120.27, 121.25, 121.43, 148.00, 148.60, 195.58; Anal. calcd for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.75; H, 4.93.

6-Amino-2,3-methylenedioxyacetophenone (2). Compound **31** (0.63 g, 3.7 mmol) was allowed to react in the same manner as described in the preparation of compound **1** to give compound **2**. Yellow solid; yield: 48.2 %; mp 102–104 °C; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.44 (*s*, 3H), 5.92 (*s*, 2H), 6.14 (*d*, *J* = 8.6 Hz,1H), 6.72 (*s*, 2H), 6.89 (*d*, *J* = 8.6 Hz,1H); ^{13}C-NMR

(DMSO-d_6, 50 MHz): δ 32.63, 101.08, 105.44, 107.71, 115.75, 136.77, 146.80, 148.78, 198.02; Anal. calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.31; H, 5.09; N, 7.83.

4-Benzyloxy-3-methoxyacetophenone (35). To a solution of acetovanillone (**33**) (4.70 g, 28.3 mmol) in MeCN (60 mL) was added K_2CO_3 (8.05 g, 58.3 mmol) and KI (0.20 g, 1.2 mmol). The mixture was stirred under N_2 atmosphere and benzyl bromide (**34**) (4.0 mL, 34 mmol) was added dropwise. The reaction mixture was reflux for 24 h and then cooled to 25 °C, then resulting precipitate was filtered off. The filtrate was evaporated and purified by column chromatography (SiO_2, *n*-hexane: CH_2Cl_2 = 1:2) to give **30**. White solid; yield: 70.3 %; mp 87–88 °C; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.51 (*s*, 3H), 3.91 (*s*, 3H), 5.20 (*s*, 2H), 6.86 (*d*, *J* = 8.2 Hz, 1H), 7.21–7.55 (*m*, 7H); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 26.19, 56.05, 70.79, 110.53, 112.13, 123.07, 127.18, 128.10, 128.68, 130.72, 136.28, 149.49, 152.41, 196.80; Anal. calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.02; H, 6.25.

4-Benzyloxy-3-methoxy-6-nitroacetophenone (36). To a solution of **35** (1.24 g, 4.83 mmol) in AcOH (15 mL) was added *f.* HNO_3 (1.5 mL, 36 mmol) dropwise at 0 ° ± 1 °C. The mixture was stirred at 25 °C for 24 h and then poured into crushed ice. The precipitate was collected and washed with H_2O. The crude was purified by column chromatography (SiO_2, *n*-hexane: EtOAc = 2:1) to give **36**. Yellow solid; yield: 68.8 %; mp 142–143 °C; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.46 (*s*, 3H), 3.95 (*s*, 3H), 5.19 (*s*, 2H), 6.74 (*s*, 1H), 7.30–7.48 (*m*, 5H), 7.64 (*s*, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 30.41, 56.67, 71.39, 108.78, 127.56, 128.56, 128.84, 133.08, 135.19, 138.21, 148.54, 154.53, 200.13; Anal. calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.82; H, 5.00; N, 4.63.

2-Amino-4-benzyloxy-5-methoxyacetophenone (3). To a solution of **36** (1.0 g, 3.32 mmol) in anhydrous EtOH (100 mL) was added Tin chloride dihydrate (3.7 g, 16.4 mmol). The mixture was reflux for 2 h and then cooled to 25 °C, and poured in 5 % $NaHCO_3$ solution. The precipitate was collected and washed with H_2O and then extracted with EtOAc. The extract was wash with H_2O, dried over $MgSO_4$ and evaporated. The crude was purified by column chromatography (SiO_2, *n*-hexane: EtOAc = 1:1) to give **7***c*. Yellow solid; yield: 72.2 %; mp 135–137 °C; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.39 (*s*, 3H), 3.66 (*s*, 3H), 5.03 (*s*, 2H), 6.38 (*s*,1H), 7.05 (*s*, 2H), 7.10 (*s*, 1H), 7.30–7.50 (*m*, 5H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 28.21, 56.94, 69.87, 100.05, 109.70, 115.40, 128.34, 128.49, 128.93, 136.83, 139.45, 148.74, 154.64, 198.06; Anal. calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.82; H, 6.30; N, 5.20.

2-(2-Fluorophenyl)-5-hydroxy-6-methoxyquinolin-4-one (37). To a solution of **16** (0.2 g, 0.67 mmol) in CH_2Cl_2 (3 mL) was added 5 mL of BCl_3 solution (1 M in CH_2Cl_2)

dropwise at 0 ° ± 1 °C. The mixture was stirred at 25 ± 1 °C for 2 h and then poured into crushed ice, extracted with EtOAc. The organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated. The crude was purified by column chromatography (SiO_2, $CHCl_3$: MeOH = 15:1) and recrystallized from MeOH to give **37**. Yellow solid; yield: 24.1 %; mp 268–270 °C; MS (EI, 70 eV): *m/z* 285 (M^+); IR (KBr): 1604.77 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.78 (*s*, 3H), 6.11 (*s*, 1H), 7.01 (*d*, *J* = 7.4 Hz,1H), 7.36–7.48 (*m*, 3H), 7.54–7.72 (*m*, 2H), 12.25 (*s*, 1H), 14.54 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 55.80, 106.22, 106.43, 112.88, 116.36 (*d*, *J* = 23 Hz), 120.81, 121.96 (*d*, *J* = 13.5 Hz), 125.04, 130.85, 132.67 (*d*, *J* = 8.6 Hz), 135.09, 141.02, 146.27, 149.29, 158.92 (*d*, *J* = 247.7 Hz), 181.97; Anal. calcd for $C_{16}H_{12}FNO_3$: C, 67.36; H, 4.24; N, 4.91. Found: C, 67.32; H, 4.26; N, 4.89.

2-(3-Fluorophenyl)-5-hydroxy-6-methoxyquinolin-4-one (38) was obtained from **17** and BCl_3. Yellow solid; yield: 26.7 %; mp 274–276 °C; MS (EI, 70 eV): *m/z* 285 (M^+); IR (KBr): 1606.70 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.77 (*s*, 3H), 6.33 (*s*, 1H), 7.11 (*d*, *J* = 8.8 Hz,1H), 7.33–7.48 (*m*, 2H), 7.51–7.76 (*m*, 3H), 12.09 (*s*, 1H), 14.56 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 57.19, 104.82, 106.97, 113.39, 115.09 (*d*, *J* = 23 Hz), 118.06 (*d*, *J* = 21 Hz), 121.07, 124.32, 131.64 (*d*, *J* = 9.0 Hz), 135.61, 136.16 (*d*, *J* = 8.0 Hz), 141.49, 149.64, 150.12, 162.64 (*d*, *J* = 242.5 Hz), 182.69; Anal. calcd for $C_{16}H_{12}FNO_3$: C, 67.36; H, 4.24; N, 4.91. Found: C, 67.35; H, 4.24; N, 4.92.

2-(4-Fluorophenyl)-5-hydroxy-6-methoxyquinolin-4-one (39) was obtained from **18** and BCl_3. Yellow solid; yield: 23.0 %; mp 307–309 °C; MS (EI, 70 eV): *m/z* 285 (M^+); IR (KBr): 1610.56 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.76 (*s*, 3H), 6.25 (*s*, 1H), 7.08 (*d*, *J* = 9.0 Hz,1H), 7.34–7.43 (*m*, 3H), 7.82–7.89 (*m*, 2H), 12.01 (*s*, 1H), 14.60 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 57.19, 104.53, 106.84, 113.23, 116.47 (*d*, *J* = 22 Hz), 120.99, 130.55 (*d*, *J* = 9.0 Hz), 135.62, 141.45, 149.69, 150.64, 164.02 (*d*, *J* = 247 Hz), 182.59; Anal. calcd for $C_{16}H_{12}FNO_3$: C, 67.36; H, 4.24; N, 4.91. Found: C, 67.36; H, 4.24; N, 4.92.

2-(2-Fluorophenyl)-5,6-dihydroxyquinolin-4-one (40). To a solution of **19** (0.1 g, 0.35 mmol) in anhydrous MeOH (30 mL) was hydrogenated in the presence of 10 % Pd/C (0.2 g) at 25 ± 2 °C for 40 h. The catalyst was filtered off and the filtrate was evaporated. The crude was purified by column chromatography (SiO_2, EtOAc: MeOH = 30:1) to give **40**. White solid; yield: 13.7 %; mp 152–154 °C; MS (EI, 70 eV): *m/z* 271 (M^+); IR (KBr): 1622.13 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 6.03 (*s*, 1H), 7.15 (*d*, *J* = 8.8 Hz,1H), 7.30–7.70 (*m*, 6H), 9.72 (*s*, 1H), 11.76 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 107.67, 108.57, 116.75 (*d*, *J* = 21.5 Hz), 120.54, 122.67, 123.36, 125.42, 126.70, 131.22, 132.49, 134.35, 144.30, 154.29, 159.43

(*d*, *J* = 248.5 Hz), 176.82; Anal. calcd for $C_{15}H_{10}FNO_3$: C, 66.42; H, 3.72; N, 5.16. Found: C, 66.38; H, 3.70; N, 5.15.

2-(3-Fluorophenyl)-5,6-dihydroxyquinolin-4-one (41) was obtained from **20**. White solid; yield: 15.0 %; mp 307–308 °C; MS (EI, 70 eV): *m/z* 271 (M^+); IR (KBr): 1608.63 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 6.25 (*s*, 1H), 7.15 (*d*, *J* = 8.8 Hz, 1H), 7.30–7.50 (*m*, 2H), 7.50–7.80 (*m*, 4H), 9.72 (*s*, 1H), 11.60 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 106.38, 107.57, 114.65 (*d*, *J* = 23 Hz), 117.38 (*d*, *J* = 21.5 Hz), 120.91, 122.62, 123.91, 126.81, 131.52 (*d*, *J* = 8.5 Hz), 134.45, 137.17, 147.66, 154.36, 162.70 (*d*, *J* = 242 Hz), 176.82; Anal. calcd for $C_{15}H_{10}FNO_3$: C, 66.42; H, 3.72; N, 5.16. Found: C, 66.43; H, 3.74; N, 5.13.

2-(4-Fluorophenyl)-5,6-dihydroxyquinolin-4-one (42) was obtained from **21**. White solid; yield: 13.9 %; mp 332–334 °C; MS (EI, 70 eV): *m/z* 271 (M^+); IR (KBr): 1614.42 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 6.18 (*s*, 1H), 7.14 (*dd*, *J* = 9.0, 2.8 Hz, 1H), 7.33–7.42 (*m*, 3H), 7.59 (*d*, *J* = 8.8 Hz, 1H), 7.79–7.86 (*m*, 2H), 9.70 (*s*, 1H), 11.59 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 106.24, 107.68, 116.39 (*d*, *J* = 21.5 Hz), 120.71, 122.48, 126.73, 130.19 (*d*, *J* = 8.5 Hz), 131.38, 134.42, 148.24, 154.20, 163.70 (*d*, *J* = 247.5 Hz), 176.81; Anal. calcd for $C_{15}H_{10}FNO_3$: C, 66.42; H, 3.72; N, 5.16. Found: C, 66.47; H, 3.69; N, 5.14.

2-(2-Fluorophenyl)-7-hydroxy-6-methoxyquinolin-4-one (43). Compound **22** (0.3 g, 0.80 mmol) was allowed to react in the same manner as described in the preparation of compound **40** to give **43**. White solid; yield: 61.3 %; mp 277–279 °C; MS (EI, 70 eV): *m/z* 285 (M^+); IR (KBr): 1622.13 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.82 (*s*, 3H), 6.04 (*s*, 1H), 7.01 (*s*, 1H), 7.32–7.50 (*m*, 3H), 7.50–7.67 (*m*, 2H), 10.22 (*s*, 1H), 11.68 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 55.52, 102.72, 105.37, 108.20, 116.28 (*d*, *J* = 22.5 Hz), 118.07, 122.94, 124.92, 130.75, 131.99 (*d*, *J* = 7.95 Hz), 136.45, 143.61, 146.58, 151.59, 158.98 (*d*, *J* = 246.9 Hz), 175.30; Anal. calcd for $C_{16}H_{12}FNO_3$: C, 67.36; H, 4.24; N, 4.91. Found: C, 67.37; H, 4.26; N, 4.90.

2-(3-Fluorophenyl)-7-hydroxy-6-methoxyquinolin-4-one (44) was obtained from **23**. White solid; yield: 44.8 %; mp 326–328 °C; MS (EI, 70 eV): *m/z* 285 (M^+); IR (KBr): 1606.70 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.81 (*s*, 3H), 6.24 (*s*, 1H), 7.12 (*s*, 1H), 7.27–7.42 (*m*, 2H), 7.47–7.70 (*m*, 3H), 10.20 (*s*, 1H), 11.44 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 55.92, 103.35, 104.70, 106.67, 114.59 (*d*, *J* = 23 Hz), 117.26 (*d*, *J* = 21 Hz), 118.85, 123.85, 131.47 (*d*, *J* = 8.0 Hz), 136.85, 137.16, 146.94, 147.33, 151.93, 162.69 (*d*, *J* = 242.5 Hz), 176.37; Anal. calcd for $C_{16}H_{12}FNO_3$: C, 67.36; H, 4.24; N, 4.91. Found: C, 67.32; H, 4.22; N, 4.93.

2-(4-Fluorophenyl)-7-hydroxy-6-methoxyquinolin-4-one (45) was obtained from **24**. White solid; yield: 42.5 %; mp 352–354 °C; MS (EI, 70 eV): *m/z* 285 (M^+); IR (KBr): 1610.56 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.80 (*s*, 3H), 6.19 (*s*, 1H), 7.11 (*s*, 1H), 7.20–7.50

(*m*, 3H), 7.70–7.90 (*m*, 2H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 55.89, 103.50, 104.55, 106.18, 116.30 (*d*, *J* = 21.5 Hz), 118.41, 130.03 (*d*, *J* = 8.5 Hz), 131.57, 137.22, 147.00, 148.01, 152.21, 163.58 (*d*, *J* = 246 Hz), 175.93; Anal. calcd for $C_{16}H_{12}FNO_3$: C, 67.36; H, 4.24; N, 4.91. Found: C, 67.39; H, 4.20; N, 4.89.

2-(3-Fluorophenyl)-6-methoxyquinoline-4,5-diyl bis(dibenzyl phosphate) (48).

Method A: To a stirred solution of **38** (0.12 g, 0.42 mmol) in dry THF (20 mL) was added NaH (96 mg, 4 mmol) at 0 ° ± 1 °C. After it was stirred for 1 h, tetrabenzyl pyrophosphate (**46**) (430 mg, 0.8 mmol) was added and stirring was continued for 25 min. The reaction mixture was filtered and washed with CH_2Cl_2. The filtrate was concentrated under vacuum at a temperature below 30 °C. The residue was purified by column chromatography (SiO_2, *n*-hexane: EtOAc) to give **48**. Liquid; yield: 95.0 %; **Method B**: To a stirred solution of of **38** (1.85 g, 6.5 mmol) in acetonitrile (50 mL) was added CCl_4 (10 eq.) at -10 °C. N,N-diisopropylethylamine (DIPEA)(4.2 eq.) followed by N,N-dimethylaminopyridine (DMAP)(0.2 eq.) were added. One minute later, dropwise addition of dibenzyl phosphate (**47**) was begun. When the reaction was complete as determined by TLC, 0.5 M aqueous KH_2PO_4 was added and the mixture was allowed to warm to room temperature and extracted with EtOAc. The organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated. The crude was purified by column chromatography (EA: n-hex = 1:1) to give 48. Liquid; yield: 96.0 %. Compound **48**: MS (EI, 70 eV): *m/z* 805 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.87 (*s*, 3H), 5.10 (*s*, 2H), 5.14 (*s*, 2H), 5.18 (*s*, 2H), 5.22 (*s*, 2H), 7.20–7.36 (*m*, 21H), 7.47–7.60 (*m*, 1H), 7.72–7.84 (*m*, 4H), 8.01 (*d*, *J* = 9.4 Hz, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 57.27, 69.63, 69.74, 70.12, 70.23, 110.20, 113.57, 114.03, 116.23, 116.92, 117.35, 119.48, 123.28, 128.10, 128.38, 128.70, 128.79, 128.85, 128.95, 131.35, 131.51, 135.79, 135.94, 136.32, 136.47, 140.41, 140.56, 145.39, 149.74, 149.82, 153.44, 153.57, 153.92, 160.71, 165.56; Anal. ($C_{44}H_{38}FNO_9P_2$) C, H, N.

2-(3-Fluorophenyl)-6-methoxyquinoline-4,5-diyl bis(dihydrogen phosphate) (49). A suspension of **48** (153 mg, 0.19 mmol) in anhydrous MeOH (10 mL) was hydrogenated in the presence of 10 % Pd/C (80 mg) at 25 °C for 15 min. The catalyst and precipitate were collected and dissolved in 10 % $NaHCO_3$ solution and then filtered. The filtrate was acidified with dil aq HCl and the precipitate was then collected and washed with acetone to give **49**. Yellow solid; yield: 87 %; mp >300 °C; MS (ESI): *m/z* 444 ($M-H)^-$; ^{1}H-NMR (D_2O, 200 MHz): δ 3.85 (*s*, 3H), 7.29 (*t*, *J* = 8.0 Hz, 1H), 7.43–7.68 (*m*, 4H), 7.72–7.92 (*m*, 2H); Anal. ($C_{16}H_{14}FNO_9P_2$) C, H, N.

2-(3-Fluorophenyl)-6-methoxyquinoline-4,5-diyl bis(disodium phosphate) (50). To a stirred solution of $NaHCO_3$ (0.67 g, 8.0 mmol) in H_2O (20 mL) was added **49** (0.89 g, 2.0 mmol) at 0

° ± 1 °C. After the addition was complete, the reaction mixture was removed from the ice bath, stirred at 25 °C for 10 min and the filtered though celite, after no dissolution from the solid was observed. The resulting filtrate (15 mL) was poured into acetone (60 mL), and kept it in an ice bath for 1 h. The precipitate was collected and washed with ice-cooled acetone (10 mL×5). The solid was dried under vacuum to give **50**. White solid; yield: 52.3%; mp >300 °C; MS(ESI): *m/z* 534 $(M + H)^+$; ^{1}H-NMR (D_2O, 200 MHz): δ 3.81 (*s*, 3H), 7.10 (*t*, *J* = 8.2 Hz, 1H), 7.34–7.52 (*m*, 2H), 7.60–7.72 (*m*, 4H); Anal. ($C_{16}H_{10}FNNa_4O_9P_2$) C, H, N.

Dibenzyl 2-(3-fluorophenyl)-6-methoxy-4-oxo-1,4- dihydroquinolin-5-yl phosphate (51). A suspension of **48** (2.42 mg, 3.0 mmol) in anhydrous MeOH (10 mL) was stirred at 25 °C for 24 h. The reaction mixture was concentrated under vacuum at a temperature below 30 °C. The residue was purified by column chromatography (SiO_2, *n*-hexane: EtOAc) to give **51**. Yellow solid; yield: 80.0 %; mp 136–138 °C; MS (ESI): *m/z* 544.5 $(M-H)^-$; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.75 (*s*, 3H), 5.28 (*s*, 2H), 5.31 (*s*, 2H), 6.27 (*s*, 1H), 7.26–7.50 (*m*, 11H), 7.50–7.78 (*m*, 6H); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 57.19, 69.32, 69.44, 108.51, 114.46, 114.93, 116.74, 117.38, 119.24, 123.92, 128.04, 128.51, 128.82, 131.49, 131.65, 136.74, 137.07, 137.23, 147.00, 160.29, 176.88; Anal. ($C_{30}H_{25}FNO_6P$) C, H, N.

2-(3-Fluorophenyl)-6-methoxy-4-oxo-1,4-dihydroquinolin-5-yl dihydrogen phosphate (52). Compound **51** (0.25 g, 0.46 mmol) was allowed to react in the same manner as described in the preparation of compound **49** to give **52**. Yellow solid; yield: 63.7 %; mp 179–181 °C; MS(ESI): *m/z* 366 $(M + H)^+$; ^{1}H-NMR (D_2O + NaOD, 200 MHz): δ 3.76 (*s*, 3H), 6.53 (*s*, 1H), 7.05 (*t*, *J* = 8.4 Hz, 1H), 7.24–7.60 (*m*, 5H); Anal. ($C_{16}H_{13}FNO_6P$) C, H, N.

Sodium 2-(3-fluorophenyl)-6-methoxy-4-oxo-1,4-dihydroquinolin-5-yl phosphate (53). Compound **52** (0.73 g, 2.0 mmol) was allowed to react in the same manner as described in the preparation of compound **50** to give **53**. Yellow solid; yield: 48.0 %; mp >300 °C; MS(ESI): *m/z* 410 $(M + H)^+$; ^{1}H-NMR (D_2O, 200 MHz): δ 3.72 (*s*, 3H), 6.54 (*s*, 3H), 6.99 (*t*, *J* = 7.8 Hz, 1H), 7.15–7.55 (*m*, 5H); Anal. ($C_{16}H_{11}FNNa_2O_6P$) C, H, N.

I-2. Anticancer activity

***In vitro* tests of compounds**

MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assays.[21, 22] HL-60, HCT-116, Hep 3B, H460, Detroit 551 and HT29/FuR cells were treated with tested compounds for the indicated periods. After treatment, cells were washed once with PBS and incubated with MTT (Sigma, St. Louis, MO, USA) for 2 h. The formazan precipitate was dissolved in 150 μL of DMSO, and the absorbance was measured with an ELISA reader at 570 nm.

Results

The cytotoxicity of 5,6-(6,7-) disubstituted 2-(fluorophenyl)quinolin-4-ones (**16–21, 37–45**) and CHM-2133, were screened against HL-60, HCT-116, Hep3B, H-460 and Detroit 551 normal human cell, and the results were summarized in **Table 1**. Among 5, 6-dimethoxy derivatives (**16–18**), the 3-fluoro derivative (**17**) exhibited the strongest cytotoxicity, though relatively weaker than that of our positive control CHM-2133. Meanwhile, both compounds **19** and **20**, having methylenedioxy entity bridging the 5,6-position of their quinoline ring, demonstrated significant cytotoxicity, although weaker than CHM-2133. Then, while all of the three 5-hydroxy-6-methoxy derivatives (**37–39**) showed significant cytotoxicity, compounds **37** and **38**, with 2'- or 3'-fluorosubstituent on 2-phenyl group, demonstrated greater cytotoxicity, but lower toxicity toward Detroit 551 normal human cell than CHM-2133. Following the same trend, it was found that, among 5,6-dihydroxy (**40–42**) and 7-hydroxy-6-methoxy (**43-45**) derivatives, those with 2'-fluoro (**40,43**) and 3'-fluoro group (**41**, **44**) demonstrated greater cytotoxicity. In general, the cytotoxicity of 4'-fluorophenyl derivatives (**18**, **21**, **39**, **42** and **45**) was found to be weaker than 2'-fluorophenyl derivatives (**16**, **19**, **37**, **40** and **43**) and 3'-fluorophenyl derivatives (**17**, **20**, **38**, **41**and **44**). Among them, compounds **37** and **38** are considered the most promising anticancer agents. None of the tested compounds showed noticeable cytotoxicity toward the Detroit 551 normal human cells. Below and **Table 1** shows structures and cytotoxicities of CHM-2133 and target compounds **16–45**.

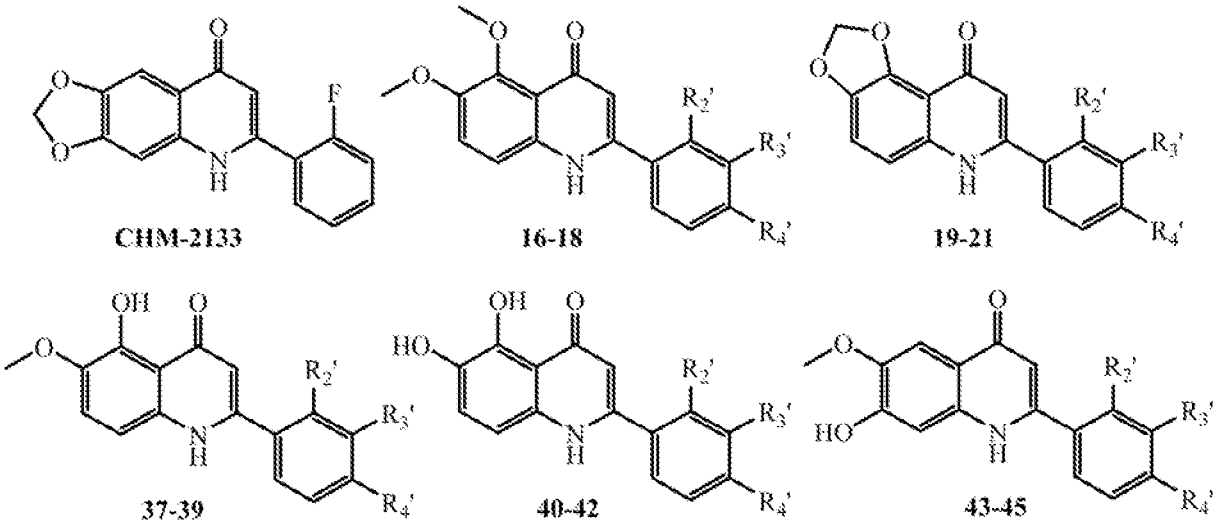


Table 1

				IC_{50} [a](μM)					
Comp'd	R_2	R_3	R_4	HL-60	HCT116	Hep3B	H460	Detroit 551	HT29/5FuR

CHM-21	-	-	-	0.08	0.15	0.13	0.14	8.2	-
33									
16	F	H	H	3.7	> 20	> 20	> 20	> 20	2.03
17	H	F	H	1.3	1.2	2.6	3.5	100	1.96
18	H	H	F	2.0	> 20	> 20	> 20	> 20	2.02
19	F	H	H	1.0	2.1	1.9	4.5	> 10	0.69
20	H	F	H	0.7	2.5	2.4	3.2	> 5	0.82
21	H	H	F	> 10	> 10	> 10	> 10	> 10	0.53
37	F	H	H	0.067	0.05	0.05	0.11	10	0.20
38	H	F	H	0.039	0.073	0.078	0.088	> 50	0.26
39	H	H	F	1.8	2.4	11.0	8.8	> 25	0.33
40	F	H	H	0.5	0.6	3.9	4.1	> 100	1.63
41	H	F	H	0.3	8.2	6.9	6.1	> 100	0.53
42	H	H	F	38.6	> 100	100	100	> 100	NA[b]
43	F	H	H	1.3	5.8	5.3	4.4	29.7	0.29
44	H	F	H	0.9	1.1	5.3	4.8	10	0.30
45	H	H	F	38.2	> 100	> 100	> 100	> 100	0.37

Human tumor cells were treated with different concentrations of samples for 48 h.
[a] Data was presented as IC_{50} (μM, the concentration of 50 % proliferation-inhibitory effect).
[b] NA = Not assayed.

In vivo antitumor activity assay.

The Hep-3B tumor cell line was purchased from American Type Culture Collection (ATCC™ HB-8064, human ovarian carcinoma cells). The culture medium contained DMEM, 90 %; Fetal Bovine Serum, 10 % and 1 % penicillin-streptomycin. The tumor cells were incubated in an atmosphere containing 5 % CO_2 at 37°C.

Balb/c Nude mice used in this study were male, 4-6 weeks age, weighing 18-20g and provided by National Animal Center. All animals were housed in Individually Ventilated Cages Racks (IVC Racks, 36 Mini Isolator system) under Specific Pathogen-Free (SPF) condition throughout the experiment. Each cage (in cm, 26.7 length × 20.7 width × 14.0 height) was sterilized with autoclave and contained 8 mice, and then the animals were maintained in a hygienic environment under controlled temperature (20-24°C) and humidity (40 %-70 %) with 12 hour light/dark cycle. The animals were given free access to sterilized lab chow and sterilized distilled water *ad libitum*. All aspects of this work, i. e., housing, experimentation and disposal of animals were performed in general accordance with the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, D. C., 1996).

In the xenograft tumor model of human ovarian carcinoma cell lines (Hep-3B, ATCC HB-8064) in male Balb/c Nude mice, the compounds **50** at doses at 7.5, 15 and 30 mg/kg (i.v. or p.o., bid) was administered five days per week for four consecutive weeks by p.o. or i.v. and ceased at Day 28. The compounds **53** at doses at 7.5, 15 and 30 mg/kg (i.v. or p.o., qd) was administered five days per week for four consecutive weeks and ceased at Day 28. The tumor size, body weight was

monitored and recorded for 28 days. Human ovarian carcinoma cells (HEP-3B, ATCC HB-8064) with 2 x 10^6 cells in 0.1 ml were injected subcutaneously into the right flank of the mice. When the tumor growth reached >100 mm^3 in volume (assumed as day 0), the tumor-bearing animals were assigned into several groups (8 animals in each group) for study.

The body weight and tumor size were measured and recorded every 7 days during the experimental periods of 28 days. Tumor volume (mm^3) was estimated according to the formula of length × $(width)^2$ × 0.5 in mm^3. Tumor growth inhibition was calculated as T/C (treatment/control) by the following formula: T/C = (Tn – T0)/(Cn – C0) x 100% (T0: Tumor volume of treated group in Day 0; Tn: Tumor volume of treated group in Day n; C0: Tumor volume of control group in Day 0; Cn: Tumor volume of control group in Day n).

Results

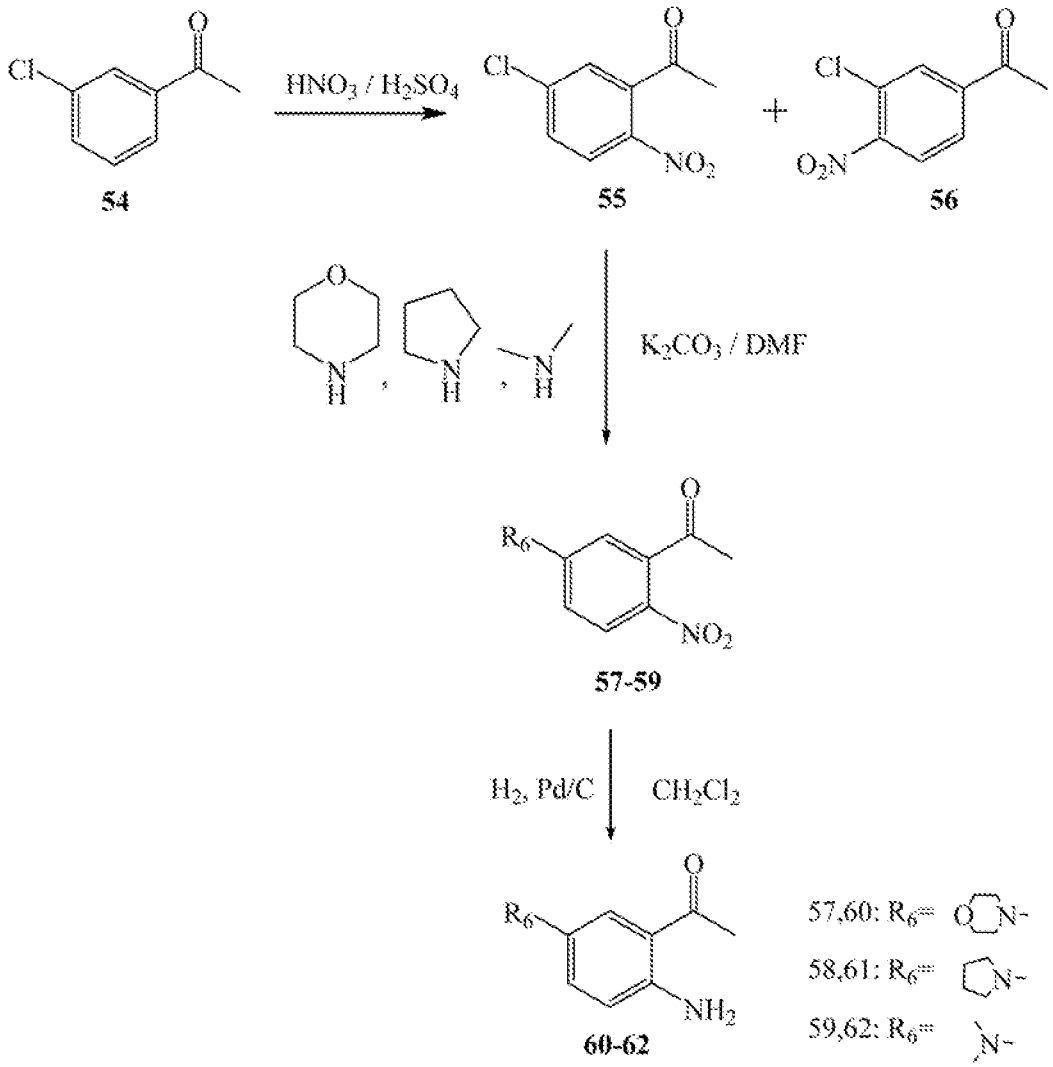
***In vivo* antitumor activity of compounds 50 and 53**. The water soluble diphosphate of **38** (**50**) was evaluated in Hep3B xenograft nude mice model administrated by p.o. and i.v. routes. Results in FIG. 4 (A–F) indicated that the antitumor activity of compound **50** followed dose- and time-dependent manner, and at 7.5 mg/kg (i.v. or p.o., bid) its antitumor activity exceeded that of doxorubicin (5 mg/kg, i.v., qd; 10 mg/kg, p.o., qd). During the course of antitumor evaluation, no significant body weight changes were detected either in tested or control mice (FIGs. 4C and 4F). At the same time, the antitumor activity of monophosphate derivative of compound **38** (**53**) was evaluated with the same animal model by oral route at the dose of 7.5, 15, 30 mg/kg/day. As shown by the results in FIG. 5A, compound **53** induced dose- and time-dependent inhibition of Hep3B tumor growth. Significant tumor growth suppression, at an extent exceeding that observed after 10 mg/kg/day oral dosing of doxorubicin, was detected after 7.5 mg/kg/day oral dosing of compound **53**. Near complete tumor suppression was observed after 30 mg/kg/day oral dosing. Again during the course of antitumor evaluation, no significant body weight changes were detected in either the tested or the control mice. Similarly, the dose- and time-dependent antitumor test result by i.v. administration, summarized in FIG. 5B, resembled that administrated through p.o. route, and showed slight better antitumor activity in general.

II. B Series

Chemical synthesis

The intermediates, 5-alkylamino-2-aminoacetophenones (**60**–**62**) were prepared according to the methods reported before. As shown in Scheme 6, the starting 3-chloroacetophenone (**54**) was first nitrated with HNO_3/H_2SO_4 to form the 5-chloro-2-nitroacetophenone (**55**) and 5-chloro-4-nitroacetophenone (**56**). Compound **55** was reacted separately with various alkylamines to yield the corresponding 5-alkylamino-2-nitroacetophenones (**57**–**59**). Catalytic hydrogenation of

compounds **57**–**59** yielded the corresponding 5-alkylamino-2-aminoacetophenones (**60**–**62**). L. Li, K. K. Wang, S. C. Kuo, T. S. Wu, D. Lednicer, C. M. Lin, E. Hamel and K. H. Lee, J. Med. Chem., 37, 1126-35. (1994), which is herein incorporated by reference in its entirety.



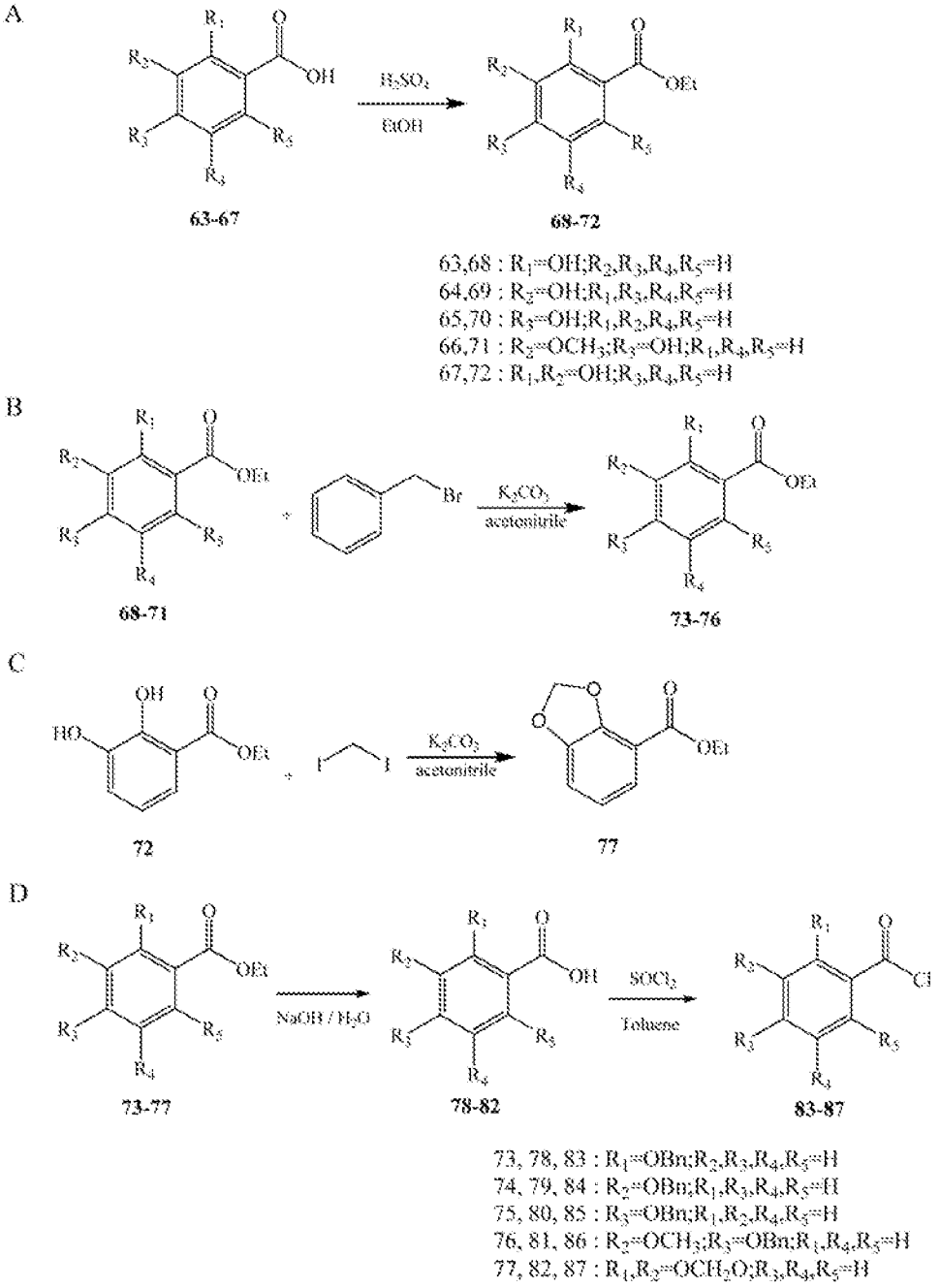
Scheme 6

The synthesis of other intermediated, substituted benzoyl chlorides (**83**–**91**) is illustrated in Scheme 7 and Scheme 8. Esterification of substituted benzoic acids (**63**–**67**) yielded the corresponding ester (**68**–**72**). Compounds **68**–**71** were treated with benzyl bromide to yield the corresponding benzyloxy derivatives (**73**–**76**). On the other hand, compound **72** was treated with diiodomethane to afford ethyl 5,6-methylenedioxobenzoate (**77**). When compounds **73**–**77** were hydrolyzed with NaOH to yield the corresponding acids (**78**–**82**) which were allowed to react with $SOCl_2$ to afford the corresponding acid chlorides (**83**–**87**).

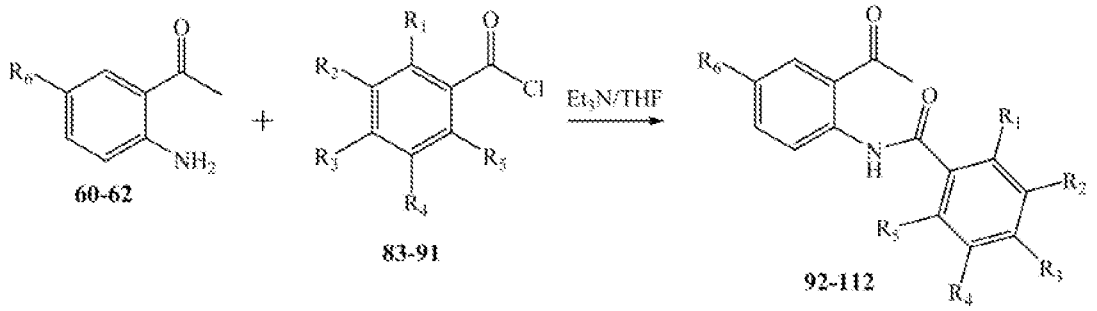
Finally, as shown in Scheme 8, 5-alkylamino-2-aminoacetophenones (**60**–**62**) were reacted separately with substituted benzoyl chlorides (**83**–**91**) to yield the corresponding amides (**92**–**112**),

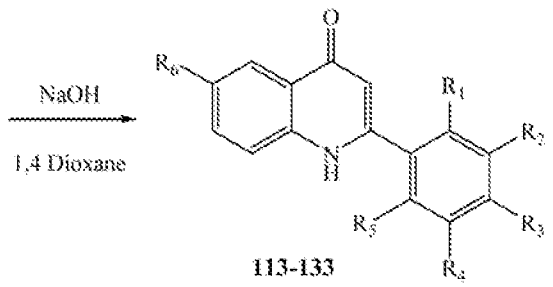
which were subsequently cyclized in dioxane in the presence of NaOH, to afford the target compounds ((**113–133**).

The compound **138** was derived into a phosphate (**147**) following the synthetic method in Scheme 10. As illustrated, compound **138** was first reacted with tetrabenylpyrophosphate **46** in THF, in the presence of NaH, to give bis(dibenzylphosphate) (**145**) which, without further purification, was subsequently dissolved in MeOH and stirred at 25 °C to yield a monophosphate (**146**). The structure of compound **146** was confirmed by the chemical shift of its proton on the 3-position (δ 6.39) in the ^{1}H-NMR spectrum. Subsequently, compound **146** was debenzylated catalytically to afford a stable monophosphoric acid (**147**).



Scheme 7

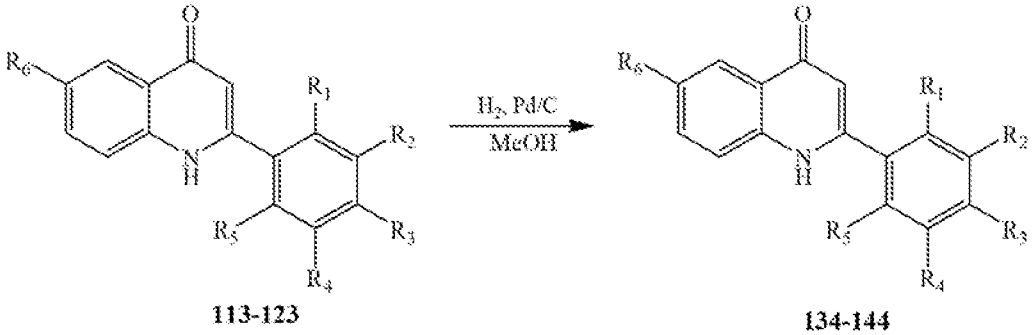




83, 92-94, 113-115: R_1=OBn;R_2,R_3,R_4,R_5=H
84, 95-97, 116-118: R_2=OBn;R_1,R_3,R_4,R_5=H
85, 98-100, 119-121: R_3=OBn;R_1,R_2,R_4,R_5=H
86, 101, 102, 122, 123: R_2=OCH_3;R_3=OBn;R_1,R_4,R_5=H
87, 103, 104, 124, 125: R_1,R_2=OCH_2O;R_3,R_4,R_5=H
88, 105, 106, 126, 127: R_1,R_2=OCH_3;R_3,R_4,R_5=H
89, 107, 108, 128, 129: R_1,R_4=OCH_3;R_2,R_3,R_5=H
90, 109, 110, 130, 131: R_1=OCH_3;R_2,R_3,R_4,R_5=H
91, 111, 112, 132, 133: R_3=OCH_3;R_1,R_2,R_4,R_5=H

60, 92, 95, 98, 101, 103, 105, 107, 109, 111, 113, 116, 119, 122, 124, 126, 128, 130, 132: R_6=
61, 93, 96, 99, 102, 104, 106, 108, 110, 112, 114, 117, 120, 123, 125, 127, 129, 131, 133: R_6=
62, 94, 97, 100, 115, 118, 121: R_6=

Scheme 8

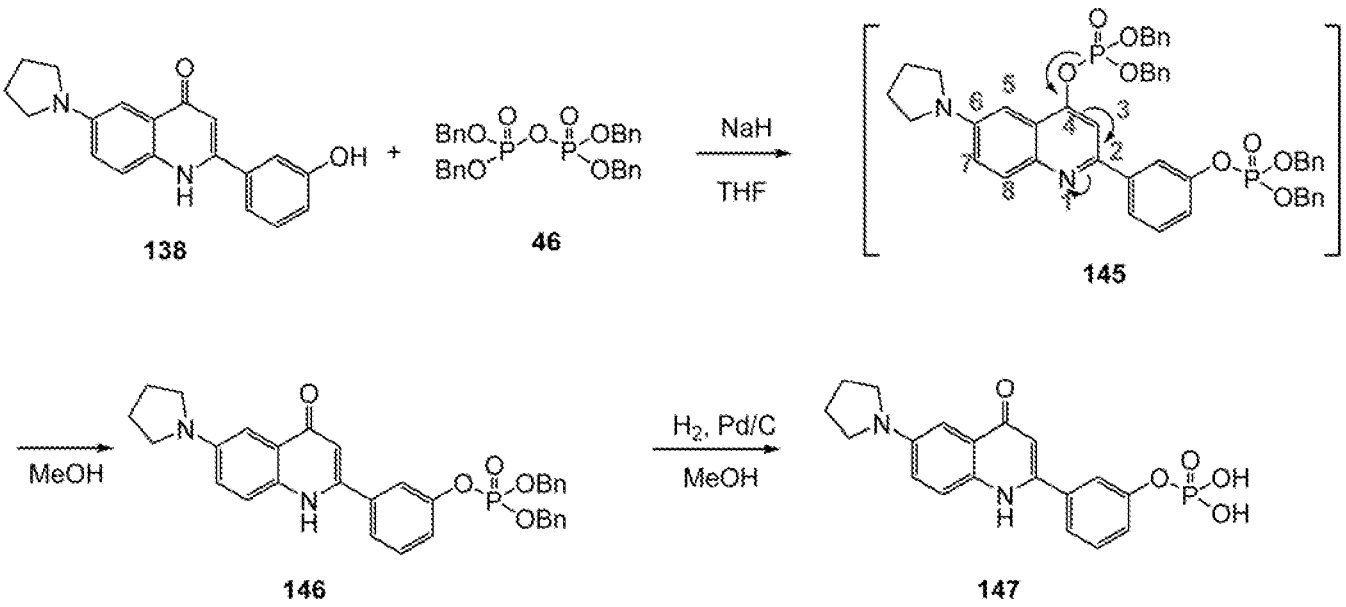


113-115: R_1=OBn;R_2,R_3,R_4,R_5=H
116-118: R_2=OBn;R_1,R_3,R_4,R_5=H
119-121: R_3=OBn;R_1,R_2,R_4,R_5=H
122, 123: R_2=OCH_3;R_3=OBn;R_1,R_4,R_5=H

134-136: R_1=OH;R_2,R_3,R_4,R_5=H
137-139: R_2=OH;R_1,R_3,R_4,R_5=H
140-142: R_3=OH;R_1,R_2,R_4,R_5=H
143, 144: R_2=OCH_3;R_3=OH;R_1,R_4,R_5=H

113, 116, 119, 122, 134, 137, 140, 143: R_6=
114, 117, 120, 123, 135, 138, 141, 144: R_6=
115, 118, 121, 136, 139, 142: R_6=

Scheme 9



138 46 145

146 147

Scheme 10

Examples

General Experimental Procedures. All of the solvents and reagents were obtained commercially and used without further purification. The progress of all reactions was monitored by TLC on 2 × 6 cm pre-coated silica gel 60 F_{254} plates of thickness 0.25 mm (Merck). The chromatograms were visualized under UV 254~366 nm. The following adsorbent was used for column chromatography: silica gel 60 (Merck, particle size 0.040~0.063 mm). Melting points were determined with a Yanaco MP-500D melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu IR-Prestige-21 spectrophotometers as KBr pellets. NMR spectra were obtained on a Bruker Avance DPX-200 FT-NMR spectrometer in $CDCl_3$ or DMSO. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; and m, multiplet. MS spectra were measured with an HP 5995 GC-MS instrument. Elemental analyses (C, H, and N) were carried out at the instruments center of National Chung Hsing University, Taichung, Taiwan and performed on a Perkin-Elmer 2400 Series II CHNS/O analyzer or Elementar vario EL III Heraeus CHNOS Rapid F002 and the results were within ±0.4% of the calculated values.

5-Chloro-2-nitroacetophenone (55). 65%HNO_3 (80 ml) was stirred at -5 °C±1 °C and 98%H_2SO_4 (10 mlx10) was added dropwise. To the stirring solution of HNO_3/H_2SO_4 was added 3-chloroacetophenone (**54**) (12.0g, 77.6 mmol). The mixture was stirred at -5□±1□ for 3 h and poured into crushed ice, and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (silica gel, *n*-hexane/EtOAc =15:1) to give **55** as yellow solid (9.3 g, 46.6 mmol).Yield: 55.8%; mp 47-49 °C; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.48 (*s*, 3H), 7.32 (*d*, *J* = 2.4 Hz, 1H), 7.49 (*dd*, *J* = 8.8,2.2 Hz, 1H),

8.00 (*d*, *J* = 8.8 Hz, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 198.27, 143.78, 141.05, 139.44, 130.55, 127.36, 125.91, 30.06; Anal. Calcd for $C_8H_6ClNO_3$: C,48.14; H,3.03; N,7.02.

5-Morpholino-2-nitroacetophenone (57). To a solution of **55** (3.0g, 15.0mmol) in DMF (25 ml) were added K_2CO_3 (8.3g, 60.1mmol) and morpholine (3.2g, 37.5mmol). The mixture was refluxed for 3h and then poured into crushed ice. The precipitate was collected and washed with H_2O. The crude product was purified by column chromatography(silica gel, CH_2Cl_2: *n*-hexane = 2:1) to give **57** as yellow solid (3.4 g, 13.6 mmol).Yield: 90.4%; mp 124-126 °C; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.45 (*s*, 3H), 3.33-3.38 (*m*, 4H), 3.78-3.82 (*m*, 4H), 6.53 (*d*, *J* = 2.8 Hz, 1H), 6.78 (*dd*, *J* = 9.4, 2.8 Hz, 1H), 8.02 (*d*, *J* = 9.4 Hz, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 201.30, 154.60, 141.53, 134.90, 127.04, 112.88, 109.83, 66.20, 46.84, 30.52; Anal. Calcd for $C_{12}H_{14}N_2O_4$: C,57.59; H,5.64; N,11.19.

5-Pyrrolidino-2-nitroacetophenone (58) was obtained from 30 and pyrrolidine, using the same synthetic procedure as for **57** to give **58** as yellow solid (3.2 g, 13.7 mmol); yield 90.9%; mp 119-121 °C; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.04 (*m*, 4H), 2.45 (*s*, 3H), 3.37 (*m*, 4 H), 6.19 (*d*, *J* = 2.6 Hz, 1H), 6.44 (*dd*, *J* = 9.4, 2.6 Hz,1H), 8.02 (*d*, *J* = 9.4 Hz, 1H); ^{13}C- NMR ($CDCl_3$, 200 MHz) *δ*: 201.80, 151.61, 142.16, 132.54,127.37, 111.08, 107.87, 48.07, 30.58, 25.37; Anal. Calcd for $C_{12}H_{14}N_2O_3$: C,61.53; H,6.02; N,11.96.

5-Dimethylamino-2-nitroacetophenone (59) was obtained from 30 and dimethylamine hydrochloride, using the same synthetic procedure as for **57** to give **59** as yellow solid (2.3 g, 11.0 mmol); yield 88.2%; mp 125-127 °C; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.45 (*s*, 3H), 3.08 (*s*, 6H), 6.31 (*d*, *J*= 2.8 Hz, 1H), 6.58 (*dd*, *J*= 9.4, 2.8 Hz,1H), 8.02 (*d*, *J*= 9.4 Hz, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 201.76, 153.98, 141.88, 133.02, 127.19, 110.83, 107.66, 40.30, 30.56

5-Morpholino-2-aminoacetophenone (60). A solution of **57** (1.5g, 5.9mmol)in CH_2Cl_2(30 ml) was hydrogenated in the presence of 10% Pd/C (0.4g) at 25°C for 8h. The catalyst was filtered off and the filtrate was evaporated to give **60** as yellow solid.(1.25 g, 5.68 mmol); yield 94.6%; ^{1}H-NMR ($CDCl_3$, 200 MHz): δδ 2.45 (*s*, 3H), 2.9 (*m*, 4H), 3.68 (*m*, 4H), 6.67 (*d*, *J* = 8.8 Hz, 1H), 6.78 (br, 2H), 7.02-7.11 (*m*, 2H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 200.44, 145.61, 141.51, 126.37, 119.26, 118.40, 118.22, 66.96, 51.57, 27.93; Anal. Calcd for $C_{12}H_{16}N_2O_2$: C,65.43; H,7.32; N,12.72.

5-Pyrrolidino-2-aminoacetophenone (61) was obtained from **58**, using the same synthetic procedure as for **60** to give **61** as orange solid (1.2 g, 5.9 mmol); yield 91.8%; ^{1}H-NMR ($CDCl_3$-d_6, 200 MHz): δ 1.86 (*m*, 4H), 2.45 (*s*, 3H), 3.10 (*m*, 4H), 6.42 (br, 2H), 6.62-6.77 (*m*, 3H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 200.56, 143.11, 139.23, 121.91, 118.59, 117.86, 113.03, 48.57, 28.47, 25.9; Anal. Calcd for $C_{12}H_{16}N_2O$: C,70.56; H,7.90; N,13.71.

5-Dimethylamino-2-aminoacetophenone (62) was obtained from **59**, using the same synthetic procedure as for **60** to give **62** as orange solid (1.8 g, 10.1 mmol); yield 91.5%; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.45 (*s*, 3H), 2.71 (*s*, 6H), 6.64-6.69 (*m*, 2H), 6.96-7.00 (*m*, 3H); ^{13}C- NMR (DMSO-d_6, 50 MHz) *δ*: 200.49, 144.66, 141.42, 124.49, 118.46, 117.37, 115.79, 42.34, 28.42

Ethyl 2-hydroxybenzoate (68). To a solution of 2-hydroxybenzoic acid **(63)**(5.0g, 36.2mmol) in anhydrous EtOH (150 ml) was added 98%H_2SO_4 (4 ml). The mixture was refluxed for 4h and concentrated. The residue was extracted with CH_2Cl_2 dried over $MgSO_4$ and evaporated. The crude was purified by distillation to give **68** as colorless liquid. (5.85 g, 35.21mmol).Yield: 97.25%; MS (EI, 70 eV): *m/z* 166.2 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.39 (*t*, *J* = 7.2 Hz, 3H), 4.37 (*q*, *J* = 7.2, 7.0 Hz, 2H), 6.81 (*t*, *J* = 6.6 Hz, 1H), 6.89 (*d*, *J* = 8.0 Hz, 1H), 7.42 (*t*, *J* = 7.2 Hz, 1H), 7.82 (*dd*, J_1 = 8.0, 1.8 Hz, 1H), 10.83 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 170.20, 161.64, 135.56, 129.89, 119.06, 117.53, 61.40, 14.18; Anal. Calcd for $C_9H_{10}O_3$: C,65.05; H,6.07.

Ethyl 3-hydroxybenzoate (69) was obtained from **64**, using the same synthetic procedure as for **38** to give **39** as white solid. (3.4 g, 20.5 mmol); yield 94.2%; mp 60-62 °C; MS (EI, 70 eV): *m/z* 166.2 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.36 (*t*, *J* = 7.2 Hz, 3H), 4.35 (*q*, *J* = 7.2, 7.0 Hz, 2H), 5.55 (*s*, 1H), 7.07 (*dd*, *J* = 2.6, 1.2 Hz, 1H), 7.27 (*d*, *J* = 7.8 Hz, 1H), 7.55 -7.62 (*m*, 2H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 167.15, 156.07, 131.50, 129.69, 121.36, 120.36, 116.36, 61.43, 14.23; Anal. Calcd for $C_9H_{10}O_3$: C,65.05; H,6.07.

Ethyl 4-hydroxybenzoate (70) was obtained from **65**, using the same synthetic procedure as for **68** to give **70** as white solid.(5.3 g, 31.9 mmol); yield 88.2%; mp 105-107 °C; MS (EI, 70 eV): *m/z* 166.2 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.36 (*t*, *J* = 7.2 Hz, 3H), 4.33 (*q*, *J* = 7.2, 7.0 Hz, 2H), 6.84 (*d*, *J* = 1.8 Hz, 1H), 6.88 (*d*, *J* = 1.8 Hz, 1H), 7.90 (*d*, *J* = 1.8 Hz, 1 H), 7.95 (*d*, *J* = 1.8 Hz, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 167.13, 160.38, 131.91, 122.44, 115.26, 61.01, 14.30; Anal. Calcd for $C_9H_{10}O_3$: C,65.05; H,6.07.

Ethyl 3-methoxy-4-hydroxybenzoate (71) was obtained from **66**, using the same synthetic procedure as for **68** to give **71** as brown liquid. (6.3 g, 32.1 mmol); yield 90.9%; MS (EI, 70 eV): *m/z* 196.2 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.35 (*t*, *J* = 7.2 Hz, 3H), 3.93 (*s*, 3H), 4.32 (*q*, *J* = 7.2, 7.0 Hz, 2H), 6.90 (*d*, *J* = 8.2 Hz, 1H), 7.53 (*d*, *J* = 1.8 Hz, 1H), 7.62 (*dd*, *J*= 8.2, 1.8 Hz, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 166.44, 149.91, 146.13, 124.10, 122.62, 113.99, 111.70, 60.79, 56.09, 14.37; Anal. Calcd for $C_{10}H_{12}O_4$: C,61.22; H,6.16.

Ethyl 2,3-dihydroxybenzoate (72) was obtained from **67,** using the same synthetic procedure as for **68** to give **72** as white solid. (5.4 g, 29.6 mmol); yield 91.4%; mp 92-94 °C; MS

(EI, 70 eV): *m/z* 182.2 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.40 (*t*, *J* = 7.2 Hz, 3H), 4.38 (*q*, *J* = 7.2, 7.0 Hz, 2H),5.18 (br, 1H), 6.70-7.40 (*m*, 3H), 10.97 (br, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 170.38, 148.90, 145.00, 120.55,119.71, 119.45, 119.10, 112.63,61.61, 14.13; Anal. Calcd for $C_{10}H_{12}O_4$: C,59.34; H,5.53.

Ethyl 2-(benzyloxy)benzoate (73). To a solution of **68** (5.8 g, 34.9 mmol) in CH_3CN (150ml) was added K_2CO_3 (10.6 g, 76.8 mmol). The mixture was added benzyl bromide (6.57g, 38.39mmol) and refluxed for 8h under N_2 atmosphere. The reaction mixture was cooled to 25 □ and poured into H_2O (500ml), and then extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated. The crude products were purified by distillation to give **73** as colorless liquid. (8.5g, 33.2 mmol).Yield: 94.71%; MS (EI, 70 eV): *m/z* 256.3 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.33 (*t*, *J* = 7.2 Hz, 3H), 4.35 (*q*, *J* = 7.2, 7.0 Hz, 2H), 5.15 (*s*, 2H), 7.00 (*d*, *J* = 8.0 Hz, 2H), 7.32-7.45 (*m*, 5H), 7.49 (*d*, *J* = 8.2 Hz, 1H), 7.82 (*dd*, *J* = 8.2, 1.8 Hz, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 166.60, 158.01, 136.77, 133.25, 131.69, 128.49, 127.80, 126.99, 121.20, 120.56, 113.75, 70.57, 60.93, 14.29; Anal. Calcd for $C_{16}H_{16}O_3$: C,74.98; H,6.29.

Ethyl 3-(benzyloxy)benzoate (74) was obtained from **69,** using the same synthetic procedure as for **73** to give **74** as colorless liquid. (4.05 g, 15.80 mmol); yield 77.3%; MS (EI, 70 eV): *m/z* 256.3 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.39 (*t*, *J* = 7.2 Hz, 3H), 4.37 (*q*, *J* = 7.2, 7.0 Hz, 2H), 5.08 (*s*, 2H), 7.17-7.72 (*m*, 9H); ^{13}C- NMR ($CDCl_3$, 200 MHz) *δ*:166.42, 158.76, 136.66, 131.90, 129.48, 128.67, 128.14, 127.62, 122.24, 119.96, 115.26, 70.14, 61.09, 14.38; Anal. Calcd for $C_{16}H_{16}O_3$: C,74.98; H,6.29.

Ethyl 4-(benzyloxy)benzoate (75) was obtained from **70**, using the same synthetic procedure as for **73** to give **75** as colorless liquid. (7.6 g, 29.6 mmol); yield 92.5%; MS (EI, 70 eV): *m/z* 256.3 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.35 (*t*, *J* = 7.2 Hz, 3H), 4.32 (*q*, *J* = 7.2, 7.0 Hz, 2H), 5.09 (*s*, 2H), 6.95 (*d*, *J* = 2.0 Hz,1H), 6.98 (*d*, *J* = 2.0 Hz, 1H), 7.31-7.41 (*m*, 5H), 7.95 (*d*, *J*= 2.0 Hz, 1H), 7.99 (*d*, *J* = 2.0 Hz, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 166.36, 162.39, 136.28, 131.55, 129.02, 128.67, 128.19, 127.48, 123.18, 114.41, 70.08, 60.65, 14.37; Anal. Calcd for $C_{16}H_{16}O_3$: C,74.98; H,6.29.

Ethyl 4-(benzyloxy)-3-methoxybenzoate (76) was obtained from **71**, using the same synthetic procedure as for **73** to give **76** as brown solid. (8.5 g, 29.7 mmol); yield 91.5%; mp 73-75 °C; MS (EI, 70 eV): *m/z* 286.4 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δδ 1.35 (*t*, *J* = 7.2 Hz, 3H), 3.91 (*s*, 3H), 4.32 (*q*, *J* = 7.2, 7.0 Hz, 2H), 5.18 (*s*, 2H), 6.85 (*d*, *J* = 8.4 Hz, 1H), 7.27-7.62 (*m*, 7H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 166.38, 152.01, 149.12, 136.40, 128.64, 128.05, 127.22, 123.29, 112.46, 70.77, 60.79, 56.07, 14.39; Anal. Calcd for $C_{17}H_{18}O_4$: C,71.31; H,6.34.

Ethyl 2,3-methylenedioxybenzoate (77) was obtained from **72** and diiodomethane, using the same synthetic procedure as for **73** to give **77** as colorless liquid. (2.8 g, 14.4 mmol); yield 87.6%; mp 90-92 °C; MS (EI, 70 eV): *m/z* 194.1 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.35 (*t*, *J* = 7.2 Hz, 3H), 4.34 (*q*, *J* = 7.2, 7.0 Hz, 2H), 6.04 (*s*, 2H), 6.80 (*t*, *J* = 7.8 Hz, 3H), 6.92 (*dd*, *J* = 7.8, 1.4 Hz, 1H), 7.37 (*dd*, *J* = 7.8, 1.4 Hz, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 164.42, 148.68, 148.41, 122.66, 121.10, 113.28, 112.12, 101.83, 60.98, 14.30; Anal. Calcd for $C_{10}H_{10}O_4$:C,61.85; H,5.19.

2-(Benzyloxy)benzoic acid (78). To a suspension of **73** (4.0g, 15.6mmol) in H_2O (150ml) were added NaOH(3.1g, 78.0 mmol) and EtOH (5 ml). The mixture was reflux for 12h, and cooled to 25 °C. The solid was filtered out and the filtrate was acidified with 2N HCl. The precipitate was collected and washed with H_2O. The crude product was recrystallized from to give **78** as white solid. (3.0 g, 13.2 mmol).Yield: 84.6%; mp 73-75 °C; MS (EI, 70 eV): *m/z* 228.3 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 5.27 (*s*, 2H), 7.08-7.54 (*m*, 8H), 6.93 (*dd*, *J* = 8.0, 1.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) *δ*: 165.43, 157.40, 135.02, 134.34, 133.88, 129.16, 127.92, 122.44, 118.09, 113.11, 72.23; Anal. Calcd for $C_{14}H_{12}O_3$: C,73.67; H,5.30.

3-(Benzyloxy)benzoic acid (79) was obtained from **74**, using the same synthetic procedure as for **48** to give **49** as white solid. (3.1 g, 13.6 mmol).Yield: 87.4%; mp 120-122 °C; MS (EI, 70 eV): *m/z* 228.3 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.37 (br, 1H), 5.12 (*s*, 2H), 7.19-7.50 (*m*, 9H); ^{13}C- NMR (DMSO-d_6, 50 MHz) *δ*: 167.55, 18.77, 137.26, 132.69, 130.19, 128.90, 128.33, 128.10, 122.25, 120.15, 115.36; Anal. Calcd for $C_{14}H_{12}O_3$: C,73.67; H,5.30.

4-(Benzyloxy)benzoic acid (80) was obtained from **75**, using the same synthetic procedure as for **78** to give **80** as white solid. (6.2 g, 27.2 mmol).Yield: 92.0%; mp 195-197 °C; MS (EI, 70 eV): *m/z* 228.3 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 5.10 (*s*, 2H), 6.96 (*d*, *J* = 2.0 Hz, 1H), 7.00 (*d*, *J* = 2.0 Hz, 1H), 7.28-7.44 (*m*, 5H), 7.82 (*d*, *J* = 2.0 Hz, 1H), 7.86 (*d*, *J* = 2.0 Hz, 1H); ^{13}C- NMR (DMSO-d_6, 50 MHz) *δ*: 168.50, 161.37, 137.20, 131.53, 128.91, 128.37, 128.21, 127.00, 114.55, 69.78; Anal. Calcd for $C_{14}H_{12}O_3$: C,73.67; H,5.30.

4-(Benzyloxy)-3-methoxybenzoic acid (81) was obtained from **76,** using the same synthetic procedure as for **78** to give **81** as white solid. (7.6 g, 29.4 mmol).Yield: 99.5%; mp 159-162 °C; MS (EI, 70 eV): *m/z* 258.3 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.76 (*s*, 3H), 5.11 (*s*, 2H), 7.10 (*d*, *J* = 8.4 Hz, 1H), 7.29-7.43 (*m*, 6H), 7.50 (*dd*, *J* = 8.4, 1.8 Hz, 1H); ^{13}C- NMR (DMSO-d_6, 50 MHz) *δ*: 167.53, 152.03, 149.01, 136.99, 128.92, 128.38, 123.68, 123.47, 112.86, 112.58, 70.30, 55.94; Anal. Calcd for $C_{15}H_{14}O_4$: C,69.76; H,5.46.

2,3-Methylenedioxybenzoic acid (82) was obtained from 77, using the same synthetic procedure as for **78** to give **82** as white solid. (2.3 g, 13.8 mmol).Yield: 96.0%; mp 188-190 °C;

MS (EI, 70 eV): *m/z* 166.2 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 6.07 (*s*, 2H), 7.05 (*d*, *J* =8.2 Hz, 1H), 7.25 (*t*, *J* =7.6 Hz, 1H), 7.06 (*dd*, *J* = 7.6, 1.2 Hz, 1H), 7.23 (*dd*, *J* = 7.6, 1.2 Hz, 1H), 12.95 (br, 1H); ^{13}C- NMR (DMSO-d_6, 50 MHz) *δ*: 165.56, 148.91, 148.51, 122.94, 121.58, 113.80, 112.46, 102.11; Anal. Calcd for $C_8H_6O_4$: C,57.84; H,3.64.

2-Benzyloxybenzoyl chloride (83). To a suspension of **78** (3.1g, 13.6mmol) in dry toluene (150 ml)was added $SOCl_2$ (12.9g, 109.1mmol). The mixture was reflux for 8h and evaporated to give **83** as yellow liquid to use directly in the next step. (2.55 g, 10.3 mmol).Yield: 79.07%.

3-Benzyloxybenzoyl chloride (84) was obtained from **79**, using the same synthetic procedure as for **53** to give **54** as yellow liquid to use directly in the next step. (2.5 g, 10.1 mmol).Yield: 74.2%.

4-Benzyloxybenzoyl chloride (85) was obtained from **80**, using the same synthetic procedure as for **53** to give **55** as yellow liquid to use directly in the next step. (2.4 g, 9.7 mmol).Yield: 79.5%.

4-Benzyloxy-3-methoxybenzoyl chloride (86) was obtained from **81**, using the same synthetic procedure as for **83** to give **86** as brown liquid to use directly in the next step. (4.5 g, 16.3 mmol).Yield: 84.6%.

2,3-Methylenedioxybenzoyl chloride (87) was obtained from **82**, using the same synthetic procedure as for **83** to give **87** as white solid to use directly in the next step. (1.7 g, 9.2 mmol).Yield: 76.5%.

2,3-Dimethoxybenzoyl chloride (88) was obtained from **83**, using the same synthetic procedure as for **53** to give **58** as yellow liquid to use directly in the next step. (2.8 g, 14.0 mmol).Yield: 84.8%.

2,5-Dimethoxybenzoyl chloride (89) was obtained from **84**, using the same synthetic procedure as for **55** to give **59** as yellow liquid to use directly in the next step. (2.3 g, 11.5 mmol).Yield:83.5%.

***N*-(2-Acetyl-4-morpholinophenyl)-2-benzyloxybenzamide (92).** To a solution of **60** (1.3g, 5.9mmol) in THF (150 ml) was added Et_3N (8 ml). The mixture was stirred at 0 °C and **83** (1.7g, 7.1 mmol) was added dropwise. The reaction mixture was stirred at 25 °C for 2 h and poured into crushed ice and extracted with CH_2Cl_2.The extract was washed with H_2O, dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2) to give **92** as yellow solid. (2.1 g, 4.9 mmol).Yield: 83.3%; mp 144-146 °C; MS (EI, 70 eV): *m/z* 430.2 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.51 (*s*, 3H), 3.14 (*m*, 4H), 3.87 (*m*, 4H), 5.46 (*s*, 2H), 6.95-7.05 (*m*, 2H), 7.15 (*dd*, *J* = 9.2, 3.0 Hz, 1H), 7.22-7.44 (*m*, 7H), 8.10 (*dd*, *J* = 7.6, 1.8 Hz, 1H), 8.37 (*d*, *J* = 9.2 Hz, 1H), 12.25 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 201.16, 164.61,

156.37, 136.77, 132.69, 132.11, 128.54, 127.79, 126.98, 125.30, 123.69, 122.22, 121.16, 117.82, 113.28, 70.46, 66.78, 49.94, 28.58; Anal. Calcd for $C_{26}H_{26}N_2O_4$; C,72.54; H,6.09; N,6.51.

***N*-(2-Acetyl-4-pyrrolidinophenyl)-2-benzyloxybenzamide (93)** was obtained from **61** and **83**, using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, $CHCl_3$ / *n*-hexane =10:1)to give **93** as yellow solid. (1.6 g, 3.9 mmol); yield 76.4%; mp 160-161 °C; MS (EI, 70 eV): *m/z* 414.2 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.02 (*m*, 4H), 2.51 (*s*, 3H), 3.30 (*m*, 4H),5.45 (*s*, 2H), 6.85-7.45(*m*, 10H), 8.1 (*dd*, *J* = 7.8, 1.6 Hz, 1H), 8.67 (*d*, *J* = 9.2 Hz,1H), 12.07 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 201.71, 164.15, 156.31, 143.73, 136.68, 132.02, 128.52, 127.74, 12.700, 125.89, 124.04, 121.10, 117.30, 113.25, 112.63, 70.45, 47.89, 28.62, 25.44; Anal. Calcd for $C_{26}H_{26}N_2O_3$; C,75.34; H,6.32; N,6.76.

***N*-(2-Acetyl-4-dimethylaminophenyl)-2-benzyloxybenzamide (94)** was obtained from **62** and **53**, using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, $CHCl_2$) to give **94** as yellow solid. (2.2 g, 5.7 mmol); yield 77.7%; mp 132-134 °C; MS (EI, 70 eV): *m/z* 388.2 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.51 (*s*, 3H), 2.95 (*s*, 6H), 5.46 (*s*, 2H), 7.00 (*dd*, *J* = 9.2, 2.6 Hz, 1H), 7.05-7.45(*m*, 9H), 8.10 (*dd*, *J* = 7.8, 1.8 Hz, 1H), 8.71 (*d*, *J* = 9.2 Hz, 1H), 12.13 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 201.55, 164.34, 156.34, 146.04, 136.83, 132.49, 132.05, 130.31, 128.53, 127.77, 127.01, 125.03, 123.95, 123.85, 121.12, 118.81, 114.34, 113.28, 70.47, 41.03, 28.59; Anal. Calcd for $C_{24}H_{24}N_2O_3$; C,74.21; H,6.23; N,7.21.

***N*-(2-Acetyl-4-morpholinophenyl)-3-benzyloxybenzamide (95)** was obtained from **60** and **84,** using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, $CHCl_3$/ *n*-hexane =8:1) to give **95** as yellow solid. (1.15 g, 2.67 mmol); yield 84.1%; mp 140-142 °C; MS (EI, 70 eV): *m/z* 430.2 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.67 (*s*, 3H), 3.13 (*m*, 4H), 3.9 (*m*, 4H), 5.13 (*s*, 2H), 6.95 (*m*, 1H), 7.05 (*m*, 1H), 7.22 (*m*, 1H), 7.23-7.41(*m*,7H), 8.10 (*m*, 1H), 8.37 (*d*, *J* = 9.2 Hz, 1H), 12.35 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 203.05, 165.46, 159.14, 136.66, 136.48, 134.56, 129.82, 128.60, 128.06, 127.61, 123.38, 122.94, 122.04, 119.47, 119.09, 118.41, 113.44, 70.14, 66.75, 49.87, 28.58; Anal. Calcd for $C_{26}H_{26}N_2O_4$; C,72.54; H,6.09; N,6.51.

***N*-(2-Acetyl-4-pyrrolidinophenyl)-3-benzyloxybenzamide (96)** was obtained from **61** and **84**, using the same synthetic procedure as for **92.** The crude product was purified by column chromatography (silica gel, CH_2Cl_2/ *n*-hexane =5:1) to give **96** as yellow solid. (1.05g, 2.53 mmol); yield 74.1%; mp 131-133 °C; MS (EI, 70 eV): *m/z* 414.2 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.02 (*m*, 4H), 2.67 (*s*, 3H), 3.30 (*m*, 4H), 5.14 (*s*, 2H), 6.83-7.67 (*m*, 11H), 8.78 (*d*, *J* = 9.2 Hz, 1H), 12.20 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 203.51, 165.07, 159.12, 143.54, 136.88,

136.75, 129.71, 128.59, 128.02, 127.62, 123.32, 122.33, 119.41, 118.85, 118.54, 113.34, 110.89, 70.13, 47.99, 28.57, 25.42; Anal. Calcd for $C_{26}H_{26}N_2O_3$; C,75.34; H,6.32; N,6.76.

***N*-(2-acetyl-4-dimethylaminophenyl)-3-(benzyloxy)benzamide (97)** was obtained from **62** and **84**, using the same synthetic procedure as for **92.** The crude product was purified by column chromatography (silica gel, CH_2Cl_2) to give **97** as yellow solid. (1.6g, 4.1 mmol); yield 73.4%; mp 147-149 °C; MS (EI, 70 eV): *m/z* 388.2 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.66 (*s*, 3H), 2.94 (*s*, 6H), 5.14 (*s*, 2H), 6.83 (*d*, *J*= 6.4 Hz, 1H), 7.13-7.69 (*m*, 10 H), 7.57-7.67 (*m*, 2H), 8.80 (*d*, *J*= 9.2 Hz, 1H), 12.26 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 203.43, 165.18, 159.12, 146.03, 136.74, 131.68, 129.75, 128.60, 128.04, 127.63, 123.11, 122.11, 119.78, 119.43, 118.90, 114.71, 113.38, 70.12, 40.88, 28.57; Anal. Calcd for $C_{24}H_{24}N_2O_3$; C,74.21; H,6.23; N,7.21.

***N*-(2-Acetyl-4-morpholinophenyl)-4-benzyloxybenzamide (98)** was obtained from **60** and **85**, using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, EtOAc/ CH_2Cl_2 =1:2) to give **98** as yellow solid. (1.5 g, 3.5 mmol); yield 64.0%; mp 172-175 °C; MS (EI, 70 eV): *m/z* 430.2 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.67 (*s*, 3H), 3.14 (*m*, 4H), 3.88 (*m*, 4H), 5.05 (*s*, 2H), 6.99-7.43 (*m*, 9H), 7.97 (*d*, *J* = 2.0 Hz, 1H), 8.00 (*d*, *J* = 2.0 Hz,1H), 8.86 (*d*, *J* = 9.2 Hz, 1H), 12.30 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 203.13, 165.27, 163.55, 161.66, 146.00, 136.37, 135.19, 132.83, 129.28, 128.67, 128.17, 127.48, 123.68, 122.71, 122.01, 118.62, 114.86, 70.13, 66.70, 50.09, 28.63; Anal. Calcd for $C_{26}H_{26}N_2O_4$; C,72.54; H,6.09; N,6.51.

***N*-(2-Acetyl-4-pyrrolidinophenyl)-4-benzyloxybenzamide (99)** was obtained from **61** and **85**, using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, EtOAc/ CH_2Cl_2 =1:4) to give **99** as yellow solid. (1.6 g, 3.9 mmol); yield 71.7%; mp 175-178 °C; MS (EI, 70 eV): *m/z* 414.2 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.03 (*m*, 4H), 2.66 (*s*, 3H), 3.29 (*m*, 4H), 5.12 (*s*, 2H), 6.84 (*d*, *J* = 9.2 Hz, 1H), 7.07 -6.97 (*m*, 3H), 7.40-7.33 (*m*, 5H), 7.98 (*d*, *J* = 7.6 Hz,1H), 8.01 (*d*, *J* = 3.2 Hz, 1H), 8.78 (*d*, *J* = 9.2 Hz, 1H), 12.15 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ*: 203.62, 164.90, 162.20, 161.40, 143.38, 136.46, 130.93, 129.14, 128.66, 128.13, 127.92, 127.49, 123.11, 122.27, 118.68, 114.76, 113.23, 70.10, 47.95, 28.63, 25.42; Anal. Calcd for $C_{26}H_{26}N_2O_3$; C,75.34; H,6.32; N,6.76.

***N*-(2-Acetyl-4-dimethylaminophenyl)-4-(benzyloxy)benzamide (100)** was obtained from **62** and **85**, using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, CH_2Cl_2) to give **100** as yellow solid. (1.7g, 4.4 mmol); yield 65.0%; mp 139-140 °C; MS (EI, 70 eV): *m/z* 388.2 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.66 (*s*, 3H), 2.94 (*s*, 6H), 5.10 (*s*, 2H), 7.00-7.06 (*m*, 3H), 7.17 (*d*, *J* = 2.8 Hz, 1H), 7.33-7.44 (*m*, 5H), 7.97 (*d*, *J* = 1.6 Hz, 1H), 8.00 (*d*, *J* = 1.6 Hz, 1H), 8.80 (*d*, *J* = 9.2 Hz, 1H), 12.19 (*s*, 1H); ^{13}C-

NMR ($CDCl_3$, 50 MHz) δ: 203.50, 165.00, 161.49, 145.80, 136.44, 132.21, 129.19, 128.66, 128.14, 127.78, 127.49, 122.91, 122.06, 120.06, 114.80, 70.11, 40.97, 28.60; Anal. Calcd for $C_{24}H_{24}N_2O_3$; C,74.21; H,6.23; N,7.21.

***N*-(2-Acetyl-4-morpholinophenyl)-4-(benzyloxy)-3-methoxybenzamide (101)** was obtained from **60** and **86**, using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, CH_2Cl_2 / *n*-hexane =5:1) to give **101** as yellow solid. (1.9 g, 4.1 mmol); yield 82.6%; mp 192-194 °C; MS (EI, 70 eV): *m/z* 460.2 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.67 (*s*, 3H), 3.13(*m*, 4H), 3.86(*m*, 4H), 5.22(*s*, 2H), 6.93 (*d*, *J* = 8.4 Hz, 1H),7.54 (*dd*, *J* = 9.2, 2.8 Hz,1H), 7.30-7.45 (*m*,6H), 7.54 (*dd*, *J* = 8.4, 2.0 Hz, 1H), 7.61 (*d*, *J* = 2.0 Hz, 1H), 8.84 (*d*, *J* = 9.2 Hz, 1H), 12.15 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) δ: 203.09, 165.26, 151.16, 149.59, 136.52, 134.94, 128.65, 128.02, 127.90, 127.21, 123.58, 122.72, 121.90, 120.03, 118.43, 112.91, 111.14, 70.88, 66.77, 56.08, 49.95, 28.59; Anal. Calcd for $C_{27}H_{28}N_2O_5$; C,70.42; H,6.13; N,6.08.

***N*-(2-Acetyl-4-pyrrolidinophenyl)-4-(benzyloxy)-3-methoxybenzamide (102)** was obtained from **61** and **86,** using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, CH_2Cl_2 / *n*-hexane =3:1) to give **102** as yellow solid. (2.0 g, 4.5 mmol); yield 83.6%; mp 152-154 °C; MS (EI, 70 eV): *m/z* 444.6 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.04 (*m*, 4H), 2.66 (*s*, 3H), 3.30 (*m*, 4H), 3.98 (*s*, 3H), 5.22 (*s*, 2H), 6.84 (*dd*, *J* = 9.2, 2.8 Hz, 1H), 6.92 (*d*, *J* = 8.4 Hz,1H), 7.97 (*m*, 1H), 7.24-7.45 (*m*, 5H), 7.53 (*dd*, *J* = 8.4, 2.0 Hz, 1H), 7.63 (*d*, *J* = 2.0 Hz, 1H), 8.77 (*d*, *J* = 9.2 Hz, 1H), 12.17 (*s*, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 203.09, 165.26, 151.16, 149.59, 136.52, 134.94, 128.65, 128.02, 127.90, 127.21, 123.58, 122.72, 121.90, 120.03, 118.43, 112.91, 111.14, 70.88, 66.77, 56.08, 49.95, 28.59; Anal. Calcd for $C_{27}H_{28}N_2O_4$; C,72.95; H,6.35; N,6.30.

***N*-(2-Acetyl-4-morpholinophenyl)benzo[*d*][1,3]dioxole-4-carboxamide (103)** was obtained from **60** and **87**, using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, $CHCl_3$ / *n*-hexane =10:1) to give **103** as yellow solid. (1.06 g, 2.88 mmol); yield 79.3 %; mp 150-152 °C; MS (EI, 70 eV): *m/z* 368.5 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.62 (*s*, 3H), 3.15 (*m*, 4H), 3.89 (*m*, 4H), 6.17 (*s*, 2H), 6.90-6.96 (*m*, 2H), 7.50 (*dd*, *J* = 9.2, 2.8 Hz, 1H), 7.50 (*dd*, *J* = 6.6, 2.8 Hz, 1H), 7.38 (*m*, 1H), 8.70 (*d*, *J* = 9.2 Hz, 1H), 11.87 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) δ: 2201.77, 162.60, 148.12, 145.80, 133.50, 124.69, 123.63, 122.57, 121.95, 121.78, 118.29, 116.95, 111.51, 101.79, 66.60, 50.07, 28.59; Anal. Calcd for $C_{20}H_{20}N_2O_5$; C,65.21; H,5.47; N,7.60.

***N*-(2-Acetyl-4-pyrrolidinophenyl)benzo[*d*][1,3]dioxole-4-carboxamide (104)** was obtained from **61** and **87**, using the same synthetic procedure as for **92**. The crude product was purified by

column chromatography (silica gel, CH_2Cl_2 / *n*-hexane =8:1) to give **104** as yellow solid. (0.8 g, 2.3 mmol); yield 57.9%; mp 139-141 °C; MS (EI, 70 eV): *m/z* 352.1 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.01 (*m*, 4H), 2.61 (*s*, 3H), 3.31 (*m*, 4H), 6.17 (*s*, 2H), 6.81-7.01 (*m*, 4H), 7.50 (*dd*, *J* = 6.2, 3.2 Hz, 1H), 8.60 (*d*, *J* = 9.2 Hz, 1H), 11.87 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) δ 202.25, 162.21, 148.06, 145.67, 125.24, 124.01, 121.98, 121.68, 117.32, 111.22, 101.70, 48.37, 48.56, 25.38; Anal. Calcd for $C_{20}H_{20}N_2O_4$; C,68.17; H,5.72; N,7.95.

***N*-(2-Acetyl-4-morpholinophenyl)-2,3-dimethoxybenzamide (105)** was obtained from **60** and **88**, using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, $CHCl_3$ / *n*-hexane =10:1) to give **105** as yellow solid. (1.5 g, 3.9 mmol); yield 78.2 %; mp 146-148 °C; MS (EI, 70 eV): *m/z* 384.5 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.61 (*s*, 3H), 3.15 (*m*, 4H), 3.87 (*m*, 4H), 3.99 (*s*, 3H), 4.05 (*s*, 3H), 6.99- 7.62 (*m*, 5H), 8.78 (*d*, *J* =9.2 Hz, 1H), 12.15 (*s*, 1H);^{13}C- NMR ($CDCl_3$, 200 MHz) δ 201.30, 164.52, 152.94, 147.73, 146.29, 133.20, 128.39, 125.43, 124.01, 123.71, 122.50, 122.19, 117.98, 115.51, 66.67, 61.61, 56.09, 50.03, 28.58; Anal. Calcd for $C_{21}H_{24}N_2O_5$; C,65.61; H,6.29; N,7.29.

***N*-(2-Acetyl-4-pyrrolidinophenyl)-2,3-dimethoxybenzamide (106)** was obtained from **61** and **88**, using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, CH_2Cl_2 / *n*-hexane =10:1) to give **106** as yellow solid. (1.4 g, 3.8 mmol); yield 77.6 %; mp 137-140 °C; MS (EI, 70 eV): *m/z* 368.5 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.00 (*m*, 4H), 2.59 (*s*, 3H), 3.28 (*m*, 4H), 3.86 (*s*, 3H), 3.98 (*s*, 3H), 6.74 (*m*, 4H), 7.14-6.92 (*m*, 3H), 7.59 (*dd*, *J* =7.6, 1.8 Hz, 1H), 8.63(*d*, *J* =9.0 Hz, 1H), 11.96 (*s*, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 201.83, 164.07, 152.92, 147.66, 143.71, 128.76, 125.96, 124.00, 123.94, 122.46, 117.32, 115.24, 112.79, 61.58, 56.08, 48.03, 28.59, 25.39; Anal. Calcd for $C_{21}H_{24}N_2O_4$; C,68.46; H,6.57; N,7.60.

***N*-(2-Acetyl-4-morpholinophenyl)-2,5-dimethoxybenzamide (107)** was obtained from **60** and **89**, using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, $CHCl_3$ / EtOAc =8:1) to give **107** as yellow solid. (1.67 g, 4.3 mmol); yield 79.7%; mp 172-174 °C; MS (EI, 70 eV): *m/z* 384.5 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.61 (*s*, 3H), 3.15 (*m*, 4H), 3.80 (*s*, 3H), 3.87 (*m*, 4H), 4.07 (*s*, 3H), 6.95-7.32 (*m*, 4H), 7.73 (*d*, *J* =2.8 Hz, 1H), 8.78 (*d*, *J* = 9.2 Hz, 1H), 12.25 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) δ 201.21, 164.05, 153.63, 151.95, 146.52, 132.80, 125.75, 123.96, 122.95, 122.01, 119.69, 117.66, 115.69, 112.79, 66.79, 56.12, 55.83, 49.86, 28.76; Anal. Calcd for $C_{21}H_{24}N_2O_5$; C,65.61; H,6.29; N,7.29.

***N*-(2-Acetyl-4-pyrrolidinophenyl)-2,5-dimethoxybenzamide (108)** was obtained from **61** and **89,** using the same synthetic procedure as for **92**. The crude product was purified by column

chromatography (silica gel, CH_2Cl_2 / *n*-hexane =8:1) to give **108** as yellow solid. (1.6 g, 4.3 mmol); yield 73.8 %; mp 137-140 °C; MS (EI, 70 eV): *m/z* 368.5 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.01 (*m*, 4H), 2.60 (*s*, 3H), 3.29 (*m*, 4H), 3.80 (*s*, 3H), 4.06 (*s*, 3H), 6.77 (*dd*, *J* = 9.2, 3.0 Hz, 1H), 6.89-6.97 (*m*, 3H), 7.74 (*d*, *J* = 2.8 Hz, 1H), 8.64 (*d*, *J* = 9.2 Hz, 1H), 12.08 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 200 MHz) *δ* 201.75, 163.61, 153.61, 151.91, 143.69, 128.64, 126.30, 124.32, 123.30, 119.36, 117.20, 115.62, 112.78, 56.15, 55.83, 47.94, 28.77, 25.42; Anal. Calcd for $C_{21}H_{24}N_2O_4$; C,68.46; H,6.57; N,7.60.

***N*-(2-Acetyl-4-morpholinophenyl)-2-methoxybenzamide (109)** was obtained from **60** and **90**, using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, CH_2Cl_2 / *n*-hexane =10:1) to give **109** as yellow solid. (1.4 g, 3.9 mmol); yield 72.6 %; mp 158-160 °C; MS (EI, 70 eV): *m/z* 354.5 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.60 (*s*, 3H), 3.12 (*m*, 4H), 3.85 (*m*, 4H), 4.09 (*s*, 3H), 6.96-7.07 (*m*, 2H), 7.13 (*dd*, *J* = 9.2, 3.0 Hz, 1H), 7.34-7.43 (*m*, 2H), 8.14 (*dd*, *J* = 7.6, 1.8 Hz, 1H), 8.80 (*d*, *J* = 9.2 Hz, 1H), 12.23 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ* 201.25, 164.33, 157.56, 146.18, 133.01, 132.25, 125.46, 123.83, 122.63, 122.18, 120.89, 117.92, 111.31, 66.69, 55.58, 49.98, 28.76; Anal. Calcd for $C_{20}H_{22}N_2O_4$; C,67.78; H,6.26; N,7.90.

***N*-(2-Acetyl-4-pyrrolidinophenyl)-2-methoxybenzamide (110)** was obtained from **61** and **90**, using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, CH_2Cl_2) to give **110** as yellow solid. (1.1 g, 3.3 mmol); yield 83.1%; mp 168-170 °C; MS (EI, 70 eV): *m/z* 338.5 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.96 (*m*, 4H), 2.64 (*s*, 3H), 3.27 (*m*, 4H), 4.05 (*s*, 3H), 6.81 (*dd*, *J* = 9.0, 2.6 Hz, 1H), 7.00-7.53 (*m*, 4H), 7.96 (*dd*, *J* = 7.8, 1.8 Hz,1H), 8.50 (*d*, *J* = 9.0 Hz, 1H), 11.87 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ* 202.81, 163.21, 157.44, 144.08, 133.51, 131.70, 127.89, 126.64, 123.70, 122.76, 121.13, 117.04, 113.42, 112.51, 56.17, 47.94, 29.37, 25.38; Anal. Calcd for $C_{20}H_{22}N_2O_3$; C,70.99; H,6.55; N,8.28.

***N*-(2-Acetyl-4-morpholinophenyl)-2-methoxybenzamide (111)** was obtained from **60** and **91**, using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, CH_2Cl_2 / EtOAc =15:1) to give **111** as yellow solid. (1.1 g, 3.1 mmol); yield 76.0 %; mp 185-187 °C; MS (EI, 70 eV): *m/z* 354.5 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.67 (*s*, 3H), 3.13 (*m*, 4H), 3.84 (*s*, 3H),3.86 (*m*, 4H), 6.95 (*d*, *J* = 2.0 Hz, 1H), 6.98 (*d*, *J* = 2.0 Hz, 1H), 7.21 (*dd*, *J* = 9.2, 2.8 Hz, 1H), 7.38 (*d*, *J* = 2.8 Hz, 1H), 7.97 (*d*, *J* = 2.0 Hz, 1H), 8.00 (*d*, *J* = 2.0 Hz, 1H), 8.85 (*d*, *J* = 9.2 Hz, 1H), 12.29 (*s*, 1H); ^{13}C- NMR ($CDCl_3$, 50 MHz) *δ* 203.11, 165.30, 162.48, 146.21, 135.01, 1229.24, 127.29, 123.61, 122.72, 121.99, 118.39, 113.95, 66.78, 55.42, 49.95, 28.61; Anal. Calcd for $C_{20}H_{22}N_2O_4$; C,67.78; H,6.26; N,7.90.

***N*-(2-Acetyl-4-pyrrolidinophenyl)-4-methoxybenzamide (112)** was obtained from **61** and **91**, using the same synthetic procedure as for **92**. The crude product was purified by column chromatography (silica gel, CH_2Cl_2 / *n*-hexane =10:1) to give **112** as yellow solid. (1.2 g, 3.5 mmol); yield 72.5%; mp 174-175 °C; MS (EI, 70 eV): *m/z* 338.5 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz): CH_2Cl_2 / *n*-hexane =10:1; ^{13}C- NMR ($CDCl_3$, 50 MHz) δ 203.60, 164.95, 162.25, 143.27, 132.19, 129.12, 127.67, 123.10, 122.24, 118.74, 113.87, 55.39, 48.02, 28.60, 25.38; Anal. Calcd for $C_{20}H_{22}N_2O_3$; C,70.99; H,6.55; N,8.28.

2-(2-Benzyloxyphenyl)-6-morpholinoquinolin-4-one (113). To a solution of **92** (1.2 g, 2.7mmol) in 1,4 dioxane (150ml) was added NaOH (0.9g, 21.4mmol). The mixture was refluxed for 5 h, concentrated and added 10% NH_4Cl (100ml). The precipitate was collected and washed with H_2O and acetone. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **113** as yellow solid (1.3 g, 3.2 mmol).Yield: 65.4%; mp 281-283 °C; MS (EI, 70 eV): *m/z* 412.4 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.15 (*m*, 4H), 3.77 (*m*, 4H), 5.12 (*s*, 2H), 6.30 (*s*, 1H), 7.36-7.50 (*m*,11H), 7.66 (*d*, *J* = 9.2 Hz, 1H), 11.57 (*s*, 1H); Anal. Calcd for $C_{26}H_{24}N_2O_3$; C,75.71; H,5.86; N,6.79.

2-(2-Benzyloxyphenyl)-6-pyrrolidinoquinolin-4-one (114) was obtained from **93**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **114** as yellow solid. (0.7 g, 1.8 mmol).Yield: 61.1%; mp 293-295 °C; MS (EI, 70 eV): *m/z* 396.4 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 1.99 (*m*, 4H), 3.34 (*m*, 4H), 5.21 (*s*, 2H), 6.33 (*s*, 1H), 7.00-7.50 (*m*,11H), 7.68 (*d*, *J* = 9.0 Hz, 1H), 11.63 (*s*, 1H); Anal. Calcd for $C_{26}H_{24}N_2O_2$; C,78.76; H,6.10; N,7.07.

2-(2-Benzyloxyphenyl)-6-dimethylaminoquinolin-4-one (115) was obtained from **94**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **115** as yellow solid. (1.2 g, 1.8 mmol).Yield: 61.1%; mp 210-212 °C; MS (EI, 70 eV): *m/z* 370.2 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.91 (*s*, 6H), 5.13 (*s*, 2H), 6.02 (*s*, 1H), 7.07 (*t*, *J* = 7.4 Hz, 1H), 7.17 (*d*, *J* = 2.6 Hz, 1 H), 7.22-7.48 (*m*,9H), 7.53 (*d*, *J* = 9.2 Hz, 1H), 11.67 (*s*, 1H); Anal. Calcd for $C_{24}H_{22}N_2O_2$; C,77.81; H,5.99; N,7.56.

2-(3-Benzyloxyphenyl)-6-morpholinoquinolin-4-one (116) was obtained from **95,** using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **116** as yellow solid. (0.8 g, 1.9 mmol).Yield: 61.1%; mp 283-285 °C; MS (EI, 70 eV): *m/z* 412.4 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.15 (*m*, 4H), 3.77 (*m*, 4H), 5.12 (*s*, 2H), 6.30 (*s*, 1H), 7.36-7.50 (*m*,11H),7.66 (*d*, *J*=9.2 Hz,1H), 11.57 (*s*, 1H); Anal. Calcd for $C_{26}H_{24}N_2O_3$; C,75.71; H,5.86; N,6.79.

2-(3-Benzyloxyphenyl)-6-pyrrolidinoquinolin-4-one (117) was obtained from **96**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **117** as yellow solid. (0.38 g, 0.95 mmol).Yield: 66.3%; mp 320-322 °C; MS (EI, 70 eV): *m/z* 396.4 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.07 (*m*, 4H), 3.34 (*m*, 4H), 5.21 (*s*, 2H), 6.35 (*s*, 1H), 6.87-7.49 (*m*,10H),7.70 (*d*, *J*=9.0 Hz,1H), 7.78 (*d*, *J*=8.6Hz, 1H), 11.50 (*s*, 1H); Anal. Calcd for $C_{26}H_{24}N_2O_2$; C,78.76; H,6.10; N,7.07.

2-(3-Benzyloxyphenyl)-6-dimethylaminoquinolin-4-one (118) was obtained from **97**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **118** as yellow solid. (1.3 g, 3.5 mmol).Yield: 65.6%; mp 307-308 °C; MS (EI, 70 eV): *m/z* 370.2 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δδ 2.91 (*s*, 6H), 5.13 (*s*, 2H), 6.02 (*s*, 1H), 7.07 (*t*, *J*=7.4 Hz,1H), 7.17 (*d*, *J*=2.6 Hz,1 H), 7.22-7.48 (*m*,9H),7.53 (*d*, *J*=9.2 Hz, 1H), 11.67 (*s*, 1H); Anal. Calcd for $C_{24}H_{22}N_2O_2$; C,77.81; H,5.99; N,7.56.

2-(4-Benzyloxyphenyl)-6-morpholinoquinolin-4-one (119) was obtained from **98**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **119** as yellow solid. (0.5 g, 1.2 mmol).Yield: 52.2%; mp 320-323 °C; MS (EI, 70 eV): *m/z* 412.4 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.14 (*m*, 4H), 3.77 (*m*, 4H), 5.21 (*s*, 2H), 6.24 (*s*, 1H),7.16-7.49 (*m*,9H),7.66 (*d*, *J*=9.0 Hz,1H), 7.76 (*d*, *J*=8.6Hz, 1H), 11.48 (*s*, 1H); Anal. Calcd for $C_{26}H_{24}N_2O_3$; C,75.71; H,5.86; N,6.79.

2-(4-Benzyloxyphenyl)-6-pyrrolidinoquinolin-4-one (120) was obtained from **99**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **120** as yellow solid. (0.6 g, 1.5 mmol).Yield: 57.5%; mp 330-332 °C; MS (EI, 70 eV): *m/z* 396.2 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 1.99 (*m*, 4H), 3.34 (*m*, 4H), 5.21 (*s*, 2H), 6.33 (*s*, 1H), 7.00-7.50 (*m*,11H), 7.68 (*d*, *J* = 9.0 Hz, 1H), 11.63 (*s*, 1H); Anal. Calcd for $C_{26}H_{24}N_2O_2$; C,78.76; H,6.10; N,7.07.

2-(4-Benzyloxyphenyl)-6-dimethylaminoquinolin-4-one (121) was obtained from **100**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **121** as yellow solid. (1.2 g, 3.2 mmol).Yield: 78.7%; mp 283-285 °C; MS (EI, 70 eV): *m/z* 370.2 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 2.92 (*s*, 6H), 5.17 (*s*, 2H), 6.17 (*s*, 1H), 7.14 (*d*, *J*=8.6 Hz,2 H), 7.24 (*dd*, *J*=8.8, 2.4 Hz, 1H), 7.29-7.46 (*m*,6H),7.53 (*d*, *J*=9.0 Hz, 1H), 7.73 (*d*, *J*=8.6 Hz,2 H), 11.38 (*s*, 1H); Anal. Calcd for $C_{24}H_{22}N_2O_2$; C,77.81; H,5.99; N,7.56.

2-(4-(Benzyloxy)-3-methoxyphenyl)-6-morpholinoquinolin-4-one (122) was obtained from **101**, using the same synthetic procedure as for **113**. The crude product was purified by column

chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **122** as yellow solid.(0.5 g, 1.1 mmol).Yield: 52.1%; mp 300-301 °C; MS (EI, 70 eV): *m/z* 442.2 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.11 (*m*, 4H), 3.74 (*m*, 4H), 5.15 (*s*, 2H), 6.28 (*s*, 1H), 7.16 (*d*, *J*=8.2 Hz, 2H), 7.25-7.45 (*m*, 9H), 7.68 (*d*, *J*=9.0 Hz, 1H), 11.48 (*br*, 1H); Anal. Calcd for $C_{27}H_{26}N_2O_4$; C,72.28; H,5.92; N,6.23.

2-(4-(Benzyloxy)-3-methoxyphenyl)-6-pyrrolidinoquinolin-4-one (123) was obtained from **102**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **123** as yellow solid. (1.3 g, 3.1 mmol).Yield: 65.2%; mp 304-306 °C; MS (EI, 70 eV): *m/z* 426.6 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 1.99 (*m*, 4H), 3.33 (*m*, 4H), 3.89 (*s*, 3H), 5.18 (*s*, 2H), 6.25 (*s*, 1H), 7.02-7.09 (*m*,2H),7.19 (*d*, *J*=8.2 Hz,1H), 7.33-7.45 (*m*,2H), 7.64 (*d*, *J*=8.8Hz, 1H), 11.34 (*s*, 1H); Anal. Calcd for $C_{27}H_{26}N_2O_3$; C,76.03; H,6.14; N,6.57.

2-(Benzo[*d*][1,3]dioxol-4-yl)-6-morpholinoquinolin-4-one (124) was obtained from **103,** using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **124** as yellow solid. (0.5 g, 1.4 mmol).Yield: 52.6%; mp 350-352 °C; MS (EI, 70 eV): *m/z* 350.5 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.16 (*m*, 4H), 3.77 (*m*, 4H), 6.15 (*s*, 2H), 6.43 (*s*, 1H), 7.04 (*d*, *J*=7.8 Hz,1H), 7.09 (*dd*, *J*=7.8,1.8 Hz,1H), 7.28 (*d*, *J*=7.0 Hz,1H), 7.40 (*d*, *J*=2.8 Hz,1H), 7.50 (*dd*, *J*=9.2,2.8 Hz,1H), 7.67 (*d*, *J*=9.2 Hz,1H), 11.54 (*s*, 1H); Anal. Calcd for $C_{20}H_{18}N_2O_4$; C,68.56; H,5.18; N,8.00.

2-(Benzo[*d*][1,3]dioxol-4-yl)-6-pyrrolidinoquinolin-4-one (125) was obtained from **104**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **125** as yellow solid. (0.2 g, 0.6 mmol).Yield: 52.6%; mp 330-332 °C; MS (EI, 70 eV): *m/z* 334.4 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 1.95 (*m*, 4H), 3.16 (*m*, 4H), 6.11 (*s*, 2H), 6.25 (*s*, 1H), 6.96-7.06 (*m*,2H), 7.19(*d*, *J*=6.8 Hz,1H), 7.57 (*d*, *J*=9.0Hz, 1H), 11.39 (*s*, 1H); Anal. Calcd for $C_{20}H_{18}N_2O_3$; C,71.84; H,5.43; N,8.38.

2-(2,3-Dimethoxyphenyl)-6-morpholinoquinolin-4-one (126) was obtained from **105**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **126** as yellow solid. (0.5 g, 1.4 mmol).Yield: 52.5%; mp 235-236 °C; MS (EI, 70 eV): *m/z* 366.5 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.11 (*m*, 4H), 3.60 (*s*, 3H), 3.83 (*m*, 4H), 3.96 (*s*, 3H), 5.98 (*s*, 1H), 6.96 -7.447 (*m*,5H), 7.54 (*d*, *J*=9.6 Hz,1H), 11.63 (*s*, 1H); ^{13}C- NMR (DMSO-d_6, 50 MHz) δ 176.63, 153.13, 147.90, 147.02,

146.66, 134.72, 129.90, 126.00, 124.84, 123.01, 121.98, 119.96, 114.93, 108.72, 107.52, 66.53, 61.13, 56.43, 49.47; Anal. Calcd for $C_{21}H_{22}N_2O_4$; C,68.84; H,6.05; N,7.65.

2-(2,3-Dimethoxyphenyl)-6-pyrrolidinoquinolin-4-one (127) was obtained from **106**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **127** as yellow solid. (0.3 g, 0.9 mmol).Yield: 52.5%; mp 258-260 °C; MS (EI, 70 eV): *m/z* 350.5 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 1.95 (*m*, 4H), 3.23 (*m*, 4H), 3.60 (*s*, 3H), 3.84 (*s*, 3H), 5.92 (*s*, 1H), 6.97 -7.19 (*m*,5H), 7.54 (*d*, *J*=8.4 Hz,1H), 11.48 (*s*, 1H); ^{13}C- NMR (DMSO-d_6, 50 MHz) δ 176.49, 153.13, 146.67, 146.07, 144.85, 132.16, 126.71, 124.78, 122.02, 119.99, 119.12, 114.77, 107.83, 103.18, 61.10, 56.43, 48.11, 25.44; Anal. Calcd for $C_{21}H_{22}N_2O_3$; C,71.98; H,6.33; N,7.99.

2-(2,5-Dimethoxyphenyl)-6-morpholinoquinolin-4-one (128) was obtained from **107**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **128** as yellow solid. (0.7 g, 1.9 mmol).Yield: 61.2%; mp 275-277 °C; MS (EI, 70 eV): *m/z* 366.2 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.14 (*m*, 4H), 3.75 (*m*, 10H), 6.03 (*s*, 1H), 7.03 -7.49 (*m*,5H), 7.67 (*d*, *J*=9.0 Hz,1H), 11.57 (*s*, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz) δ 176.67, 153.49, 150.98, 147.80, 147.00, 134.68, 125.97, 124.87, 122.89, 119.92, 116.57, 113.71, 108.93, 107.46, 66.53, 56.64, 49.45; Anal. Calcd for $C_{21}H_{22}N_2O_4$; C,68.84; H,6.05; N,7.65.

2-(2,5-Dimethoxyphenyl)-6-pyrrolidinoquinolin-4-one (129) was obtained from **108**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **129** as yellow solid. (0.9 g, 0.9 mmol).Yield: 59.2%; mp 272-274 °C; MS (EI, 70 eV): *m/z* 350.2 (M^+); IR (KBr): 1606.77 (C=O), 2978.22 (-NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 1.95 (*m*, 4H), 3.25 (*m*, 4H), 3.71 (*s*, 3H), 3.72 (*s*, 3H), 5.94 (*s*, 2H), 6.99-7.11 (*m*, 5H), 7.49 (*d*, *J*=8.6 Hz,1H), 11.43 (*s*, 1H); Anal. Calcd for $C_{21}H_{22}N_2O_3$; C,71.98; H,6.33; N,7.99.

2-(2-Methoxyphenyl)-6-morpholinoquinolin-4-one (130) was obtained from **109**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **130** as yellow solid. (0.6 g, 1.8 mmol).Yield: 57.5%; mp 262-264 °C; MS (EI, 70 eV): *m/z* 336.5 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.10 (*m*, 4H), 3.74 (*m*, 4H), 3.76 (*s*, 3H), 5.97 (*s*, 1H), 7.05 (*t*, *J*=7.6 Hz,1H), 7.16 (*d*, *J*=8.2 Hz,1H), 7.40-7.54 (*m*, 5H),11.55 (*s*, 1H); ^{13}C- NMR (DMSO-d_6, 50 MHz) δ 176.61, 156.96, 147.79, 147.42, 134.82, 131.73, 130.69, 125.89, 124.39, 122.89, 121.06, 119.97, 112.34, 108.85, 107.44, 66.54, 56.16, 49.48; Anal. Calcd for $C_{20}H_{20}N_2O_3$; C,71.41; H,5.99; N,8.33.

2-(2-Methoxyphenyl)-6-pyrrolidinoquinolin-4-one (131) was obtained from **110**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **131** as yellow solid. (0.7 g, 2.2 mmol).Yield: 62.3%; mp 312-313 °C; MS (EI, 70 eV): *m/z* 320.2 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 1.98 (*m*, 4H), 3.25 (*m*, 4H), 3.77 (*s*, 3H), 5.91 (*s*, 1H), 7.00-7.51(*m*,7H), 11.43 (*s*, 1H); ^{13}C- NMR (DMSO-d_6, 50 MHz) δ 176.58, 156.97, 146.43, 144.75, 132.13, 131.60, 130.69, 126.65, 124.53, 121.04, 119.93, 119.05, 112.33, 108.03, 103.16, 56.15, 48.09, 25.45; Anal. Calcd for $C_{20}H_{20}N_2O_2$; C,74.98; H,6.29; N,8.74.

2-(4-Methoxyphenyl)-6-morpholinoquinolin-4-one (132) was obtained from **111**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **132** as yellow solid. (0.5 g, 1.8 mmol).Yield: 65.9%; mp 302-304 °C; MS (EI, 70 eV): *m/z* 336.2 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 3.10 (*m*, 4H), 3.74 (*m*, 4H), 3.80(*s*, 3H), 6.22 (*s*, 1H), 7.06 (*d*, *J*=8.8 Hz,2H), 7.38 (*d*, *J*=2.4 Hz,1H), 7.43 (*dd*, *J*=9.2,2.8 Hz,1H), 7.64 (*d*, *J*=9.2 Hz,1H), 7.74 (*d*, *J*=8.8 Hz,2H), 11.45 (*s*, 1H); Anal. Calcd for $C_{20}H_{20}N_2O_3$; C,71.41; H,5.99; N,8.33.

2-(4-Methoxyphenyl)-6-pyrrolidinoquinolin-4-one (133) was obtained from **112**, using the same synthetic procedure as for **113**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **133** as yellow solid. (0.4 g, 1.2 mmol).Yield: 74.0%; mp 312-313 °C; MS (EI, 70 eV): *m/z* 320.2 (M^+); Anal. Calcd for $C_{20}H_{20}N_2O_2$; C,74.98; H,6.29; N,8.74.

2-(2-Hydroxyphenyl)-6-morpholinoquinolin-4-one (134). To a suspension of **113** (0.4 g, 1.0 mmol) in MeOH (400 ml) was hydrogenated in the presence of 10%Pd/C (0.1g) at 25□ for 3 h. The catalyst was filtered off and the filtrate was evaporated. The crude product was purified by column chromatography (SiO_2,$CHCl_3$:MeOH=25:1) to give **134** as yellow solid. (0.3g, 0.9 mmol).Yield: 81.5%; mp 290-291 °C; MS (EI, 70 eV): *m/z* 322.2 (M^+); IR (KBr): 1612.56 (C=O), 2969.54 (-NH) cm^{-1}; ^{1}H-NMR (MeOD-d_4, 400 MHz) δ 3.30 (*m*, 4H), 3.87 (*m*, 4H), 4.48 (*s*, 1H), 6.64 (*s*, 1H), 7.02 (*d*, *J*=8.8 Hz, 1H), 7.04 (*d*, *J*=8.8 Hz, 1H), 7.40 (*t*, *J*=8.0 Hz, 1H), 7.60 (*d*, *J*=8.8 Hz, 2H), 7.65 (*d*, *J*=2.0 Hz, 1H), 7.72 (*d*, *J*=9.2 Hz, 1H); Anal. Calcd for $C_{19}H_{18}N_2O_3$; C,70.79; H,5.63; N,8.69.

2-(2-Hydroxyphenyl)-6-pyrrolidinoquinolin-4-one (135) was obtained from **114**, using the same synthetic procedure as for **134**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **135** as yellow solid. (0.2 g, 0.7 mmol).Yield: 86.6%; mp 304-306 °C; MS (EI, 70 eV): *m/z* 306.2 (M^+); IR (KBr): 1612.56 (C=O), 2969.54 (-NH) cm^{-1}; ^{1}H-NMR (MeOD-d_4, 400 MHz): δ 3.25 (*m*, 4H), 3.87 (*m*, 4H), 6.29 (*s*, 1H), 6.87 (*d*, *J*=3.2

Hz,1H), 6.91 (*dd*, *J*=8.8, 3.2 Hz, 1H), 7.03 (*d*, *J*=8.8 Hz,1H), 7.45 (*d*, *J*=2.8 Hz,1H), 7.48 (*dd*, *J*=9.2, 2.8 Hz, 1H), 7.61 (*d*, *J*=9.2 Hz, 1H), 9.45 (*br*, 1H), 11.72 (*br*, 1H); Anal. Calcd for $C_{19}H_{18}N_2O_2$; C,74.49; H,5.92; N,9.14.

2-(2-Hydroxyphenyl)-6-dimethylaminoquinolin-4-one (136) was obtained from **115**, using the same synthetic procedure as for **134**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **136** as yellow solid. Yield: 86.6 %; mp 296-298 °C; MS (EI, 70 eV): *m/z* 280.1 (M^+); IR (KBr): 1597.13 (C=O), 2908.78 (-NH) cm^{-1}; ^{1}H-NMR (MeOD-d_4, 200 MHz) δ 3.02 (*s*, 6H), 6.56 (*s*, 1H), 6.92-6.99 (*m*, 2H), 7.27-7.38 (*m*, 3H), 7.50 (*dd*, *J*=8.2, 1.8 Hz,1H), 7.60 (*d*, *J*=8.2 Hz,1H); Anal. Calcd for $C_{17}H_{16}N_2O_2$; C,72.84; H,5.75; N,9.99.

2-(3-Hydroxyphenyl)-6-morpholinoquinolin-4-one (137) was obtained from **116**, using the same synthetic procedure as for **134**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **81a** as yellow solid. (0.3 g, 0.9 mmol).Yield: 89.7%; mp 357-360 °C; MS (EI, 70 eV): *m/z* 322.2 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 3.13 (*m*, 4H), 3.75 (*m*, 4H), 6.20 (*s*, 1H), 6.81 (*d*, *J*=7.8 Hz,1H), 7.15-7.22 (*m*,2H), 7.33 (*d*, *J*=7.8 Hz,1H),7.43 (*d*, *J*=2.6Hz, 1H), 7.48 (*dd*, *J*=9.0,2.6 Hz, 1H), 7.69 (*d*, *J*=9.0 Hz,1H), 9.86 (*s*, 1H), 11.56 (*s*, 1H); ^{13}C- NMR (DMSO-d_6, 50 MHz) δ 176.78, 158.20, 149.47, 147.95, 136.28, 134.96, 130.59, 125.97, 122.95, 120.39, 118.36, 117.63, 114.38, 107.24, 106.22, 66.52, 49.32, 43.47; Anal. Calcd for $C_{19}H_{18}N_2O_3$; C,70.79; H,5.63; N,8.69.

2-(3-Hydroxyphenyl)-6-pyrrolidinoquinolin-4-one (138) was obtained from **117**, using the same synthetic procedure as for **134**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **138** as yellow solid. (0.14 g, 0.45 mmol).Yield: 90.9%; mp 364-367 °C; MS (EI, 70 eV): *m/z* 306.3 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 1.80 (*m*, 4H), 3.29 (*m*, 4H), 6.14 (*s*, 1H), 6.92 (*d*, *J*=7.0 Hz,1H), 7.02 (*d*, *J*=7.0 Hz,1H), 7.09 (*dd*, *J*=9.2,2.4 Hz, 1H), 7.15-7.21 (*m*, 2H), 7.34 (*t*, *J*=7.8 Hz, 1H), 7.65 (*d*, *J*=9.2 Hz,1H), 9.84 (*s*, 1H), 11.46 (*s*, 1H); ^{13}C- NMR (DMSO-d_6, 50 MHz) δ 176.78, 158.20, 149.47, 147.95, 136.28, 134.96, 130.59, 125.97, 122.95, 120.39, 118.36, 117.63, 114.38, 107.24, 106.22, 66.52, 49.32, 43.47; Anal. Calcd for $C_{19}H_{18}N_2O_2$; C,74.49; H,5.92; N,9.14.

2-(3-Hydroxyphenyl)-6-dimethylaminoquinolin-4-one (139) was obtained from **118**, using the same synthetic procedure as for **134**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **139** as yellow solid. (0.4 g, 1.4 mmol).Yield: 75.6%; mp 342-344 °C; MS (EI, 70 eV): *m/z* 280.1 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 2.93 (*s*, 6H), 6.23 (*s*, 1H), 6.92 (*d*, *J*=8.0 Hz,1H),7.16-7.35 (*m*, 6H), 7.70 (*d*, *J*=9.2 Hz,1H), 9.93 (*s*, 1H), 11.46 (*s*, 1H); ^{13}C- NMR (DMSO-d_6, 50 MHz) δ 175.86, 158.25, 148.99, 147.63, 136.34,

133.33, 130.52, 126.09, 120.64, 120.22, 118.32, 117.58, 114.39, 105.55, 103.94, 38.69; Anal. Calcd for $C_{17}H_{16}N_2O_2$; C,72.84; H,5.75; N,9.99.

2-(4-Hydroxyphenyl)-6-morpholinoquinolin-4-one (140) was obtained from **119**, using the same synthetic procedure as for **134**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **140** as yellow solid. (0.1 g, 0.3 mmol).Yield: 64.5%; mp 340-342 °C; MS (EI, 70 eV): *m/z* 322.2 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 3.16 (*m*, 4H), 3.74 (*m*, 4H), 6.24 (*s*, 1 H), 6.95 (*d*, *J*=8.6 Hz,2H), 7.40 (*d*, *J*=2.6 Hz,1H), 7.45 (*dd*, *J*=9.0,2.6 Hz,1H), 7.69 (*d*, *J*=9.0 Hz,3H), 10.05 (*s*, 1H), 11.50 (br *s*, 1H); ^{13}C- NMR (DMSO-d_6, 50 MHz) δ 176.38, 159.90, 149.38, 147.81, 135.04, 129.15, 125.76, 125.31, 122.78, 120.23, 116.18, 107.35, 105.34, 66.54, 49.37; Anal. Calcd for $C_{19}H_{18}N_2O_3$; C,70.79; H,5.63; N,8.69.

2-(4-Hydroxyphenyl)-6-pyrrolidinoquinolin-4-one (141) was obtained from **120**, using the same synthetic procedure as for **134**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **141** as yellow solid. (0.1 g, 0.7 mmol).Yield: 64.9%; mp 304-306 °C; MS (EI, 70 eV): *m/z* 306.3 (M^+); IR (KBr): 1613.52 (C=O), 3132.53 (-NH), 3438.26 (-OH) cm^{-1}; ^{1}H-NMR (DMSO-d_6,400 MHz) δ 2.02 (*m*, 4H), 3.37 (*m*, 4H), 6.93 (*s*, 1H), 7.04 (*d*, *J*=8.4 Hz, 2H), 7.42 (*dd*, *J*=9.2, 2.0 Hz, 1H), 7.76 (*d*, *J*=8.4 Hz, 1H), 7.83 (*d*, *J*=8.4 Hz, 2H), 8.14 (*d*, *J*=9.2 Hz,1H), 10.48 (*s*, 1H); Anal. Calcd for $C_{19}H_{18}N_2O_2$; C,74.49; H,5.92; N,9.14.

2-(4-Hydroxyphenyl)-6-dimethylaminoquinolin-4-one (142) was obtained from **121**, using the same synthetic procedure as for **134**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **142** as yellow solid. Yield: 74.2 %; mp 321-323 °C; MS (EI, 70 eV): *m/z* 280.1 (M^+); IR (KBr): 1617.38 (C=O), 3132.53 (-NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 3.03 (*s*, 6H), 7.01 (*d*, *J*=8.6 Hz, 2H), 7.08 (*d*, *J*=2.8 Hz, 1H), 7.40 (*d*, *J*=6.0 Hz, 1H), 7.64 (*dd*, *J*=9.4, 2.6 Hz,1H), 7.84 (*d*, *J*=8.8 Hz, 2H), 8.22 (*d*, *J*=9.4 Hz, 1H), 11.30 (*br*, 1H), 14.35 (*br*, 1H); Anal. Calcd for $C_{17}H_{16}N_2O_2$; C,72.84; H,5.75; N,9.99.

2-(4-Hydroxy-3-methoxyphenyl)-6-morpholinoquinolin-4-one (143) was obtained from **122**, using the same synthetic procedure as for **134**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **143** as yellow solid. (0.15 g, 0.3 mmol).Yield: 63.0%; mp 297-299 °C; MS (EI, 70 eV): *m/z* 352.1 (M^+); ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 3.15 (*m*, 4H), 3.77 (*m*, 4H), 3.88(*s*, 3H),6.28 (*s*, 1H), 6.92 (*d*, *J*=8.2 Hz,1H), 7.27 (*dd*, *J*=8.2,1.8 Hz,1H),7.33 (*d*, *J*=1.8 Hz, 1H), 7.43 (*d*, *J*=2.6 Hz, 1H), 7.47 (*dd*, *J*=8.8,2.6 Hz, 1H), 7.67 (*d*, *J*=8.8 Hz,1H), 9.60 (*s*, 1H), 11.40 (*s*, 1H); ^{13}C- NMR (DMSO-d_6, 50 MHz) δ 176.85, 149.22, 148.29, 147.75, 137.15, 134.84, 125.98, 125.64, 122.71, 120.63, 120.00,

116.13, 111.65, 107.50, 105.68, 66.55, 56.31, 49.37; Anal. Calcd for $C_{20}H_{20}N_2O_4$; C,68.17; H,5.72; N,7.95.

2-(4-Hydroxy-3-methoxyphenyl)-6-pyrrolidinoquinolin-4-one (144) was obtained from **123**, using the same synthetic procedure as for **134**. The crude product was purified by column chromatography (silica gel, $CHCl_3$:MeOH=25:1) to give **144** as yellow solid. Yield: 63.7 %; mp 310-312 °C; MS (EI, 70 eV): *m/z* 336.2 (M^+); IR (KBr): 1605.81 (C=O), 3163.39 (-NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ 2.04 (*m*, 4H), 3.25 (*m*, 4H), 3.85 (*s*, 3H), 6.19 (*s*, 1H), 6.89 (*d*, *J*=8.2 Hz, 1H), 6.98 (*d*, *J*=2.6 Hz, 1H), 7.03 (*dd*, *J*=8.2, 2.6 Hz, 1H), 7.22 (*dd*, *J*=8.8, 2.6 Hz, 1H), 7.30 (*d*, *J*=2.6 Hz, 1H), 7.61 (*d*, *J*=8.8 Hz, 1H), 9.53 (*s*, 1H), 11.27 (*s*, 1H); Anal. Calcd for $C_{20}H_{20}N_2O_3$; C,71.41; H,5.99; N,8.33.

Dibenzyl 3-(4-oxo-6-(pyrrolidin-1-yl)-1,4-dihydroquinolin-2-yl)phenyl phosphate (146). To a stirred solution of **138** (0.61 g, 2.0 mmol) in dry THF (20 mL) was added NaH (500 mg, 12.5 mmol) at 0 ± 1 °C. After the mixture was stirred for 1 h, tetrabenzyl pyrophosphate (**46**) (2.15 g, 4.0 mmol) was added and stirring was continued for 30 min. The reaction mixture was filtered and washed with CH_2Cl_2. The filtrate was concentrated under vacuum at a temperature below 30 °C to give crude product (**145**). Then, the crude product in anhydrous MeOH (50 mL) was stirred at 25 °C for 24 h. The precipitates were collected and purified by column chromatography (SiO_2, CH_2Cl_2: EtOAc = 3:7) to give **146** (0.37 g, 0.65 mmol). Yellow solid; yield: 32.7 %; mp 169–171 °C; MS (ESI): *m/z* 567.4 $(M + H)^+$; ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.97 (*m*, 4H), 3.27 (*m*, 4H), 5.04 (*s*, 2H), 5.09 (*s*, 2H), 6.39 (*s*, 1H), 6.93 (*dd*, *J*=9.0, 2.6 Hz, 1H), 7.05 (*d*, *J*=7.8 Hz, 1H), 7.19-7.46 (*m*, 14H), 7.52 (*d*, *J*=8.8 Hz, 1H); Anal. ($C_{33}H_{31}N_2O_5P$) C, H, N.

3-(4-Oxo-6-(pyrrolidin-1-yl)-1,4-dihydroquinolin-2-yl)phenyl dihydrogen phosphate (147). A suspension of **146** (200 mg, 0.36 mmol) in anhydrous MeOH (10 mL) was hydrogenated in the presence of 10% Pd/C (100 mg) at 25 °C for 20 min. The catalyst and precipitate were collected and dissolved in 10% $NaHCO_3$ solution and then filtered. The filtrate was acidified with dil aq HCl and the precipitate was then collected and washed with acetone to give **147** (97 mg, 0.25 mmol). Yellow solid; yield: 69.8 %; mp >300 °C; MS(ESI): *m/z* 387.1 $(M + H)^+$; ^{1}H-NMR (D_2O + NaOD, 200 MHz): δ 1.78 (*m*, 4H), 3.08 (*m*, 4H), 6.70 (*s*, 1H), 7.12–7.20 (*m*, 3H), 7.28 (*t*, *J* = 7.8 Hz, 1H), 7.40 (*d*, *J*=7.6 Hz, 1H), 7.49 (*s*, 1H), 7.61 (*d*, *J*=9.8 Hz, 1H); Anal. ($C_{19}H_{19}N_2O_5P$) C, H, N.

II-2. Anticancer activity

In vitro test

HL-60, Hep 3B, H460, MES-SA, MES-SA/D x5 and Detroit 551 cells were treated with vehicle or test compounds for 48 h. The cell growth rate was determined by MTT (3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyltetrazolium bromide) reduction assay. After 48 h incabution, the cell growth rate was measured by scanning with an ELISA reader with a 570 nm filter and the IC_{50} values of test compounds were calculated.

Results

The B-1 series of compounds has the following formula:

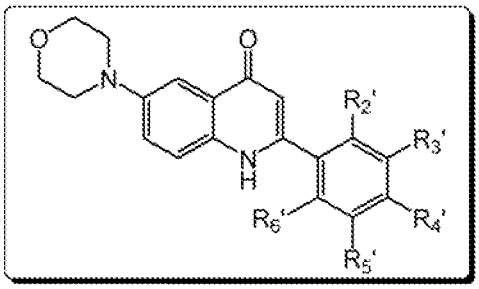


Table 2 shows the B-1 series of compounds inhibited proliferation of human cancer cells.

Table 2

					$IC_{50}(\mu M)$						
Cpd	R_2'	R_3'	R_4'	R_5'	HL-60	Hep 3B	H460	MES-SA	MES-SA/Dx5	Ratio Of SA/Dx5	Detroit 551
124	OCH_2O		H	H	0.72	1.5	2.13	2.35	2.1	0.89	>2.5
126	OCH_3	OCH_3	H	H	5.22	9.8	17.45	5.0	17.465	3.49	>50
128	OCH_3	H	H	OCH_3	1.2	3.11	3.47	2.03	8.205	4.04	16.6
130	OCH_3	H	H	H	2.48	NA	7.36	2.5	9.708	3.88	>20
132	H	H	OCH_3	H	> 2.5	> 2.5	> 2.5	NA	NA	NA	> 2.5
134	OH	H	H	H	2.1	8.78	8.3	2.38	10.419	4.38	>100
137	H	OH	H	H	0.23	11.5	24.8	3.61	7.3	2.02	10
140	H	H	OH	H	1.64	>10	>10	NA	NA	NA	> 10
143	H	OCH_3	OH	H	3.9	50	50	NA	NA	NA	50
143a	OCH_3	H	H	OH	93.8	>100	84.8	NA	NA	NA	> 100
143b	OH	H	H	OH	56.2	59.32	> 100	NA	NA	NA	> 100

*: Cancer cell were treated with test compound for 48 hrs.

The B-2 series of compounds has the following formula:

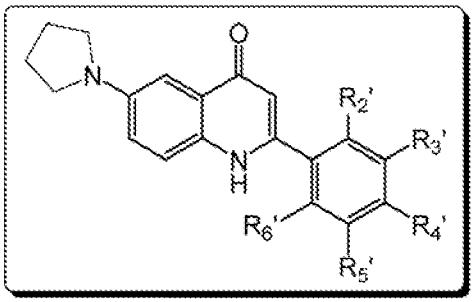


Table 3 shows the B-2 series of compounds inhibited proliferation of human cancer cells.

Table 3

					$IC_{50}(\mu M)$						
Cpd.	R_2'	R_3'	R_4'	R_5'	HL-60	Hep 3B	H460	MES-SA	MES-SA/Dx5	Ratio Of SA/Dx5	Detroit 551
125	OCH_2O		H	H	0.08	0.2	0.2	0.1	0.183	1.83	>2.5
127	OCH_3	OCH_3	H	H	0.53	1.2	1.78	0.802	1.71	2.13	>20
129	OCH_3	H	H	OCH_3	0.006	0.22	0.19	0.229	0.216	0.94	5.0
131	OCH_3	H	H	H	0.13	0.3	0.57	0.445	0.451	1.01	>10
133	H	H	OCH_3	H	> 1.0	> 1.0	> 1.0	NA	NA	NA	> 1.0
135	OH	H	H	H	0.36	1.31	0.86	0.846	1.0	1.18	25
138	H	OH	H	H	0.009	0.28	0.4	0.734	0.32	0.23	1.39
141	H	H	OH	H	0.04	1.1	1.56	NA	NA	NA	> 25
144	H	OCH_3	OH	H	0.038	0.38	0.56	NA	NA	NA	> 2.5
144a	OCH_3	H	H	OH	1.62	7.38	6.5	3.69	25	6.78	9.1
144b	OH	H	H	OH	NA	NA	NA	NA	NA	NA	NA

*: Cancer cell were treated with test compound for 48 hrs.

The B-3 series of compounds has the following formula:

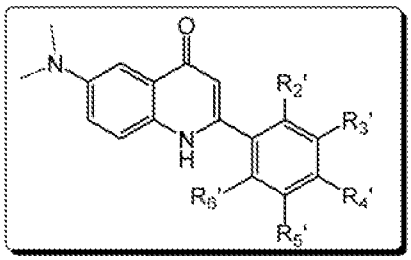


Table 4 shows the B-3 series of compounds inhibited proliferation of human cancer cells.

Table 4

					$IC_{50}(\mu M)$						
Cpd.	R_2'	R_3'	R_4'	R_5'	HL-60	Hep 3B	H460	MES-SA	MES-SA/Dx5	Ratio Of SA/Dx5	Detroit 551
136	OH	H	H	H	3.02	7.1	5.4	NA	NA	NA	100
139	H	OH	H	H	0.06	1.0	6.2	0.931	0.852	0.92	10
142	H	H	OH	H	0.64	9.0	0.56	NA	NA	NA	75

*: Cancer cell were treated with test compound for 48 hrs.

In vivo antitumor activity assay

The Hep-3B tumor cell line was purchased from American Type Culture Collection (ATCC HB-8064, human ovarian carcinoma cells). A culture medium of 90% DMEM, 10% Fetal Bovine Serum, supplemented with 1% penicillin-streptomycin, was used. The tumor cells were incubated in an atmosphere containing 5% CO_2 at 37 °C.

Balb/c Nude mice used in this study were male, 4 ~ 6 weeks age, weighing 18 ~ 20 g and provided by National Animal Center. All animals were housed in individually ventilated cages racks (IVC Racks, 36 Mini Isolator system) under specific pathogen-free (SPF) conditions throughout the experiment. Each cage (in cm, 26.7 length × 20.7 width × 14.0 height) was sterilized with autoclave and contained eight mice. The animals were maintained in a hygienic environment under controlled temperature (20 ~ 24 °C) and humidity (40% ~ 70%) with a 12 hour light/dark cycle. The animals were given free access to sterilized lab chow and sterilized distilled water *ad libitum*. All aspects of this work, i.e., housing, experimentation and disposal of animals, were performed in general accordance with the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, D. C., 1996).

In the xenograft tumor model of human ovarian carcinoma cell lines (Hep-3B, ATCC HB-8064) in male Balb/c Nude mice, compound **147** prepared in 9 % (w/v) $NaHCO_3$ solution at doses of 7.5, 15 and 30 mg/kg (iv or po, qd) was administered five days per week for four consecutive weeks and ceased at Day28. The tumor size and body weight were monitored and recorded for 28 days. Human ovarian carcinoma cells (HEP-3B, ATCC HB-8064) with 2×10^6 cells in 0.1 mL were injected subcutaneously into the right flank of the mice. When the tumor growth reached >100 mm^3 in volume (assumed as day 0), the tumor-bearing animals were assigned into several groups (six animals in each group) for study.

The body weight and tumor size were measured and recorded every seven days during the experiment periods of 28 days. Tumor volume (mm^3) was estimated according to the formula of length × $(width)^2$ × 0.5 in mm^3. Tumor growth inhibition was calculated as T/C (treatment/control) by the following formula: T/C = (Tn – T0)/(Cn – C0) x 100% (T0: Tumor volume of treated group in Day 0; Tn: Tumor volume of treated group in Day n; C0: Tumor volume of control group in Day 0; Cn: Tumor volume of control group in Day n).

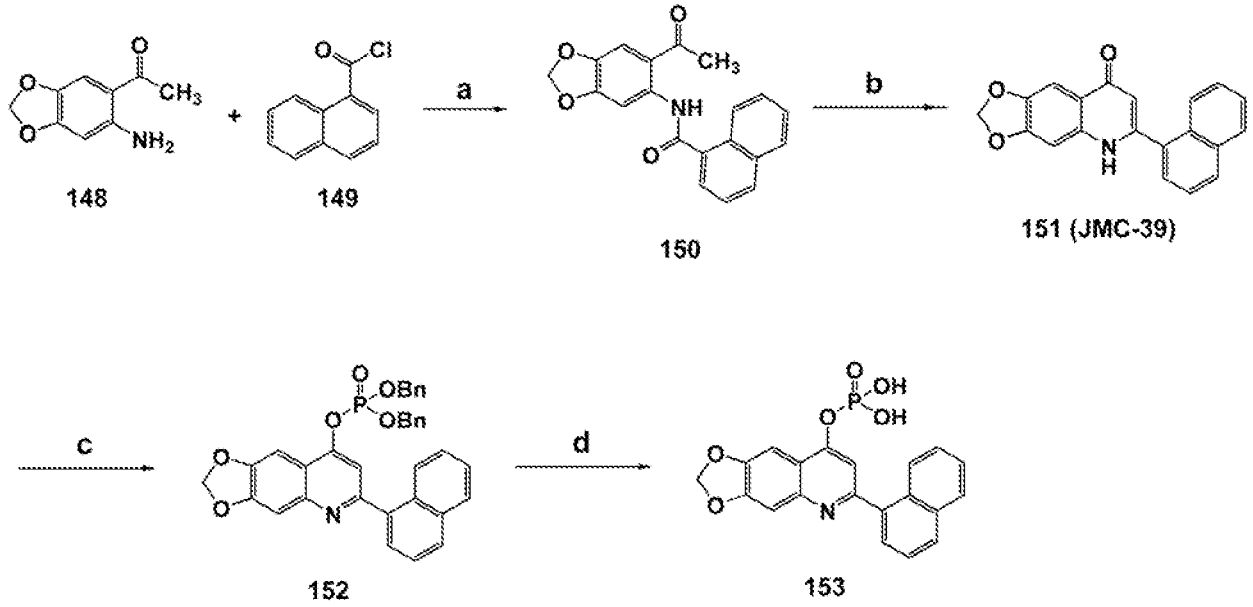
Results

The monophosphate (**147**) of **138** was evaluated in the Hep3B xenograft nude mice model by oral route (po) at dosages of 7.5, 15 and 30 mg/kg/day. As shown by the results in FIG. 6 (A–C), compound **147** induced dose- and time-dependent inhibition of Hep3B tumor growth. At the 7.5 mg/kg dose, the Hep3B inhibitory activity of **147** was found to exceed that of 10 mg/kg doxorubicin, and at the 30 mg/kg dose of **147**, the weight of Hep3B tumor was reduced to 26.3% of that of the control (FIG. 6B). During the course of antitumor evaluation, no significant body weight changes were detected in either the tested or the control group (FIG. 6C). Comparison of the antitumor activity of **147** administered through two different routes showed that the iv route yielded slightly greater activity than the po route (FIG. 7A~7C).

III. C series

Chemical synthesis

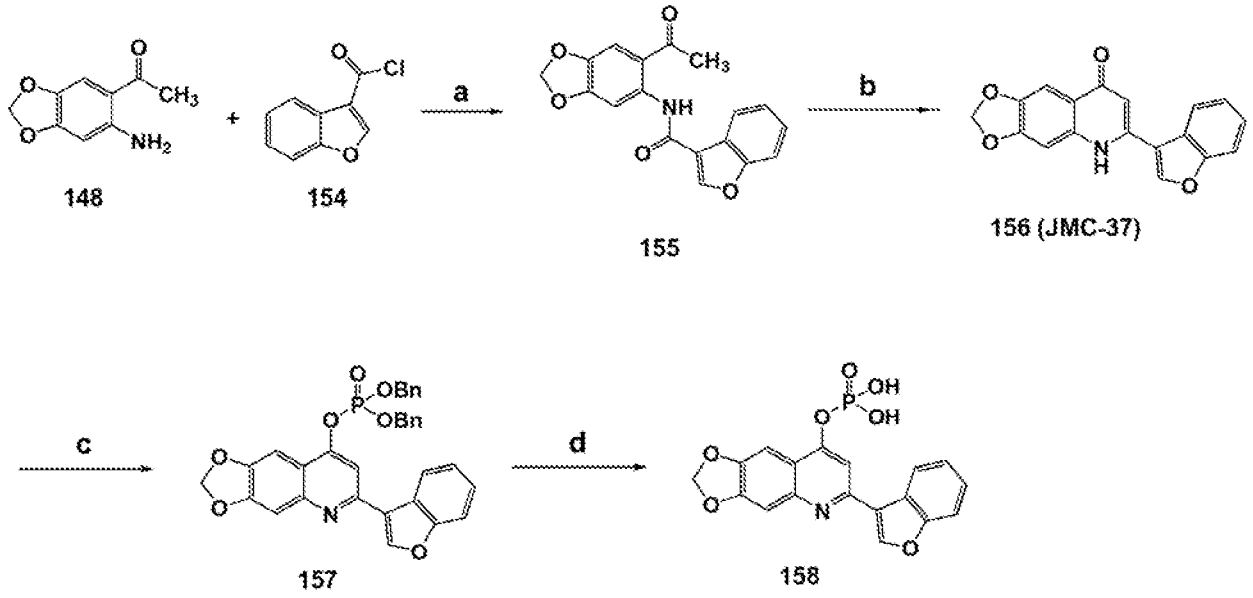
The synthetic procedure of target compounds **153** is illustrated in Scheme 11. The starting 2-amino-4,5-methylenedioxy-acetophenone (**148**) was first reacted with naphthalene-1-carbonyl chloride (**149**) to give *N*-(6-Acetyl-1,3-benzodioxol-5-yl)naphthalene-1-carboxamide (**150**). Then, the intermediate (**150**) was subjected to cyclization in dioxane, in the presence of NaOH, to afford 2-(1-Naphthalenyl)-6,7-methylenedioxyquinolin-4-one (**151**). Compound **151** was first reacted with tetrabenzylpyrophosphate in THF, in the presence of NaH, to yield Dibenzyl 2-(1-naphthalenyl)-6,7-methylenedioxyquinolin-4-yl Phosphate (**152**). Compound **152** was then subjected to catalytic hydrogenation in MeOH to give its diphosphoric acid (**153**).



Reagents and conditions: (a) toluene/triethylamine, 22-25 °C; (b) *t*-BuOK/*t*-BuOH, reflux; (c) tetrabenzyl pyrophosphate, NaH/THF;(d) H_2, Pd/C, MeOH

Scheme 11

The synthetic procedure of target compounds **158** is illustrated in Scheme 12. The starting 2-amino-4,5-methylenedioxy acetophenone (**148**) was first reacted with benzo[*b*]furan-3-carbonyl chloride (**154**) to give *N*-(6-Acetyl-1,3-benzodioxol-5-yl)-1-benzofuran-3-carboxamide (**155**). Then, the intermediates (**155**) was subjected to cyclization in dioxane, in the presence of NaOH, to afford 2-(3-Benzo[*b*]furyl)-6,7-methylenedioxyquinolin-4-one (**156**). Compound **156** was first reacted with tetrabenzylpyrophosphate in THF, in the presence of NaH, to yield dibenzyl 2-(3-benzo[*b*]furyl)-6,7-methylenedioxyquinolin-4-yl phosphate (**157**). Compound **157** was then subjected to catalytic hydrogenation in MeOH to give its diphosphoric acid (**158**).



Reagents and conditions: (a) toluene/triethylamine, 22-25 °C; (b) *t*-BuOK/*t*-BuOH, reflux; (c) tetrabenzyl pyrophosphate, NaH/THF;(d) H_2, Pd/C, MeOH

Scheme 12

Examples

General Experimental Procedures. All of the reagents and solvents were obtained commercially and used without further purification. Reactions were monitored by thin-layer chromatography, using Merck plates with fluorescent indicator (TLC Silica gel 60 F_{254}). The following adsorbent was used for column chromatography: silica gel 60 (Merck, particle size 0.063-0.200 mm). Melting points were determined on a Yanaco MP-500D melting point apparatus and were uncorrected. IR spectra were recorded on Shimadzu IRPrestige-21 spectrophotometers as KBr pellets. NMR spectra were obtained on a Bruker Avance DPX-200 FT-NMR spectrometer in $CDCl_3$ or DMSO. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet and m, multiplet. EI-MS spectra were measured with an HP 5995 GC–MS instrument. ESI-MS spectra were measured with a Finnigan LCQ ion-trap mass spectrometer (TSQ

Quantum, Thermo Finnigan Corporation, San Jose, CA). Elemental analyses (C, H, and N) were performed on a Perkin-Elmer 2400 Series II CHNS/O analyzer, and the results were within ±0.4% of the calculated values.

***N*-(6-Acetyl-1,3-benzodioxol-5-yl)naphthalene-1-carboxamide (150).** Into solutions of **149** (5.0 mmol) in 200 mL of dry toluene were added triethylamine (4 mL) and 2-amino-4,5-methylenedioxy acetophenone (**148**) (5 mmol). The mixtures were stirred at 20 ± 2 °C for 24 h and then evaporated. The residues were washed with acetone and EtOH and then recrystallized from acetone or EtOH to form **150**. Obtained as a grayish-white solid; mp 143-144 °C; ESI-MS (Positive mode): *m/z* 334 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6, δ): 2.59 (3H, s), 6.20 (2H, s), 7.60-7.68 (4H, m), 7.87 (1H, d, *J* = 7.2Hz), 8.05-8.07 (1H, m), 8.15 (1H, d, *J* = 8.0 Hz), 8.33-8.38 (2H, m), 12.52 (1H, s); IR (KBr): 1647, 1672 (C=O) cm^{-1}.

2-(1-Naphthalenyl)-6,7-methylenedioxyquinolin-4-one (151). Into a suspension of **150** (2.95 mmol) in *t*-butyl alcohol (100 mL) was added potassium *t*-butoxide (1.66 g, 14.7 mmol). The mixture was refluxed under argon for 12 h, cooled, and poured into a 10% ammonium chloride solution (100 mL). The solid precipitate was collected and washed with EtOH. The crude product was purified by flash chromatography (silica gel, CH2Cl2:EtOH 16:1-10:1). Yield 52% from **150** as a grayish-white solid; mp >350 °C; ESI-MS (Positive mode): *m/z* 316 $[M+H]^+$; ^{1}H-NMR(DMSO-d_6, δ): 6.08 (1H,s), 6.15 (2H, s), 7.03 (1H, s), 7.46 (1H, s), 7.56-7.63 (2H, m),7.63-7.70 (2H, m), 7.83 (1H, d, *J* = 7.6 Hz), 8.06 (1H, d, *J* =7.6 Hz), 8.11 (1H, d, *J*=7.6 Hz), 11.90 (1H, s). IR (KBr): 1653(C=O) cm^{-1}; Anal. Calcd for $C_{20}H_{13}NO_3$: C, 76.18; H, 4.16; N, 4.44. Found: C, 75.60; H, 3.94; N, 4.29.

Dibenzyl 2-(1-naphthalenyl)-6,7-methylenedioxyquinolin-4-yl Phosphate (152). A suspension of **151** (1.20 g, 3.81 mmol) in anhydrous MeOH (10 mL) was stirred at 25 °C for 24 h. The precipitates were collected and purified by silica gel column chromatography eluted by *n*-hexane and EtOAc to give **152**. Orange oil; yield: 63.7%; ESI-MS (Positive mode): *m/z* 576 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 5.21 (4H, dd, *J* = 8.30, 8.15 Hz), 6.17 (2H, s), 7.23 (1H, s), 7.28-7.37 (9H, m), 7.40-7.60 (7H, m), 7.95 (2H, m), 8.09 (1H, d, *J* = 8.20 Hz).

2-(1-Naphthalenyl)-6,7-methylenedioxyquinolin-4-yl Dihydrogen Phosphate (153). A suspension of **152** (894.8 mg, 1.55 mmol) in anhydrous MeOH (40 mL) was hydrogenated in the presence of 10% Pd/C (456.7 mg) at 25 °C for 15 min. The catalyst and precipitate were collected and dissolved in 10% $NaHCO_3$ solution and then filtered. The filtrate was acidified with dil aq HCl and the precipitate was then collected and washed with acetone to give **153**.Yellow solid; yield: 94.1%; ESI-MS (Negative mode): *m/z* 394 $[M-H]^-$; ^{1}H-NMR (D_2O + NaOD, 500 MHz): δ 6.13 (2H, s), 7.26 (1H, s), 7.50 (1H, ddd, *J* = 8.23, 7.33, 1.20 Hz),

7.55-7.58 (2H, m), 7.62-7.70 (3H, m), 7.98 (1H, d, J=8.53 Hz), 8.02 (1H, d, J=8.96 Hz); ^{13}C-NMR (D_2O + NaOD, 125 MHz): δ 98.65, 102.15, 103.54, 109.80, 110.00, 118.35, 125.66, 126.37, 126.84, 127.40, 128.34, 128.97, 130.89, 133.50, 138.15, 146.58, 147.34, 151.27, 158.15, 158.23.

***N*-(6-Acetyl-1,3-benzodioxol-5-yl)-1-benzofuran-3-carboxamide (155).** Into solutions of **154** (5.0 mmol) in 200 mL of dry toluene were added triethylamine (4 mL) and 2-amino-4,5-methylenedioxy acetophenone (**148**) (5 mmol). The mixtures were stirred at 20 ± 2 °C for 24 h and then evaporated. The residues were washed with acetone and EtOH and then recrystallized from acetone or EtOH to form **155**. Obtained as a pale-yellow solid; mp 144-145°C; ESI-MS (Positive mode): m/z 324 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.63 (3H, s), 6.19 (2H, s),7.41-7.50 (2H, m), 7.68 (1H, s), 7.75 (1H, dd, J = 1.6, 6.8 Hz), 8.15 (1H, dd, J = 2.0, 8.8 Hz), 8.27 (1H, s), 8.71 (1H, s), 12.63 (1H, s); IR (KBr): 1635, 1677 (C=O) cm^{-1}.

2-(3-Benzo[*b*]furyl)-6,7-methylenedioxyquinolin-4-one (156). Into a suspension of **155** (2.95 mmol) in *t*-butyl alcohol (100 mL) was added potassium *t*-butoxide (1.66 g, 14.7 mmol). The mixture was refluxed under argon for 12 h, cooled, and poured into a 10% ammonium chloride solution (100 mL). The solid precipitate was collected and washed with EtOH. The crude product was purified by flash chromatography (silica gel, CH_2Cl_2: EtOH 16:1-10:1). Obtained as a pale-yellow solid from **155**; yield 17%; mp >315°C; ESI-MS (Positive mode): m/z 306 $[M+H]^+$; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.12 (2H, s), 6.49 (1H, s), 7.13 (1H, s), 7.36-7.45 (3H, m), 7.69 (1H, d, J = 8.0 Hz), 8.14 (1H, s), 8.52 (1H, s); IR (KBr): 1626 (C=O) cm^{-1}; Anal. Calcd for $C_{18}H_{11}NO_4$: C, 70.82; H, 3.63; N, 4.59. Found: C, 70.52; H, 3.95; N, 4.21.

Dibenzyl 2-(3-benzo[*b*]furyl)-6,7-methylenedioxyquinolin-4-yl Phosphate (157). To a stirred solution of **151** (0.04 g, 0.13 mmol) in dry tetrahydrofuran (40 mL) was added NaH 60% in mineral oil (48.0 mg, 2.0 mmol) at 0 ±1°C. After the mixture was stirred for 1 h, tetrabenzyl pyrophosphate (139.8 mg, 0.26 mmol) was added and stirring was continued for 60 min. The reaction mixture was filtered and washed with tetrahydrofuran. The filtrate was concentrated under vacuum at a temperature below 30 °C. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc) to give **157**. Obtained as a white solid from **156**; yield: 86.8%; ESI-MS (Positive mode): m/z 566 $[M+H]^+$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.24 (4H, dd, J = 9.5, 9.5 Hz), 6.15 (2H, s), 7.16 (1H, s), 7.34-7.42 (12H, m), 7.45 (1H, s), 7.58 (1H, d, J = 9.5 Hz), 7.59 (1H, s), 8.02 (1H, s), 8.47 (1H, d, J = 7.5 Hz); ^{13}C-NMR (D_2O + NaOD, 125 MHz): δ 70.67, 70.63, 97.30, 100.00, 101.87, 105.93, 106.72, 111.48, 116.94, 121.76, 122.62, 123.51, 124.82, 125.66, 128.20, 128.72, 128.96, 134.98, 144.59, 147.92, 148.43, 150.97, 151.43, 153.47, 156.06.

2-(3-Benzo{*b*}furyl)-6,7-methylenedioxyquinolin-4-yl Dihydrogen Phosphate (158). A suspension of **157** (80.1 mg, 0.14 mmol) in anhydrous MeOH (40 mL) was hydrogenated in the presence of 10% Pd/C (40.0 mg) at 25 °C for 15 min. The catalyst and precipitate were collected and dissolved in 10% $NaHCO_3$ solution and then filtered. The filtrate was acidified with dil aq HCl and the precipitate was then collected and washed with acetone to give **158**. Obtained as white solid; yield: 46.3%; ESI-MS (Positive mode): *m/z* 386 $[M+H]^+$, 408 $[M+Na]^+$; ESI-MS (Negative mode): *m/z* 384 $[M-H]^-$; ^{1}H-NMR (D_2O + NaOD, 500 MHz): δ 6.12 (2H, s), 7.32 (1H, s), 7.42 (2H, m), 7.56 (1H, s), 7.63 (1H, d, *J* =8.0 Hz), 7.78 (1H, s), 8.29 (1H, d, *J* =7.0 Hz), 8.40 (1H, s).

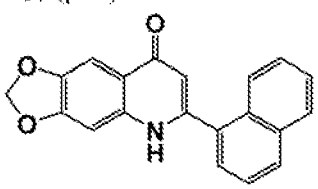
III-2. Anticancer activity

In vitro test

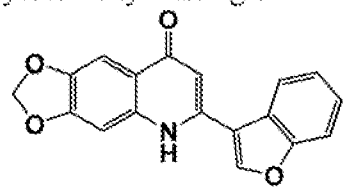
MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assays. HL-60, HCT-116, A549, Hep 3B, KB, Kb-VIN and DU145 cells were treated with tested compounds for the indicated periods. After treatment, cells were washed once with PBS and incubated with MTT (Sigma, St. Louis, MO, USA) for 2 h. The formazan precipitate was dissolved in 150 μL of DMSO, and the absorbance was measured with an ELISA reader at 570 nm.

Results

Table 5 shows IC_{50} (μM) Values from *In Vitro* Cytotoxicity Testing of **151** and **156**.



151 (JMC-39)



156 (JMC-37)

Table 5

Compound	HL-60	HCT-116	A549	Hep 3B	KB	Kb-VIN	DU145
151	0.07	0.07	0.13	0.07	0.13	0.19	0.13
156	0.03	0.05	2.98	0.09	1.05	0.59	1.87

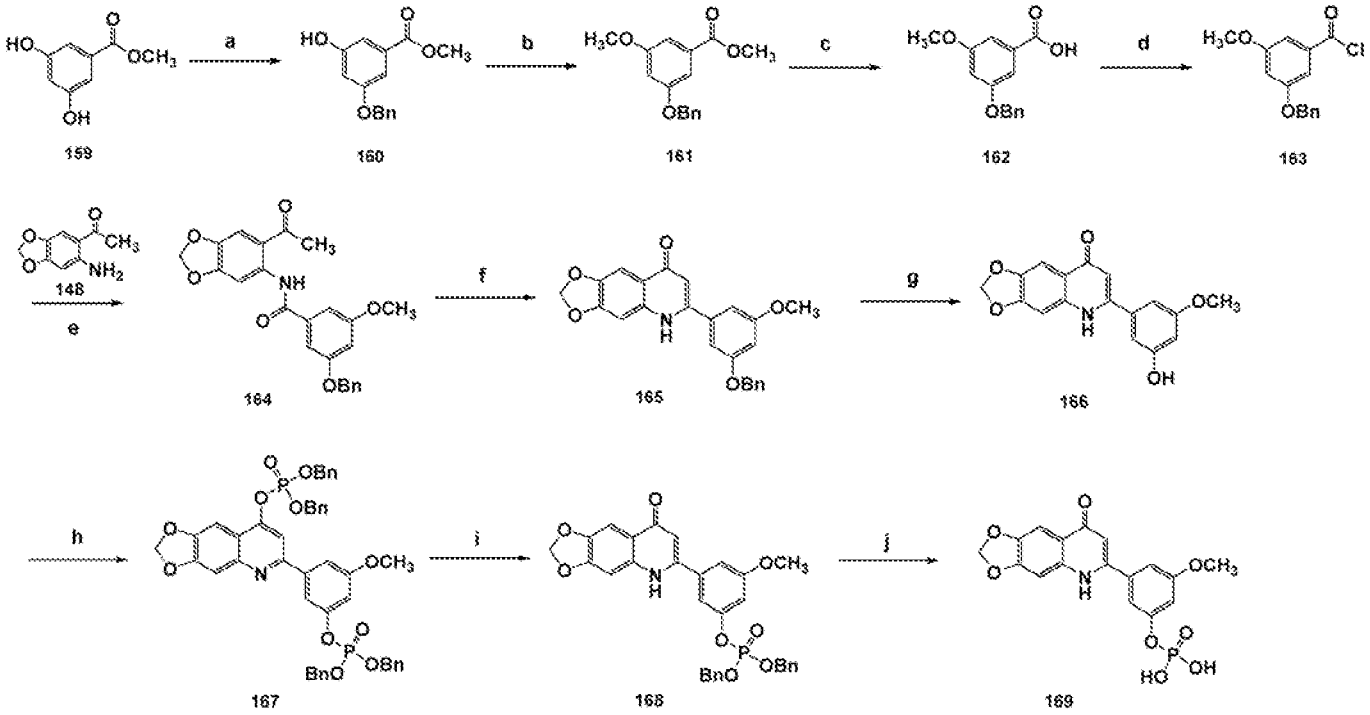
* Not assayed

IV. D series

Chemical synthesis

The compound **159** was derived into a phosphate (**169**) following the synthetic method in Scheme 13. As illustrated, 3-(Benzyloxy)-5-methoxybenzoyl chloride (**163**) obtained from **159** with steps a-d was reacted with 2-amino-4,5-methylenedioxy acetophenone (**148**) in THF/triethylamine,

to give *N*-(6-acetylbenzo[*d*][1,3]dioxol-5-yl)-3-(benzyloxy)-5-methoxybenzamide (**164**). Compound **164** was further refluxed in NaOH/1,4-dioxane to yield **165**. Subsequently, by following the steps g-j, target compound **169** was afforded as white solid.



Reagents and conditions: (a) benzyl bromide, K_2CO_3, acetone; (b) iodomethane, K_2CO_3, acetone; (c) NaOH, H_2O, ethanol; (d) thionyl chloride, dimethyl formamide, toluene;(e) THF/triethylamine, 22-25 °C; (f) NaOH, 1,4-dioxane, reflux; (g) H2, Pd/C, MeOH;(h) tetrabenzyl pyrophosphate, NaH/THF; (i) MeOH, 48hrs; (j) H2, Pd/C, MeOH

Scheme 13

Examples

General Experimental Procedures. All of the reagents and solvents were obtained commercially and used without further purification. Reactions were monitored by thin-layer chromatography, using Merck plates with fluorescent indicator (TLC Silica gel 60 F_{254}). The following adsorbent was used for column chromatography: silica gel 60 (Merck, particle size 0.063-0.200 mm). Melting points were determined on a Yanaco MP-500D melting point apparatus and were uncorrected. IR spectra were recorded on Shimadzu IRPrestige-21 spectrophotometers as KBr pellets. NMR spectra were obtained on a Bruker Avance DPX-200 FT-NMR spectrometer in $CDCl_3$ or DMSO. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet and m, multiplet. EI-MS spectra were measured with an HP 5995 GC–MS instrument. ESI-MS spectra were measured with a Finnigan LCQ ion-trap mass spectrometer (TSQ Quantum, Thermo Finnigan Corporation, San Jose, CA). Elemental analyses (C, H, and N) were performed on a Perkin-Elmer 2400 Series II CHNS/O analyzer, and the results were within ±0.4% of the calculated values.

Methyl 3-(benzyloxy)-5-hydroxybenzoate (160)

A mixture of 8.40 g (0.05 mmol) methyl 3, 5-dihydroxybenzoate (**159**) and 7.60 g (0.055 mmol) of potassium carbonate in 250 mL of acetone was stirred at room temperature for 30 min. Then 8.55 g (0.05 mmol) of benzyl bromide dissolved in 100 mL of acetone was added. The suspension was refluxed for 24 h. The solid was filtered, and the filtrate was evaporated. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/ EtOAc = 9/1) to give **160**.

Obtained as a white solid from methyl 3,5-dihydroxybenzoate (**159**); yield 34%; ^{1}H NMR (400 MHz, $CDCl_3$): δ3.92 (3H, s), 5.05 (2H, s), 6.77 (1H, dd, J = 2.35, 2.20 Hz), 7.13 (1H, s), 7.27-7.28 (2H, m), 7.34-7.45 (5H, m); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 52.34, 70.27, 107.44, 108.08, 109.48, 127.53 (2C), 128.11, 128.60 (2C), 131.99, 136.41, 137.45, 156.80, 160.00.

Methyl 3-(benzyloxy)-5-methoxybenzoate (161)

A suspension of 4.0 g (0.0165 mmol) methyl 3-(benzyloxy)-5-hydroxybenzoate (**160**), 6.84 g (0.0495 mmol) potassium carbonate, and 11.71 g (0.0825 mmol) iodomethane in the 200 mL of acetone was stirred at room temperature for 24 h. After the mixture was filtered and evaporated, the residue was washed with water. The methyl 3-(benzyloxy)-5-methoxybenzoate (**161**) was obtained as a white solid.

Obtained as a white solid from methyl 3-(benzyloxy)-5-hydroxybenzoate (**160**); yield 85%; ^{1}H NMR (200 MHz, $CDCl_3$): δ3.83 (3H, s), 3.92 (3H, s), 5.09 (2H, s), 6.74 (1H, t, J = 2.45 Hz), 7.21 (1H, dd, J = 2.45, 1.22 Hz), 7.29 (1H, dd, J = 2.45, 1.22 Hz), 7.34-7.48 (5H, m); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 52.22, 55.55, 70.24, 106.53, 107.47, 107.98, 127.54, 128.09, 128.59, 131.99, 136.44, 159.75, 160.61.

3-(Benzyloxy)-5-methoxybenzoic acid (162)

4.45 g (0.0174 mmol) of methyl 3-(benzyloxy)-5-methoxybenzoate (**161**) was suspended in 120 mL of 95% ethanol and 5mL water. An amount of 2.00 g (0.05 mmol) of sodium hydroxide was added. The mixture was heated at reflux for 1 h. After the mixture was evaporated, the residue was quenched with 150 mL of water. The solution was neutralized with dil aq HCl and then the precipitate was collected and washed with water and acetone to give **162**.

Obtained as a white solid from methyl 3-(benzyloxy)-5-methoxybenzoate (**161**); yield 90 %; ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.81 (3H, s), 5.09 (2H, s), 6.74 (1H, t, J = 2.45 Hz), 7.25 (1H, dd, J = 2.45, 1.35 Hz), 7.20 – 7.46 (6H, m); ^{13}C-NMR (DMSO-d_6, 50 MHz): δ 55.89, 69.94, 106.19, 107.57, 108.17, 128.12, 128.33, 128.90, 133.34, 137.22, 138.78, 159.88, 160.80, 167.36, 176.99.

3-(Benzyloxy)-5-methoxybenzoyl chloride (163)

3-(Benzyloxy)-5-methoxybenzoic acid (**162**) (2.57 g, 0.01 mmol) and thionyl chloride (4.80g, 0.04 mmol) were suspended in 200 mL of dry toluene. The reaction mixture was stirred for 30 min

and then dimethyl formamide (3 drops) was added. The mixture was stirred for 24 h and then evaporated to dryness. The residue was directly used for the next step without further purification.

***N*-(6-acetylbenzo[*d*][1,3]dioxol-5-yl)-3-(benzyloxy)-5-methoxybenzamide (164)**

Into solutions of **163** (2.77 g, 0.01 mmol) in 200 mL of dry tetrahydrofuran were added triethylamine (10 mL) and 2-amino-4,5-methylenedioxy acetophenone (**148**) (1.79 g, 0.01 mmol). The mixtures were stirred at room temperature for 24 h and then evaporated. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/ EtOAc = 3/1) to give **164**.

Obtained as a grayish white solid from 3-(benzyloxy)-5-methoxybenzoyl chloride (**163**) and 2-amino-4,5-methylenedioxy acetophenone (**148**); yield 75 %; ESI-MS (Positive mode): *m/z* 442 $[M+Na]^+$; ^{1}H NMR (DMSO-d_6, 500 MHz): δ2.64 (3H, s), 3.84 (3H, s), 5.20 (2H, s), 6.19 (2H, s), 6.87 (1H,s), 7.09 (1H, s), 7.16 (1H, s), 7.37 (1H, d, J = 7.43 Hz), 7.43 (1H, t, J = 7.43 Hz), 7.49 (1H, d, J = 7.43 Hz), 7.68 (1H, s), 8.34 (1H, s), 13.06 (1H, s); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ 29.32, 55.99, 70.12, 98.96, 100.77, 102.91, 105.03, 105.67, 106.45, 111.25, 116.53, 128.28, 128.30, 128.95, 136.90, 137.05, 138.27, 143.11, 152.68, 160.28, 161.20, 164.99, 200.00.

2-(3-Benzyloxy-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-one (165)

Into a suspension of **164** (3.33 g, 0.0079 mmol) in 200 mL of 1,4-dioxane was added sodium hydroxide (2.50 g, 0.0635 mmol). The mixture was refluxed for 24 h. After the reaction mixture was evaporated, 100 mL of 10% ammonium chloride solution was added. The mixture was stirred for 12 h, and then the precipitate was collected and washed with water and acetone.

Obtained as a grayish white solid; yield 75 %; mp 235-238°C; ESI-MS (Positive mode): *m/z* 402 $[M+H]^+$; ESI-MS (Negative mode): *m/z* 400 $[M-H]^-$; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.85 (3H, s), 5.22 (2H, s), 6.16 (2H, s), 6.31 (1H, s, br), 6.79 (1H, s), 6.95 (1H, s), 7.04 (1H, s), 7.21 (1H, s), 7.36 -7.50 (6H, m), 11.50 (1H, s, br); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ 56.04, 70.10, 97.72, 101.76, 102.40, 103.14, 105.95, 106.60, 107.15, 110.00, 120.46, 128.25, 128.42, 128.96, 137.27, 137.82, 145.66, 151.57, 160.31, 161.23, 175.40.

2-(3-Hydroxy-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-one (166)

A suspension of 0.5 g (1.245 mmol) of **165** and 0.25 g of palladium (10 wt % on activated carbon) in 60 mL of methanol was stirred at room temperature under hydrogen gas atmosphere for 24 h. The precipitate were collected and dissolved in 10% NaOH solution and then filtered. The filtrate was acidified with dil aq HCl and the precipitate was then collected and washed with acetone and water to give **166**.

Obtained as white solid; yield: 77%; mp > 300 °C; ESI-MS (Positive mode): *m/z* 312 $[M+H]^+$, 408 $[M+Na]^+$; ESI-MS (Negative mode): *m/z* 310 $[M-H]^-$; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.80 (3H, s), 6.16 (2H, s), 6.24 (1H, s, br), 6.52 (1H, s), 6.77 (1H, s), 6.78 (1H, s), 7.22

(1H,s), 7.40 (1H,s), 9.91 (1H, s), 11.56 (1H, s, br); ^{13}C-NMR (DMSO-d_6, 125 MHz): δ 55.77, 97.83, 101.52, 102.39, 103.29, 104.31, 106.74, 107.17, 120.79, 136.78, 137.77, 145.69, 149.27, 151.57, 159.38, 161.24, 175.93.

Dibenzyl 2-(3-([bis-[(benzyl)oxy]]phosphoryl)oxy-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-yl phosphate (167)

A suspension of 203.9 mg (0.65 mmol) of **166**, 131.0 mg of NaH 60% in mineral oil and 705.4 mg (1.31 mmol) of tetrabenzyl pyrophosphate in 20 mL of dry tetrahydrofuran. The mixture was stirred at room temperature for 10 min. The reaction mixture was filtered and washed with tetrahydrofuran. The filtrate was concentrated under vacuum at a temperature below 30 °C.

Obtained as a yellow oil; yield: 85 %; ESI-MS (Positive mode): *m/z* 832 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$, 200 MHz):δ 3.77 (3H, s), 5.12 (4H, d, *J* = 8.31 Hz), 5.17 (4H, d, *J* = 9.54 Hz), 6.09 (2H, s), 6.78 (1H, m), 7.10 (1H, s), 7.23 (1H, s), 7.27-7.40 (22H, m), 7.52 (1H, d, *J* = 0.98 Hz); ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 55.64, 70.01, 70.12, 70.53, 70.65, 97.16, 101.90, 106.07, 106.62, 110.04, 111.41, 111.52, 117.39, 117.53, 128.09, 128.14, 128.59, 128.67, 128.90, 134.91, 135.02, 135.38, 135.52, 141.49, 151.49, 151.64, 151.78, 153.74, 153.87, 154.86, 160.82.

2-(3-([bis-[(benzyl)oxy]]phosphoryl)oxy-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-one (168)

A suspension of 0.92 g (1.11 mmol) of **167** in 100 mL of methanol was stirred at 25 °C for 48 h. The precipitates were collected and purified by column chromatography (SiO_2, EtOAc) to give **168**.

Obtained as a white solid; yield: 45 %; ESI-MS (Positive mode): *m/z* 572 $[M+H]^+$, 594$[M+Na]^+$; ESI-MS (Negative mode): *m/z* 570 $[M-H]^-$; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 3.64 (3H, s), 5.07 (4H, d, *J* = 9.20 Hz), 5.99 (2H, s), 6.37 (1H, s), 6.79 (1H, s), 7.09 (1H, s), 7.18 (1H, s), 7.27-7.29 (22H, m), 7.59 (1H, s); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 55.57, 70.39, 70.43, 97.35, 101.83, 102.25, 107.57, 107.76, 107.82, 109.93, 110.00, 110.80, 110.90, 121.03, 128.09, 128.66, 128.87, 134.98, 134.02, 145.92, 148.07, 151.35, 151.40, 151.91, 160.90, 177.41.

2-(3-(dihydrogen)phosphate-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-one (169)

A suspension of 38.9 mg (0.068 mmol) of **168** and 20 mg of palladium (10 wt % on activated carbon) in 20 mL of anhydrous methanol was stirred at room temperature under hydrogen gas atmosphere for 15 min. The precipitate were collected and dissolved in 10% $NaHCO_3$ solution and then filtered. The filtrate was acidified with dil aq HCl and the precipitate was then collected and washed with acetone to give **169**.

Obtained as white solid; yield: 80 %; ESI-MS (Negative mode): *m/z* 390 $[M-H]^-$; ^{1}H NMR (D_2O + NaOD, 500 MHz): δ 3.88 (3H, s), 6.01 (2H, s), 6.78 (1H, s), 6.93 (1H, s), 7.14

(1H, s), 7.15 (1H, s), 7.25 (1H, s), 7.44 (1H, s); ^{13}C-NMR (D_2O + NaOD, 125 MHz): δ 55.74, 99.41, 101.53, 103.57, 105.41, 106.64, 107.14, 112.32, 120.87, 142.31, 145.41, 147.13, 150.33, 155.24, 157.79, 159.78, 172.61.

IV-2. Anticancer activity

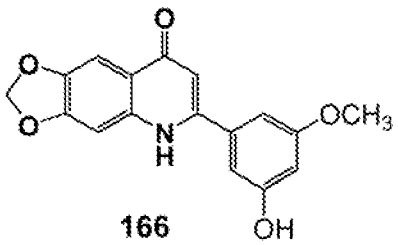
In vitro tests

MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assays. HL-60, Hep 3B, H460, A498, Colo205 and Detroit 551 cells were treated with tested compounds for the indicated periods. After treatment, cells were washed once with PBS and incubated with MTT (Sigma, St. Louis, MO, USA) for 2 h. The formazan precipitate was dissolved in 150 µL of DMSO, and the absorbance was measured with an ELISA reader at 570 nm.

Results

Table 6 shows IC_{50} (µM) Values from *In Vitro* Cytotoxicity Testing of **166**.

Table 6

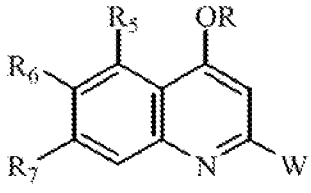


166

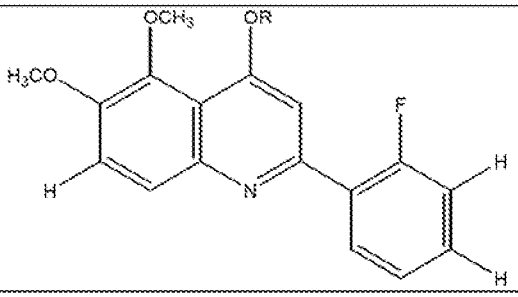
Compound	HL-60	Hep 3B	H460	A498	Colo205	Detroit 551
166	0.4	> 50	> 50	> 50	> 50	> 50

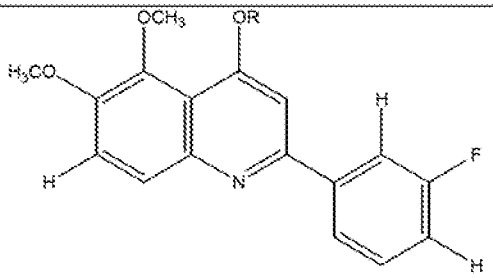
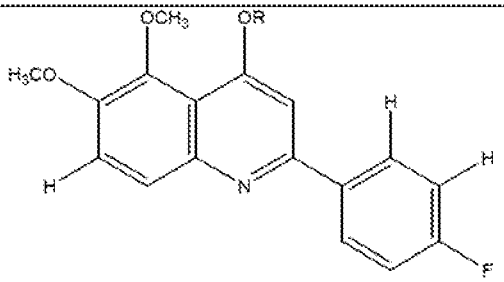
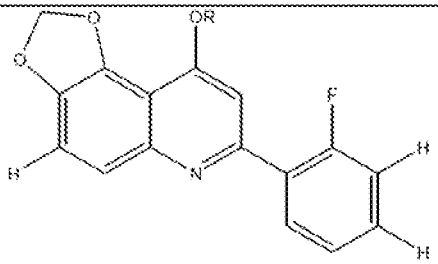
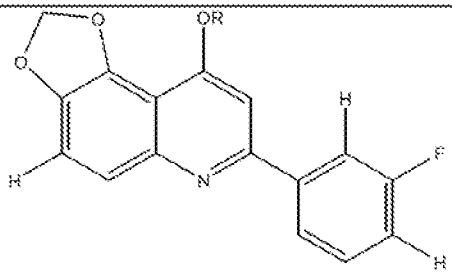
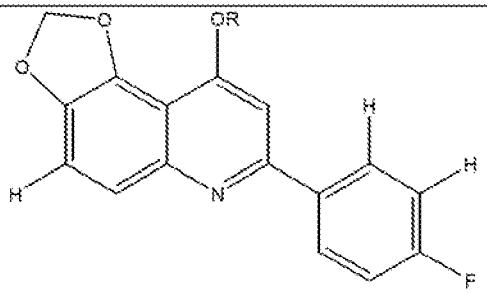
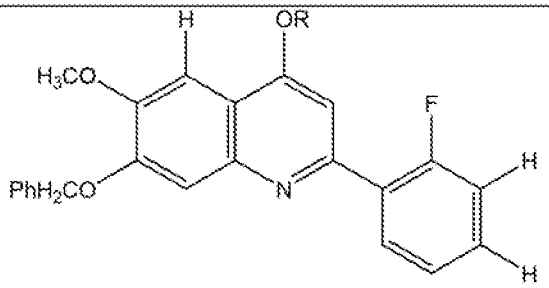
Representative compounds of the present invention are shown in Table 7 below.

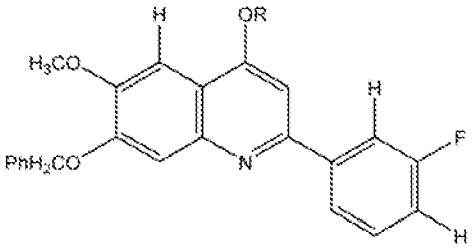
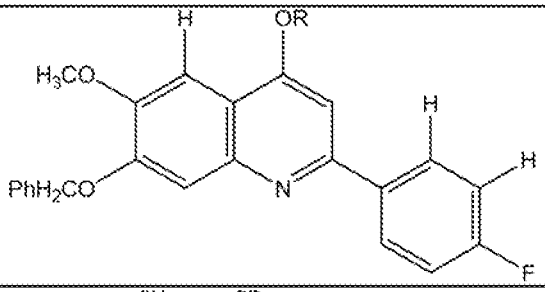
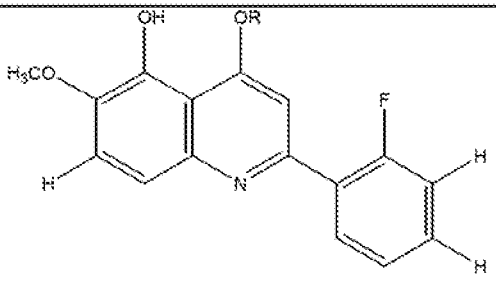
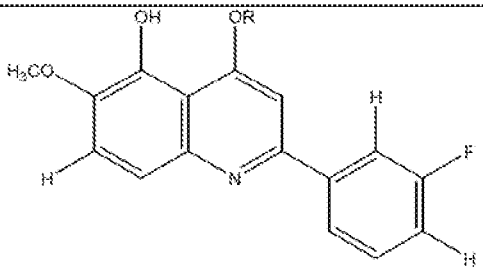
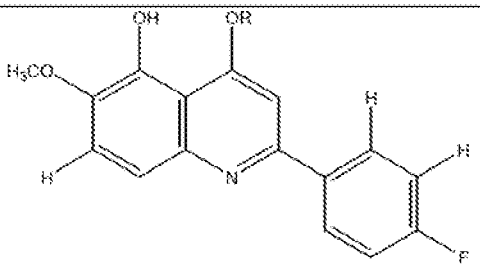
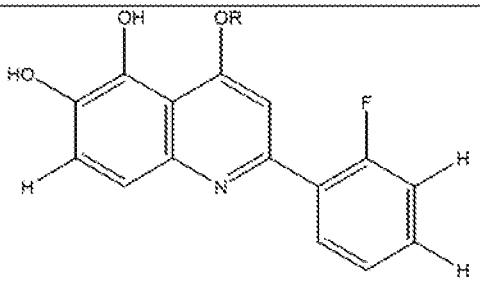
Table 7

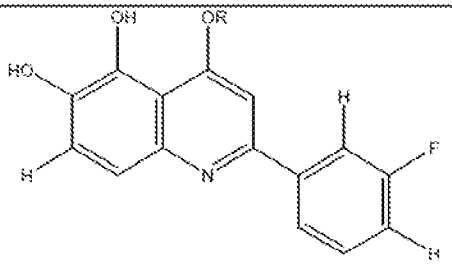
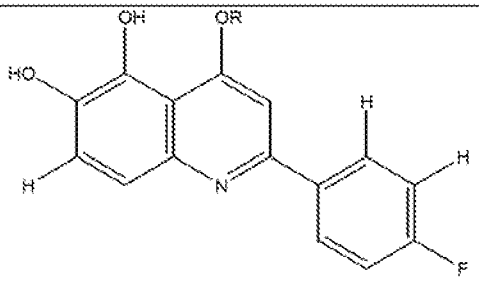
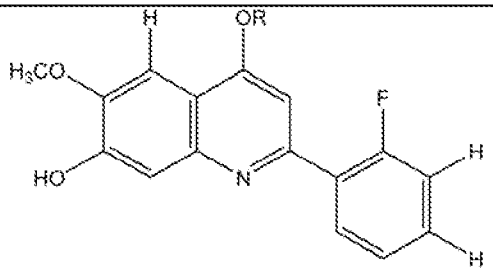
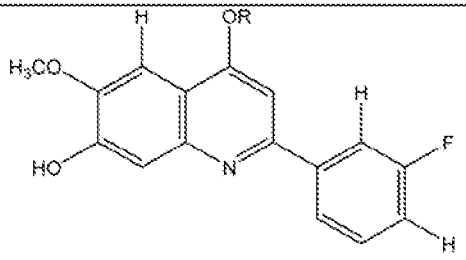
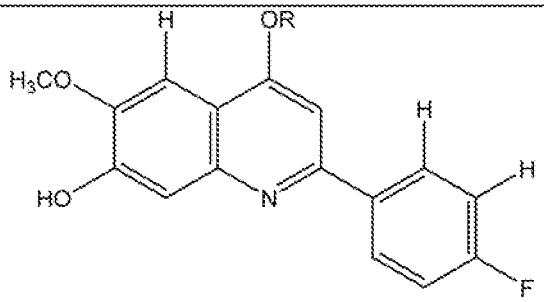
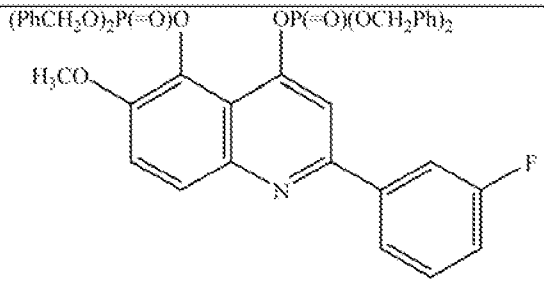


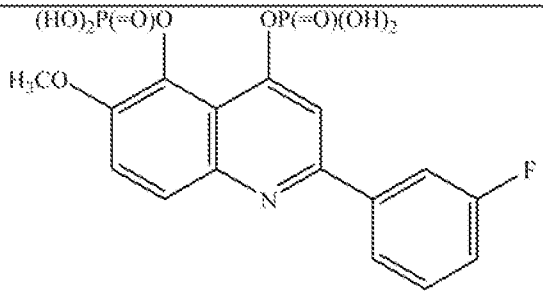
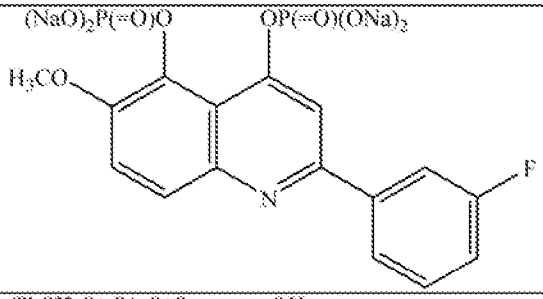
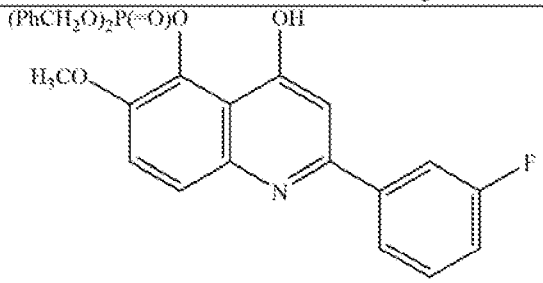
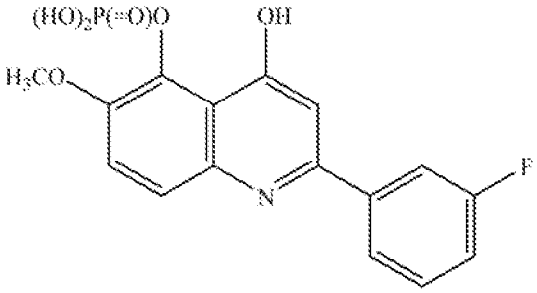
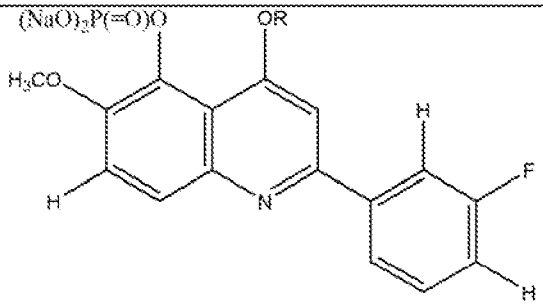
(Formula I)

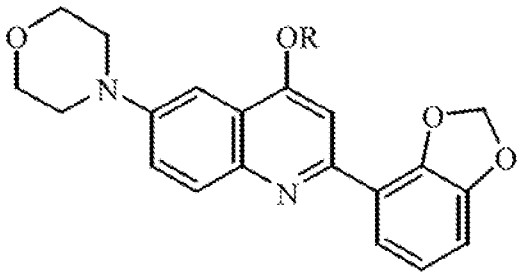
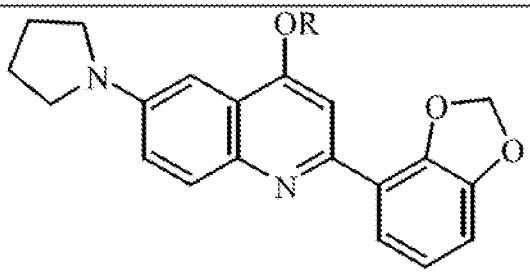
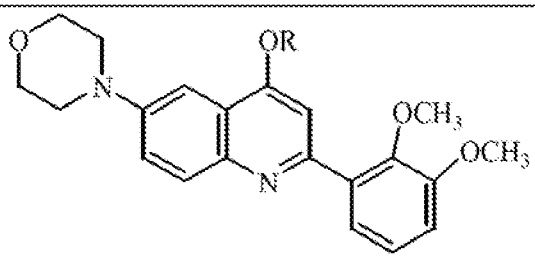
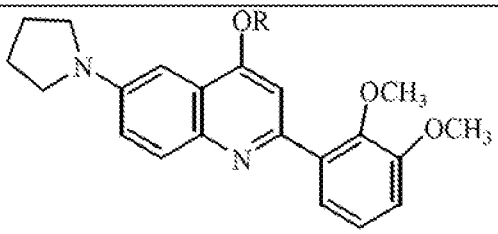
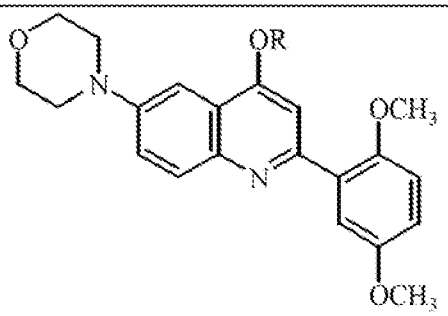
Comp'd	Structure	Name	Substituent on Formula I
16		2-(2-Fluorophenyl)-5,6-dimethoxyquinolin-4-one	R = H W = 2-fluorophenyl R5 = methoxy R6 = methoxy

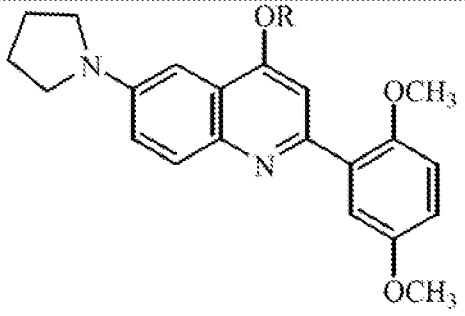
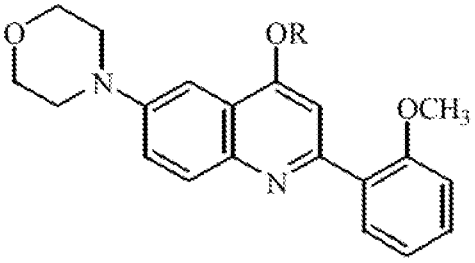
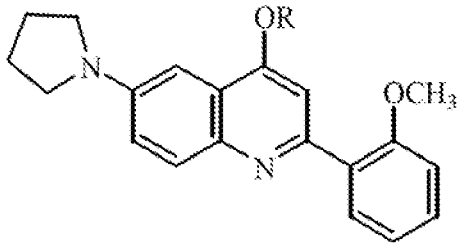
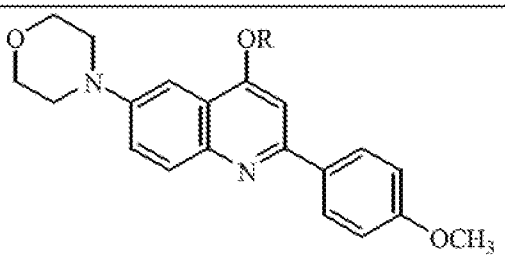
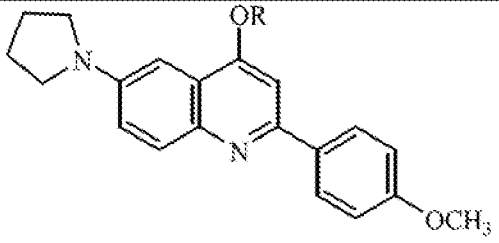
			R7 = hydrogen
17		2-(3-Fluorophenyl)-5,6-dimethoxyquinolin-4-one	R = H W = 3-fluorophenyl R5 = methoxy R6 = methoxy R7 = hydrogen
18		2-(4-Fluorophenyl)-5,6-dimethoxyquinolin-4-one	R = H W = 4-fluorophenyl R5 = methoxy R6 = methoxy R7 = hydrogen
19		2-(2-Fluorophenyl)-5,6-methylenedioxy quinolin-4-one	R = H W = 2-fluorophenyl R5, R6 = methylenedioxy R7 = hydrogen
20		2-(3-Fluorophenyl)-5,6-methylenedioxy quinolin-4-one	R = H W = 3-fluorophenyl R5, R6 = methylenedioxy R7 = hydrogen
21		2-(4-Fluorophenyl)-5,6-methylenedioxy quinolin-4-one	R = H W = 4-Fluorophenyl R5, R6 = methylenedioxy R7 = hydrogen
22		7-Benzyloxy-2-(2-fluorophenyl)-6-methoxyquinolin-4-one	R = H W = 2-fluorophenyl R5 = hydroxyl R6 = methoxy R7 = O-benzyl R7 = hydrogen

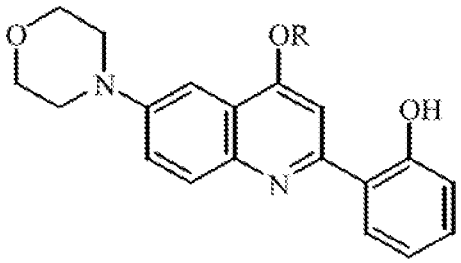
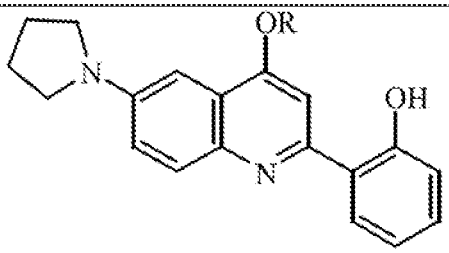
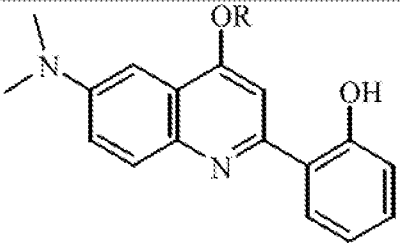
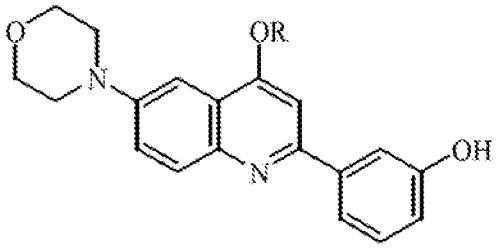
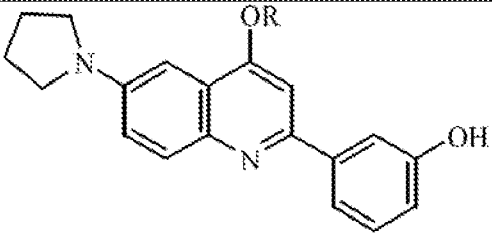
23		7-Benzyloxy-2-(3-fluorophenyl)-6-methoxyquinolin-4-one	R = H W = 3-fluorophenyl R5 = hydroxyl R6 = methoxy R7 = O-benzyl
24		7-Benzyloxy-2-(4-fluorophenyl)-6-methoxyquinolin-4-one	R = H W = 4-fluorophenyl R5 = hydroxyl R6 = methoxy R7 = O-benzyl
37		2-(2-Fluorophenyl)-5-hydroxy-6-methoxyquinolin-4-one	R = H W = 2-fluorophenyl R5 = hydroxyl R6 = methoxy R7 = hydrogen
38		2-(3-Fluorophenyl)-5-hydroxy-6-methoxyquinolin-4-one	R = H W = 3-fluorophenyl R5 = hydroxyl R6 = methoxy R7 = hydrogen
39		2-(4-Fluorophenyl)-5-hydroxy-6-methoxyquinolin-4-one	R = H W = 4-fluorophenyl R5 = hydroxyl R6 = methoxy R7 = hydrogen
40		2-(2-Fluorophenyl)-5,6-dihydroxyquinolin-4-one	R = H W = 2-fluorophenyl R5 = hydroxyl R6 = hydroxyl R7 = hydrogen

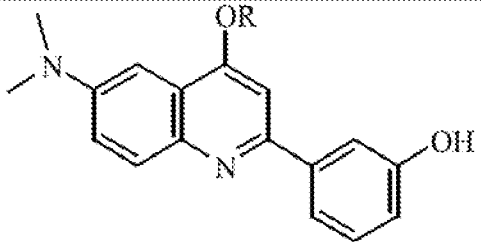
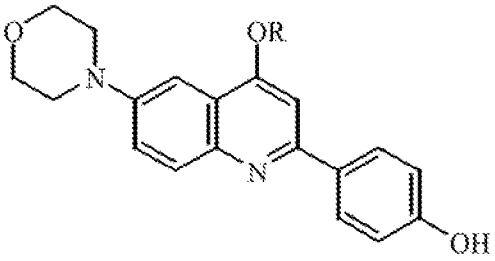
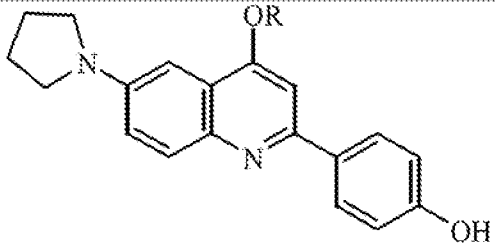
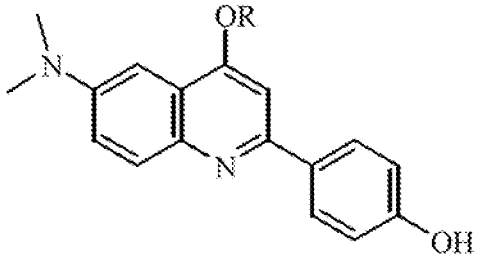
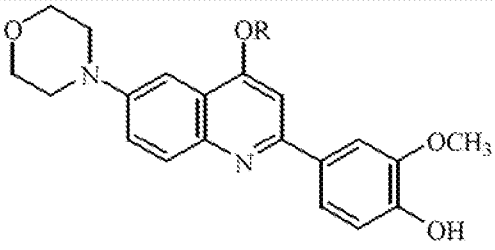
41		2-(3-Fluorophenyl)-5,6-dihydroxyquinolin-4-one	R = H W = 3-fluorophenyl R5 = hydroxyl R6 = hydroxyl R7 = hydrogen
42		2-(4-Fluorophenyl)-5,6-dihydroxyquinolin-4-one	R = H W = 4-fluorophenyl R5 = hydroxyl R6 = hydroxyl R7 = hydrogen
43		2-(2-Fluorophenyl)-7-hydroxy-6-methoxyquinolin-4-one	R = H W = 2-fluorophenyl R5 = hydroxyl R6 = methoxy R7 = hydroxyl
44		2-(3-Fluorophenyl)-7-hydroxy-6-methoxyquinolin-4-one	R = H W = 3-fluorophenyl R5 = hydroxyl R6 = methoxy R7 = hydroxyl
45		2-(4-Fluorophenyl)-7-hydroxy-6-methoxyquinolin-4-one	R = H W = 4-fluorophenyl R5 = hydroxyl R6 = methoxy R7 = hydroxyl
48		2-(3-Fluorophenyl)-6-methoxyquinoline-4,5-diyl bis(dibenzyl phosphate)	R= PO(O-benzyl)2 W= 3-fluorophenyl R5 = OR8 R6 = methoxy R7 = hydrogen R8 = P(=O)(O-benzyl)2

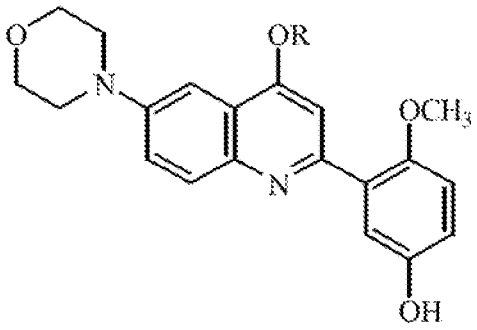
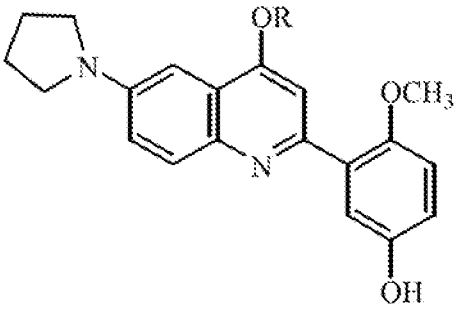
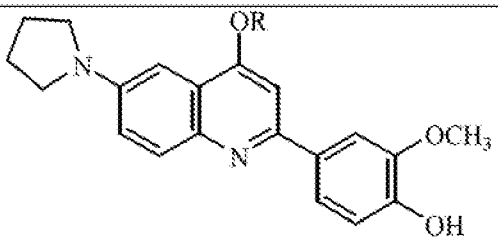
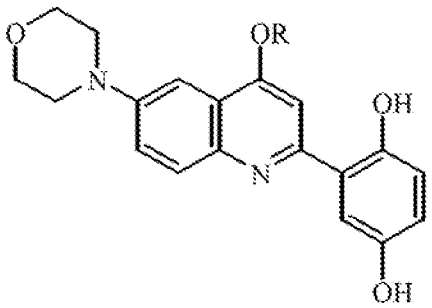
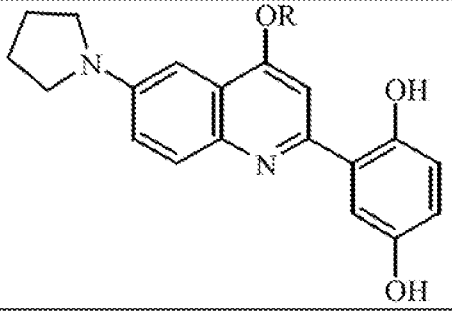
49		2-(3-Fluorophenyl)-6-methoxyquinoline-4,5-diyl bis(dihydrogen phosphate)	R= PO(OH)2 W= 3-fluorophenyl R5 = OR8 R6 = methoxy R7 = hydrogen R8 = - P(=O)(OH)$_2$
50		2-(3-Fluorophenyl)-6-methoxyquinoline-4,5-diyl bis(disodium phosphate)	R= PO(ONa)2 W= 3-fluorophenyl R5 = OR8 R6 = methoxy R7 = hydrogen R8 = P(=O)(ONa)$_2$
51		Dibenzyl 2-(3-fluorophenyl)-6-methoxy-4-oxo-1,4-dihydroquinolin-5-yl phosphate	R = H W = 3-fluorophenyl R5 = OR8 R6 = methoxy R7 = hydrogen R8 = P(=O)(O-benzyl)2
52		2-(3-Fluorophenyl)-6-methoxy-4-oxo-1,4-dihydroquinolin-5-yl dihydrogen phosphate	R = H W = 3-fluorophenyl R5 = OR8 R6 = methoxy R7 = hydrogen R8 = P(=O)(OH)2
53		Sodium 2-(3-fluorophenyl)-6-methoxy-4-oxo-1,4-dihydroquinolin-5-yl phosphate	R = H W = 3-fluorophenyl R5 = OR8 R6 = methoxy R7 = hydrogen R8 = P(=O)(ONa)2

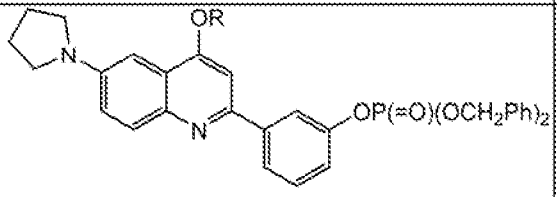
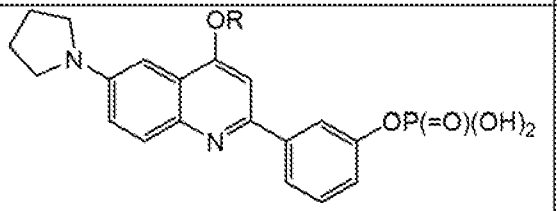
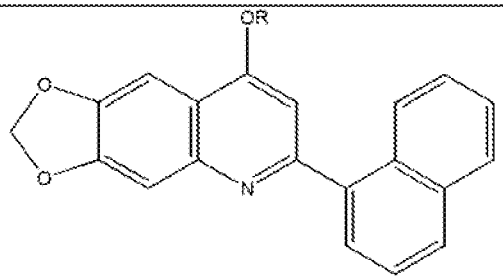
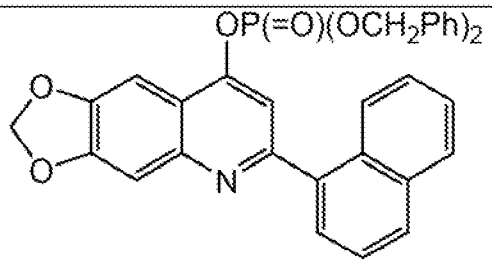
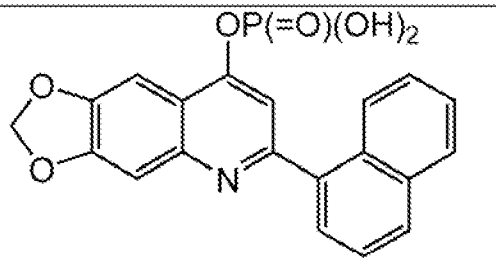
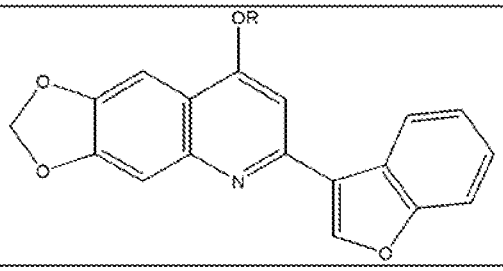
124		2-(benzo[d] [1,3] dioxol-81-yl)-6-morpholinoquinolin-4-one	R = H W= benzo[d] [1,3]dioxol-4-yl, R5= hydrogen R6 = N-morpholino R7 = hydrogen
125		2-(benzo[d] [1,3] dioxol-4-yl)-6-pyrrolidinoquinolin-4-one	R = H W= benzo[d] [1,3]dioxol-4-yl, R5= hydrogen R6 = N-pyrrolindino R7 = hydrogen
126		2-(2,3-dimethoxyphenyl)-6-morpholinoquinolin-4-one	R = H W= 2,3-dimethoxyphenyl R5= hydrogen R6 = N-morpholino R7 = hydrogen
127		2-(2,3-dimethoxyphenyl)-6-pyrrolidinoquinolin-4-one	R = H W= 2,3-dimethoxyphenyl R5= hydrogen R6 = N-pyrrolindino R7 = hydrogen
128		2-(2,5-dimethoxyphenyl)-6-morpholinoquinolin-4-one	R = H W= 2,5-dimethoxyphenyl R5= hydrogen R6 = N-morpholino R7 = hydrogen

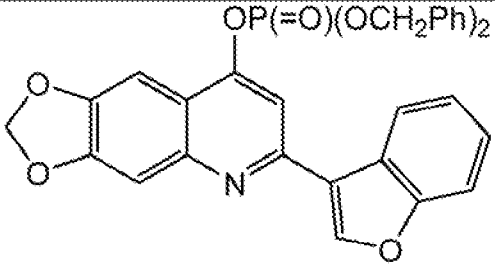
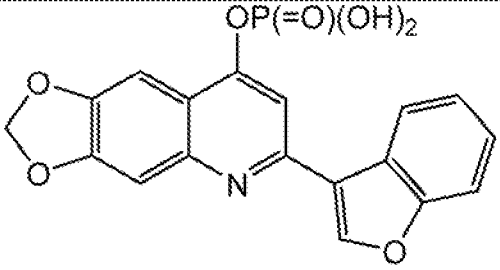
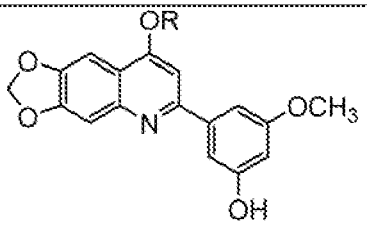
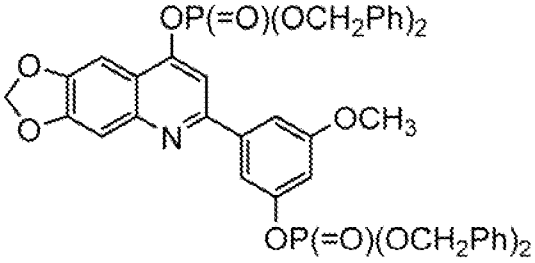
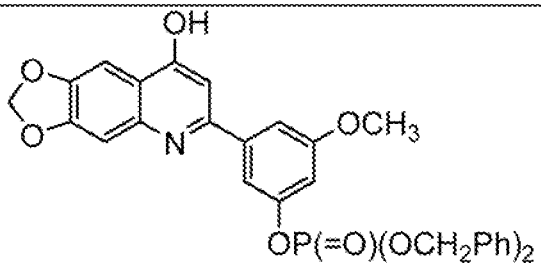
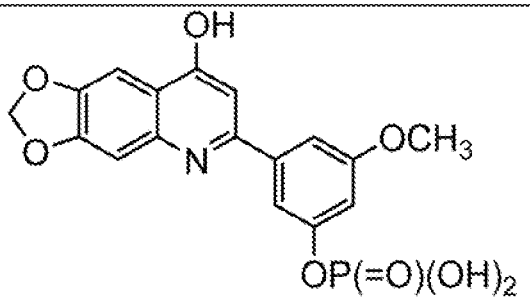
129		2-(2,5-dimethoxyphenyl)-6-pyrrolidinoquinolin-4-one	R = H W= 2,5-dimethoxyphenyl R5= hydrogen R6 = N-pyrrolindino R7 = hydrogen
130		2-(2-methoxyphenyl)-6-morpholinoquinolin-4-one	R = H W = 2-methoxyphenyl R5= hydrogen R6 = N-morpholino R7 = hydrogen
131		2-(2,5-dimethoxyphenyl)-6-pyrrolidinoquinolin-4-one	R = H W= 2-methoxyphenyl R5= hydrogen R6 = N-pyrrolindino R7 = hydrogen
132		2-(4-methoxyphenyl)-6-morpholinoquinolin-4-one	R = H W= 4-methoxyphenyl R5= hydrogen R6 = N-morpholino R7 = hydrogen
133		2-(4-methoxyphenyl)-6-pyrrolidinoquinolin-4-one	R = H W= 4-methoxyphenyl R5= hydrogen R6 = N-pyrrolindino R7 = hydrogen

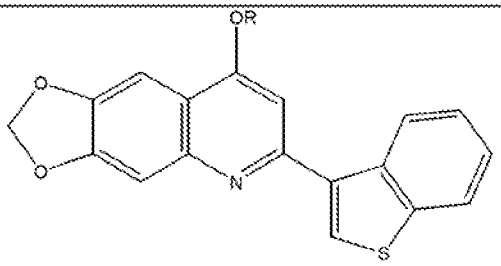
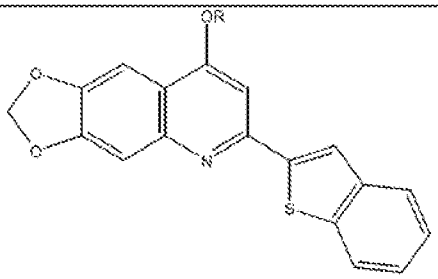
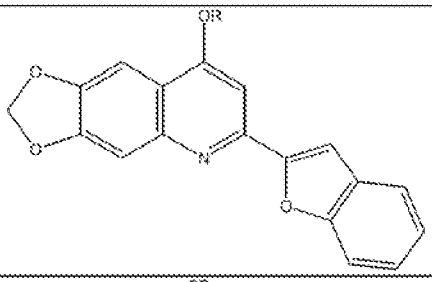
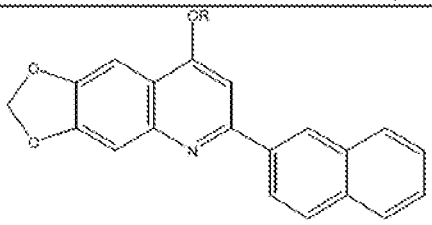
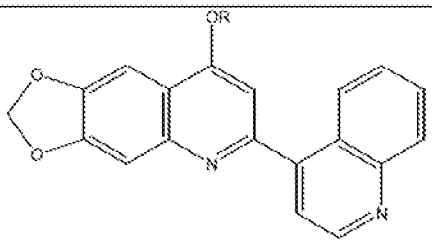
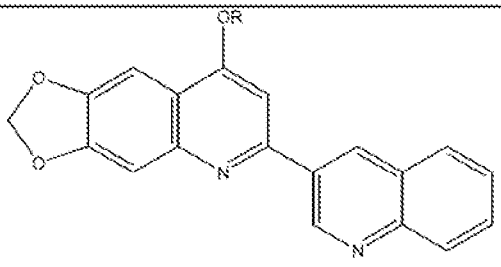
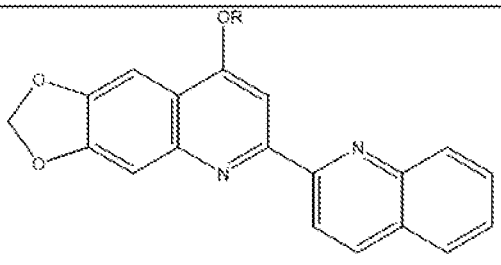
134		2-(2-Hydroxyphenyl)-6-morpholinoquinolin-4-one	R = H W= 2-hydroxyphenyl R5= hydrogen R6 = N-morpholino R7 = hydrogen
135		2-(2-hydroxyphenyl)- -6-pyrrolidinoquinolin-4-one	R = H W= 2-hydroxyphenyl R5= hydrogen R6 = N-pyrrolindino R7 = hydrogen
136		2-(2-hydroxyphenyl)-6-dimethylaminoquinolin-4-one	R = H W= 2-hydroxyphenyl R5= hydrogen R6 = N,N-dimethylamino R7 = hydrogen
137		2-(3-Hydroxyphenyl)-6-morpholinoquinolin-4-one	R = H W= 3-hydroxyphenyl R5= hydrogen R6 = N-morpholino R7 = hydrogen
138		2-(3-hydroxyphenyl)-6-pyrrolidinoquinolin-4-one	R = H W= 3-hydroxyphenyl R5= hydrogen R6 = N-pyrrolindino R7 = hydrogen

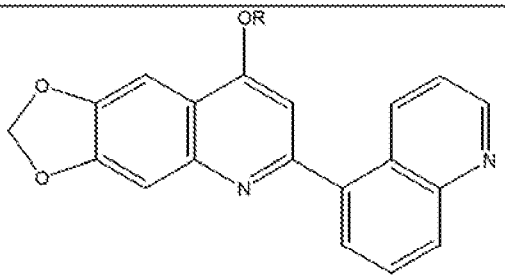
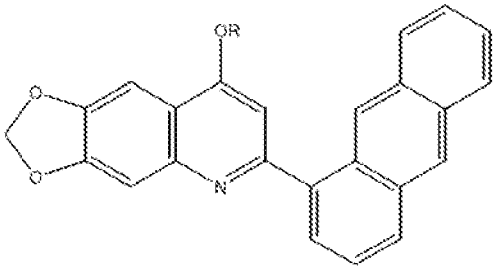
139		2-(3-hydroxyphenyl)-6-dimethylaminoquinolin-4-one	R = H W= 3-hydroxyphenyl R5= hydrogen R6 = N,N-dimethylamino R7 = hydrogen
140		2-(4-Hydroxyphenyl)-6-morpholinoquinolin-4-one	R = H W= 4-hydroxyphenyl R5= hydrogen R6 = N-morpholino R7 = hydrogen
141		2-(4-hydroxyphenyl)-6-pyrrolidinoquinolin-4-one	R = H W= 4-hydroxyphenyl R5= hydrogen R6 = N-pyrrolindino R7 = hydrogen
142		2-(4-hydroxyphenyl)-6-dimethylaminoquinolin-4-one	R = H W= 4-hydroxyphenyl R5= hydrogen R6 = N,N-dimethylamino R7 = hydrogen
143		2-(4-hydroxy-3-methoxyphenyl)-6-morpholinoquinolin-4-one	R = H W= 4-hydroxy-3-methoxyphenyl R5= hydrogen R6 = N-morpholino R7 = hydrogen

143a		2-(5-hydroxy-2-methoxyphenyl)-6-morpholinoquinolin-4-one	R = H W= 5-hydroxy-2-methoxyphenyl R5= hydrogen R6 = N-morpholino R7 = hydrogen
143b		2-(5-hydroxy-2-methoxyphenyl)--6-pyrrolidinoquinolin-4-one	R = H W= 5-hydroxy-2-methoxyphenyl R5= hydrogen R6 = N-pyrrolindino R7 = hydrogen
144		2-(4-hydroxy-3-methoxyphenyl)-6-pyrrolidinoquinolin-4-one	R = H W= 4-hydroxy-3-methoxyphenyl R5= hydrogen R6 = N-pyrrolindino R7 = hydrogen
144a		2-(2,5-dihydroxy-phenyl)-6-morpholinoquinolin-4-one	R, R5 and R7 = H W= 2,5-dihydroxyphenyl R6 = N-morpholino
144b		2-(2,5-dihydroxy-phenyl)--6-pyrrolidinoquinolin-4-one	R , R5 and R7 = H W= 2,5-dihydroxyphenyl R6 = N-pyrrolindino

146		Dibenzyl 3-(4-oxo-6-(pyrrolidin-1-yl)-1,4-dihydroquinolin-2-yl)phenyl phosphate	R = H W= 3-OR8-phenyl R5= hydrogen R6 =N-pyrrolindino R8 = P(=O)(O-benzyl)2
147		3-(4-Oxo-6-(pyrrolidin-1-yl)-1,4-dihydroquinolin-2-yl)phenyl dihydrogen phosphate	R = H W= 3-OR8-phenyl R5= hydrogen R6 =N-pyrrolindino R8 = P(=O)(OH)2
151 (JMC-39)		2-(1-Naphthalenyl)-6,7-methylenedioxyquinolin-4-one	R = H W= naphtha-1-yl R5= hydrogen R6 and R7 = methylenedioxy
152		Dibenzyl 2-(1-naphthalenyl)-6,7-methylenedioxyquinolin-4-yl phosphate	R = P(=O)(O-benzyl)2 W= naphtha-1-yl R5= hydrogen R6 and R7 = methylenedioxy
153		2-(1-Naphthalenyl)-6,7-methylenedioxyquinolin-4-yl dihydrogen phosphate	R = P(=O)(OH)2 W= naphtha-1-yl R5= hydrogen R6 and R7 = methylenedioxy
156 (JMC-37)		2-(3-Benzo[*b*]furyl)-6,7-methylenedioxyquinolin-4-one	R = H W= benzo[b]furan-3-yl R5= hydrogen R6 and R7 = methylenedioxy

157		Dibenzyl 2-(3-benzo[*b*]furyl)-6,7-methylenedioxy quinolin-4-yl phosphate	R = P(=O)(O-benzyl)2 W= benzo[b]furan-3-yl R5= hydrogen R6 and R7 = methylenedioxy
158		2-(3-Benzo[*b*]furyl)-6,7-methylenedioxy quinolin-4-yl dihydrogen phosphate	R = P(=O)(OH)2 W= benzo[b]furan-3-yl R5= hydrogen R6 and R7 = methylenedioxy
166		2-(3-Hydroxy-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-one	R and R5 = H W= 3-OR8-5-methoxyphenyl R6 and R7 = methylenedioxy
167		Dibenzyl 2-(3-([bis-[(benzyl)oxy]]phosphoryl)oxy-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-yl phosphate	R and R8 = P(=O)(O-benzyl)2 W= 3-OR8-5-methoxyphenyl R5= hydrogen R6 and R7 = methylenedioxy
168		2-(3-([bis-[(benzyl)oxy]]phosphoryl)oxy-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-one	R and R5 = H W= 3-OR8-5-methoxyphenyl R6 and R7 = methylenedioxy R8= P(=O)(O-benzyl)2
169		2-(3-(dihydrogen)phosphate-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-one	R and R5 = H W= 3-OR8-5-methoxyphenyl R6 and R7 = methylenedioxy R8= P(=O)(OH)2

JMC-1		2-(3-Benzo[*b*]thienyl)-6,7-methylenedioxyquinolin-4-one	R and R5 = H W= benzo[b]thiophen-3-yl R6 and R7 = methylenedioxy
JMC-36		2-(2-Benzo[*b*]thienyl)-6,7-methylenedioxyquinolin-4-one	R and R5 = H W= benzo[b]thiophen-2-yl R6 and R7 = methylenedioxy
JMC-38		2-(2-Benzo[*b*]furyl)-6,7-methylenedioxy quinolin-4-one	R and R5 = H W= benzo[b]furan-2-yl R6 and R7 = methylenedioxy
JMC-40		2-(2-Naphthalenyl)-6,7-methylenedioxy quinolin-4-one	R and R5 = H W= naphtha-2-yl R6 and R7 = methylenedioxy
JMC-41		2-(4-Quinolinyl)-6,7-methylenedioxyquinolin-4-one	R and R5 = H W= quinolin-4-yl R6 and R7 = methylenedioxy
JMC-42		2-(3-Quinolinyl)-6,7-methylenedioxyquinolin-4-one	R and R5 = H W= quinolin-3-yl R6 and R7 = methylenedioxy
JMC-43		2-(2-Quinolinyl)-6,7-methylenedioxyquinolin-4-one	R and R5 = H W= quinolin-2-yl R6 and R7 = methylenedioxy

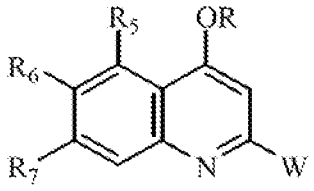
JMC-44		2-(5-Quinolinyl)-6,7-methylenedioxyquinolin-4-one	R = H
			W= quinolin-5-yl
			R5= hydrogen
			R6 and R7 = methylenedioxy
JMC-45		2-(1-Anthracenyl)-6,7-methylenedioxyquinolin-4-one	R = H
			W= anthracen-1-yl
			R5= hydrogen
			R6 and R7 = methylenedioxy

The foregoing description of the exemplary embodiments of the invention has been presented only for the purposes of illustration and description and is not intended to be exhaustive or to limit the invention to the precise forms disclosed. The embodiments and examples were chosen and described in order to explain the principles of the invention and their practical application so as to enable others skilled in the art to utilize the invention and various embodiments and with various modifications as are suited to the particular use contemplated. Accordingly, the scope of the present invention is defined by the appended claims rather than the foregoing description and the exemplary embodiments described therein.

CLAIMS

What is claimed is:

1. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, prodrug, solvate, or metabolite thereof,

wherein

R is hydrogen, $P(=O)(OH)_2$, $P(=O)(O(C_1\text{-}C_{18})alkylene(C_6\text{-}C_{20})aryl)_2$, $P(=O)(OH)(OM)$, $P(=O)(OM)_2$, $P=O(O_2M)$, $S(=O)(OH)_2$, $S(=O)(O(C_1\text{-}C_{18})alkylene(C_6\text{-}C_{20})aryl)_2$, $S(=O)(OH)(OM)$, $S(=O)(OM)_2$;

M is a monovalent or divalent metal ion, or alkylammonium ion,

W is $(C_6\text{-}C_{20})$aryl, $(C_6\text{-}C_{20})$heteroaryl, $(C_1\text{-}C_{18})alkyl(C_6\text{-}C_{20})aryl$, $(C_1\text{-}C_{18})alkyl(C_6\text{-}C_{20})heteroaryl$, $hydroxy(C_6\text{-}C_{20})aryl$, $hydroxy(C_6\text{-}C_{20})heteroaryl$, $(C_1\text{-}C_{18})alkoxy(C_6\text{-}C_{20})aryl$, $(C_1\text{-}C_{18})alkoxy(C_6\text{-}C_{20})heteroaryl$, $(C_1\text{-}C_{18})alkylenedioxy(C_6\text{-}C_{20})aryl$, $(C_1\text{-}C_{18})alkylenedioxy(C_6\text{-}C_{20})heteroaryl$, $halo(C_6\text{-}C_{20})aryl$, $halo(C_6\text{-}C_{20})heteroaryl$, $(C_1\text{-}C_{18})alkylamino(C_6\text{-}C_{20})aryl$, $(C_1\text{-}C_{18})alkylamino(C_6\text{-}C_{20})heteroaryl$, $(C_1\text{-}C_{18})cycloalkylamino(C_6\text{-}C_{20})aryl$, or $(C_1\text{-}C_{18})cycloalkylamino(C_6\text{-}C_{20})heteroaryl$, and their OR_8 substutes;

R_5 is $(C_1\text{-}C_{18})$alkoxy, hydrogen, hydroxyl, $O\text{-}(C_1\text{-}C_{18})alkyl(C_6\text{-}C_{20})aryl$, halo or OR_8, or R_5 and R_6 are $(C_1\text{-}C_{18})$dioxy provided that R_7 is hydrogen;

R_6 is hydroxyl, $O\text{-}(C_1\text{-}C_{18})alkyl(C_6\text{-}C_{20})aryl$, halo, OR_8, $(C_1\text{-}C_{18})$alkoxy, $(C_1\text{-}C_{18})$alkylamino, or $(C_1\text{-}C_{18})$cycloalkylamino, or R_6 and R_7 are $(C_1\text{-}C_{18})$dioxy provided that R_5 is hydrogen;

R_7 is hydrogen, hydroxyl, halo or OR_8, or $O\text{-}(C_1\text{-}C_{18})alkyl(C_6\text{-}C_{20})aryl$; and

R_8 is $P(=O)(OH)_2$, $P(=O)(O(C_1\text{-}C_{18})alkyl(C_6\text{-}C_{20})aryl)_2$, $P(=O)(OH)(OM)$, or $P(=O)(OM)_2$. $P=O(O_2M)$; M is a monovalent or divalent (ex: Mg, Ca) metal ion, alkylammonium ion (ex: N^+R).

2. The compound of claim 1, wherein:

R is hydrogen, $P(=O)(OH)(ONa)$, or $P(=O)(ONa)_2$;

M is sodium;

W is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, benzo[d] [1,3]dioxol-4-yl, 2,3-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 4-hydroxy-3-methoxyphenyl, 5-hydroxy-2-methoxyphenyl, 2,5-dihydroxyphenyl, benzo[b]thiophen-3-yl, benzo[b]thiophen-2-yl, benzo[b]furan-3-yl, naphtha-1-yl, naphtha-2-yl, quinolin-4-yl, quinolin-3-yl, quinolin-2-yl, quinolin-5-yl, or anthracen-1-yl, and their OR_8 substutes;

R_5 is hydrogen, methoxy, hydroxyl, halo or OR_8, or R_5 and R_6 are methylenedioxy provided that R_7 is hydrogen;

R_6 is N,N-dimethylamino, hydroxyl, halo or OR_8, methoxy, N-morpholino, or N-pyrrolindino, or R_6 and R_7 are methylenedioxy provided that R_5 is hydrogen;

R_7 is hydrogen, hydroxyl, halo or OR_8, or O-benzyl; and

R_8 is $P(=O)(OH)_2$, $P(=O)(O\text{-benzyl})_2$, $P(=O)(OH)(ONa)$, or $P(=O)(ONa)_2$.

3. The compound of claim 2, wherein:

R is hydrogen;

W is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl;

R_5 is hydrogen, methoxy, hydroxyl, or OR_8;

R_6 is hydroxyl or methoxy;

R_7 is hydrogen, hydroxyl, or O-benzyl; and

R_8 is hydrogen.

4. The compound of claim 2, wherein:

R is hydrogen;

W is benzo[d] [1,3]dioxol-4-yl, 2,3-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 4-hydroxy-3-methoxyphenyl, 5-hydroxy-2-methoxyphenyl, or 2,5-dihydroxyphenyl;

R_5 is hydrogen, methoxy, hydroxyl, or OR_8;

R_6 is hydroxyl or methoxy;

R_7 is hydrogen, hydroxyl, or O-benzyl; and

R_8 is hydrogen.

5. The compound of claim 2, wherein:

R is hydrogen;

W is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl;

R_5 and R_6 are methylenedioxy provided that R_7 is hydrogen; and

R_8 is hydrogen.

6. The compound of claim 2, wherein:

R is hydrogen;

W is benzo[b]thiophen-3-yl, benzo[b]thiophen-2-yl, benzo[b]furan-3-yl, naphtha-1-yl, naphtha-2-yl, quinolin-4-yl, quinolin-3-yl, quinolin-2-yl, quinolin-5-yl, or anthracen-1-yl; and

R_6 and R_7 are methylenedioxy provided that R_5 is hydrogen.

7. The compound of claim 2, wherein:

R is hydrogen, $P(=O)(OH)_2$, $P(=O)(O\text{-benzyl})_2$,

W is naphthalene, dibenzyl-3-phenyl phosphate, 3-phenyl dihydrogen phosphate, 3-([bis-[(benzyl)oxy]]phosphoryl)oxy-5-methoxyphenyl, 3-(dihydrogen)phosphate-5-methoxyphenyl; and

R_6 and R_7 are methylenedioxy provided that R_5 is hydrogen.

8. The compound of claim 1, wherein the compound is selected from the group consisting of:

2-(2-Fluorophenyl)-5,6-dimethoxyquinolin-4-one,

2-(3-Fluorophenyl)-5,6-dimethoxyquinolin-4-one,

2-(4-Fluorophenyl)-5,6-dimethoxyquinolin-4-one,

2-(2-Fluorophenyl)-5,6-methylenedioxyquinolin-4-one,

2-(3-Fluorophenyl)-5,6-methylenedioxyquinolin-4-one,

2-(4-Fluorophenyl)-5,6-methylenedioxyquinolin-4-one,

2-(2-Fluorophenyl)-5-hydroxy-6-methoxyquinolin-4-one,

2-(3-Fluorophenyl)-5-hydroxy-6-methoxyquinolin-4-one,

2-(4-Fluorophenyl)-5-hydroxy-6-methoxyquinolin-4-one,

2-(2-Fluorophenyl)-5,6-dihydroxyquinolin-4-one,

2-(3-Fluorophenyl)-5,6-dihydroxyquinolin-4-one,

2-(4-Fluorophenyl)-5,6-dihydroxyquinolin-4-one,

2-(2-Fluorophenyl)-7-hydroxy-6-methoxyquinolin-4-one,

2-(3-Fluorophenyl)-7-hydroxy-6-methoxyquinolin-4-one,

2-(4-Fluorophenyl)-7-hydroxy-6-methoxyquinolin-4-one,

7-Benzyloxy-2-(2-fluorophenyl)-6-methoxyquinolin-4-one,

7-Benzyloxy-2-(3-fluorophenyl)-6-methoxyquinolin-4-one,

7-Benzyloxy-2-(4-fluorophenyl)-6-methoxyquinolin-4-one,

sodium 2-(3-fluorophenyl)-6-methoxy-4-oxo-1,4-dihydroquinolin-5-yl phosphate,

2-(benzo [d] [1,3] dioxol-4-yl)-6-pyrrolidinoquinolin-4-one,

2-(2,3-dimethoxyphenyl)-6-morpholinoquinolin-4-one,

2-(2,3-dimethoxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(2,5-dimethoxyphenyl)-6-morpholinoquinolin-4-one,

2-(2,5-dimethoxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(2-methoxyphenyl)-6-morpholinoquinolin-4-one,

2-(2,5-dimethoxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(4-methoxyphenyl)-6-morpholinoquinolin-4-one,

2-(4-methoxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(2-Hydroxyphenyl)-6-morpholinoquinolin-4-one,

2-(2-hydroxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(2-hydroxyphenyl)-6-dimethylaminoquinolin-4-0one,

2-(3-Hydroxyphenyl)-6-morpholinoquinolin-4-one,

2-(3-hydroxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(3-hydroxyphenyl)-6-dimethylaminoquinolin-4-one,

2-(4-Hydroxyphenyl)-6-morpholinoquinolin-4-one,

2-(4-hydroxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(4-hydroxyphenyl)-6-dimethylaminoquinolin-4-one,

2-(4-hydroxy-3-methoxyphenyl)-6-morpholinoquinolin-4-one,

2-(4-hydroxy-3-methoxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(5-hydroxy-2-methoxyphenyl)-6-morpholinoquinolin-4-one,

2-(5-hydroxy-2-methoxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(2,5-dihydroxy-phenyl)-6-morpholinoquinolin-4-one,

2-(2,5-dihydroxy-phenyl)-6-pyrrolidinoquinolin-4-one,

2-(3-Benzo[*b*]thienyl)-6,7-methylenedioxyquinolin-4-one,

2-(2-Benzo[*b*]thienyl)-6,7-methylenedioxyquinolin-4-one,

2-(3-Benzo[*b*]furyl)-6,7-methylenedioxyquinolin-4-one,

2-(2-Benzo[*b*]furyl)-6,7-methylenedioxyquinolin-4-one,

2-(1-Naphthalenyl)-6,7-methylenedioxyquinolin-4-one,

2-(2-Naphthalenyl)-6,7-methylenedioxyquinolin-4-one,

2-(4-Quinolinyl)-6,7-methylenedioxyquinolin-4-one,

2-(3-Quinolinyl)-6,7-methylenedioxyquinolin-4-one,

2-(2-Quinolinyl)-6,7-methylenedioxyquinolin-4-one,

2-(5-Quinolinyl)-6,7-methylenedioxyquinolin-4-one,

2-(1-Anthracenyl)-6,7-methylenedioxyquinolin-4-one,

Dibenzyl 2-(1-naphthalenyl)-6,7-methylenedioxyquinolin-4-yl phosphate,

2-(1-Naphthalenyl)-6,7-methylenedioxyquinolin-4-yl dihydrogen phosphate,

Dibenzyl 2-(3-benzo[b]furyl)-6,7-methylenedioxyquinolin-4-yl phosphate,

2-(3-Benzo[b]furyl)-6,7-methylenedioxyquinolin-4-yl dihydrogen phosphate,

Dibenzyl 3-(4-oxo-6-(pyrrolidin-1-yl)-1,4-dihydroquinolin-2-yl)phenyl phosphate,

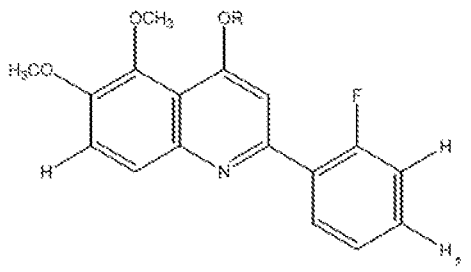
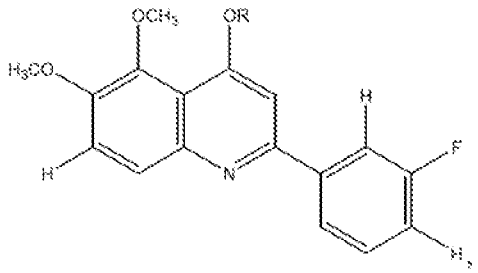
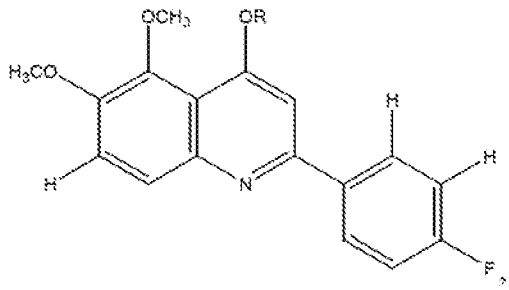
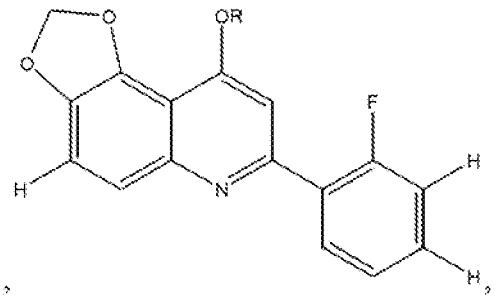
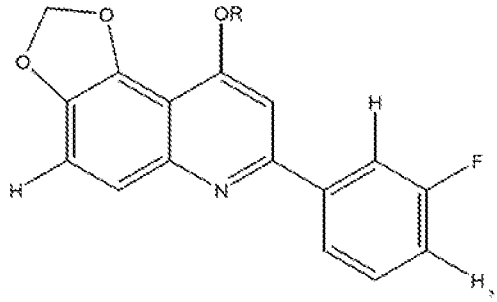
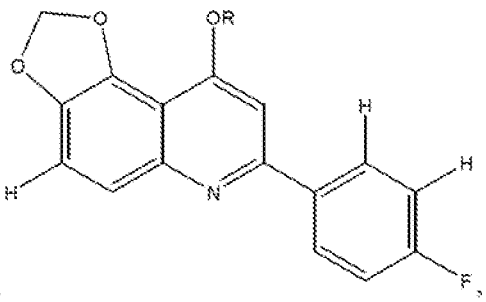
3-(4-Oxo-6-(pyrrolidin-1-yl)-1,4-dihydroquinolin-2-yl)phenyl dihydrogen phosphate,

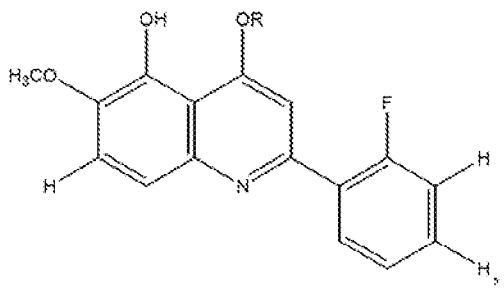
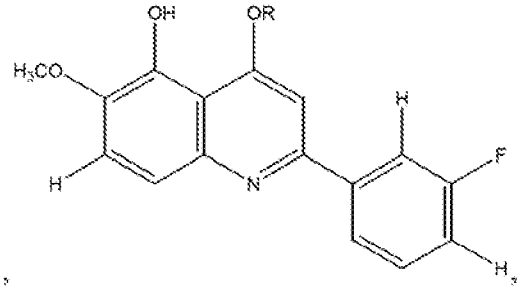
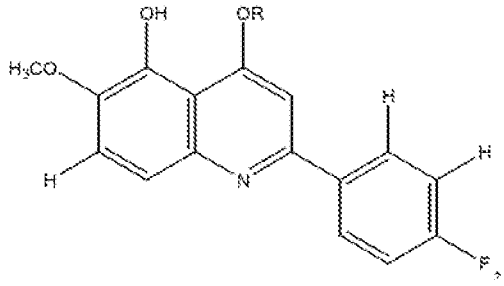
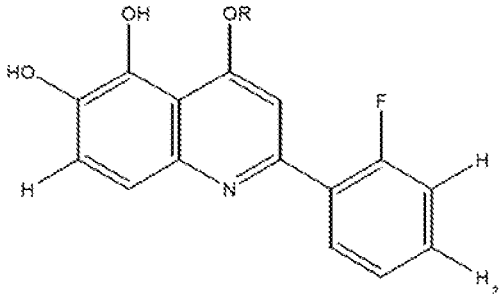
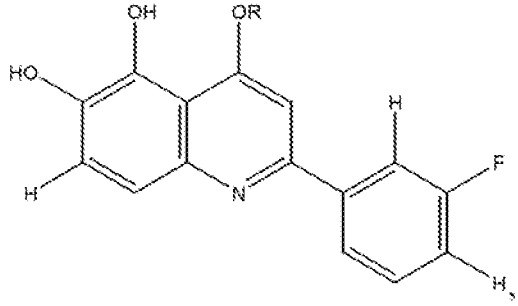
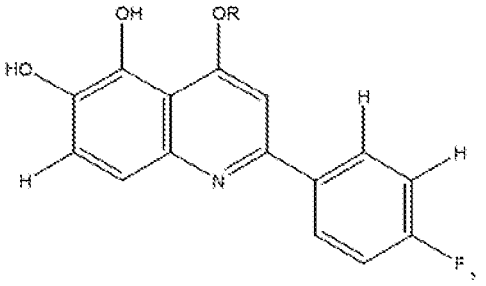
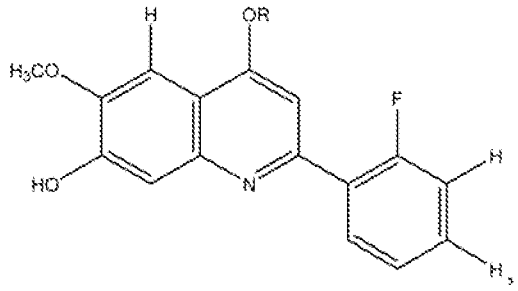
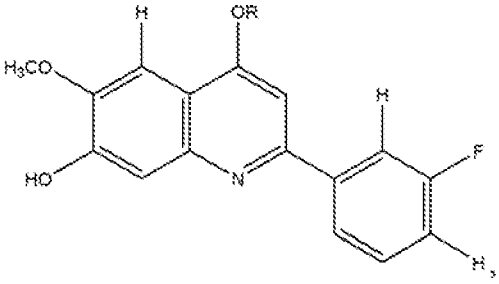
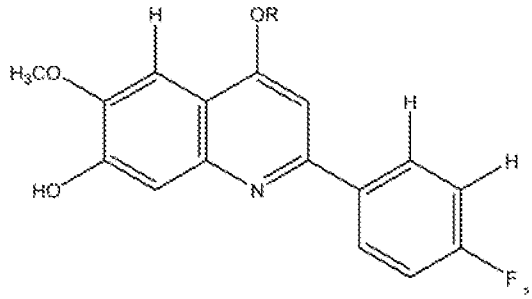
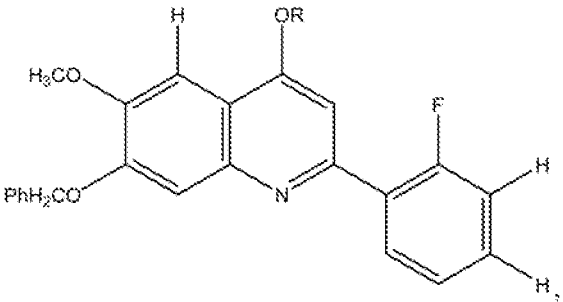
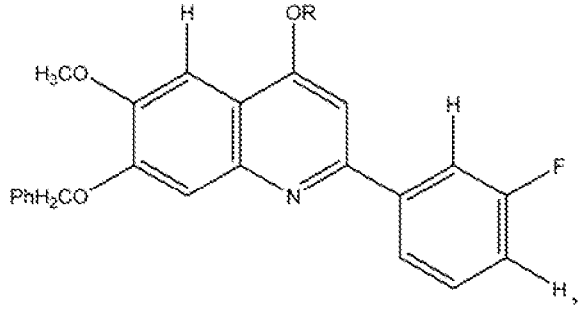
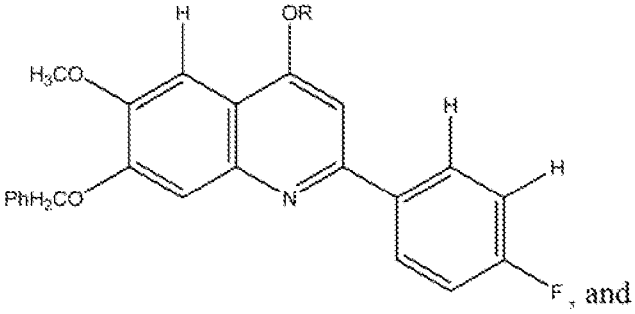
Dibenzyl 2-(3-([bis-[(benzyl)oxy]]phosphoryl)oxy-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-yl phosphate,

2-(3-([bis-[(benzyl)oxy]]phosphoryl)oxy-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-one, and

2-(3-(dihydrogen)phosphate-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-one, or a pharmaceutically acceptable salt, prodrug, solvate, or metabolite thereof.

9. The compound of claim 1, wherein the compound is selected from the group consisting of

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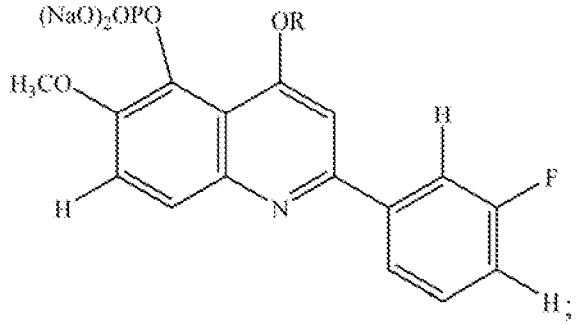
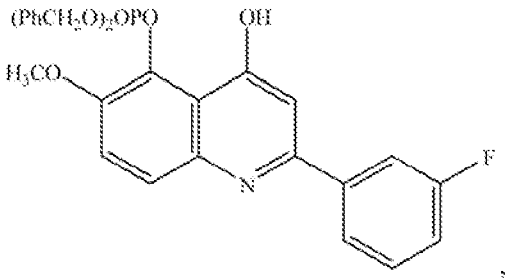


wherein R = H, or a pharmaceutically acceptable salt, prodrug, solvate, or metabolite thereof.

10. The compound of claim 1, wherein the compound is selected from the group consisiting of



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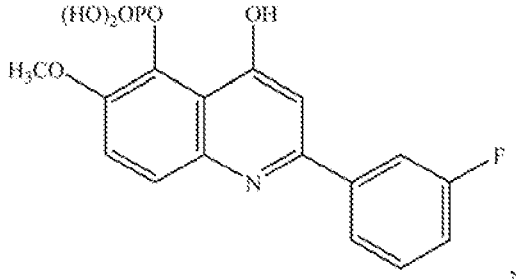

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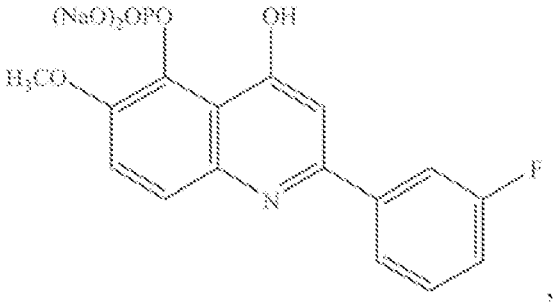

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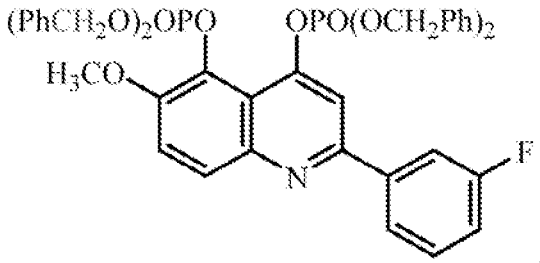

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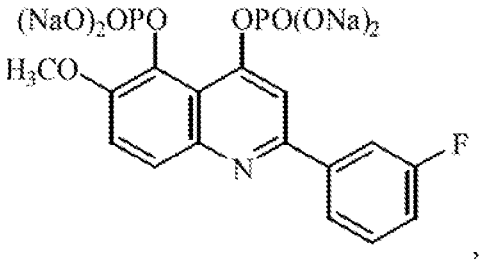
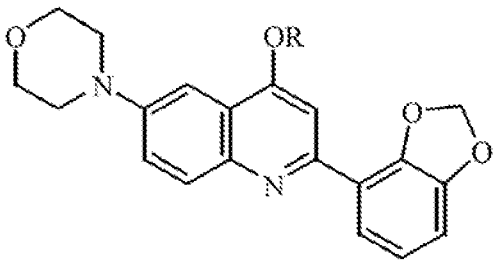


,

or a pharmaceutically acceptable salt, prodrug, solvate, or metabolite thereof.

11. The compound of claim 1, wherein the compound is selected from the group consisting of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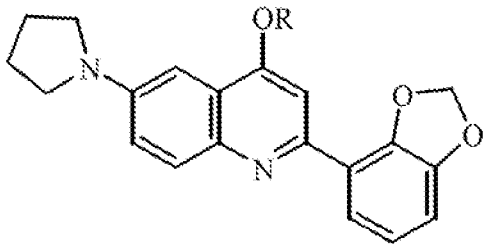
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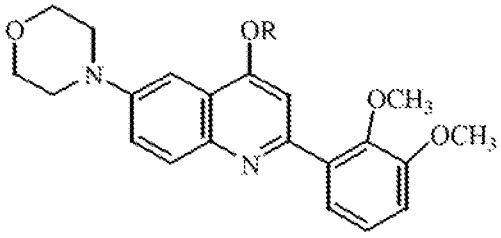
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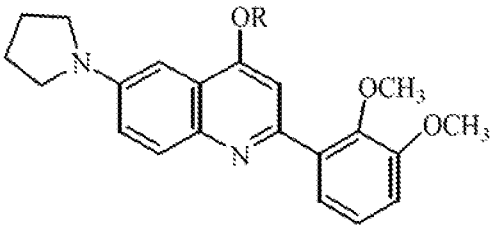
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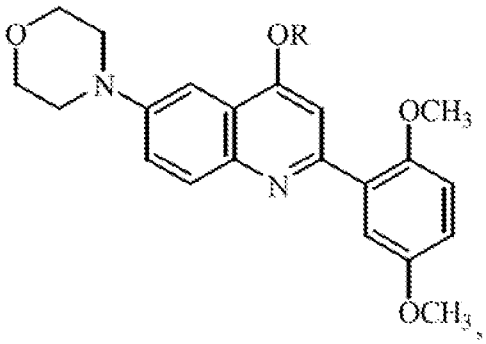
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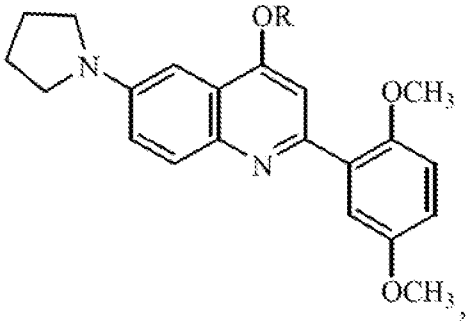
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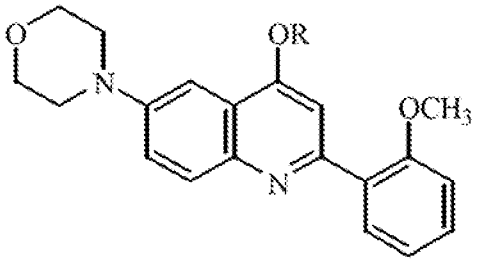
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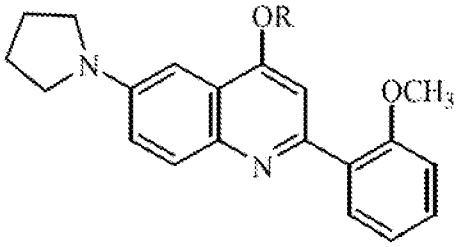
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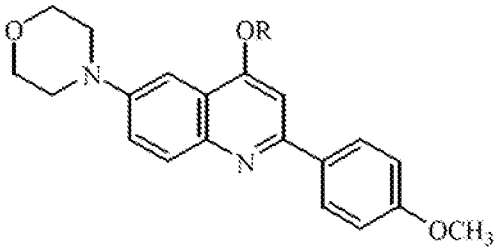
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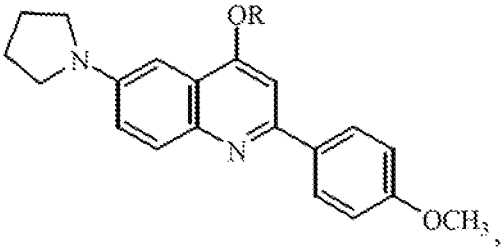
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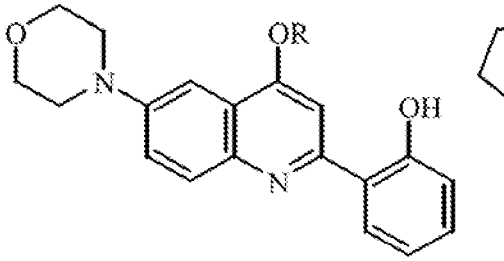
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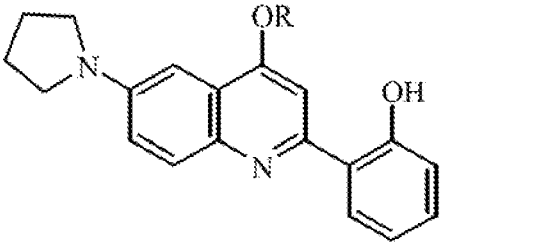
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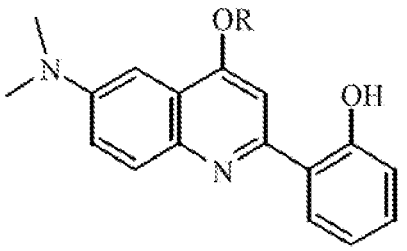
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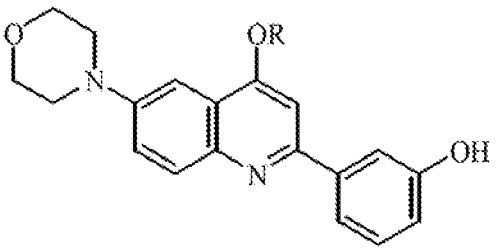
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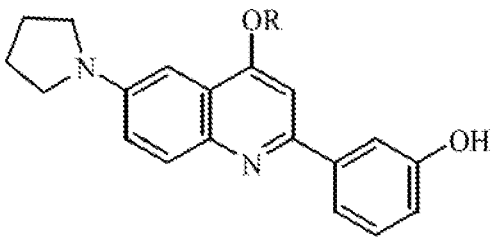
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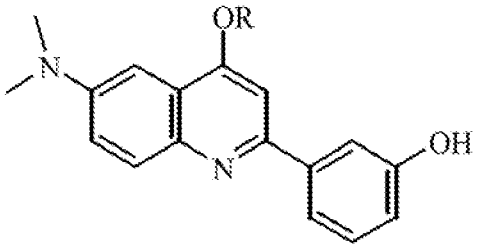
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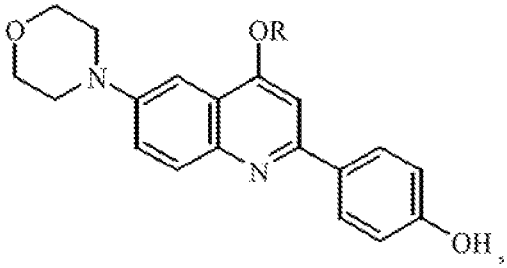
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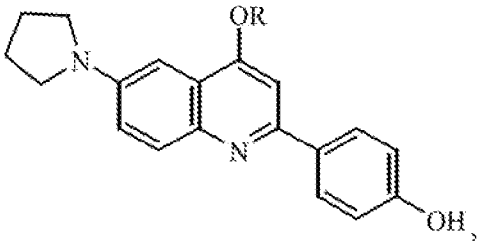
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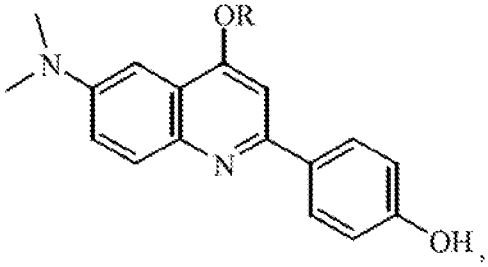
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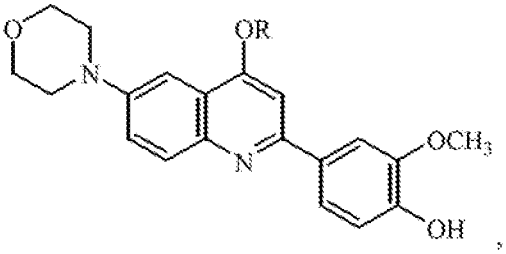
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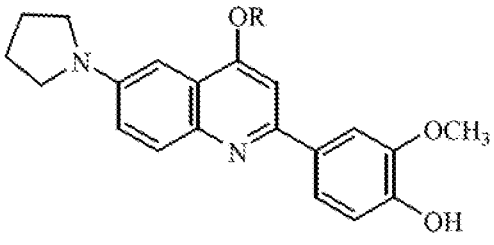
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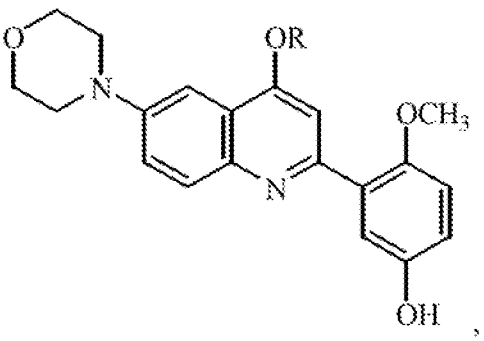
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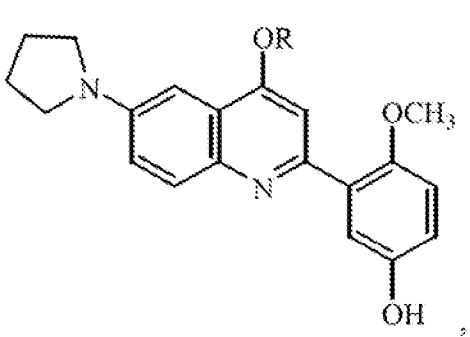
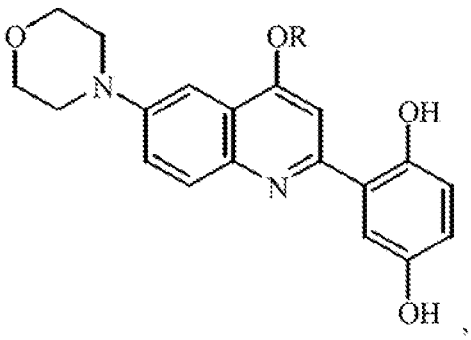
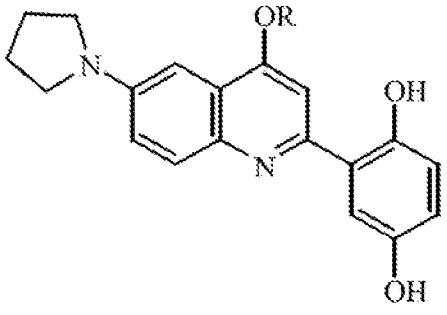
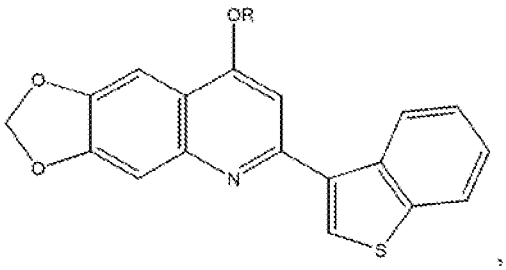
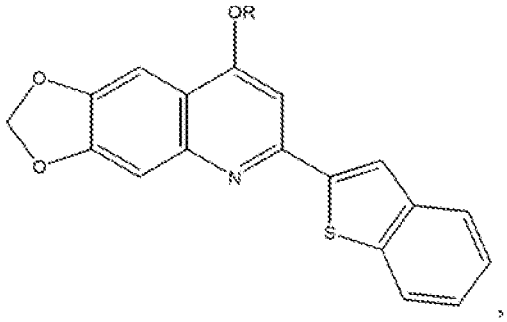
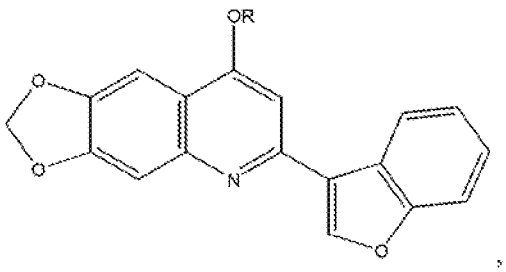
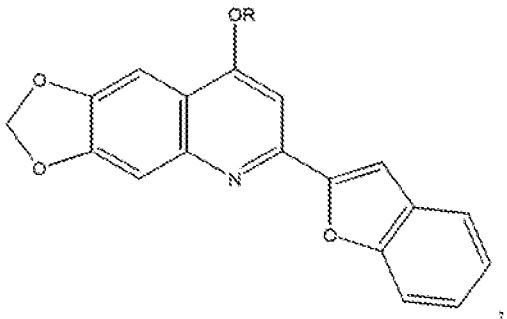
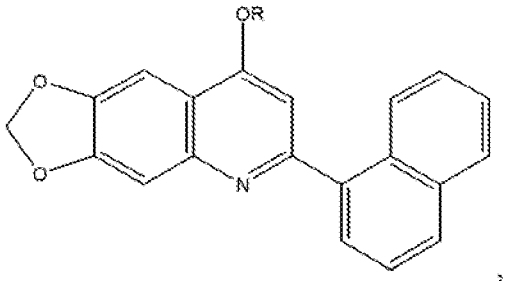
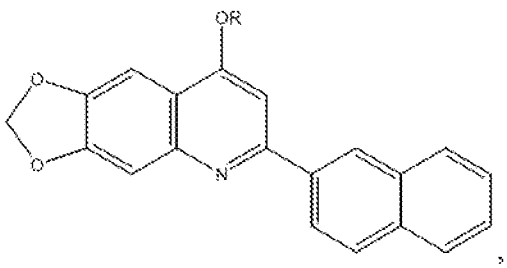
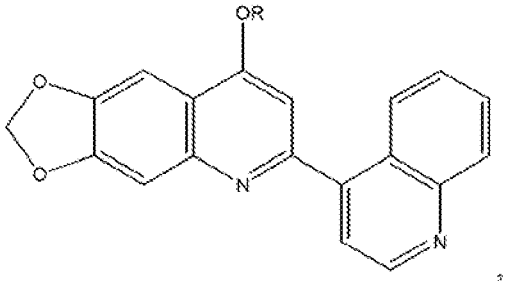
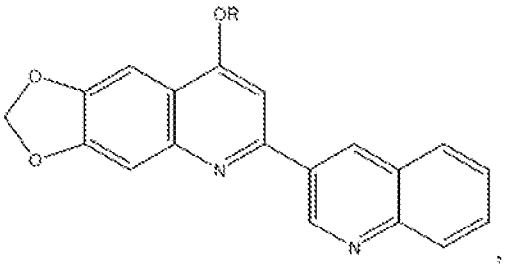
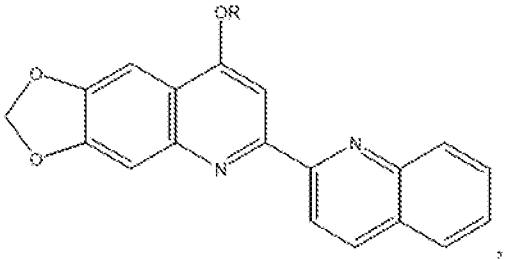
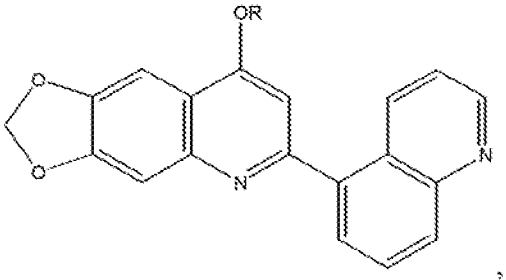




and ;

wherein R = H, or a pharmaceutically acceptable salt, prodrug, solvate, or metabolite thereof.

12. The compound of claim 1, wherein the compound is selected from the group consisting of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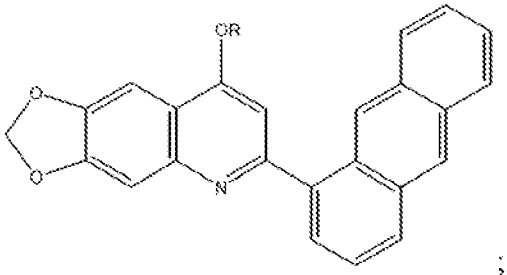
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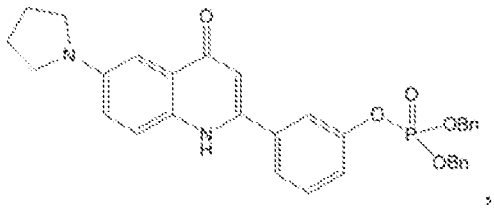
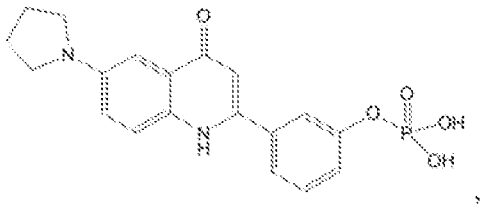
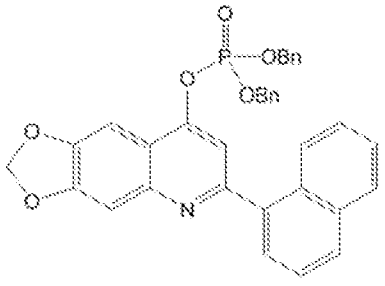
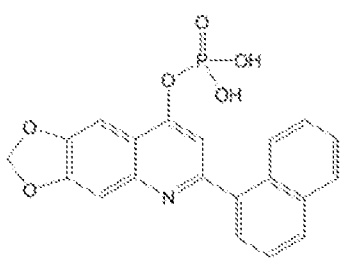
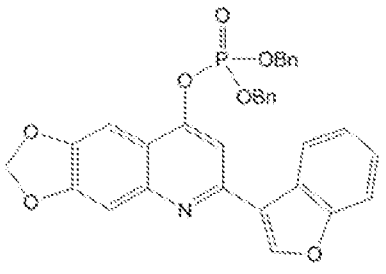
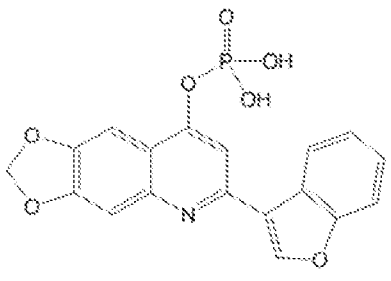
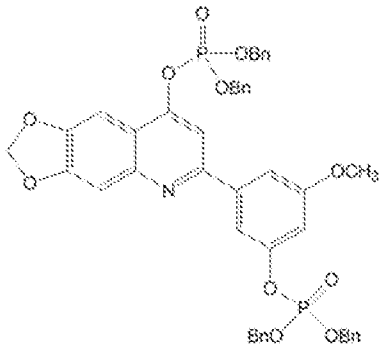
wherein R = H, or a pharmaceutically acceptable salt, prodrug, solvate, or metabolite thereof.

13. The compound of claim 1, wherein the compound is selected from the group consisting of



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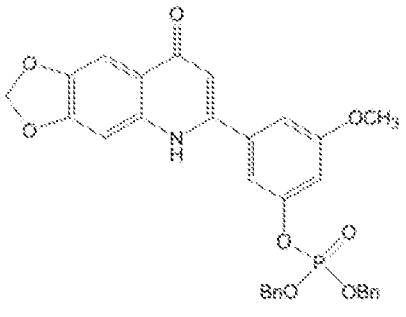

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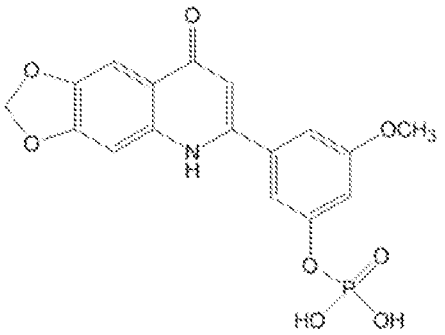

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14. The compound of claim 1, wherein the compound is 2-(3-Fluorophenyl)-6-methoxy-4-oxo-1,4-dihydroquinolin-5-yl dihydrogen phosphate, or Sodium 2-(3-fluorophenyl)-6-methoxy-4-oxo-1,4-dihydroquinolin-5-yl phosphate.

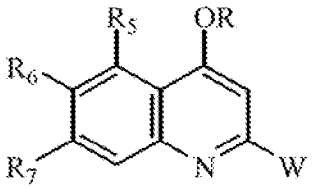
15. The compound of claim 1, with the proviso that if R5 is hydroxyl, then R6 is not (C1)alkoxy and W is not 3-fluorophenyl.

16. The compound of claim 1, wherein R5 is hydroxyl, R6 is (C1)alkoxy and W is 3-fluorophenyl.

17. A composition comprising an effective amount of a compound according to any of claims 1-16 and a pharmaceutically acceptable carrier.

18. A composition comprising an effective amount of a compound according to any of claims 1-16, for use in treating a tumor disease in a subject in need thereof.

19. A process for preparing a compound of Formula I



Formula I;

wherein

R is hydrogen;

W is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, benzo[d] [1,3]dioxol-4-yl, 2,3-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-benzyloxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3-benzyloxy-5-methoxyphenyl, 4-hydroxy-3-methoxyphenyl, 5-hydroxy-2-methoxyphenyl, 2,5-dihydroxyphenyl, benzo[b]thiophen-3-yl, benzo[b]thiophen-2-yl, benzo[b]furan-3-yl, naphtha-1-yl, naphtha-2-yl, quinolin-4-yl, quinolin-3-yl, quinolin-2-yl, quinolin-5-yl, or anthracen-1-yl;

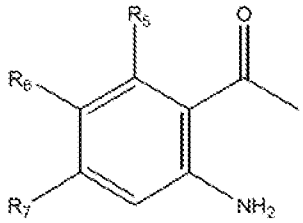
R_5 is hydrogen, methoxy, hydroxyl, or OR_8, or R_5 and R_6 are methylenedioxy provided that R_7 is hydrogen;

R_6 is N,N-dimethylamino, hydroxyl, methoxy, N-morpholino, or N-pyrrolindino, or R_6 and R_7 are methylenedioxy provided that R_5 is hydrogen;

R_7 is hydrogen, hydroxyl, or O-benzyl; and

R_8 is hydrogen; or a pharmaceutically acceptable salt, prodrug, solvate, or metabolite thereof, comprising:

reacting a compound of Formula II



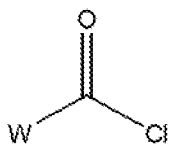
Formula II;

wherein R_5 is (C_1-C_{18})alkoxy, hydrogen, hydroxyl, O-(C_1-C_{18})alkyl(C_6-C_{20})aryl, halo or OR_8 or R_5 and R_6 are (C_1-C_{18})dioxy provided that R_7 is hydrogen;

R_6 is hydroxyl, O-(C_1-C_{18})alkyl(C_6-C_{20})aryl, halo, OR_8, (C_1-C_{18})alkoxy, (C_1-C_{18})alkylamino, or (C_1-C_{18})cycloalkylamino or R_6 and R_7 are (C_1-C_{18})dioxy provided that R_5 is hydrogen;

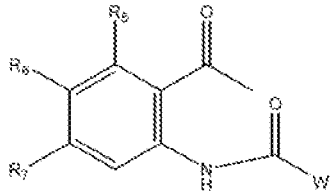
R_7 is hydrogen, halo or OR_8, hydroxyl, or O-(C_1-C_{18})alkyl(C_6-C_{20})aryl; and

R_8 is hydrogen; with a compound of Formula III



Formula III;

in the presence of a base; wherein W is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, benzo[d] [1,3]dioxol-4-yl, 2,3-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-benzyloxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3-benzyloxy-5-methoxyphenyl, 4-hydroxy-3-methoxyphenyl, 5-hydroxy-2-methoxyphenyl, 2,5-dihydroxyphenyl, benzo[b]thiophen-3-yl, benzo[b]thiophen-2-yl, benzo[b]furan-3-yl, naphtha-1-yl, naphtha-2-yl, quinolin-4-yl, quinolin-3-yl, quinolin-2-yl, quinolin-5-yl, or anthracen-1-yl to afford a compound of Formula IV



Formula IV;

wherein

R is hydrogen;

W is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, benzo[d] [1,3]dioxol-4-yl, 2,3-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-benzyloxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3-benzyloxy-5-methoxyphenyl, 4-hydroxy-3-methoxyphenyl, 5-hydroxy-2-methoxyphenyl, 2,5-dihydroxyphenyl, benzo[b]thiophen-3-yl, benzo[b]thiophen-2-yl, benzo[b]furan-3-yl, naphtha-1-yl, naphtha-2-yl, quinolin-4-yl, quinolin-3-yl, quinolin-2-yl, quinolin-5-yl, or anthracen-1-yl;

R_5 is hydrogen, methoxy, hydroxyl, or OR_8, or R_5 and R_6 are methylenedioxy provided that R_7 is hydrogen;

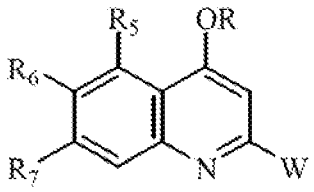
R_6 is N,N-dimethylamino, hydroxyl, methoxy, N-morpholino, or N-pyrrolindino, or R_6 and R_7 are methylenedioxy provided that R_5 is hydrogen;

R_7 is hydrogen, hydroxyl, or O-benzyl; and

R_8 is hydrogen; and

reacting a compound of Formula IV with a base to afford the compound of Formula I.

20. The process of claim 19, further comprising dealkylating the compound of Formula I to afford the compound of Formula I



Formula I

wherein

R is hydrogen;

W is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, benzo[d] [1,3]dioxol-4-yl, 2,3-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-benzyloxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3-benzyloxy-5-methoxyphenyl, 4-hydroxy-3-methoxyphenyl, 5-hydroxy-2-methoxyphenyl, 2,5-dihydroxyphenyl, benzo[b]thiophen-3-yl, benzo[b]thiophen-2-yl, benzo[b]furan-3-yl, naphtha-1-yl, naphtha-2-yl, quinolin-4-yl, quinolin-3-yl, quinolin-2-yl, quinolin-5-yl, or anthracen-1-yl;

R_5 is hydrogen, hydroxyl, or methoxy;

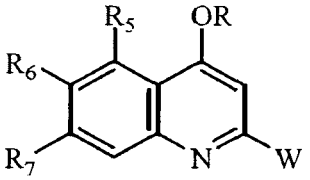
R_6 is N,N-dimethylamino, hydroxyl, methoxy, N-morpholino, or N-pyrrolindino, or R_6 and R_7 are methylenedioxy provided that R_5 is hydrogen; and

R_7 is hydrogen.

AMENDED CLAIMS
received by the International Bureau on 9 December 2011 (09.12.2011)

What is claimed is:

1. A process for preparing a compound of Formula I



Formula I;

wherein

R is hydrogen;

W is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, benzo[d] [1,3]dioxol-4-yl, 2,3-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-benzyloxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3-benzyloxy-5-methoxyphenyl, 4-hydroxy-3-methoxyphenyl, 5-hydroxy-2-methoxyphenyl, 2,5-dihydroxyphenyl, benzo[b]furan-3-yl, or naphtha-1-yl;

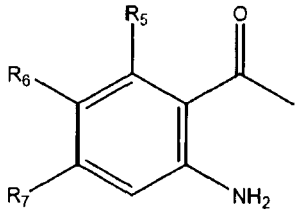
R_5 is hydrogen, methoxy, hydroxyl, or OR_8, or R_5 and R_6 are methylenedioxy provided that R_7 is hydrogen;

R_6 is N,N-dimethylamino, hydroxyl, methoxy, N-morpholino, or N-pyrrolindino, or R_6 and R_7 are methylenedioxy provided that R_5 is hydrogen;

R_7 is hydrogen, hydroxyl, or O-benzyl; and

R_8 is hydrogen; or a pharmaceutically acceptable salt, or solvate thereof, comprising:

reacting a compound of Formula II



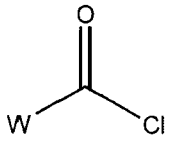
Formula II;

wherein R_5 is hydrogen, hydroxyl, methoxy, or OR_8 or R_5 and R_6 are methylenedioxy provided that R_7 is hydrogen;

R_6 is hydroxyl, N,N-dimethylamino, methoxy, N-morpholino, or N-pyrrolindino or R_6 and R_7 are methylenedioxy provided that R_5 is hydrogen;

R_7 is hydrogen, halo, OR_8, hydroxyl, or O-benzyl; and

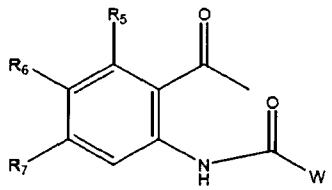
R_8 is hydrogen; with a compound of Formula III



Formula III;

in the presence of a base; wherein W is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, benzo[d] [1,3]dioxol-4-yl, 2,3-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-benzyloxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3-benzyloxy-5-methoxyphenyl, 4-hydroxy-3-methoxyphenyl, 5-hydroxy-2-methoxyphenyl, 2,5-dihydroxyphenyl, benzo[b]furan-3-yl, or naphtha-1-yl;

to afford a compound of Formula IV



Formula IV;

wherein

R is hydrogen;

W is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, benzo[d] [1,3]dioxol-4-yl, 2,3-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-benzyloxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3-benzyloxy-5-methoxyphenyl, 4-hydroxy-3-methoxyphenyl, 5-hydroxy-2-methoxyphenyl, 2,5-dihydroxyphenyl, benzo[b]furan-3-yl, or naphtha-1-yl;

R_5 is hydrogen, methoxy, hydroxyl, or OR_8, or R_5 and R_6 are methylenedioxy provided that R_7 is hydrogen;

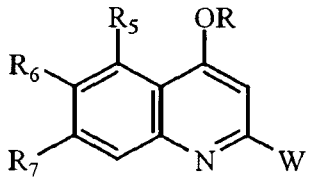
R_6 is N,N-dimethylamino, hydroxyl, methoxy, N-morpholino, or N-pyrrolindino, or R_6 and R_7 are methylenedioxy provided that R_5 is hydrogen;

R_7 is hydrogen, hydroxyl, or O-benzyl; and

R_8 is hydrogen; and

reacting a compound of Formula IV with a base to afford the compound of Formula I.

2. The process of claim 1, further comprising dealkylating the compound of Formula I to afford the compound of Formula I



Formula I

wherein

R is hydrogen;

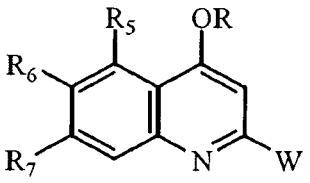
W is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, benzo[d] [1,3]dioxol-4-yl, 2,3-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-benzyloxyphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3-benzyloxy-5-methoxyphenyl, 4-hydroxy-3-methoxyphenyl, 5-hydroxy-2-methoxyphenyl, 2,5-dihydroxyphenyl, or benzo[b]furan-3-yl, naphtha-1-yl;

R_5 is hydrogen, hydroxyl, or methoxy;

R_6 is N,N-dimethylamino, hydroxyl, methoxy, N-morpholino, or N-pyrrolindino, or R_6 and R_7 are methylenedioxy provided that R_5 is hydrogen; and

R_7 is hydrogen.

3. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, or solvate thereof,

wherein:

R is hydrogen, $PO(OH)_2$, $P(=O)(O\text{-}(C_1\text{-}C_{18})alkylenephenyl))_2$, $P(=O)(OH)(OM)$, or $P(=O)(OM)_2$;

W is 2-halophenyl, 3-halophenyl, 4-halophenyl;

R_5 is hydrogen, $(C_1\text{-}C_{18})$alkoxy, hydroxyl, or OR_8;

R_6 is hydroxyl or $(C_1\text{-}C_{18})$alkoxy;

R_7 is hydrogen, hydroxyl, or $O\text{-}(C_1\text{-}C_{18})$alkylenephenyl;

R_8 is hydrogen, $PO(OH)_2$, $P(=O)(O\text{-}(C_1\text{-}C_{18})alkylenephenyl)_2$, $P(=O)(OH)(OM)$, or $P(=O)(OM)_2$, and

M is a monovalent or divalent metal ion, or alkylammonium ion.

4. The compound of claim 3, wherein:

R is hydrogen, $PO(OH)_2$, $P(=O)(O\text{-benzyl})_2$, $P(=O)(OH)(OM)$, or $P(=O)(OM)_2$;

W is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl;

R_5 is hydrogen, methoxy, hydroxyl, or OR_8;

R_6 is hydroxyl or methoxy;

R_7 is hydrogen, hydroxyl, or O-benzyl;

R_8 is hydrogen, $PO(OH)_2$, $P(=O)(O\text{-benzyl})_2$, $P(=O)(OH)(OM)$, or $P(=O)(OM)_2$, and

M is a sodium ion.

5. The compound of claim 4, wherein the compound comprises

2-(2-Fluorophenyl)-5,6-dimethoxyquinolin-4-one,

2-(3-Fluorophenyl)-5,6-dimethoxyquinolin-4-one,

2-(4-Fluorophenyl)-5,6-dimethoxyquinolin-4-one,

7-Benzyloxy-2-(2-fluorophenyl)-6-methoxyquinolin-4-one,

7-Benzyloxy-2-(3-fluorophenyl)-6-methoxyquinolin-4-one,

7-Benzyloxy-2-(4-fluorophenyl)-6-methoxyquinolin-4-one,

2-(2-Fluorophenyl)-5-hydroxy-6-methoxyquinolin-4-one,

2-(3-Fluorophenyl)-5-hydroxy-6-methoxyquinolin-4-one,

2-(4-Fluorophenyl)-5-hydroxy-6-methoxyquinolin-4-one,

2-(2-Fluorophenyl)-5,6-dihydroxyquinolin-4-one,

2-(3-Fluorophenyl)-5,6-dihydroxyquinolin-4-one,

2-(4-Fluorophenyl)-5,6-dihydroxyquinolin-4-one,

2-(2-Fluorophenyl)-7-hydroxy-6-methoxyquinolin-4-one,

2-(3-Fluorophenyl)-6-methoxyquinoline-4,5-diyl bis(dibenzyl phosphate),

2-(3-Fluorophenyl)-6-methoxyquinoline-4,5-diyl bis(dihydrogen phosphate),

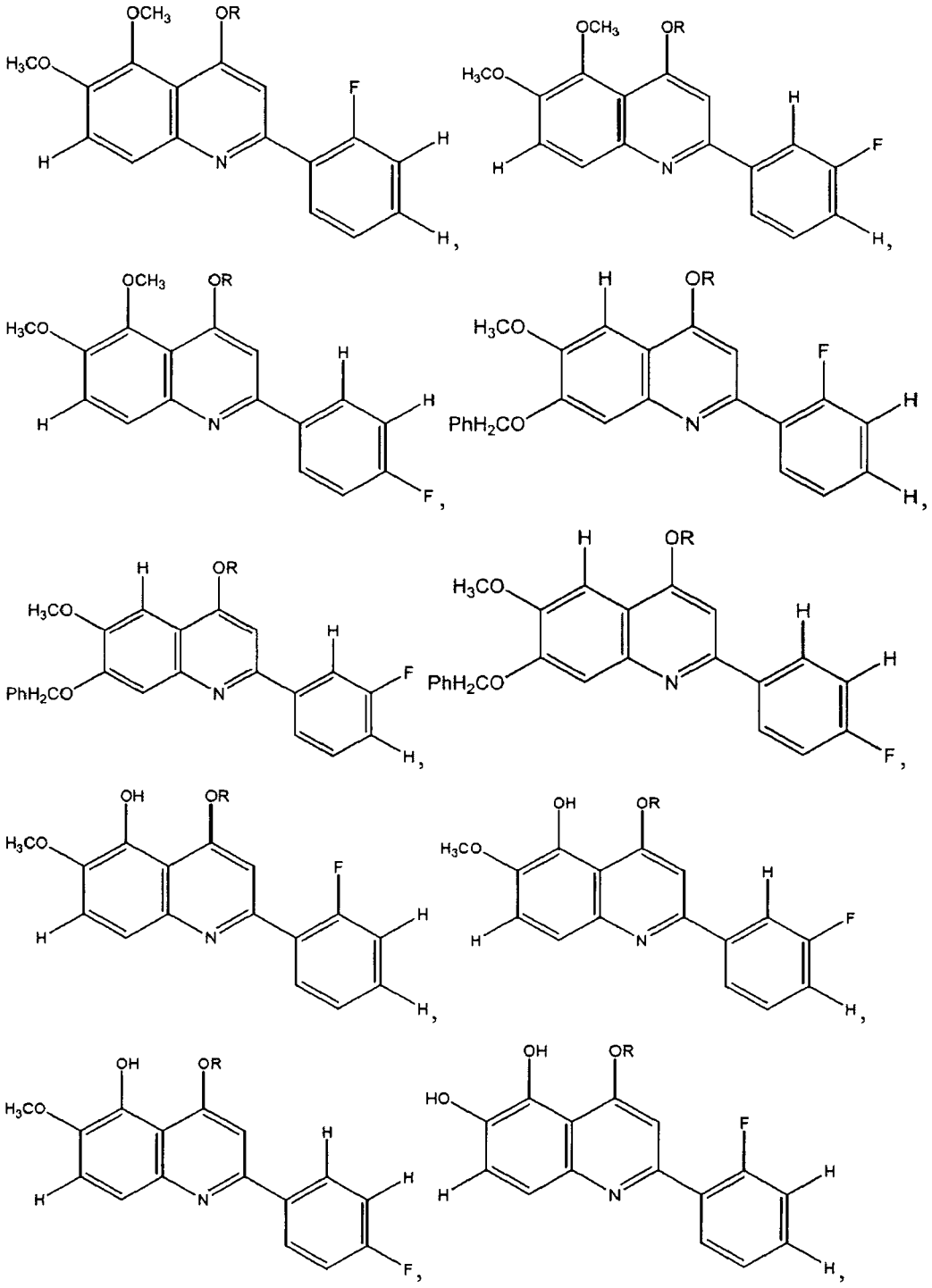
2-(3-Fluorophenyl)-6-methoxyquinoline-4,5-diyl bis(disodium phosphate),

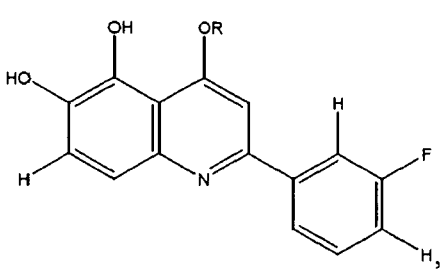
Dibenzyl 2-(3-fluorophenyl)-6-methoxy-4-oxo-1,4-dihydroquinolin-5-yl phosphate,

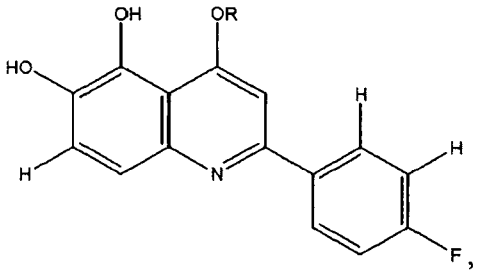
2-(3-Fluorophenyl)-6-methoxy-4-oxo-1,4-dihydroquinolin-5-yl dihydrogen phosphate, or

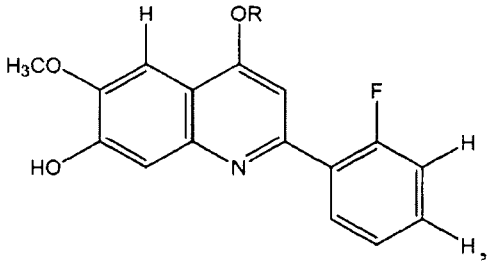
Sodium 2-(3-fluorophenyl)-6-methoxy-4-oxo-1,4-dihydroquinolin-5-yl phosphate.

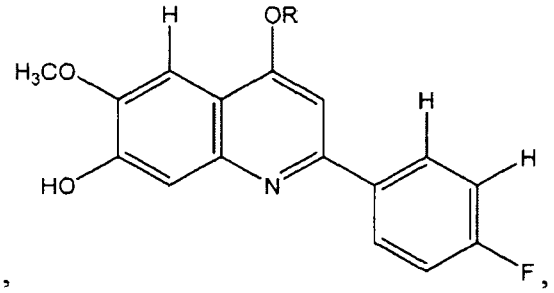
6. The compound of claim 4, wherein the compound comprises

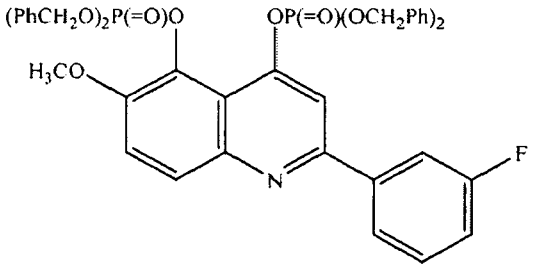












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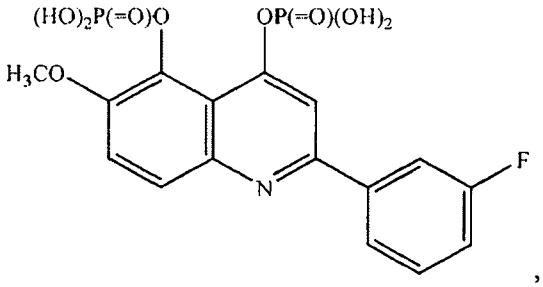

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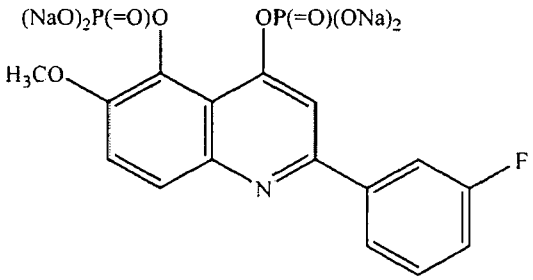

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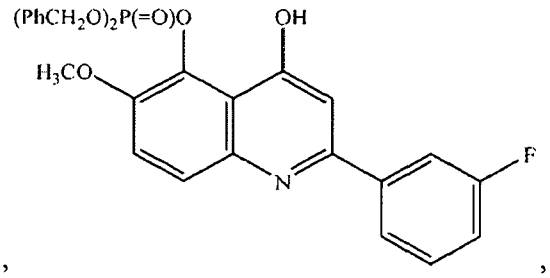

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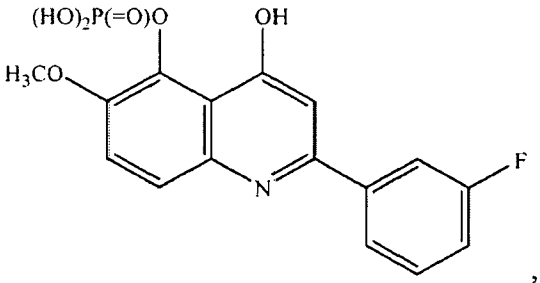
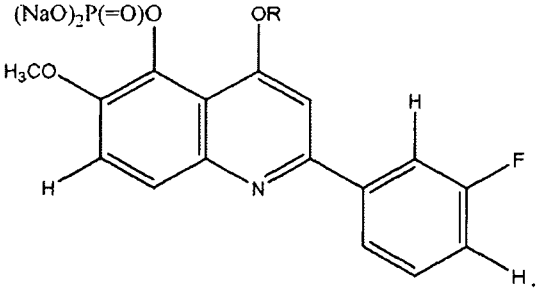


, or



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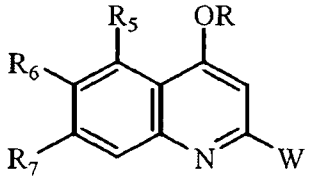
7. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, or solvate thereof,

wherein:

R is hydrogen, $PO(OH)_2$, $P(=O)(O\text{-}(C_1\text{-}C_{18})alkylenephenyl))_2$, $P(=O)(OH)(OM)$, or $P(=O)(OM)_2$;

W is benzo[d] [1,3]dioxol-4-yl, 2,3-di(C_1-C_{18})alkoxyphenyl, 2,5-di(C_1-C_{18})alkoxyphenyl, 2-(C_1-C_{18})alkoxyphenyl, 4-(C_1-C_{18})alkoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 4-hydroxy-3-(C_1-C_{18})alkoxyphenyl, 5-hydroxy-2-(C_1-C_{18})alkoxy phenyl, 3-(O-di(C_1-C_{18})alkylenephenyl))phenyl, 3-(O-dihydrogen phosphate)phenyl, or 2,5-dihydroxyphenyl;

R_5 is hydrogen;

R_6 is hydroxyl, (C_1-C_{18})alkoxy, N,N-di(C_1-C_{18})alkylamino, or N-(C_1-C_{18})cycloalkylamino;

R_7 is hydrogen.

8. The compound of claim 7, wherein:

R is hydrogen;

W is benzo[d] [1,3]dioxol-4-yl, 2,3-dimethoxyphenyl, 2,5-dimethoxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 4-hydroxy-3-methoxyphenyl, 5-hydroxy-2-methoxyphenyl, 3-(O-dibenzylphosphate)phenyl, 3-(O-dihydrogen phosphate)phenyl, or 2,5-dihydroxyphenyl;

R_5 is hydrogen;

R_6 is hydroxyl, methoxy, N,N-dimethylamino, N-morpholino, or N-pyrrolindino; and

R_7 is hydrogen.

9. The compound of claim 8, wherein the compound comprises

2-(benzo[d] [1,3] dioxol-1-yl)-6-morpholinoquinolin-4-one,

2-(benzo[d] [1,3] dioxol-4-yl)-6-pyrrolidinoquinolin-4-one,

2-(2,3-dimethoxyphenyl)-6-morpholinoquinolin-4-one,

2-(2,3-dimethoxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(2,5-dimethoxyphenyl)-6-morpholinoquinolin-4-one,

2-(2,5-dimethoxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(2-methoxyphenyl)-6-morpholinoquinolin-4-one,

2-(2,5-dimethoxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(4-methoxyphenyl)-6-morpholinoquinolin-4-one,

2-(4-methoxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(2-Hydroxyphenyl)-6-morpholinoquinolin-4-one,

2-(2-hydroxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(2-hydroxyphenyl)-6-dimethylaminoquinolin-4-one,

2-(3-Hydroxyphenyl)-6-morpholinoquinolin-4-one,

2-(3-hydroxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(3-hydroxyphenyl)-6-dimethylaminoquinolin-4-one,

2-(4-Hydroxyphenyl)-6-morpholinoquinolin-4-one,

2-(4-hydroxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(4-hydroxyphenyl)-6-dimethylaminoquinolin-4-one,

2-(4-hydroxy-3-methoxyphenyl)-6-morpholinoquinolin-4-one,

2-(5-hydroxy-2-methoxyphenyl)-6-morpholinoquinolin-4-one,

2-(5-hydroxy-2-methoxyphenyl)-6-pyrrolidinoquinolin-4-one,

2-(4-hydroxy-3-methoxyphenyl)-6-pyrrolidinoquinolin-4-one,

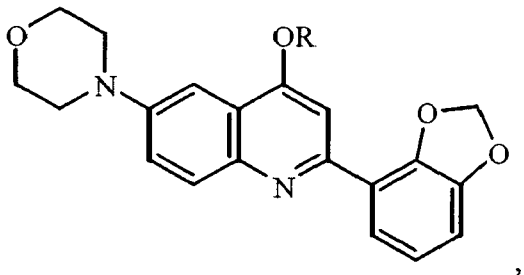
2-(2,5-dihydroxy-phenyl)-6-morpholinoquinolin-4-one,

2-(2,5-dihydroxy-phenyl)-6-pyrrolidinoquinolin-4-one,

Dibenzyl 3-(4-oxo-6-(pyrrolidin-1-yl)-1,4-dihydroquinolin-2-yl)phenyl phosphate, or

3-(4-Oxo-6-(pyrrolidin-1-yl)-1,4-dihydroquinolin-2-yl)phenyl dihydrogen phosphate.

10. The compound of claim 8, wherein the compound comprises



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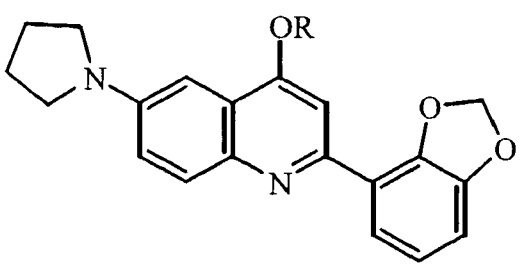

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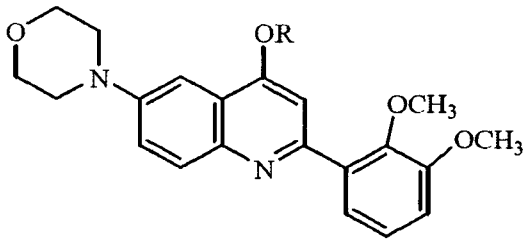
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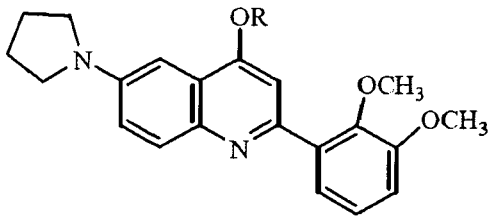
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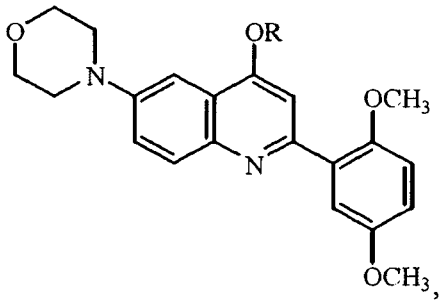
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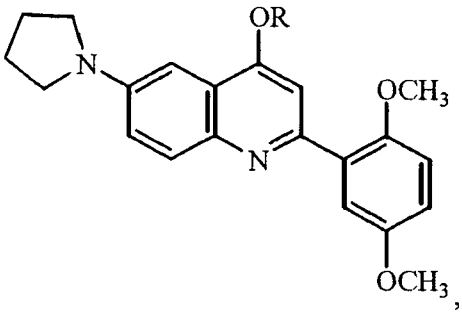
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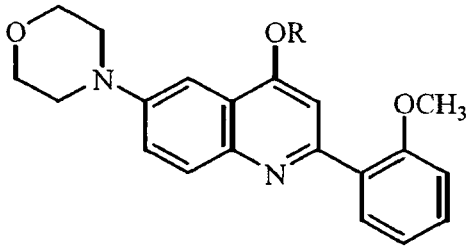
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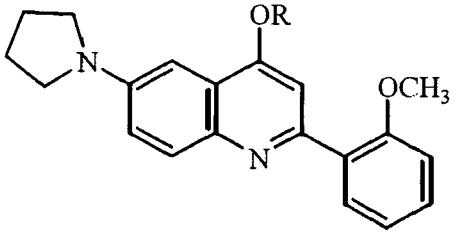
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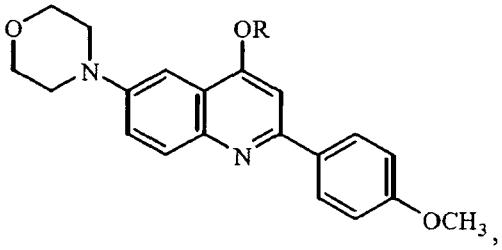
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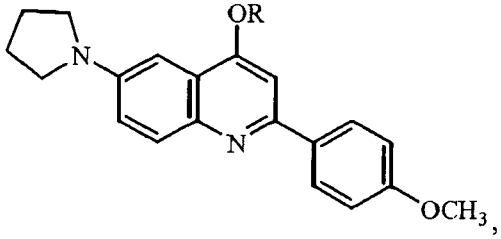
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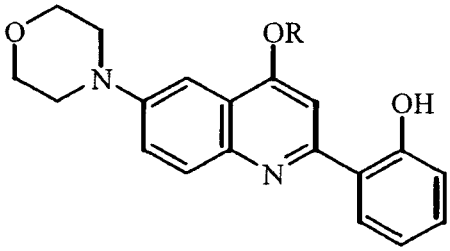
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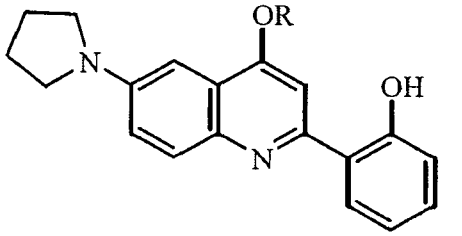
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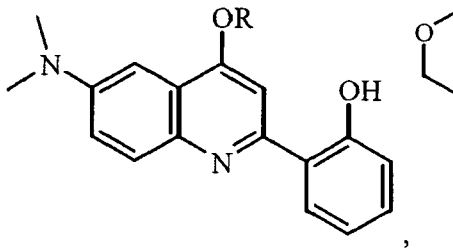
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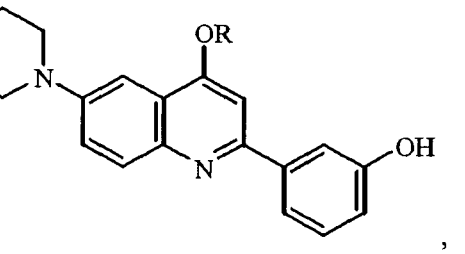
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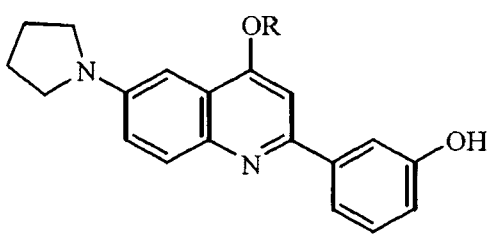
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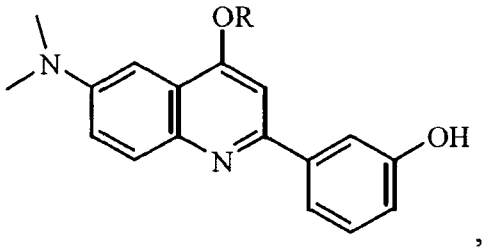
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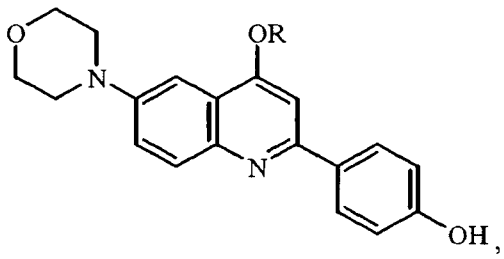
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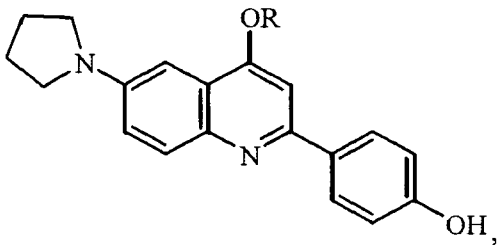
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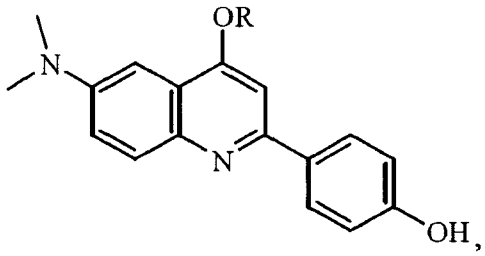
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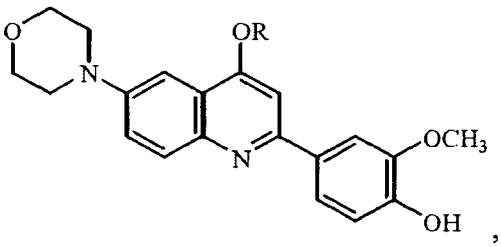
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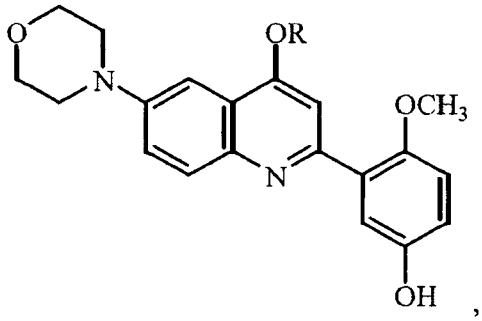
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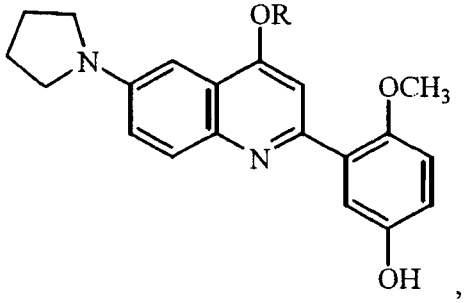
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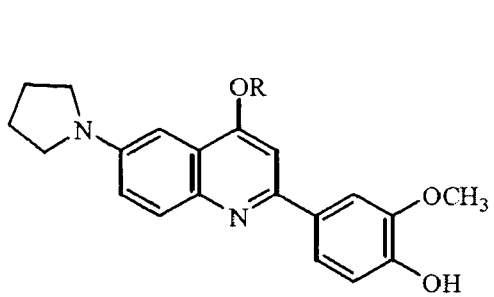
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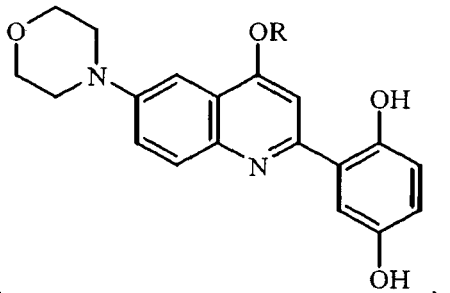
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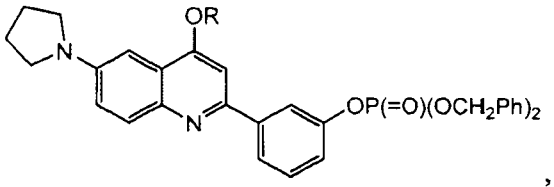

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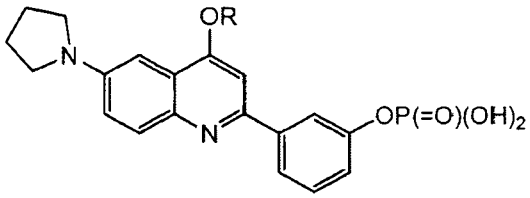

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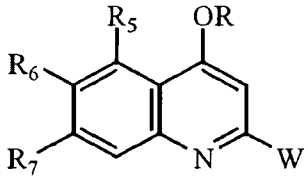
11. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, or solvate thereof,

wherein:

R is hydrogen;

W is 2-halophenyl, 3-halophenyl, 4-halophenyl;

R_5 and R_6 are (C_1-C_{18})alkylenedioxy provided that R_7 is hydrogen; and

R_8 is hydrogen.

12. The compound of claim 11,

wherein:

R is hydrogen;

W is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl;

R_5 and R_6 are methylenedioxy provided that R_7 is hydrogen; and

R_8 is hydrogen.

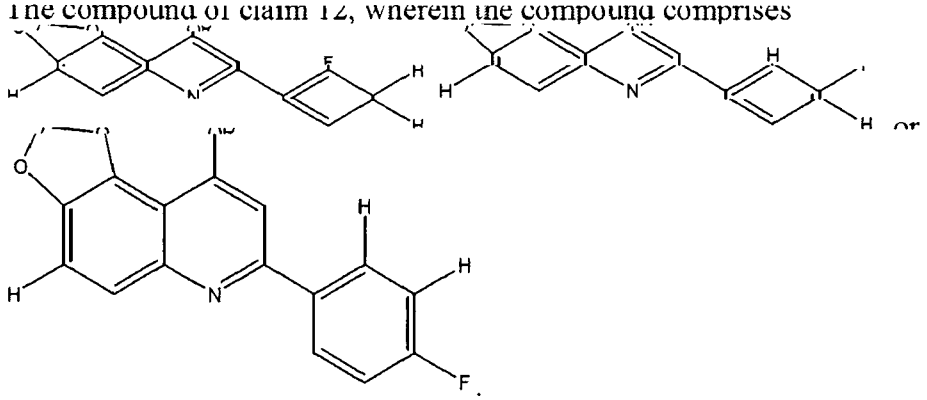
13. The compound of claim 12, wherein the compound comprises

2-(2-Fluorophenyl)-5,6-methylenedioxyquinolin-4-one,

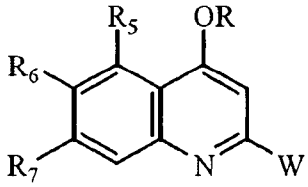
2-(3-Fluorophenyl)-5,6-methylenedioxyquinolin-4-one, or

2-(4-Fluorophenyl)-5,6-methylenedioxyquinolin-4-one.

14. The compound of claim 12, wherein the compound comprises



15. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, or solvate thereof,

wherein:

R is hydrogen, $P(=O)(OH)_2$, $P(=O)(O\text{-}(C_1\text{-}C_{18})alkylenephenyl)_2$,

W is naphtha-1-yl, benzo[b]furan-3-yl, 3-([bis-[(C_1-C_{18})alkylenephenyl)oxy]]phosphoryl)oxy-5-(C_1-C_{18})alkoxy phenyl, 3-(dihydrogen)phosphate-5-(C_1-C_{18})alkoxy phenyl; and

R_6 and R_7 are (C_1-C_{18})alkylenedioxy provided that R_5 is hydrogen.

16. The compound of claim 15,

wherein:

R is hydrogen, $P(=O)(OH)_2$, $P(=O)(O\text{-benzyl})_2$,

W is naphtha-1-yl, benzo[b]furan-3-yl, 3-([bis-[(benzyl)oxy]]phosphoryl)oxy-5-methoxyphenyl, 3-(dihydrogen)phosphate-5-methoxyphenyl; and

R_6 and R_7 are methylenedioxy provided that R_5 is hydrogen.

17. The compound of claim 15, wherein the compound comprises

Dibenzyl 2-(1-naphthalenyl)-6,7-methylenedioxyquinolin-4-yl phosphate,

2-(1-Naphthalenyl)-6,7-methylenedioxyquinolin-4-yl dihydrogen phosphate,

Dibenzyl 2-(3-benzo[b]furyl)-6,7-methylenedioxyquinolin-4-yl phosphate,

2-(3-Benzo[b]furyl)-6,7-methylenedioxyquinolin-4-yl dihydrogen phosphate,

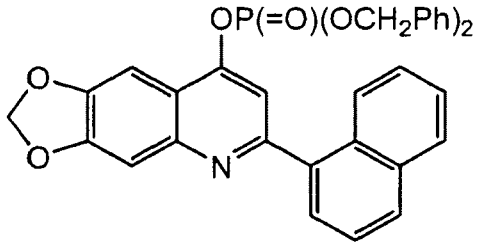
2-(3-Hydroxy-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-one,

Dibenzyl 2-(3-([bis-[(benzyl)oxy]]phosphoryl)oxy-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-yl phosphate,

2-(3-([bis-[(benzyl)oxy]]phosphoryl)oxy-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-one, or

2-(3-(dihydrogen)phosphate-5-methoxyphenyl)-6,7-methylenedioxyquinolin-4-one.

18. The compound of claim 15, wherein the compound comprises



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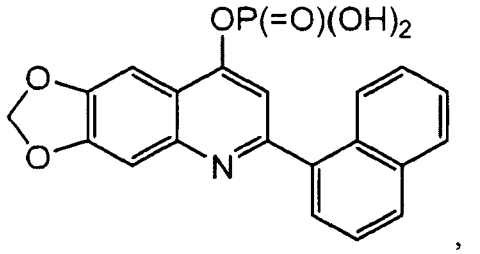

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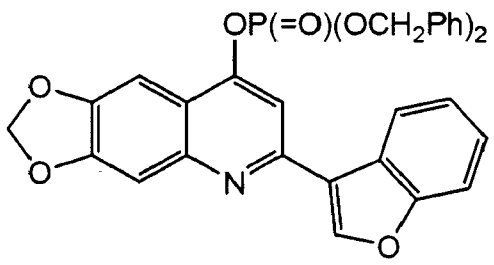

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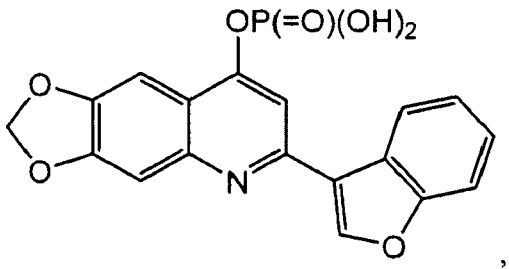

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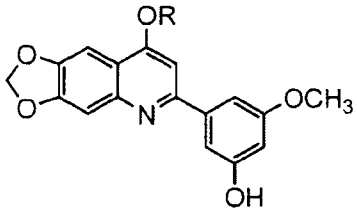

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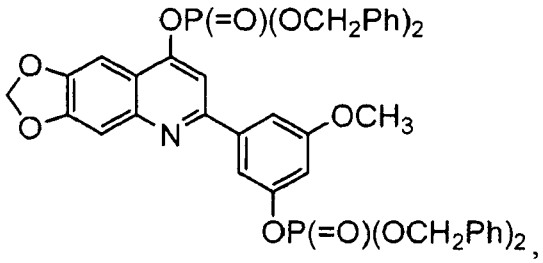

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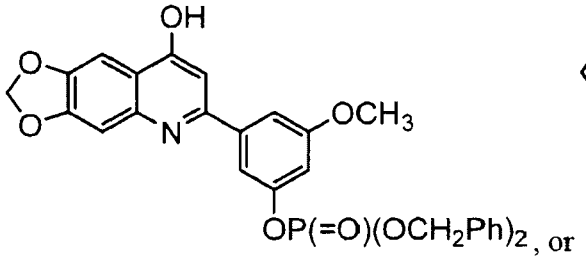

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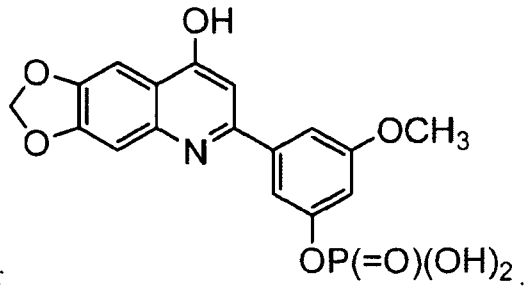

.

19. A composition comprising an effective amount of a compound according to any of claims 3-18 for use in treating cancer in a subject in need thereof.

20. The composition of claim 19, wherein the cancer is lung cancer, colon cancer, breast cancer, liver cancer, prostate cancer, ovarian cancer, leukemia, lymphoma, pancreatic cancer, skin cancer, brain tumor, kidney cancer, bladder cancer, esophagus cancer, gastric cancer, head and neck cancers cervical cancer, endometrial cancer, thyroid cancer, bone cancer, or soft tissue sarcoma.

STATEMETN UNDER ARTICLE 19

Claims 1-18 have been canceled. Claims 19-20 (currently claims 1 and 2) have been amended to more clearly point out and distinctly claim the present invention. In addition, new claims (currently claims 3-20) have been added. As a result, claims 1-20 are now pending in this application.

The basis for new claims 3-6 appears in, for example, the specification, page 1, line 27, page 2, line 13 and original claims 1-2, and compound Nos. 16-18, 22-43 and 45-53 in Table 7 in the Specification from pages 76, line 15 to page 89, line 2.

The basis for new claims 7-10 appears, for example, in the original claims 1-2 and compound Nos. 124-147 in Table 7 in the Specification from pages 76, line 15 to page 89, line 2.

The basis for new claims 11-14 appears, for example, in the original claims 1-2 and in compound Nos. 19-21 in Table 7 in the Specification from pages 76, line 15 to page 89, line 2.

The basis for new claims 15-18 appears, for example, in the original claims 1-2 and in compound Nos. 152-153, 156-158 and 166-169 in Table 7 in the Specification from pages 76, line 15 to page 89, line 2.

The basis for new claims 19-20 appears, for example, FIGs. 3A-3C.

No new subject matter is introduced by this Amendment.

It is respectfully submitted that none of the cited references disclose the subject matter of the claimed invention. Thus, the amended claims and new claims are novel and non-obvious over the cited references.

It is thus believed that the application is in condition for allowance at least for the above reasons and such allowance is respectfully requested.

If there are any errors or irregularities in this Amendment, the Authorized Officer I s respectfully requested to notify the undersigned by telefacsimile at (650) 472-9153 or by telephone at (650) 557-4464/

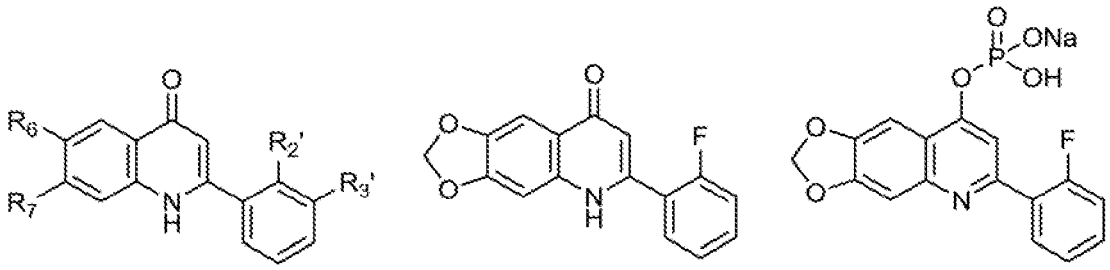

FIG. 1

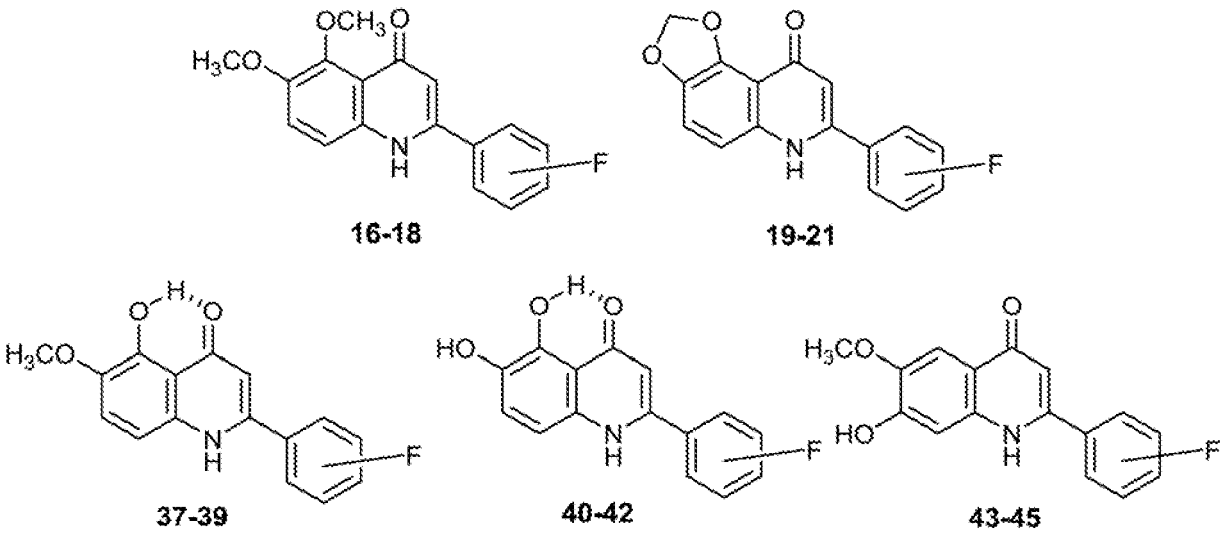

FIG. 2

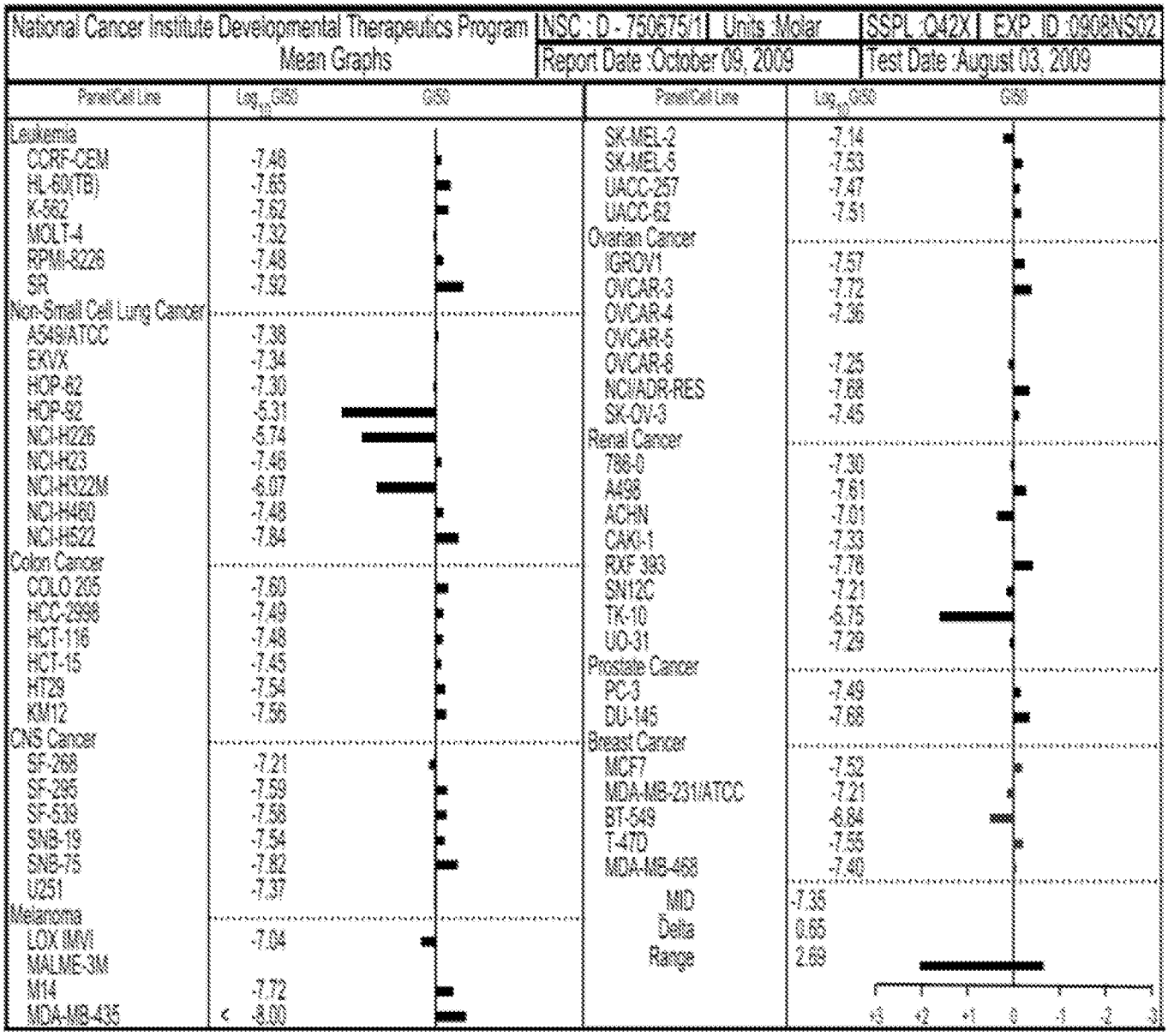
National Cancer Institute Developmental Therapeutics Program
Mean Graphs
NSC : D - 750675/1 | Units :Molar
Report Date :October 09, 2009
SSPL :O42X | EXP. ID :0908NS02
Test Date :August 03, 2009
Panel/Cell Line
Log10 GI50
GI50
Leukemia
CCRF-CEM -7.46
HL-60(TB) -7.65
K-562 -7.62
MOLT-4 -7.52
RPMI-8226 -7.46
SR -7.52
Non-Small Cell Lung Cancer
A549/ATCC -7.38
EKVX -7.34
HOP-62 -7.30
HOP-92 -5.31
NCI-H226 -5.74
NCI-H23 -7.46
NCI-H322M -6.07
NCI-H460 -7.46
NCI-H522 -7.84
Colon Cancer
COLO 205 -7.60
HCC-2998 -7.49
HCT-116 -7.46
HCT-15 -7.45
HT29 -7.54
KM12 -7.56
CNS Cancer
SF-268 -7.21
SF-295 -7.59
SF-539 -7.56
SNB-19 -7.54
SNB-75 -7.62
U251 -7.37
Melanoma
LOX IMVI -7.04
MALME-3M
M14 -7.72
MDA-MB-435 < -8.00
SK-MEL-2 -7.14
SK-MEL-5 -7.53
UACC-257 -7.47
UACC-62 -7.51
Ovarian Cancer
IGROV1 -7.57
OVCAR-3 -7.72
OVCAR-4 -7.36
OVCAR-5
OVCAR-8 -7.25
NCI/ADR-RES -7.68
SK-OV-3 -7.46
Renal Cancer
786-0 -7.38
A498 -7.61
ACHN -7.01
CAKI-1 -7.53
RXF 393 -7.78
SN12C -7.21
TK-10 -5.75
UO-31 -7.29
Prostate Cancer
PC-3 -7.49
DU-145 -7.68
Breast Cancer
MCF7 -7.52
MDA-MB-231/ATCC -7.21
BT-549 -6.64
T-47D -7.65
MDA-MB-468 -7.49
MID -7.35
Delta 0.65
Range 2.69
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FIG. 3A

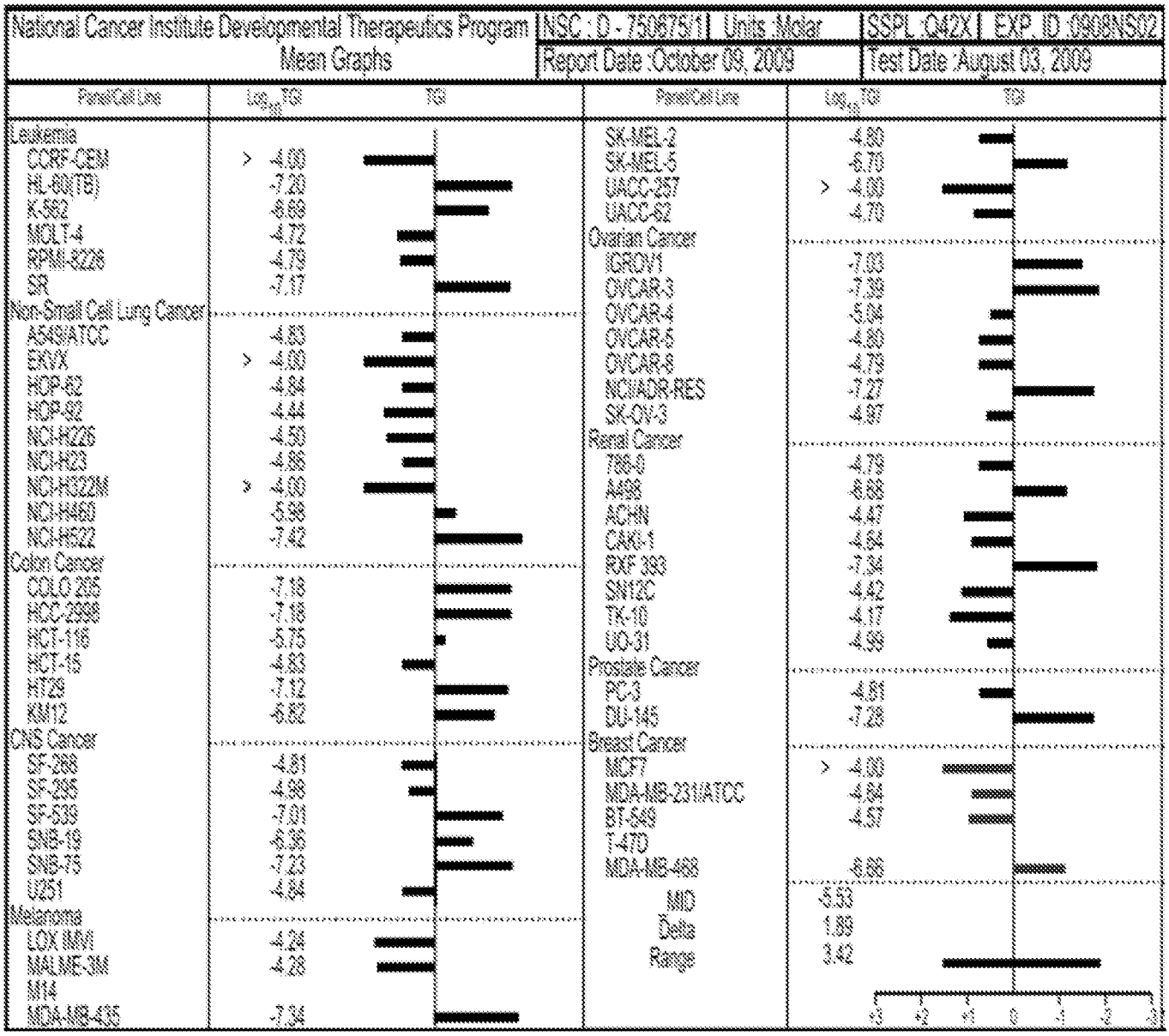

National Cancer Institute Developmental Therapeutics Program
Mean Graphs
NSC : D - 750575/1 | Units :Molar
Report Date :October 09, 2009
SSPL :042X | EXP. ID :0908NS02
Test Date :August 03, 2009
Panel/Cell Line
Log10 TGI
TGI
Leukemia
CCRF-CEM
HL-60(TB)
K-562
MOLT-4
RPMI-8226
SR
Non-Small Cell Lung Cancer
A549/ATCC
EKVX
HOP-62
HOP-92
NCI-H226
NCI-H23
NCI-H322M
NCI-H460
NCI-H522
Colon Cancer
COLO 205
HCC-2998
HCT-116
HCT-15
HT29
KM12
CNS Cancer
SF-268
SF-295
SF-539
SNB-19
SNB-75
U251
Melanoma
LOX IMVI
MALME-3M
M14
MDA-MB-435
SK-MEL-2
SK-MEL-5
UACC-257
UACC-62
Ovarian Cancer
IGROV1
OVCAR-3
OVCAR-4
OVCAR-5
OVCAR-8
NCI/ADR-RES
SK-OV-3
Renal Cancer
786-0
A498
ACHN
CAKI-1
RXF 393
SN12C
TK-10
UO-31
Prostate Cancer
PC-3
DU-145
Breast Cancer
MCF7
MDA-MB-231/ATCC
BT-549
T-47D
MDA-MB-468
MID
Delta
Range

FIG. 3B

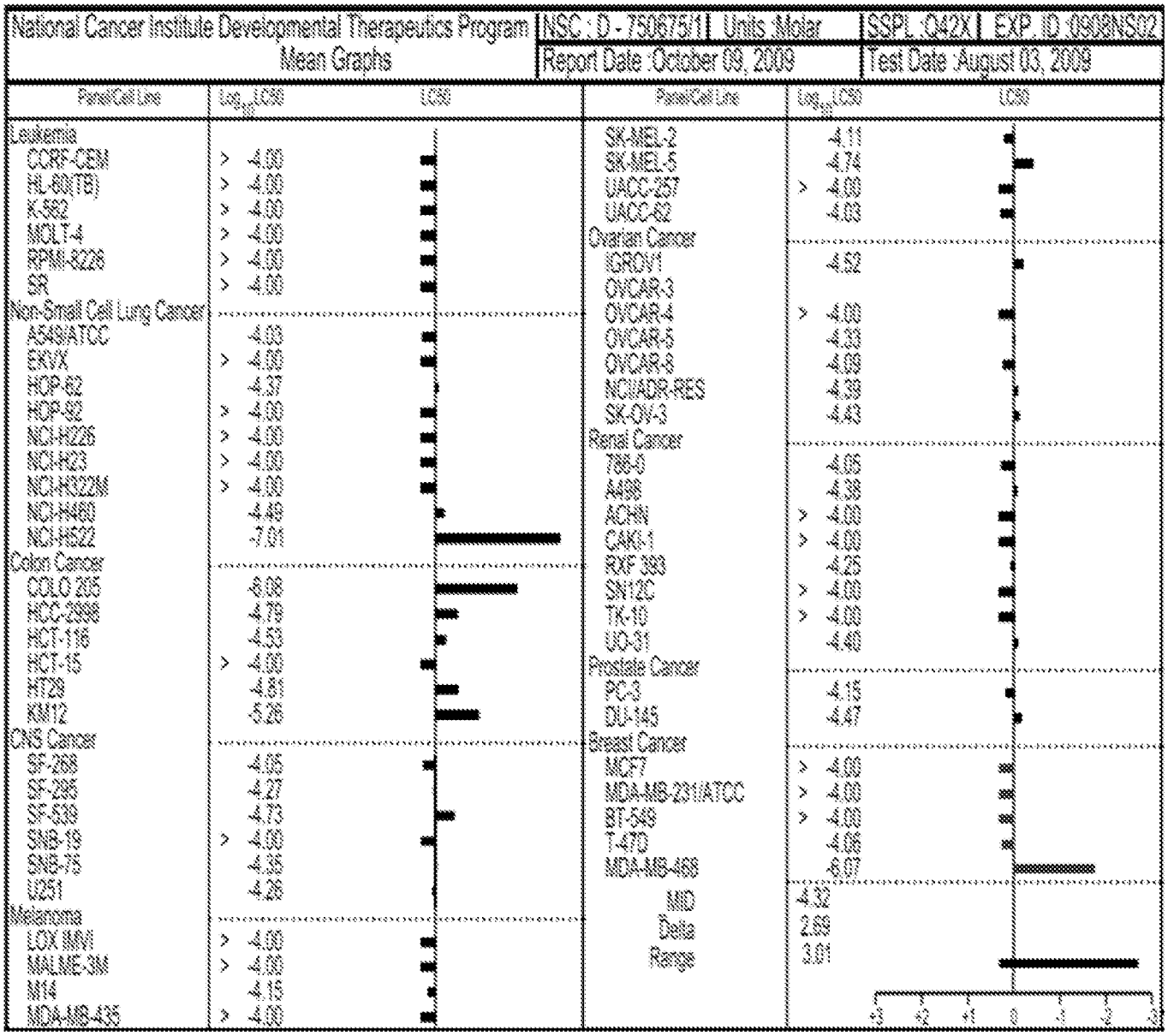

National Cancer Institute Developmental Therapeutics Program
Mean Graphs
NSC : D - 750675/1 | Units :Molar
Report Date :October 09, 2009
SSPL :042X | EXP. ID :09OSNS02
Test Date :August 03, 2009
Panel/Cell Line
Log10 LC50
LC50
Leukemia
CCRF-CEM > -4.00
HL-60(TB) > -4.00
K-562 > -4.00
MOLT-4 > -4.00
RPMI-8226 > -4.00
SR > -4.00
Non-Small Cell Lung Cancer
A549/ATCC -4.03
EKVX > -4.00
HOP-62 -4.37
HOP-92 > -4.00
NCI-H226 > -4.00
NCI-H23 > -4.00
NCI-H322M > -4.00
NCI-H460 -4.49
NCI-H522 -7.01
Colon Cancer
COLO 205 -6.08
HCC-2998 -4.79
HCT-116 -4.53
HCT-15 > -4.00
HT29 -4.81
KM12 -5.26
CNS Cancer
SF-268 -4.05
SF-295 -4.27
SF-539 -4.73
SNB-19 > -4.00
SNB-75 -4.35
U251 -4.26
Melanoma
LOX IMVI > -4.00
MALME-3M > -4.00
M14 -4.15
MDA-MB-435 > -4.00
SK-MEL-2 -4.11
SK-MEL-5 -4.74
UACC-257 > -4.00
UACC-62 -4.03
Ovarian Cancer
IGROV1 -4.52
OVCAR-3
OVCAR-4 > -4.00
OVCAR-5 -4.33
OVCAR-8 -4.09
NCI/ADR-RES -4.39
SK-OV-3 -4.43
Renal Cancer
786-0 -4.05
A498 -4.38
ACHN > -4.00
CAKI-1 > -4.00
RXF 393 -4.25
SN12C > -4.00
TK-10 > -4.00
UO-31 -4.40
Prostate Cancer
PC-3 -4.15
DU-145 -4.47
Breast Cancer
MCF7 > -4.00
MDA-MB-231/ATCC > -4.00
BT-549 > -4.00
T-47D -4.06
MDA-MB-468 -6.07
MID 4.32
Delta 2.69
Range 3.01
+3 +2 +1 0 -1 -2 -3

FIG. 3C

FIG. 4A

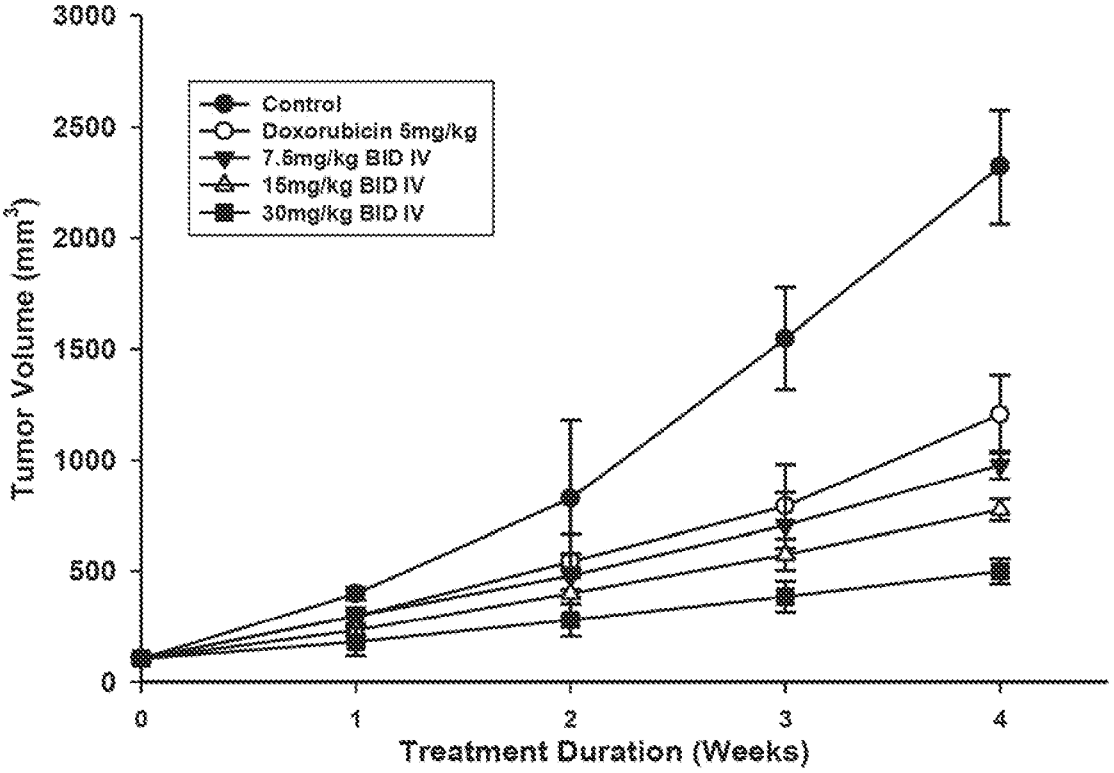

Control
Doxorubicin 5mg/kg
7.5mg/kg BID IV
15mg/kg BID IV
30mg/kg BID IV
Tumor Volume (mm3)
3000
2500
2000
1500
1000
500
0
0
1
2
3
4
Treatment Duration (Weeks)

FIG. 4B

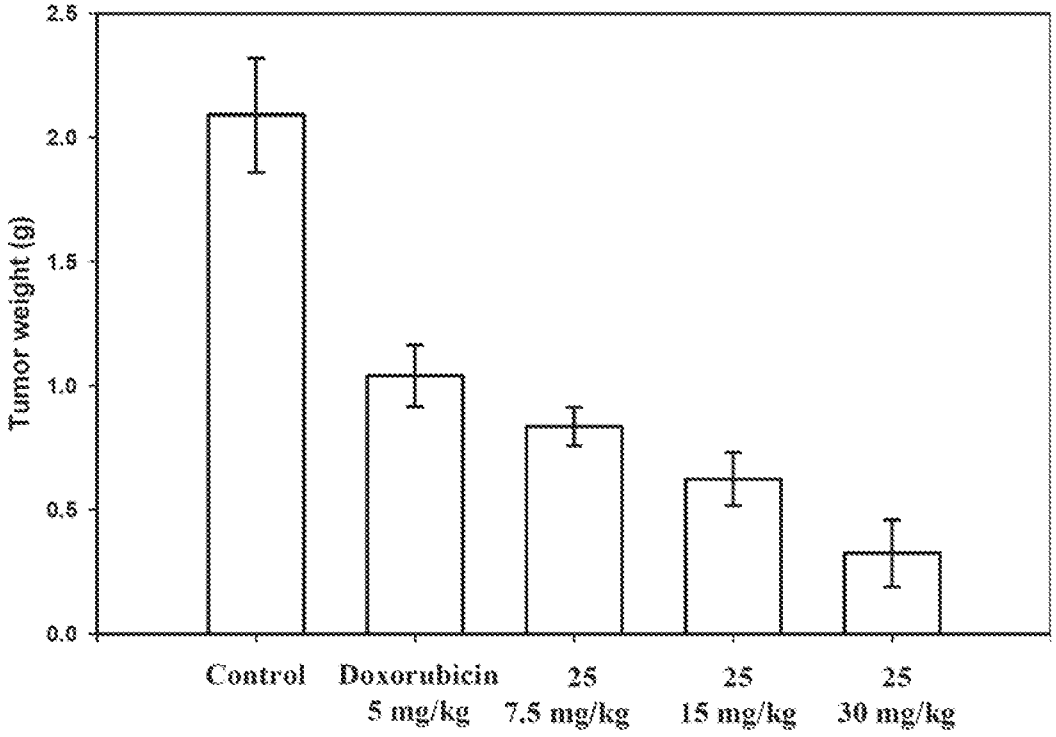

Tumor weight (g)
2.5
2.0
1.5
1.0
0.5
0.0
Control
Doxorubicin 5 mg/kg
25 7.5 mg/kg
25 15 mg/kg
25 30 mg/kg

FIG. 4C

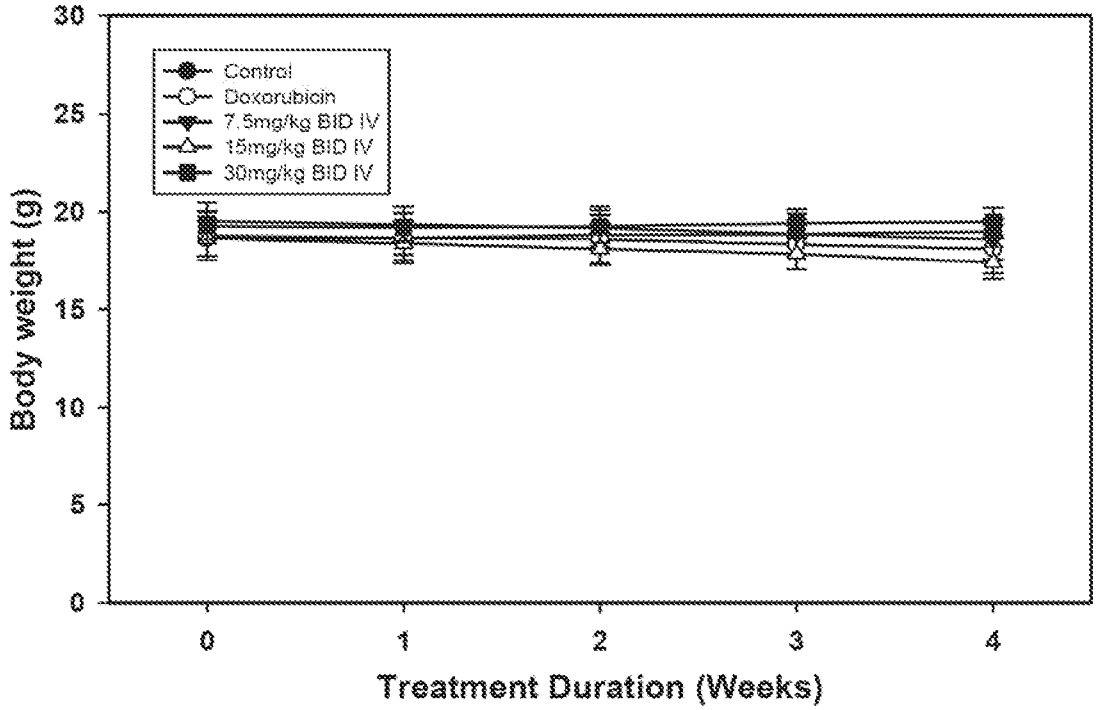

Control
Doxorubicin
7.5mg/kg BID IV
15mg/kg BID IV
30mg/kg BID IV
Body weight (g)
0
5
10
15
20
25
30
0
1
2
3
4
Treatment Duration (Weeks)

FIG. 4D

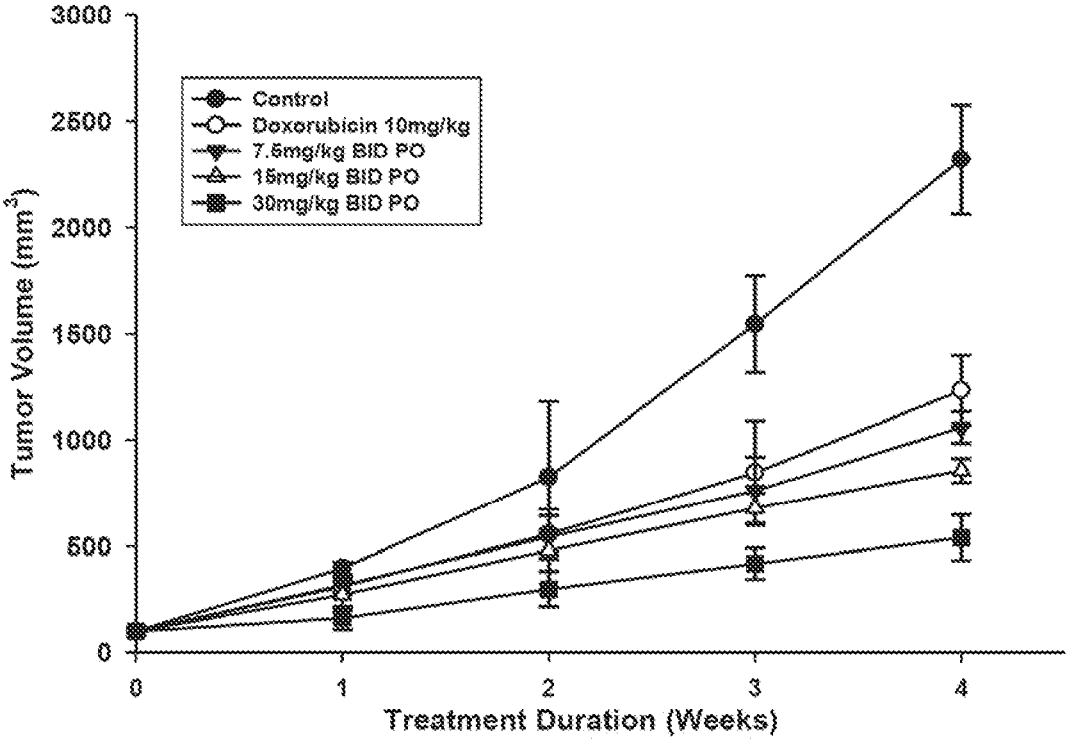

Control
Doxorubicin 10mg/kg
7.5mg/kg BID PO
15mg/kg BID PO
30mg/kg BID PO
Tumor Volume (mm3)
0
500
1000
1500
2000
2500
3000
0
1
2
3
4
Treatment Duration (Weeks)

FIG. 4E

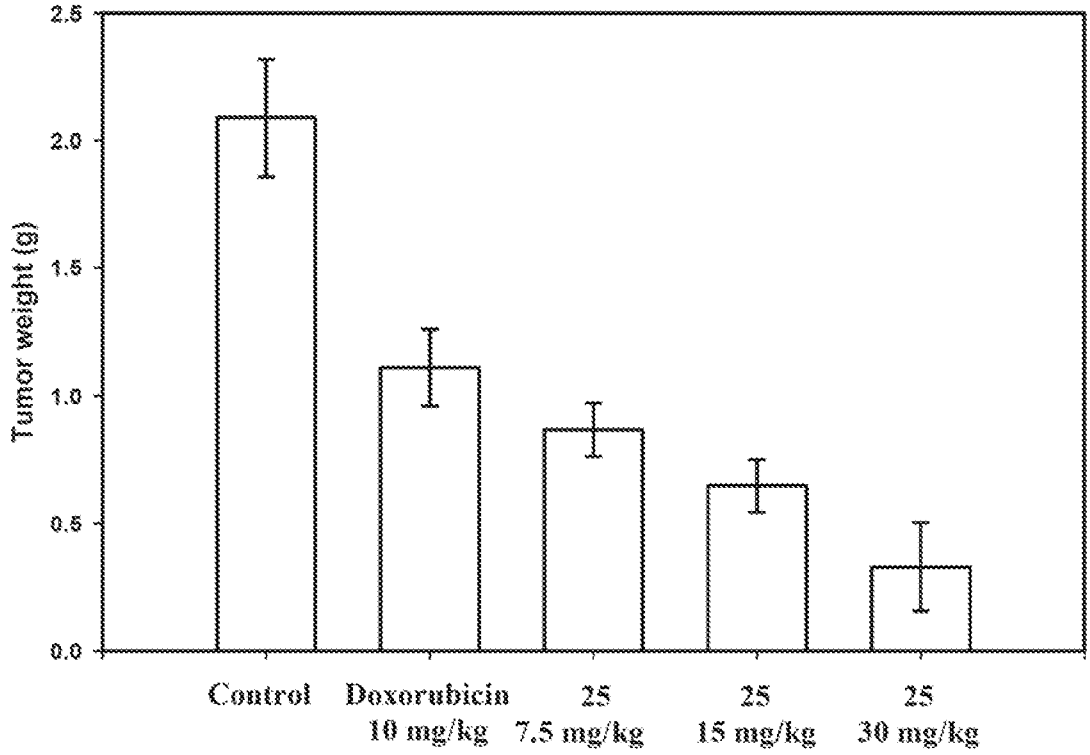

Tumor weight (g)
2.5
2.0
1.5
1.0
0.5
0.0
Control
Doxorubicin 10 mg/kg
25 7.5 mg/kg
25 15 mg/kg
25 30 mg/kg

FIG. 4F

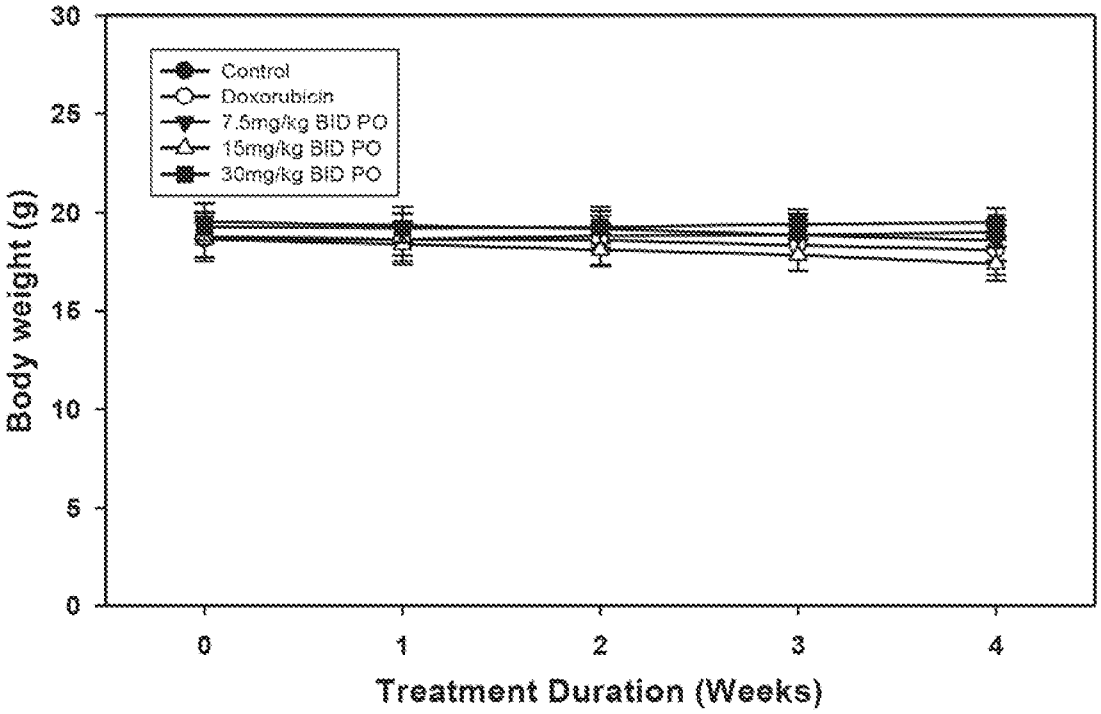

Body weight (g)
30
25
20
15
10
5
0
Control
Doxorubicin
7.5mg/kg BID PO
15mg/kg BID PO
30mg/kg BID PO
0
1
2
3
4
Treatment Duration (Weeks)

FIG. 5A

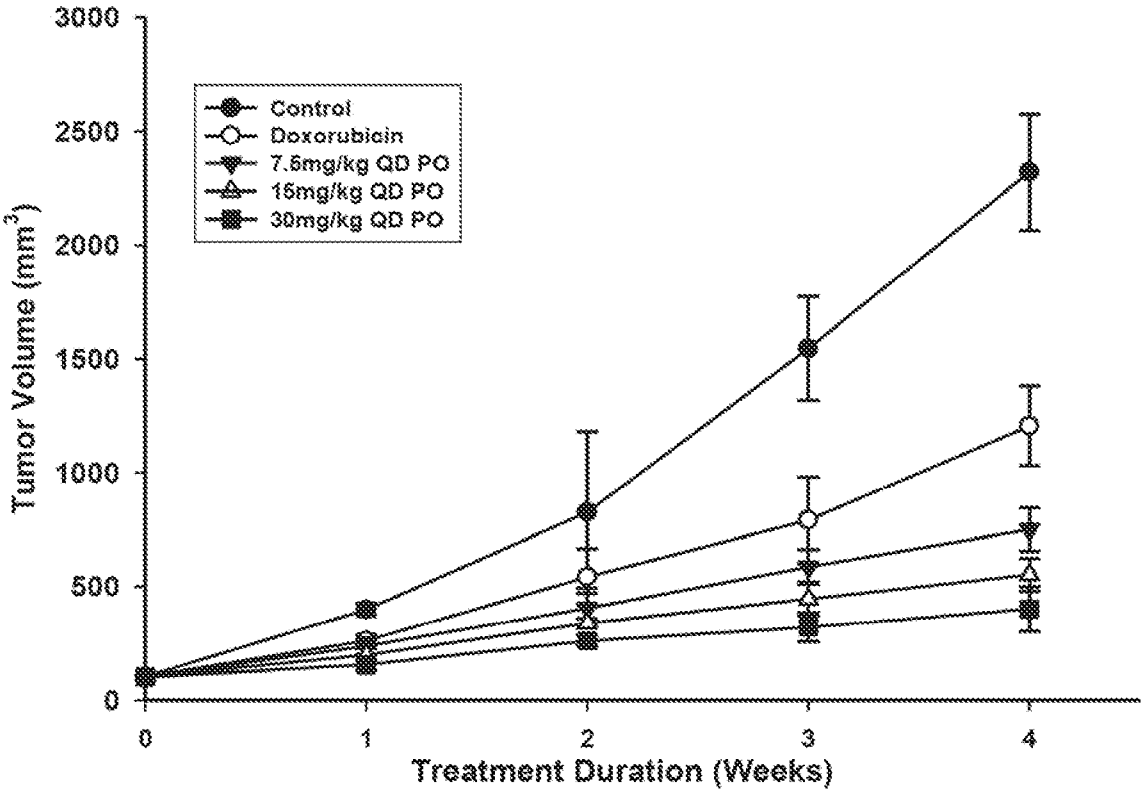

3000
2500
2000
1500
1000
500
0
Tumor Volume (mm3)
0
1
2
3
4
Treatment Duration (Weeks)
Control
Doxorubicin
7.5mg/kg QD PO
15mg/kg QD PO
30mg/kg QD PO

FIG. 5B

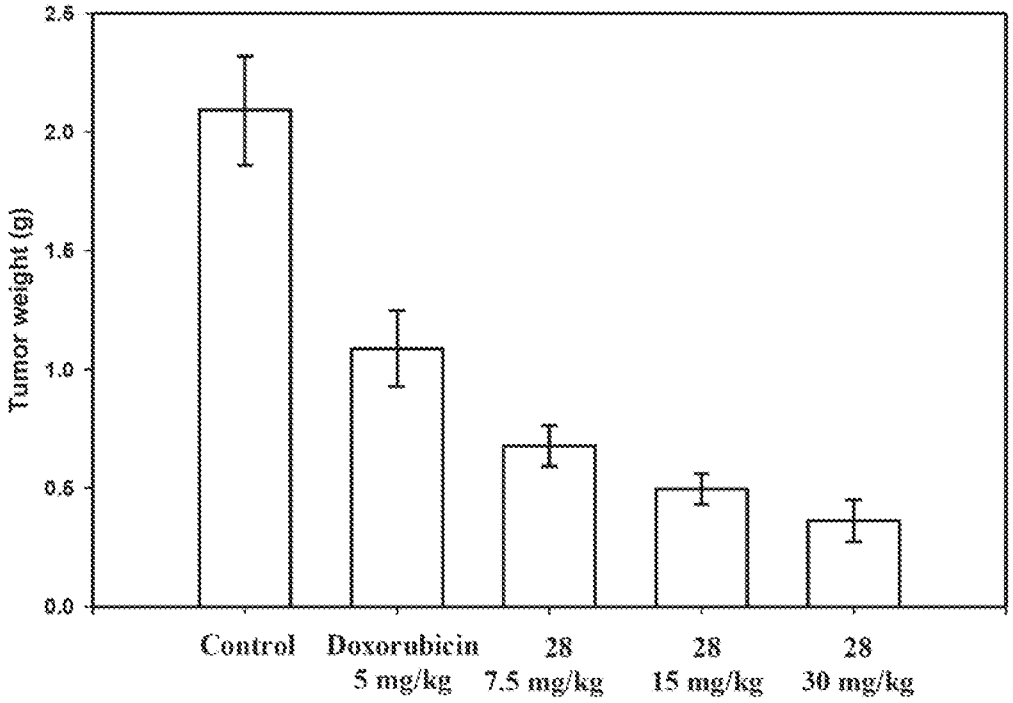

2.5
2.0
1.5
1.0
0.5
0.0
Tumor weight (g)
Control
Doxorubicin 5 mg/kg
28 7.5 mg/kg
28 15 mg/kg
28 30 mg/kg

FIG. 5C

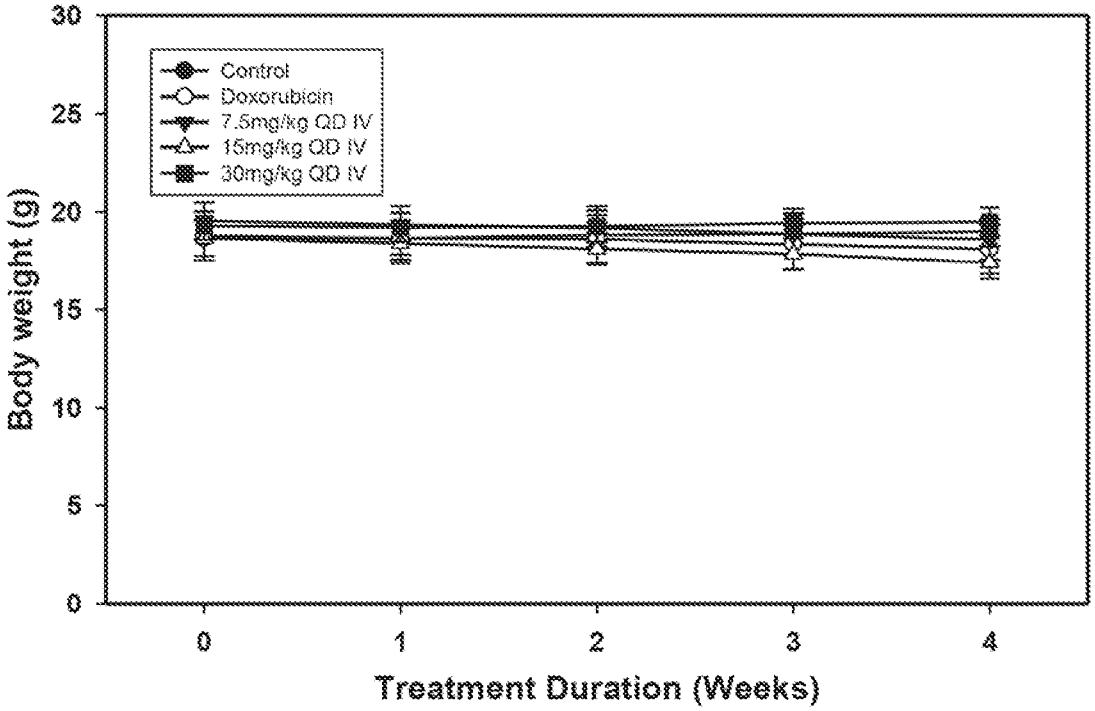

Control
Doxorubicin
7.5mg/kg QD IV
15mg/kg QD IV
30mg/kg QD IV
Body weight (g)
0
5
10
15
20
25
30
0
1
2
3
4
Treatment Duration (Weeks)

FIG. 5D

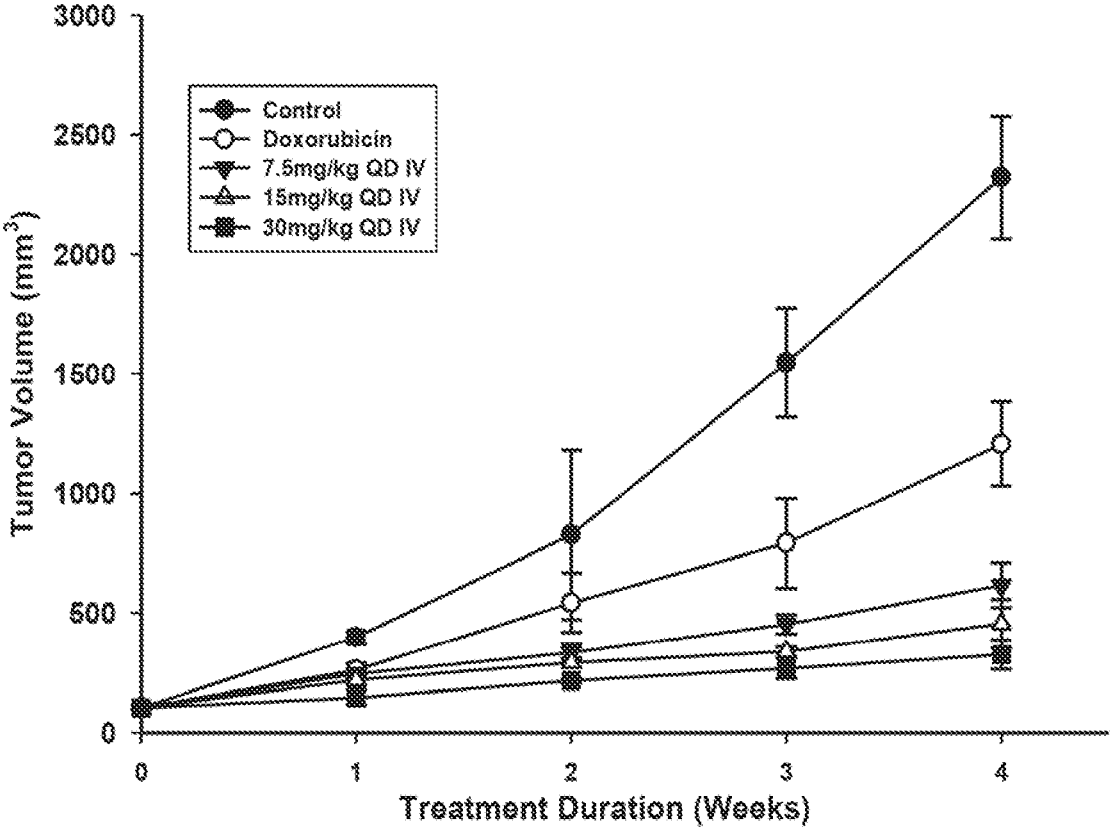

Control
Doxorubicin
7.5mg/kg QD IV
15mg/kg QD IV
30mg/kg QD IV
Tumor Volume (mm3)
0
500
1000
1500
2000
2500
3000
0
1
2
3
4
Treatment Duration (Weeks)

FIG. 5E

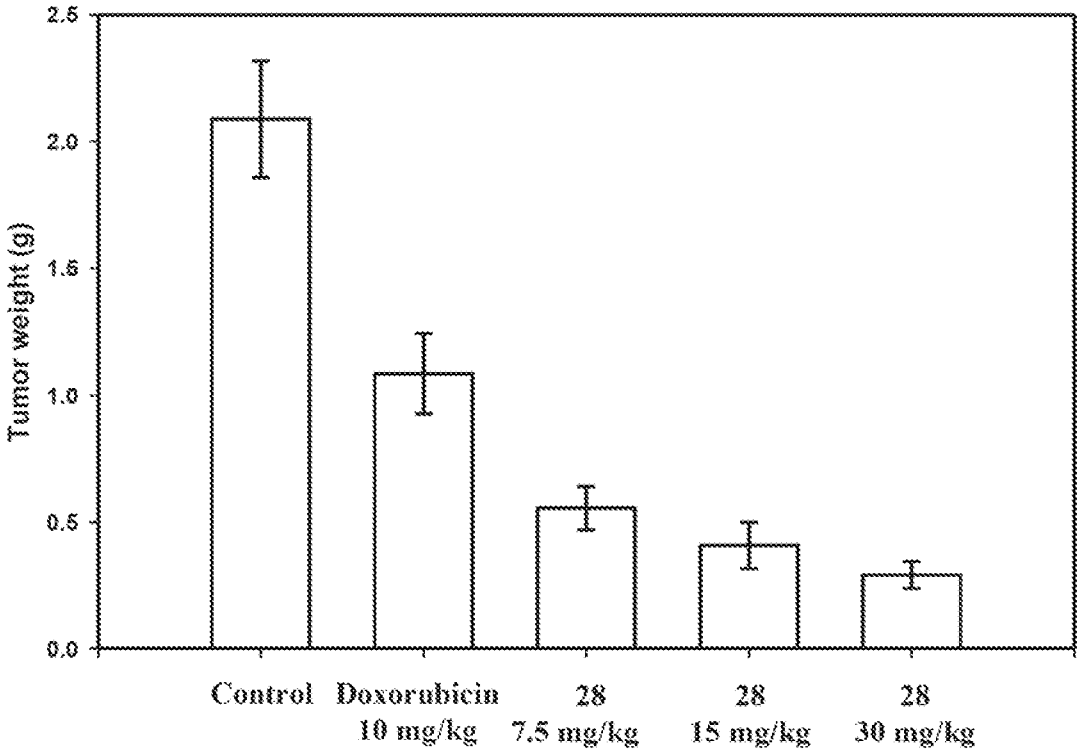

Tumor weight (g)
2.5
2.0
1.5
1.0
0.5
0.0
Control
Doxorubicin 10 mg/kg
28 7.5 mg/kg
28 15 mg/kg
28 30 mg/kg

FIG. 5F

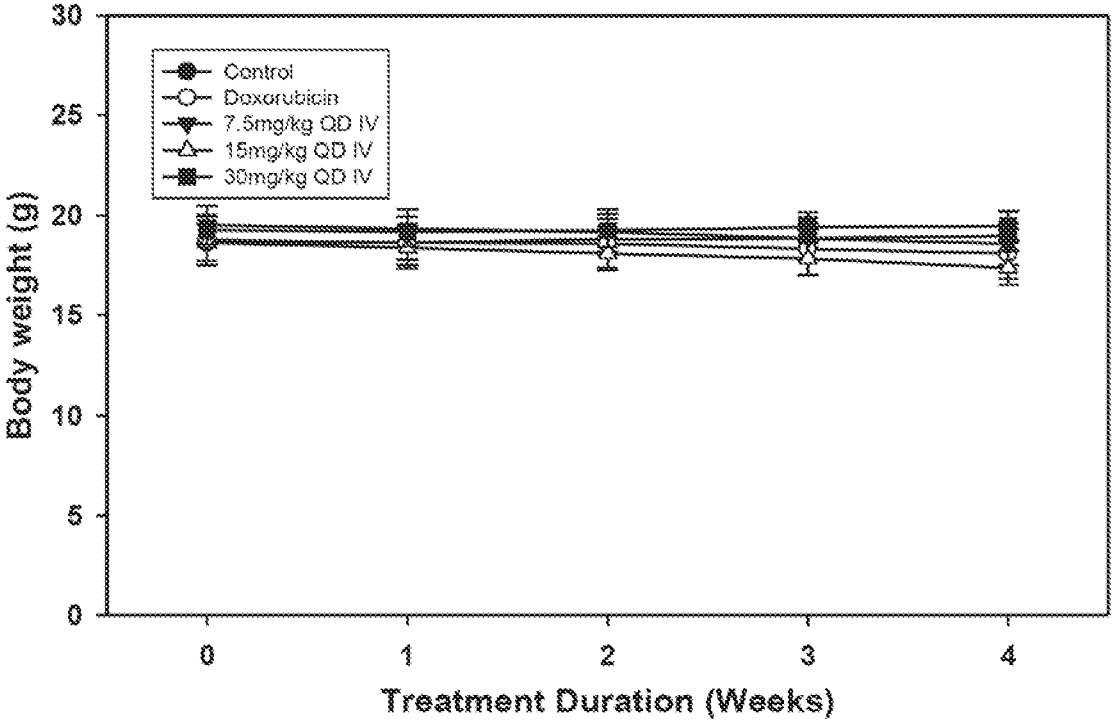

Body weight (g)
30
25
20
15
10
5
0
Control
Doxorubicin
7.5mg/kg QD IV
15mg/kg QD IV
30mg/kg QD IV
0
1
2
3
4
Treatment Duration (Weeks)

FIG. 6A

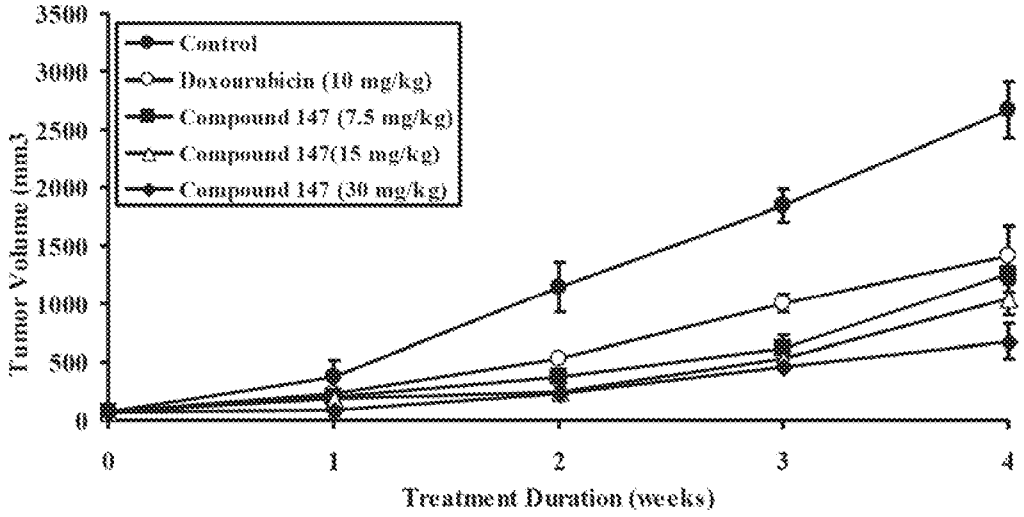


FIG. 6B

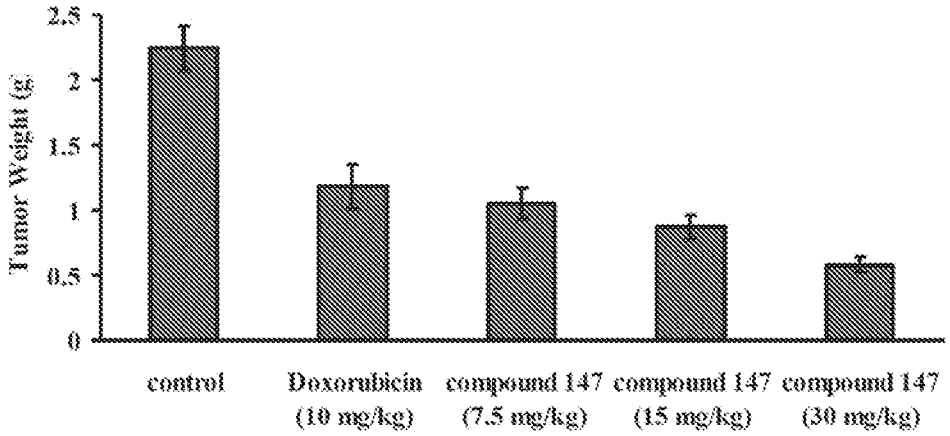


FIG. 6C

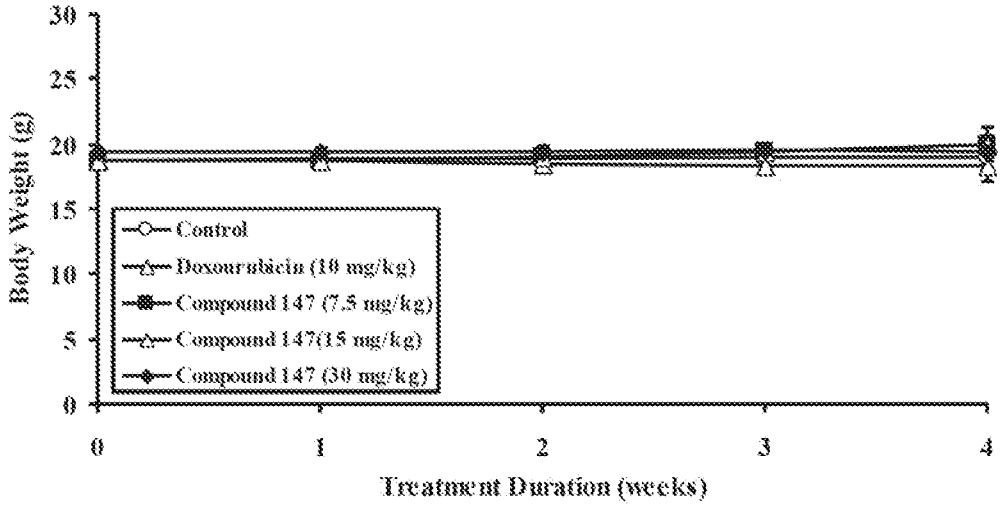


FIG. 7A

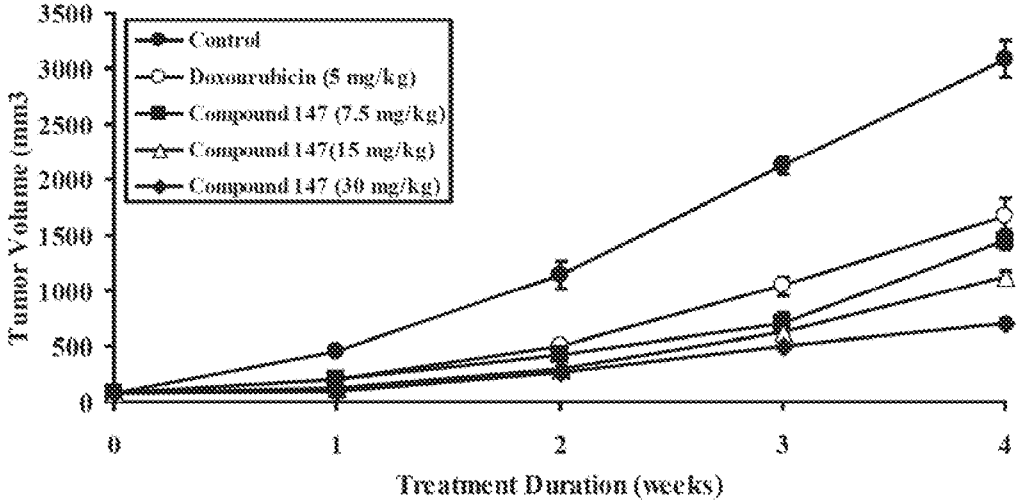


FIG. 7B

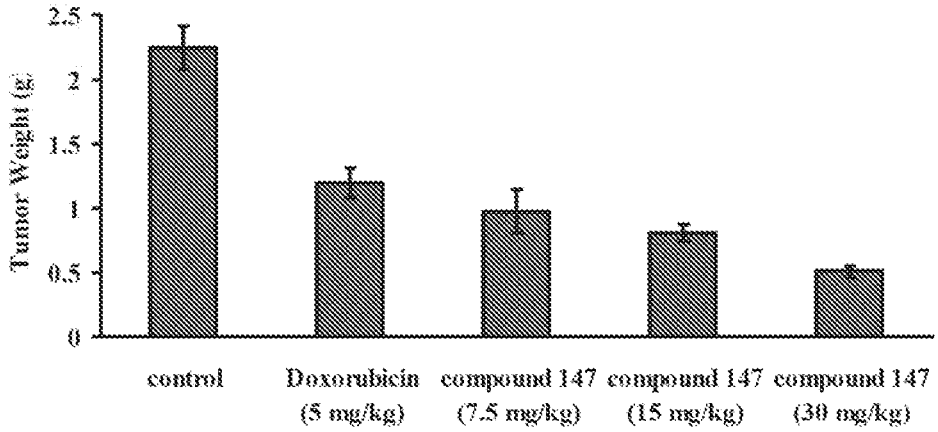
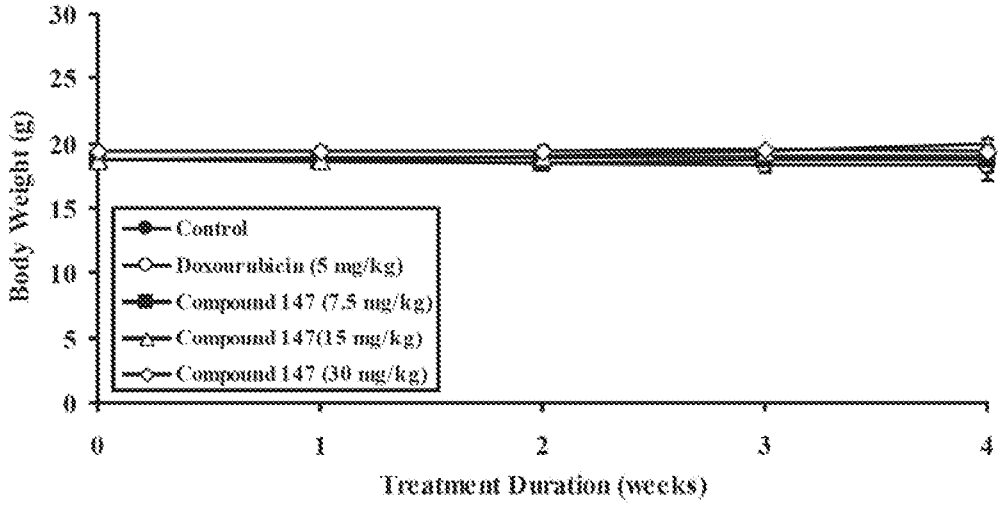


FIG. 7C



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/043985

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/22 C07D215/38 C07D401/04 C07D493/04 C07D215/233
A61K31/4709 A61K31/4741 C07F9/60 C07F9/6558 C07F9/6561
A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YU-HSUN CHANG ET AL: "Design and Synthesis of 2-(3-Benzo[b]thienyl)-6,7-methylenedioxyquinolin-4-one Analogues as Potent Antitumor Agents that Inhibit Tubulin Assembly", JOURNAL OF MEDICINAL CHEMISTRY, vol. 52, no. 15, 13 August 2009 (2009-08-13), pages 4883-4891, XP55007743, ISSN: 0022-2623, DOI: 10.1021/jm900456w cited in the application abstract page 4884; figures 3, 4; compounds B, CHM-1, CHM-1-P-Na, CHM, C page 4886; table I; compounds 1, 36-45 ----- -/--	1-20

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 September 2011	10/10/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bissmire, Stewart

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/070176 A1 (KUO SHENG-CHU; TENG CHE-MING; LEE KUO-HSIUNG [US]; HUANG LI-JIAU; CHOU) 12 June 2008 (2008-06-12) cited in the application page 1, line 10 - page 2, line 23 page 10 - page 35; claims 1-3, 5-10 claim 1	1-20
X	LI L ET AL: "Antitumor Agents. 150. 2',3',4',5',5,6,7-Substituted 2-Phenyl-4-quinolones and Related Compounds: Their Synthesis, Cytotoxicity, and Inhibition of Tubulin Polymerization", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 37, no. 8, 1 January 1994 (1994-01-01), pages 1126-1135, XP002903510, ISSN: 0022-2623, DOI: 10.1021/JM00034A010 abstract page 1128; tables 1, 2; compounds 7-23, 28-34, 36, 37-41, 44-46	1-20
X	WO 02/26730 A2 (UNIV NORTH CAROLINA [US]) 4 April 2002 (2002-04-04) page 1, line 22 - page 2, line 14 page 12; example 1; compounds 1-7, 13 claim 1	1-20
X	WO 96/10563 A1 (UNIV NORTH CAROLINA [US]) 11 April 1996 (1996-04-11) page 1, line 27 - page 3, line 14 page 7; table 1; compounds 1-19, 23-30, 34-36 claim 1	1-20

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/043985

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008070176 A1	12-06-2008	AU 2007328034 A1	12-06-2008
		CA 2670292 A1	12-06-2008
		CN 101583280 A	18-11-2009
		EP 2096924 A1	09-09-2009
		JP 2010512319 A	22-04-2010
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		US 2010168064 A1	01-07-2010
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		EP 1322615 A2	02-07-2003
		JP 2004509956 A	02-04-2004
		US 6569870 B1	27-05-2003
WO 9610563 A1	11-04-1996	US 5571822 A	05-11-1996