

COMBRETASTATIN ANALOGS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of US Provisional Patent Application No. 61/814,028, filed April 19, 2013, US Provisional Patent Application No. 61/866,878, filed August 16, 2013, and US Provisional Patent Application No. 61/901,710 filed November 8, 2013, which are each hereby incorporated by reference in their entirety.

FIELD

[0002] The present invention relates novel analogs of combretastatin, their synthesis, and their use as anti-cancer compounds.

BACKGROUND

[0003] The isolation of stilbene derivatives, termed combretastatins, from the South African tree *Combretum cafrum* has been described. Many of these combretastatins were found to be cytotoxic, with combretastatin A-4 being the most potent. This compound was found to inhibit tubulin polymerization and to competitively inhibit the binding of radiolabeled colchicines to tubulin. Investigation of combretastatins revealed that combretastatin A-4 was active against multidrug resistant (MDR) cancer cell lines. Combretastatin A-4, as well as its *trans* isomer and a number of related substances, have been found to cause mitotic arrest in cells in culture at cytotoxic concentrations. *trans*-Tetrahydroxystilbene and a number of related substances were also reported to be cytotoxic agents.

[0004] 2,3-Diarylacrylonitriles are also very important synthons for the synthesis of a wide spectrum of biologically active molecules. These compounds have been shown to possess spasmolytic, estrogenic, hypotensive, antioxidative, tuberculostatic, antitrichomonal, insecticidal and cytotoxic activities. Also, many natural products possessing a trimethoxybenzene ring, e.g., colchicines, and podophyllotoxin, were found to be potent cytotoxic agents and exert their antitumor properties based on their antitubulin character.

[0005] Although some compounds have shown biological activity, there remains a need for novel compounds for the treatment of disease.

REFERENCE TO COLOR FIGURES

[0006] The application file contains at least one photograph executed in color. Copies of this patent application publication with color photographs will be provided by the Office upon request and payment of the necessary fee.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] **FIGs. 1(A)-(C)** show various combretastatin heterocyclic *E* and *Z*-isomer analogs.

[0008] **FIGs. 2(A)-(K)** show further combretastatin heterocyclic *E* and *Z*-isomer analogs.

[0009] **FIGs. 3 (A)-(B)** show *N*-alkyl indole combretastatin heterocyclic *E* and *Z*-isomer analogs.

[0010] **FIGs. 4 (A)-(C)** show exemplary compounds comprising Formula (II).

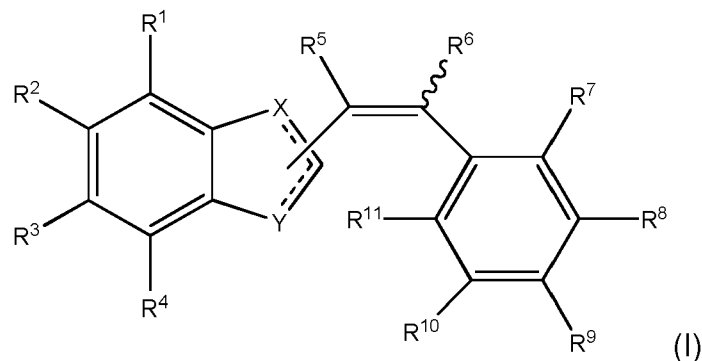
DETAILED DESCRIPTION

[0011] Briefly, the present invention relates to novel heterocyclic combretastatin analogs. The analogs generally have a heterocyclic structural feature and a stilbene (or combretastatin) structural feature, each of which may each be further derivatized. These analogs show novel and unexpected properties in terms of biological activity, and in particular showing cytotoxicity against various cancer cell lines. It is thought that this cytotoxicity is due to the ability of the compound to bind to tubulin and to inhibit tubulin polymerization. Due to this activity, the compounds described herein may be active in the treatment of a variety of diseases including in the treatment of cancer.

I. COMPOSITIONS

(a) Compound Comprising Formula (I)

[0012] One aspect of the invention provides compounds comprising Formula (I):



wherein:

R^1 , R^2 , R^3 , R^4 , R^7 , R^8 , R^9 , R^{10} , R^{11} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro;

R^5 and R^6 are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, carboxyl, ester, and cyano;

X and Y are independently chosen from O, C, CR^{12} , $CR^{12}R^{13}$, S, SR^{14} N, or NR^{15} ; and

R^{12} , R^{13} , R^{14} , and R^{15} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro.

[0013] R^1 , R^2 , R^3 , and R^4 are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro. Alkylalkylamino groups are disubstituted amine groups. Each of the alkyl groups may be the same or different. In one embodiment, both alkyl groups are lower alkyl groups. The amidine nitrogen groups may be further substituted by hydrogen, hydrocarbyl, or substituted hydrocarbyl at each position. Preferably, the amidine nitrogens are each substituted by hydrogen. Where the group is an amine, the amine may be a primary, secondary, or tertiary amine. Preferably,

amine substituents are lower alkyl groups. Ester groups may be attached to the phenyl ring at either the carbonyl end or at the oxygen end of the ester. The opposite terminus may be hydrocarbyl or substituted hydrocarbyl, and is preferably a lower alkyl.

[0014] In one embodiment, R^1 , R^2 , R^3 , and R^4 are chosen from hydrogen, hydroxyl, and alkoxy. In a preferred embodiment, R^1 and R^4 are both hydrogen. In yet another preferred embodiment, each of R^1 , R^2 , R^3 , and R^4 are hydrogen.

[0015] R^7 , R^8 , R^9 , R^{10} , and R^{11} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro. Alkylalkylamino groups are disubstituted amine groups. Each of the alkyl groups may be the same or different. In one embodiment, both alkyl groups are lower alkyl groups. The amidine nitrogen groups may be further substituted by hydrogen, hydrocarbyl, or substituted hydrocarbyl at each position. Preferably, the amidine nitrogens are each substituted by hydrogen. Where the group is an amine, the amine may be a primary, secondary, or tertiary amine. Preferably, amine substituents are lower alkyl groups. Ester groups may be attached at either the carbonyl end or at the oxygen end of the ester. The opposite terminus of the ester may be hydrocarbyl or substituted hydrocarbyl. Preferably, the ester is a lower alkyl.

[0016] In certain embodiments, R^7 , R^8 , R^9 , R^{10} , and R^{11} are chosen from hydrogen, hydroxyl, and alkoxy. In one preferred embodiment, R^7 and R^{11} are hydrogen.

[0017] In another embodiment, R^8 , R^9 , and R^{10} are independently chosen from hydrogen, methoxy, ethoxy, benzyloxy, substituted benzyloxy, hydroxyl, and lower alkyl groups. In one embodiment, R^8 , R^9 , and R^{10} are independently chosen from hydrogen, hydroxyl, and alkoxy. In one preferred embodiment, R^8 , R^9 , and R^{10} are each methoxy, and in still another preferred embodiment, R^8 and R^{10} are methoxy, and R^9 is hydrogen.

[0018] R^5 and R^6 are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, carboxyl, ester, and cyano. Ester groups may be attached at either the carbonyl end or at the oxygen end of the ester. The terminus of the ester that

is not bound to the double bond may be hydrocarbyl or substituted hydrocarbyl.

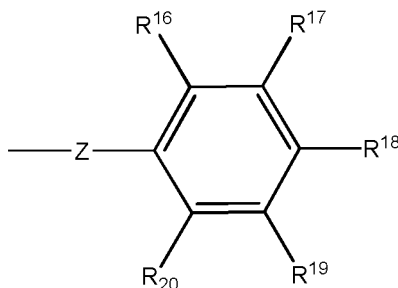
Preferably, the ester is a lower alkyl ester.

[0019] In one embodiment, R^5 is hydrogen and R^6 is chosen from hydrogen, cyano, and carboxyl. In still another embodiment, R^5 is hydrogen and R^6 is cyano. In yet another exemplary embodiment, R^5 and R^6 are hydrogen.

[0020] X and Y are independently chosen from O, C, CR^{12} , $CR^{12}R^{13}$, S, SR^{14} , N, and NR^{15} . In one embodiment, where X is chosen from C, CR^{12} , or $CR^{12}R^{13}$, then Y is not chosen from C, CR^{12} , or $CR^{12}R^{13}$. In another embodiment, X is chosen from C or S. In still another embodiment, Y is chosen from O, S, and NR^{15} . In some specific embodiments, X is C and Y is S, or X is C and Y is O, or X is C and Y is NR^{15} , or X is S and Y is N.

[0021] R^{12} , R^{13} , R^{14} , and R^{15} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro. Alkylalkylamino groups are disubstituted amine groups. Each of the alkyl groups may be the same or different. In one embodiment, both alkyl groups are lower alkyl groups. The amidine nitrogen groups may be further substituted by hydrogen, hydrocarbyl, or substituted hydrocarbyl at each position. Preferably, the amidine nitrogens are each substituted by hydrogen. Where the group is an amine, the amine may be a primary, secondary, or tertiary amine. Preferably, amine substituents are lower alkyl groups. Ester groups may be attached at either the carbonyl end or at the oxygen end of the ester. The terminus of the ester that is not bound to the aromatic ring may be hydrocarbyl or substituted hydrocarbyl. Preferably, the ester is a lower alkyl.

[0022] In one preferred embodiment, each of R^{12} , R^{13} , R^{14} , and R^{15} are hydrogen. In yet another embodiment, R^{12} , R^{13} , R^{14} , and R^{15} comprise the formula:



wherein Z is chosen from CH₂, CO, and SO₂; and

R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²⁰ are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro.

[0023] In one preferred embodiment, R¹⁶ and R²⁰ are hydrogen, while R¹⁷, R¹⁸, and R¹⁹ are chosen from amino, carboxyl, cyano, ester, halogen, alkyl, and hydrogen.

[0024] The dashed lines in the five-membered ring of the compound comprising Formula (I) indicate either a single bond or a double bond. Preferably, one of the dashed lines represents a single bond, and the other represents a double bond.

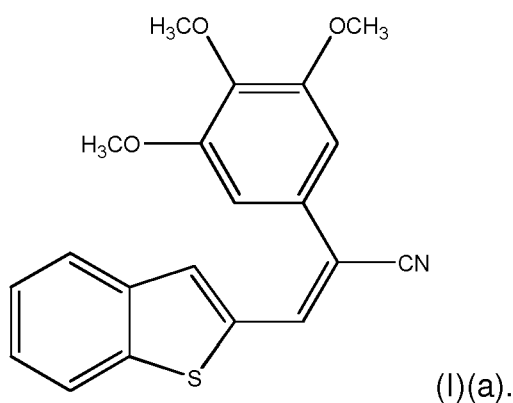
[0025] The stilbene or modified stilbene moiety may be bonded to the five-membered ring at any one of the non-fused ring positions. In various embodiments, the stilbene moiety may be attached through a bond to X, through a bond to Y, or a bond to the carbon atom between the X and Y atoms.

[0026] The wavy bond at R⁶ indicates that R⁶ may be at either geometric position on the double bond. Accordingly, the double bond may be (*E*) or (*Z*), which are defined according to the IUPAC convention. In one embodiment, the double bond may have an (*E*) configuration, and in another embodiment, the double bond may have a (*Z*) configuration.

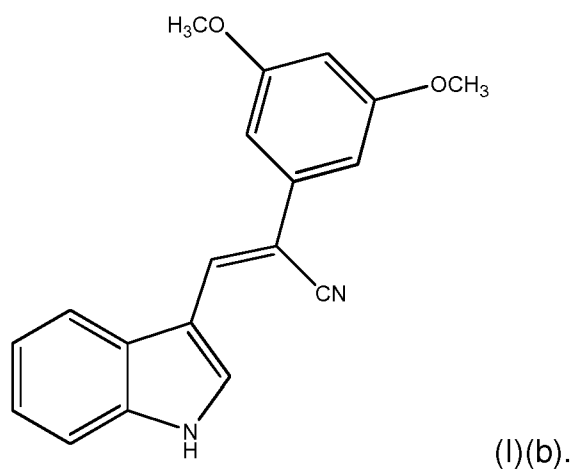
[0027] The compound comprising Formula (I) may be a free form or a salt. When the compound is in a salt form, the salt is preferably a pharmaceutically acceptable salt. Pharmaceutically acceptable salts may include, without limitation, hydrochloride, hydrobromide, phosphate, sulfate, methanesulfonate, acetate, formate, tartaric acid, bitartrate, stearate, phthalate, hydroiodide, lactate, monohydrate, mucate, nitrate, phosphate, salicylate, phenylpropionate, isobutyrate, hypophosphite, maleic, malic, citrate, isocitrate, succinate, lactate, gluconate, glucuronate, pyruvate, oxalate, fumarate, propionate, aspartate, glutamate, benzoate, terephthalate, and the like. In other embodiments, the pharmaceutically acceptable salt includes an alkaline or alkaline earth metal ion salt. In particular, sodium, potassium or other pharmaceutically

acceptable inorganic salts are used. The salt forms may be amorphous or in various polymeric forms including hydrates, or solvates with alcohols or other solvents.

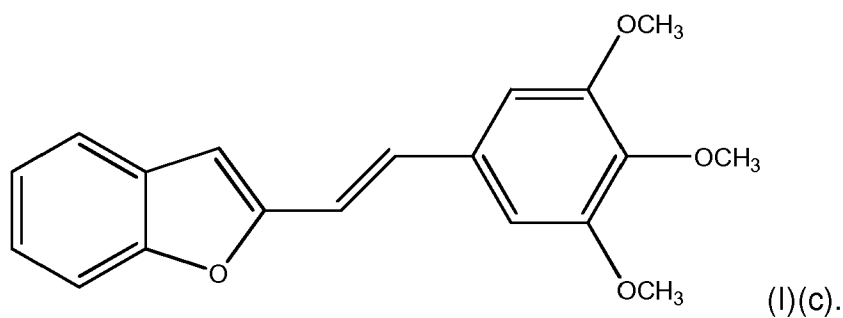
[0028] In one embodiment, the disclosure provides a compound comprising Formula (I)(a):



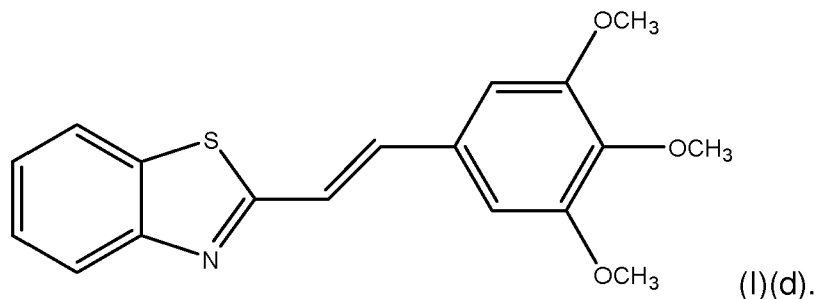
[0029] In still another embodiment, the disclosure provides a compound comprising Formula (I)(b):



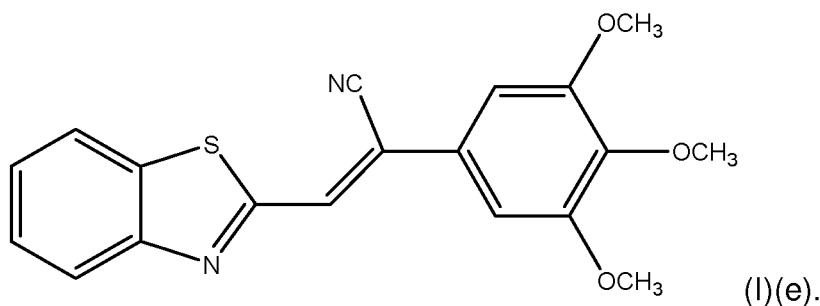
[0030] In still another embodiment, the disclosure provides a compound comprising Formula (I)(c):



[0031] In still a further embodiment, the disclosure provides a compound comprising Formula (I)(d):



[0032] In still a further embodiment, the disclosure provides a compound comprising Formula (I)(e):



[0033] Additional embodiments are shown in **FIGs. 1 to 3**.

(b) Pharmaceutical Compositions

[0034] The disclosure also provides a pharmaceutical composition comprising the compound comprising Formula (I) and at least one pharmaceutically acceptable excipient. In various embodiments, one or more of the compounds described in section (I) may be combined with at least one pharmaceutically acceptable excipient.

(i) excipient

[0035] A pharmaceutical composition of the disclosure comprises at least one pharmaceutically acceptable excipient. Non-limiting examples of suitable excipients may include diluents, binders, fillers, buffering agents, pH modifying agents, disintegrants, dispersing agents, stabilizers, preservatives, and coloring agents. The amount and types of excipients may be selected according to known principles of pharmaceutical science.

[0036] In one embodiment, the excipient may include at least one diluent. Non-limiting examples of suitable diluents may include microcrystalline cellulose (MCC), cellulose derivatives, cellulose powder, cellulose esters (i.e., acetate and butyrate mixed esters), ethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, corn starch, phosphated corn starch, pregelatinized corn starch, rice starch, potato starch, tapioca starch, starch-lactose, starch-calcium carbonate, sodium starch glycolate, glucose, fructose, lactose, lactose monohydrate, sucrose, xylose, lactitol, mannitol, malitol, sorbitol, xylitol, maltodextrin, and trehalose.

[0037] In another embodiment, the excipient may comprise a binder. Suitable binders may include, but are not limited to, starches, pregelatinized starches, gelatin, polyvinylpyrrolidone, cellulose, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinylloxazolidone, polyvinylalcohols, C12-C18 fatty acid alcohol, polyethylene glycol, polyols, saccharides, oligosaccharides, polypeptides, oligopeptides, and combinations thereof.

[0038] In another embodiment, the excipient may include a filler. Suitable fillers may include, but are not limited to, carbohydrates, inorganic compounds, and polyvinylpyrrolidone. By way of non-limiting example, the filler may be calcium sulfate, both di- and tri-basic, starch, calcium carbonate, magnesium carbonate, microcrystalline cellulose, dibasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, talc, modified starches, lactose, sucrose, mannitol, or sorbitol.

[0039] In still another embodiment, the excipient may comprise a buffering agent. Buffers may include phosphates, carbonates, citrates, and the like. Representative examples of suitable buffering agents may include, but are not limited to, MOPS, HEPES, TAPS, Bicine, Tricine, TES, PIPES, MES, Tris buffers or buffered saline salts (e.g., Tris buffered saline or phosphate buffered saline).

[0040] In various embodiments, the excipient may include a pH modifier. By way of non-limiting example, the pH modifying agent may be sodium carbonate or sodium bicarbonate.

[0041] In another alternate embodiment, the excipient may also include a preservative. Non-limiting examples of suitable preservatives may include antioxidants, such as alpha-tocopherol or ascorbate, or EDTA (ethylenediaminetetraacetic acid), EGTA (ethylene glycol tetraacetic acid), BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), and the like.

[0042] In a further embodiment, the excipient may include a disintegrant. Suitable disintegrants may include, but are not limited to, starches such as corn starch, potato starch, pregelatinized and modified starches thereof, sweeteners, clays, such as bentonite, micro-crystalline cellulose, alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya, pectin, and tragacanth.

[0043] In yet another embodiment, the excipient may include a dispersion enhancer. Suitable dispersants may include, but are not limited to, starch, alginic acid, polyvinylpyrrolidones, guar gum, kaolin, bentonite, purified wood cellulose, sodium starch glycolate, isoamorphous silicate, and microcrystalline cellulose.

[0044] In a further embodiment, the excipient may include a lubricant. Non-limiting examples of suitable lubricants may include minerals such as talc or silica; and fats such as vegetable stearin, magnesium stearate, or stearic acid.

[0045] In still another embodiment, it may be desirable to provide a coloring agent. Suitable color additives may include, but are not limited to, food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C).

[0046] The weight fraction of the excipient(s) in the composition may be about 98% or less, about 95% or less, about 90% or less, about 85% or less, about 80% or less, about 75% or less, about 70% or less, about 65% or less, about 60% or less, about 55% or less, about 50% or less, about 45% or less, about 40% or less, about 35% or less, about 30% or less, about 25% or less, about 20% or less, about 15% or less, about 10% or less, about 5% or less, about 2%, or about 1% or less of the total weight of the composition.

[0047] The pharmaceutical composition may be mixed with one or more excipients to form a solid, liquid, or cream dosage form. Methods of formulating a solid, liquid, or cream dosage form are known in the art.

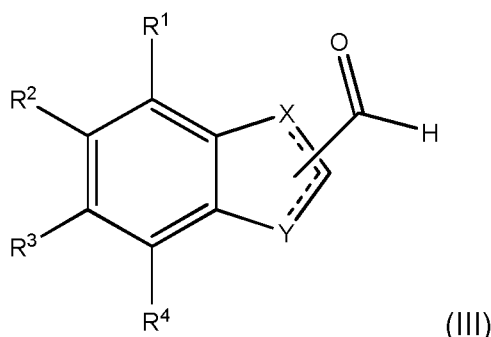
(ii) optional additional pharmaceutical ingredient

[0048] Optionally, the compound comprising Formula (I) may be combined with other compounds comprising Formula (I) or may be combined with one or more than one additional active pharmaceutical ingredients.

II. Method for Synthesis

(a) Method for Producing a Compound Comprising Formula (I)

[0049] In another embodiment, the disclosure provides a method of making the compound comprising Formula (I). The method comprises contacting a compound comprising Formula (III) with a phenylacetonitrile or a benzyl triphenyl phosphine bromide in the presence of a proton acceptor. The compound of Formula (II) comprises:



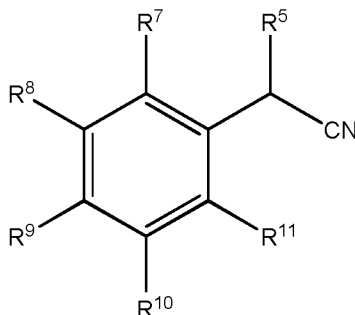
wherein, R^1 , R^2 , R^3 , R^4 , X, and Y may be chosen as described in section (I).

[0050] The compound comprising Formula (III) is an aldehyde. As indicated by the figure, the aldehyde may be connected at any of the non-fused positions of the five-membered ring including through a bond to X, through a bond to Y, or through a bond to the carbon atom between X and Y.

[0051] R^1 , R^2 , R^3 , R^4 , X and Y may be chosen as described in section (I). In some embodiments, the compound comprising Formula (III) is chosen from benzo[b]thiophene-2-carbaldehydes, benzo[b]thiophene-3-carbaldehydes, benzofuran-

2-carboxaldehydes, benzofuran-3-carboxaldehydes, indole-2-carboxaldehydes, indole-3-carboxaldehydes, and benzthiazole-2-carboxaldehydes.

[0052] In one embodiment, the compound comprising Formula (III) is contacted with a phenylacetonitrile. Phenylacetonitriles have the following generic structure:

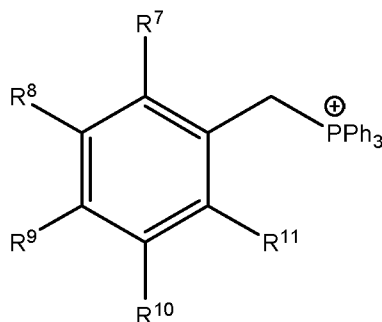


wherein, R⁵, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ may be chosen as described in section (I).

[0053] In preferred embodiments, the phenylacetonitrile is chosen from phenylacetonitrile, 3,4,5-trimethoxy phenyl acetonitrile, 3,4-dimethoxyphenylacetonitrile, and 4-hydroxy, 3,5-trimethoxyphenylacetonitrile.

[0054] The mole to mole ratio of the compound comprising Formula (III) to the phenyl acetonitrile can range over different embodiments of the invention. In one embodiment, the ratio of the compound comprising Formula (III) to the phenylacetonitrile varies from about 0.9:1 to about 1:10. In some embodiments, the mole to mole ratio of the compound comprising Formula (III) to the phenylacetonitrile is about 1:1 to about 1:1.5. In various embodiments, the mole to mole ratio of the compound comprising Formula (III) to the phenylacetonitrile is about 1:1, about 1:1.1, about 1:1.2, about 1:1.3, about 1:1.4, or about 1:1.5. In an exemplary embodiment, the mole to mole ratio of the compound comprising Formula (III) to the phenylacetonitrile is 1:1.

[0055] In another embodiment, the compound comprising Formula (III) is contacted with a benzyl triphenyl phosphine. A benzyl triphenyl phosphine generally comprises the following structure:



[0056] wherein, R^7 , R^8 , R^9 , R^{10} , and R^{11} may be chosen as described in section (I). An acceptable counterion is generally present. In preferred embodiments, the counterion is bromide.

[0057] In particular embodiments, benzyl triphenyl phosphines may include 3,4,5 trimethoxybenzyl triphenyl phosphine bromide, 3,4-dimethoxybenzyl triphenyl phosphine bromide, 4-hydroxy, and 3,5-dimethoxybenzyl triphenyl phosphine bromide.

[0058] The mole to mole ratio of the compound comprising Formula (III) to the benzyl triphenyl phosphine can range over different embodiments of the invention. In one embodiment, the ratio of the compound comprising Formula (III) to the benzyl triphenyl phosphine varies from about 0.9:1 to about 1:10. In some embodiments, the mole to mole ratio of the compound comprising Formula (III) to the benzyl triphenyl phosphine is about 1:1 to about 1:1.5. In various embodiments, the mole to mole ratio of the compound comprising Formula (III) to the benzyl triphenyl phosphine is about 1:1, about 1:1.1, about 1:1.2, about 1:1.3, about 1:1.4, or about 1:1.5. In an exemplary embodiment, the mole to mole ratio of the compound comprising Formula (III) to the benzyl triphenyl phosphine is 1:1.

[0059] The reaction is preferably carried out in a solvent and is more preferably carried out in an organic solvent. The solvent may be chosen without limitation from including alkane and substituted alkane solvents (including cycloalkanes) alcohol solvents, halogenated solvents, aromatic hydrocarbons, esters, ethers, ketones, and combinations thereof. Non-limiting examples of suitable organic solvents are acetonitrile, acetone, allyl alcohol, benzene, butyl acetate, chlorobenzene, chloroform, chloromethane, cyclohexane, cyclopentane, dichloromethane (DCM), dichloroethane, diethyl ether, dimethoxyethane (DME), dimethylformamide (DMF), dimethyl sulfoxide

(DMSO), dioxane, ethanol, ethyl acetate, ethylene dichloride, ethylene bromide, formic acid, fluorobenzene, heptane, hexane, isobutylmethylketone, isopropanol, isopropyl acetate, N-methylpyrrolidone, methanol, methylene bromide, methylene chloride, methyl iodide, methylethylketone, methyltetrahydrofuran, pentyl acetate, propanol, *n*-propyl acetate, sulfolane, tetrahydrofuran (THF), tetrachloroethane, toluene, trichloroethane, water, xylene and combinations thereof. In exemplary embodiments, the solvent is an alcohol solvent. In one preferred embodiment, the solvent is methanol.

[0060] A proton acceptor is generally added to facilitate the reaction. The proton acceptor generally has a pKa greater than about 7, or from about 7 to about 13, or more preferably from about 8 to about 10. Representative proton acceptors may include, but are not limited to, borate salts (such as, for example, NaBO_3), di- and tri-basic phosphate salts, (such as, for example, Na_2HPO_4 and NaPO_4), bicarbonate salts, carbonate salts, hydroxides, alkoxides, (including methoxide, ethoxide, propoxide, butoxide, and pentoxide, including straight chain and branched), and organic proton acceptors, (such as, for example, pyridine, triethylamine, *N*-methylmorpholine, and *N,N*-dimethylaminopyridine), and mixtures thereof. In some embodiments, the proton acceptor may be stabilized by a suitable counterion such as lithium, potassium, sodium, calcium, magnesium, and the like. In one preferred embodiment, the proton acceptor is sodium methoxide.

[0061] The amount of the proton acceptor which is added may vary. Generally, the proton acceptor is added in excess to the compound comprising Formula (III). In some embodiments, the mole to mole ratio of the compound comprising Formula (III) to the proton acceptor can range from about 1:1.1 to about 1:100. In some embodiments, the mole to mole ratio of the compound comprising Formula (III) to the proton acceptor is about 1:10, about 1:20, about 1:30, about 1:40, about 1:50, about 1:60, about 1:70, about 1:80, or about 1:100. In still other embodiments, the mole to mole ratio of the compound comprising Formula (III) to the proton acceptor is about 1:41, about 1:42, about 1:43, about 1:44, about 1:45, about 1:46, about 1:47, about 1:48, or about 1:49. In one preferred embodiment, the mole to mole ratio of the compound comprising Formula (III) to the proton acceptor is 1:47.

[0062] The amount of time over which the reaction is conducted may also vary within different embodiments. In some embodiments, the reaction may be conducted over a period of 2 hours to 8 hours. In particular embodiments, the reaction is carried out for about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, or about 8 hours. In preferred embodiments, the reaction is conducted for about 4 hours.

[0063] The temperature may vary over different embodiments, in some embodiments the temperature may range from about 20°C to about 80°C. In particular embodiments the temperature may range from about 20°C to about 30°C, from about 30°C to about 40°C, from about 40°C to about 50°C, from about 50°C to about 60°C, from about 60°C to about 70°C, or from about 70°C to about 80°C.

[0064] In some embodiments, a further isomerization step is required to convert between (*E*) and (*Z*) isomers. This step may be accomplished by methods known in the art. In one preferred embodiment, the isomers are transformed by stirring the compounds under a UV light for 12 to 72 hours.

[0065] The synthesized compounds may be used in their crude form or they may be purified. The compounds may be purified by any suitable method known in the art including through column chromatography, crystallization, distillation, extraction, and the like. In one preferred embodiment, the compounds are recrystallized from a solvent.

III. Methods of Use For the Compound Comprising Formula (I)

[0066] In still another aspect, the present disclosure provides a method of inhibiting tubulin polymerization in a subject. The method comprises administering a compound comprising Formula (I) to a subject.

[0067] Without being bound to any theory, compounds comprising Formula (I) are thought to bind to tubulin. The binding at this site is thought to inhibit tubulin polymerization, and in turn, inhibit formation of vasculature. In tumors, a developing vasculature is critical to tumor growth and migration. Accordingly, inhibition of tubulin polymerization is important to the treatment of various disease states.

[0068] In another embodiment, a method for treating cancer is provided. The method comprises administering a compound comprising Formula (I) to a subject.

Cancers treatable by the method may include, without limitation, prostate cancer, ovarian cancer, breast cancer, brain cancer, hepatic cancer, leukemia, lung cancer, colon cancer, CNS cancer, melanoma, renal cancer, pancreatic cancer, gastric cancer, lymphoma and the like.

[0069] The compounds may be administered to the subject by a variety of routes. For example, a compound comprising Formula (I) may be administered orally via a solid or liquid dosage form (tablet, gel cap, time release capsule powder, solution, or suspension in aqueous or non-aqueous liquid), parenterally (i.e., subcutaneously, intradermally, intravenously, (i.e., as a solution, suspension or emulsion in a carrier), intramuscularly, intracranially, or intraperitoneally), or topically (i.e., transdermally or transmucosally, including, but not limited to buccal, rectal, vaginal and sublingual). In one embodiment, the compounds may be administered in saline or with a pharmaceutically acceptable excipient as described in section (I). The compound may be administered as primary therapy, or as adjunct therapy, either following local intervention (surgery, radiation, local chemotherapy) or in conjunction with at least one other chemotherapeutic agent.

[0070] Suitable subjects may include, without limit, humans, as well as companion animals such as cats, dogs, rodents, and horses; research animals such as rabbits, sheep, pigs, dogs, primates, mice, rats and other rodents; agricultural animals such as cows, cattle, pigs, goats, sheep, horses, deer, chickens and other fowl; zoo animals; and primates such as chimpanzees, monkeys, and gorillas. The subject can be of any age without limitation. In a preferred embodiment, the subject may be a human.

[0071] Generally, the compound comprising Formula (I) will be administered in a therapeutically effective amount which includes prophylactic amounts or lower dosages for example, when combined with another agent. As used herein, "an effective amount" refers to doses of compound sufficient to provide circulating concentrations high enough to impart a beneficial effect on the recipient thereof. The amount to be administered depends on the lipophilicity of the specific compound selected, since it is expected that this property of compounds will cause it to partition into fat deposits of the subject. The precise

amount to be administered can be determined by the skilled practitioner in view of desired dosages, side effects, and medical history of the patient.

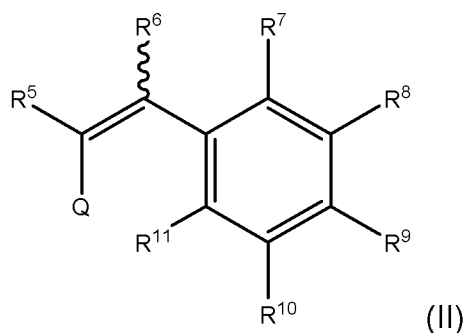
[0072] The compounds comprising Formula (I) may also be characterized by their cytotoxic effects when contacted with cells. In some embodiments, the compounds inhibit the growth of a cell. In other embodiments, the compounds kill cells. Accordingly, the compounds of the present invention may be characterized by GI_{50} values and LC_{50} values. GI_{50} refers to the molar drug concentration required to cause 50% growth inhibition compared to an untreated cell. LC_{50} refers to the concentration required to kill 50% of cells. In still another embodiment, the disclosure provides a method for inhibiting growth of a cell by contacting the cells with a compound comprising Formula (I), and in a still further embodiment, the disclosure provides a method for killing cells by contacting the cells with a compound comprising Formula (I). Cells may be chosen from, without limitation, those listed in **TABLE 1**.

[0073] In some embodiments, the compounds comprising Formula (I) have an LC_{50} of less than about 100 μ M, or less than 80 μ M, or less than about 60 μ M, or less than about 40 μ M, or less than about 20 μ M, or less than about 1 μ M. In other embodiments, the compounds comprising Formula (I) have a GI_{50} of less than about 100 μ M, or less than 80 μ M, or less than about 60 μ M, or less than about 40 μ M, or less than about 20 μ M, or less than about 1 μ M.

IV. Compositions of the Compound Comprising Formula (II)

(a) Compound Comprising Formula (II)

[0074] One aspect of the invention provides compounds comprising Formula (II):



wherein:

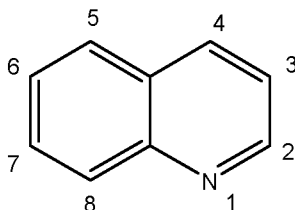
R^7 , R^8 , R^9 , R^{10} , R^{11} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkoxy, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro;

R^5 and R^6 are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, carboxyl, ester, and cyano; and

Q is a quinolinyl moiety,

with the proviso that when R^6 is cyano, R^8 and R^9 are not each OCH_3 .

[0075] Q is a quinolinyl moiety. Quinolinyl moieties are nitrogen containing heterocyclic aromatic compounds which have the structure below. The atoms of the quinolinyl moiety are numbered as shown in the figure. The quinolinyl moiety may be bonded to the remainder of the compound comprising Formula (II) via any of the numbered positions below. In some embodiments, Q is a 1-quinolinyl, a 2-quinolinyl, a 3-quinolinyl, a 4-quinolinyl, a 5-quinolinyl, a 6-quinolinyl, a 7-quinolinyl, or an 8-quinolinyl. In preferred embodiments, Q is a 2-quinolinyl or 3-quinolinyl.



[0076] The quinolinyl may be further substituted. Further substitutions may be independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro. Alkylalkylamino groups are disubstituted amine groups. Each of the alkyl groups may be the same or different. In one embodiment, both alkyl groups are lower alkyl groups. Amidine nitrogen groups may be further substituted by hydrogen, hydrocarbyl, or substituted hydrocarbyl at each position. Preferably, the amidine nitrogens are each substituted by hydrogen. Where the substitution is an amine, the amine may be a primary, secondary, or tertiary amine. Preferably, amine substituents are lower alkyl groups. Ester groups may be attached to the quinolinyl at either the carbonyl end or at

the oxygen end of the ester. The opposite terminus may be hydrocarbyl or substituted hydrocarbyl, and is preferably a lower alkyl.

[0077] R^7 , R^8 , R^9 , R^{10} , and R^{11} in the compound comprising Formula (I) are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro. Alkylalkylamino groups are disubstituted amine groups. Each of the alkyl groups may be the same or different. In one embodiment, both alkyl groups are lower alkyl groups. The amidine nitrogen groups may be further substituted by hydrogen, hydrocarbyl, or substituted hydrocarbyl at each position. Preferably, the amidine nitrogens are each substituted by hydrogen. Where the group is an amine, the amine may be a primary, secondary, or tertiary amine. Preferably, amine substituents are lower alkyl groups. Ester groups may be attached at either the carbonyl end or at the oxygen end of the ester. The opposite terminus of the ester may be hydrocarbyl or substituted hydrocarbyl. Preferably, the ester is a lower alkyl.

[0078] In certain embodiments, R^7 , R^8 , R^9 , R^{10} , and R^{11} are independently chosen from hydrogen, hydroxyl, and alkoxy, with the proviso that when R^8 and R^9 are OCH_3 , then R^{10} is not hydrogen, and when R^9 and R^{10} are OCH_3 , then R^8 is not hydrogen. In another embodiment, R^7 , R^8 , R^9 , R^{10} , and R^{11} are independently chosen from hydrogen and hydroxyl. In one preferred embodiment, R^7 and R^{11} are hydrogen. In another embodiment, R^8 , R^9 , and R^{10} are independently chosen from hydrogen, methoxy, ethoxy, benzyloxy, substituted benzyloxy, hydroxyl, and lower alkyl groups. In one embodiment, R^8 , R^9 , and R^{10} are independently chosen from hydrogen and hydroxyl. In one preferred embodiment, R^8 , R^9 , and R^{10} are each hydroxy, and in still another preferred embodiment, R^8 and R^{10} are hydroxy, and R^9 is hydrogen.

[0079] Various substitution patterns on the phenyl ring are within the scope of the present invention. In one embodiment, where R^8 and R^9 are substituted with other than hydrogen, then R^{10} is not hydrogen. In yet another embodiment, where R^9 and R^{10} are substituted with other than hydrogen then R^8 is not hydrogen. In preferred embodiments, R^8 , R^9 , and R^{10} are each substituted with other than hydrogen. In still

other preferred embodiments, R⁸ and R¹⁰ are substituted with other than hydrogen, and R⁹ is substituted with hydrogen.

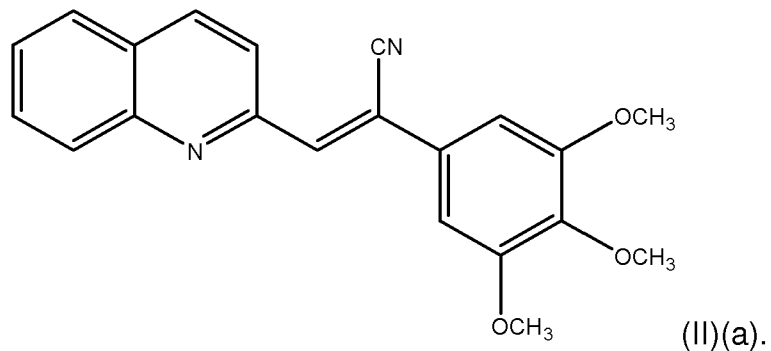
[0080] R⁵ and R⁶ are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, carboxyl, ester, and cyano. Ester groups may be attached at either the carbonyl end or at the oxygen end of the ester. The terminus of the ester that is not bound to the double bond may be hydrocarbyl or substituted hydrocarbyl. Preferably, the ester is a lower alkyl ester.

[0081] In one embodiment, R⁵ is hydrogen and R⁶ is chosen from hydrogen, cyano, and carboxyl. In still another embodiment, R⁵ is hydrogen and R⁶ is cyano. In yet another embodiment, R⁵ and R⁶ are hydrogen. In one embodiment, where R⁶ is cyano, R⁸ and R⁹ are not each OCH₃. In another embodiment, where R⁶ is cyano, R⁹ and R¹⁰ are not each methoxy.

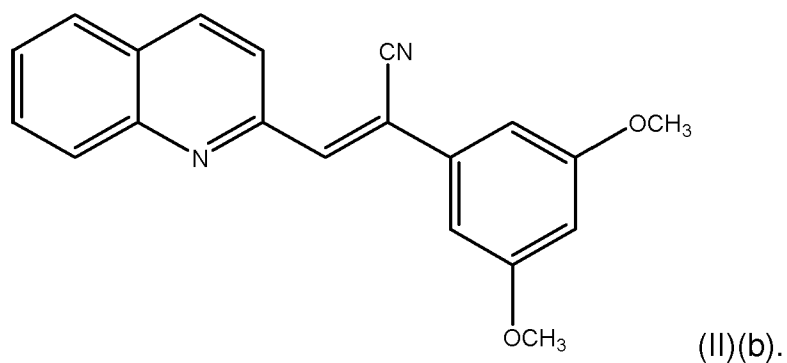
[0082] The wavy bond at R⁶ indicates that R⁶ may be at either geometric position on the double bond. Accordingly, the double bond may be (*E*) or (*Z*), which are defined according to the IUPAC convention. In one embodiment, the double bond may have an (*E*) configuration, and in another embodiment, the double bond may have a (*Z*) configuration.

[0083] The compound comprising Formula (II) may be a free form or a salt. When the compound is in a salt form, the salt is preferably a pharmaceutically acceptable salt. Pharmaceutically acceptable salts may include, without limitation, hydrochloride, hydrobromide, phosphate, sulfate, methanesulfonate, acetate, formate, tartaric acid, bitartrate, stearate, phthalate, hydroiodide, lactate, monohydrate, mucate, nitrate, phosphate, salicylate, phenylpropionate, isobutyrate, hypophosphite, maleic, malic, citrate, isocitrate, succinate, lactate, gluconate, glucuronate, pyruvate, oxalate, fumarate, propionate, aspartate, glutamate, benzoate, terephthalate, and the like. In other embodiments, the pharmaceutically acceptable salt includes an alkaline or alkaline earth metal ion salt. In particular, sodium, potassium or other pharmaceutically acceptable inorganic salts are used. The salt forms may be amorphous or in various polymeric forms including hydrates, or solvates with alcohols or other solvents.

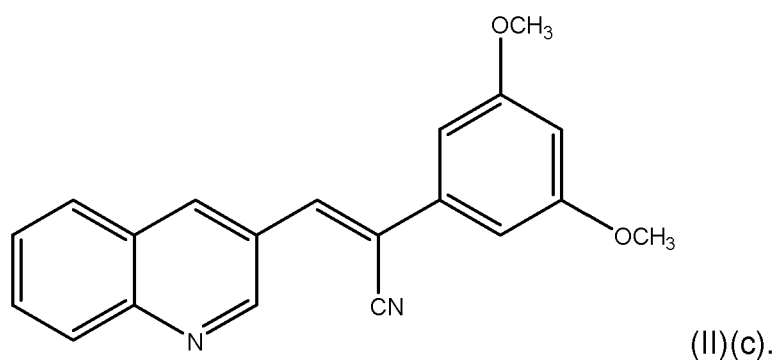
[0084] In one embodiment, the disclosure provides a compound comprising Formula (II)(a):



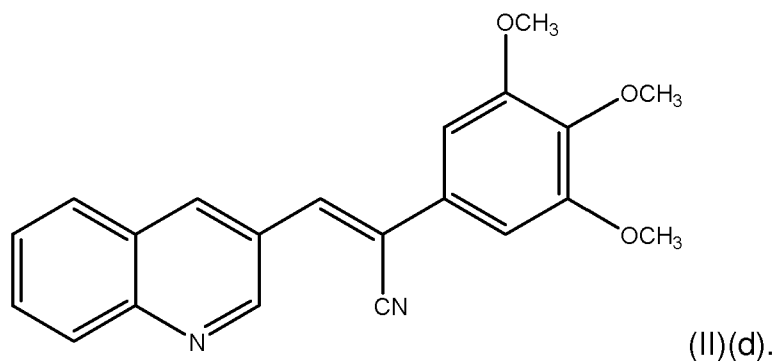
[0085] In still another embodiment, the disclosure provides a compound comprising Formula (I)(b):



[0086] In still another embodiment, the disclosure provides a compound comprising Formula (II)(c):



[0087] In still a further embodiment, the disclosure provides a compound comprising Formula (II)(d):



[0088] Additional embodiments are shown in **FIGs. 4 (A) – (C)**.

(b) Pharmaceutical Compositions

[0089] The disclosure also provides a pharmaceutical composition comprising the compound comprising Formula (II) and at least one pharmaceutically acceptable excipient. In various embodiments, one or more of the compounds described in section (I) may be combined with at least one pharmaceutically acceptable excipient.

(i) excipient

[0090] A pharmaceutical composition of the disclosure comprises at least one pharmaceutically acceptable excipient. Non-limiting examples of suitable excipients may include diluents, binders, fillers, buffering agents, pH modifying agents, disintegrants, dispersing agents, stabilizers, preservatives, and coloring agents. The amount and types of excipients may be selected according to known principles of pharmaceutical science.

[0091] In one embodiment, the excipient may include at least one diluent. Non-limiting examples of suitable diluents may include microcrystalline cellulose (MCC), cellulose derivatives, cellulose powder, cellulose esters (i.e., acetate and butyrate mixed esters), ethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, corn starch, phosphated corn starch, pregelatinized corn starch, rice starch, potato starch, tapioca starch, starch-lactose, starch-calcium carbonate, sodium starch glycolate, glucose, fructose, lactose, lactose monohydrate, sucrose, xylose, lactitol, mannitol, malitol, sorbitol, xylitol, maltodextrin, and trehalose.

[0092] In another embodiment, the excipient may comprise a binder. Suitable binders may include, but are not limited to, starches, pregelatinized starches, gelatin, polyvinylpyrrolidone, cellulose, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinylloxazolidone, polyvinylalcohols, C12-C18 fatty acid alcohol, polyethylene glycol, polyols, saccharides, oligosaccharides, polypeptides, oligopeptides, and combinations thereof.

[0093] In another embodiment, the excipient may include a filler. Suitable fillers may include, but are not limited to, carbohydrates, inorganic compounds, and polyvinylpyrrolidone. By way of non-limiting example, the filler may be calcium sulfate, both di- and tri-basic, starch, calcium carbonate, magnesium carbonate, microcrystalline cellulose, dibasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, talc, modified starches, lactose, sucrose, mannitol, or sorbitol.

[0094] In still another embodiment, the excipient may comprise a buffering agent. Buffers may include phosphates, carbonates, citrates, and the like. Representative examples of suitable buffering agents may include, but are not limited to, MOPS, HEPES, TAPS, Bicine, Tricine, TES, PIPES, MES, Tris buffers or buffered saline salts (e.g., Tris buffered saline or phosphate buffered saline).

[0095] In various embodiments, the excipient may include a pH modifier. By way of non-limiting example, the pH modifying agent may be sodium carbonate or sodium bicarbonate.

[0096] In another alternate embodiment, the excipient may also include a preservative. Non-limiting examples of suitable preservatives may include antioxidants, such as alpha-tocopherol or ascorbate, or EDTA (ethylenediaminetetraacetic acid), EGTA (ethylene glycol tetraacetic acid), BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), and the like.

[0097] In a further embodiment, the excipient may include a disintegrant. Suitable disintegrants may include, but are not limited to, starches such as corn starch, potato starch, pregelatinized and modified starches thereof, sweeteners, clays, such as bentonite, micro-crystalline cellulose, alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya, pectin, and tragacanth.

[0098] In yet another embodiment, the excipient may include a dispersion enhancer. Suitable dispersants may include, but are not limited to, starch, alginic acid, polyvinylpyrrolidones, guar gum, kaolin, bentonite, purified wood cellulose, sodium starch glycolate, isoamorphous silicate, and microcrystalline cellulose.

[0099] In a further embodiment, the excipient may include a lubricant. Non-limiting examples of suitable lubricants may include minerals such as talc or silica; and fats such as vegetable stearin, magnesium stearate, or stearic acid.

[0100] In still another embodiment, it may be desirable to provide a coloring agent. Suitable color additives may include, but are not limited to, food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C).

[0101] The weight fraction of the excipient(s) in the composition may be about 98% or less, about 95% or less, about 90% or less, about 85% or less, about 80% or less, about 75% or less, about 70% or less, about 65% or less, about 60% or less, about 55% or less, about 50% or less, about 45% or less, about 40% or less, about 35% or less, about 30% or less, about 25% or less, about 20% or less, about 15% or less, about 10% or less, about 5% or less, about 2%, or about 1% or less of the total weight of the composition.

[0102] The pharmaceutical composition may be mixed with one or more excipients to form a solid, liquid, or cream dosage form. Methods of formulating a solid, liquid, or cream dosage form are known in the art.

(ii) optional additional pharmaceutical ingredient

[0103] Optionally, the compound comprising Formula (I) may be combined with other compounds comprising Formula (I) or may be combined with one or more than one additional active pharmaceutical ingredients.

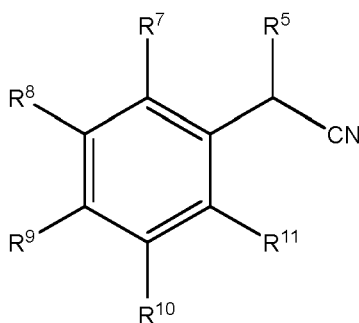
V. Method for Producing a Compound Comprising Formula (II)

[0104] In another embodiment, the disclosure provides a method of making the compound comprising Formula (II). The method comprises contacting a quinolinyl carboxaldehyde with a phenylacetonitrile or a benzyl triphenyl phosphine bromide in

the presence of a proton acceptor. A quinolinyl carboxaldehyde is a quinolinyl moiety, as described in Section (IV), which is substituted with an aldehyde moiety at one or more of the positions 1-8. Further substitution on the quinolinyl moiety may be as described in Section (II). In preferred embodiments, the quinolinyl carboxaldehyde is quinoline-2-carboxaldehyde, quinoline-3-carboxaldehyde, quinoline-4-carboxaldehyde, quinoline-5-carboxaldehyde, quinoline-6-carboxaldehyde.

[0105] The carboxaldehyde is contacted with phenylacetonitrile.

Phenylacetonitriles have the following generic structure:

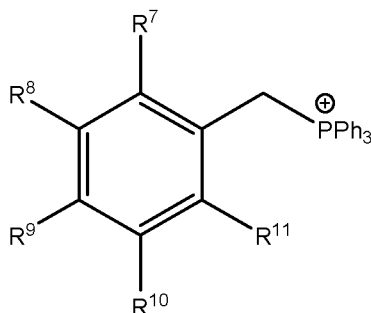


wherein, R⁵, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ may be chosen as described in section (I).

[0106] In preferred embodiments, the phenylacetonitrile is chosen from phenylacetonitrile, 3,4,5-trimethoxy phenyl acetonitrile, 3,4-dimethoxyphenylacetonitrile, and 4-hydroxy, 3,5-trimethoxyphenylacetonitrile.

[0107] The mole to mole ratio of the carboxaldehyde to the phenyl acetonitrile can range over different embodiments of the invention. In one embodiment, the ratio of the carboxaldehyde to the phenylacetonitrile varies from about 0.9:1 to about 1:10. In some embodiments, the mole to mole ratio of the carboxaldehyde to the phenylacetonitrile is about 1:1 to about 1:1.5. In various embodiments, the mole to mole ratio of the carboxaldehyde to the phenylacetonitrile is about 1:1, about 1:1.1, about 1:1.2, about 1:1.3, about 1:1.4, or about 1:1.5. In an exemplary embodiment, the mole to mole ratio of the carboxaldehyde to the phenylacetonitrile is 1:1.

[0108] In another embodiment, the compound comprising Formula (II) is contacted with a phenyl triphenyl phosphine. A phenyl triphenyl phosphine generally comprises the following structure:



wherein, R⁷, R⁸, R⁹, R¹⁰, and R¹¹ may be chosen as described in section (I).

[0109] An acceptable counter ion is generally present. In preferred embodiments, the counter ion is bromide.

[0110] In particular embodiments, phenyl triphenyl phosphines may include 3,4,5 trimethoxyphenyl triphenyl phosphine bromide, 3,4-dimethoxyphenyl triphenyl phosphine bromide, 4-hydroxy, and 3,5-dimethoxyphenyl triphenyl phosphine bromide.

[0111] The mole to mole ratio of the carboxaldehyde to the phenyl triphenyl phosphine can range over different embodiments of the invention. In one embodiment, the ratio of the carboxaldehyde to the phenyl triphenyl phosphine varies from about 0.9:1 to about 1:10. In some embodiments, the mole to mole ratio of the carboxaldehyde to the phenyl triphenyl phosphine is about 1:1 to about 1:1.5. In various embodiments, the mole to mole ratio of the carboxaldehyde to the phenyl triphenyl phosphine is about 1:1, about 1:1.1, about 1:1.2, about 1:1.3, about 1:1.4, or about 1:1.5. In an exemplary embodiment, the mole to mole ratio of the carboxaldehyde to the phenyl triphenyl phosphine is 1:1.

[0112] The reaction is preferably carried out in a solvent and is more preferably carried out in an organic solvent. The solvent may be chosen without limitation from including alkane and substituted alkane solvents (including cycloalkanes) alcohol solvents, halogenated solvents, aromatic hydrocarbons, esters, ethers, ketones, and combinations thereof. Non-limiting examples of suitable organic solvents are acetonitrile, acetone, allyl alcohol, benzene, butyl acetate, chlorobenzene, chloroform, chloromethane, cyclohexane, cyclopentane, dichloromethane (DCM), dichloroethane, diethyl ether, dimethoxyethane (DME), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), dioxane, ethanol, ethyl acetate, ethylene dichloride, ethylene bromide, formic

acid, fluorobenzene, heptane, hexane, isobutylmethylketone, isopropanol, isopropyl acetate, N-methylpyrrolidone, methanol, methylene bromide, methylene chloride, methyl iodide, methylethylketone, methyltetrahydrofuran, pentyl acetate, propanol, *n*-propyl acetate, sulfolane, tetrahydrofuran (THF), tetrachloroethane, toluene, trichloroethane, water, xylene and combinations thereof. In exemplary embodiments, the solvent is an alcohol solvent. In one preferred embodiment, the solvent is methanol.

[0113] A proton acceptor is generally added to facilitate the reaction. The proton acceptor generally has a pKa greater than about 7, or from about 7 to about 13, or more preferably from about 8 to about 10. Representative proton acceptors may include, but are not limited to, borate salts (such as, for example, NaBO_3), di- and tri-basic phosphate salts, (such as, for example, Na_2HPO_4 and NaPO_4), bicarbonate salts, carbonate salts, hydroxides, alkoxides, (including methoxide, ethoxide, propoxide, butoxide, and pentoxide, including straight chain and branched), and organic proton acceptors, (such as, for example, pyridine, triethylamine, *N*-methylmorpholine, and *N,N*-dimethylaminopyridine), and mixtures thereof. In some embodiments, the proton acceptor may be stabilized by a suitable counterion such as lithium, potassium, sodium, calcium, magnesium, and the like. In one preferred embodiment, the proton acceptor is sodium methoxide.

[0114] The amount of the proton acceptor which is added may vary. In some embodiments, the mole to mole ratio of the carboxaldehyde to the proton acceptor can range from about 1:1 to about 1:10. In some embodiments, the mole to mole ratio of the carboxaldehyde to the proton acceptor is about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:6, about 1:7, about 1:8, or about 1:10. In still other embodiments, the mole to mole ratio of the carboxaldehyde to the proton acceptor is about 1:1.2, about 1:1.3, about 1:1.4, about 1:1.5, about 1:1.6, about 1:1.7, about 1:1.8, or about 1:9. In one preferred embodiment, the mole to mole ratio of the carboxaldehyde to the proton acceptor is about 1:2.

[0115] The amount of time over which the reaction is conducted may also vary within different embodiments. In some embodiments, the reaction may be conducted over a period of 2 hours to 8 hours. In particular embodiments, the reaction

is carried out for about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, or about 8 hours. In preferred embodiments, the reaction is conducted for about 4 hours.

[0116] The temperature may vary over different embodiments, in some embodiments the temperature may range from about 20°C to about 80°C. In particular embodiments the temperature may range from about 20°C to about 30°C, from about 30°C to about 40°C, from about 40°C to about 50°C, from about 50°C to about 60°C, from about 60°C to about 70°C, or from about 70°C to about 80°C.

[0117] The synthesized compounds may be used in their crude form or they may be purified. The compounds may be purified by any suitable method known in the art including through column chromatography, crystallization, distillation, extraction, and the like. In one preferred embodiment, the compounds are recrystallized from a solvent.

VI. Methods of Use for the Compound Comprising Formula (II)

[0118] In still another aspect, the present disclosure provides a method of inhibiting tubulin polymerization in a subject. The method comprises administering a compound comprising Formula (II) to a subject.

[0119] Without being bound to any theory, compounds comprising Formula (II) are thought to bind to tubulin. The binding at this site is thought to inhibit tubulin polymerization, and in turn, inhibit formation of vasculature. In tumors, a developing vasculature is critical to tumor growth and migration. Accordingly, inhibition of tubulin polymerization is important to the treatment of various disease states.

[0120] In another embodiment, a method for treating cancer is provided. The method comprises administering a compound comprising Formula (II) to a subject. Cancers treatable by the method may include, without limitation, prostate cancer, ovarian cancer, breast cancer, brain cancer, hepatic cancer, leukemia, lung cancer, colon cancer, CNS cancer, melanoma, renal cancer, pancreatic cancer, gastric cancer, lymphoma and the like.

[0121] The compounds may be administered to the subject by a variety of routes. For example, a compound comprising Formula (II) may be administered orally via a solid or liquid dosage form (tablet, gel cap, time release capsule powder, solution,

or suspension in aqueous or non-aqueous liquid), parenterally (i.e., subcutaneously, intradermally, intravenously, (i.e., as a solution, suspension or emulsion in a carrier), intramuscularly, intracranially, or intraperitoneally), or topically (i.e., transdermally or transmucosally, including, but not limited to buccal, rectal, vaginal and sublingual). In one embodiment, the compounds may be administered in saline or with a pharmaceutically acceptable excipient as described in section (IV). The compound may be administered as primary therapy, or as adjunct therapy, either following local intervention (surgery, radiation, local chemotherapy) or in conjunction with at least one other chemotherapeutic agent.

[0122] Suitable subjects may include, without limit, humans, as well as companion animals such as cats, dogs, rodents, and horses; research animals such as rabbits, sheep, pigs, dogs, primates, mice, rats and other rodents; agricultural animals such as cows, cattle, pigs, goats, sheep, horses, deer, chickens and other fowl; zoo animals; and primates such as chimpanzees, monkeys, and gorillas. The subject can be of any age without limitation. In a preferred embodiment, the subject may be a human.

[0123] Generally, the compound comprising Formula (II) will be administered in a therapeutically effective amount which includes prophylactic amounts or lower dosages for example, when combined with another agent. As used herein, "an effective amount" refers to doses of compound sufficient to provide circulating concentrations high enough to impart a beneficial effect on the recipient thereof. The precise amount to be administered can be determined by the skilled practitioner in view of desired dosages, side effects, and medical history of the patient.

[0124] The compounds comprising Formula (II) may also be characterized by their cytotoxic effects when contacted with cells. In some embodiments, the compounds inhibit the growth of a cell. In other embodiments, the compounds kill cells. Accordingly, the compounds of the present invention may be characterized by GI_{50} values and LC_{50} values. GI_{50} refers to the molar drug concentration required to cause 50% growth inhibition compared to an untreated cell. LC_{50} refers to the concentration required to kill 50% of cells. In still another embodiment, the disclosure provides a

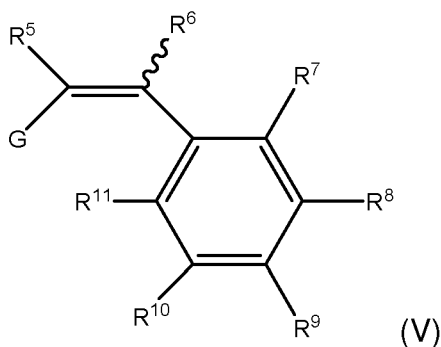
method for inhibiting growth of a cell by contacting the cells with a compound comprising Formula (II), and in a still further embodiment, the disclosure provides a method for killing cells by contacting the cells with a compound comprising Formula (II). Cells may be chosen from, without limitation, those listed in **TABLE 2**.

[0125] In some embodiments, the compounds comprising Formula (I) have an LC_{50} of less than about $100\mu\text{M}$, or less than $80\mu\text{M}$, or less than about $60\mu\text{M}$, or less than about $40\mu\text{M}$, or less than about $20\mu\text{M}$, or less than about $1\mu\text{M}$. In other embodiments, the compounds comprising Formula (II) have a GI_{50} of less than about $100\mu\text{M}$, or less than $80\mu\text{M}$, or less than about $60\mu\text{M}$, or less than about $40\mu\text{M}$, or less than about $20\mu\text{M}$, or less than about $1\mu\text{M}$.

VII. Compositions of the Compound Comprising Formula (V)

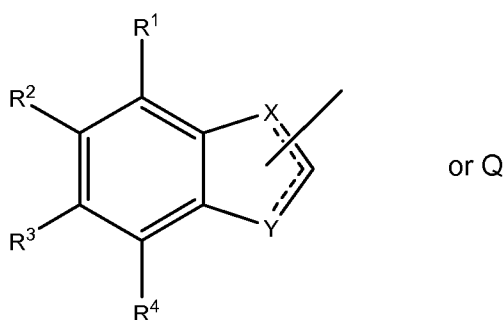
(a) Compound Comprising Formula (V)

[0126] One aspect of the invention provides compounds comprising Formula (V):



wherein:

G is chosen from



Q is a quinolinyl moiety;

R^1 , R^2 , R^3 , R^4 , R^7 , R^8 , R^9 , R^{10} , R^{11} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro;

R^5 and R^6 are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, carboxyl, ester, and cyano;

X and Y are independently chosen from O, C, CR^{12} , $CR^{12}R^{13}$, S, SR^{14} N, or NR^{15} ; and

R^{12} , R^{13} , R^{14} , and R^{15} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro.

[0127] All variables are as described in Sections (I) and (IV).

[0128] The compound comprising Formula (V) may be used as a polymerase inhibitor, as described in Sections (III) and (VI). The compositions may be formulated as a pharmaceutical composition as described in Sections (I) and (IV).

DEFINITIONS

[0129] When introducing elements of the embodiments described herein, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

[0130] The term "acyl," as used herein alone or as part of another group, denotes the moiety formed by removal of the hydroxyl group from the group COOH of an organic carboxylic acid, e.g., $RC(O)-$, wherein R is R^1 , R^1O- , R^1R^2N- , or R^1S- , R^1 is hydrocarbyl, heterosubstituted hydrocarbyl, or heterocyclo, and R^2 is hydrogen, hydrocarbyl, or substituted hydrocarbyl.

[0131] The term "acyloxy," as used herein alone or as part of another group, denotes an acyl group as described above bonded through an oxygen linkage (O), e.g., $RC(O)O-$ wherein R is as defined in connection with the term "acyl."

[0132] The term “allyl,” as used herein not only refers to compound containing the simple allyl group ($\text{CH}_2=\text{CH}-\text{CH}_2-$), but also to compounds that contain substituted allyl groups or allyl groups forming part of a ring system.

[0133] The term “alkyl” as used herein refers to straight or branched chain alkyl groups having in the range of about 1 to about 10 carbon atoms. A substituted alkyl group has one or more heteroatom substituents as described in the definition of substituted hydrocarbyl.

[0134] The term “alkylaryl” refers to alkyl substituted aryl groups, and “substituted alkylaryl” refers to alkylaryl groups further bearing one or more substituents.

[0135] The term “alkenyl” as used herein describes groups which are preferably lower alkenyl containing from two to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain or cyclic and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, hexenyl, and the like.

[0136] The term “alkoxide” or “alkoxy” as used herein is the conjugate base of an alcohol. The alcohol may be straight chain, branched, cyclic, and includes aryloxy compounds.

[0137] The term “alkynyl” as used herein describes groups which are preferably lower alkynyl containing from two to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain and include ethynyl, propynyl, butynyl, isobutynyl, hexynyl, and the like.

[0138] The term “aromatic” as used herein alone or as part of another group denotes optionally substituted homo- or heterocyclic conjugated planar ring or ring system comprising delocalized electrons. These aromatic groups are preferably monocyclic (e.g., furan or benzene), bicyclic, or tricyclic groups containing from 5 to 14 atoms in the ring portion. The term “aromatic” encompasses “aryl” groups defined below.

[0139] The terms “aryl” or “Ar” as used herein alone or as part of another group denote optionally substituted homocyclic aromatic groups, preferably monocyclic or bicyclic groups containing from 6 to 12 carbons in the ring portion, such as phenyl, biphenyl, naphthyl, substituted phenyl, substituted biphenyl, or substituted naphthyl.

[0140] The term "arylalkynyl" refers to aryl-substituted alkynyl groups and "substituted arylalkynyl" refers to arylalkynyl groups further bearing one or more substituents.

[0141] The term "aroyl" refers to aryl-substituted species such as benzoyl and "substituted aroyl" refers to aroyl moieties further bearing one or more substituents as set forth above.

[0142] The term "cycloalkyl" refers to cyclic ring-containing moieties containing in the range of about 3 up to 7 carbon atoms and "substituted cycloalkyl" refers to cycloalkyl moieties further bearing one or more substituents.

[0143] The terms "halide" or "halo" as used herein alone or as part of another group refer to chlorine, bromine, fluorine, and iodine.

[0144] The term "heteroatom" refers to atoms other than carbon and hydrogen.

[0145] The term "heteroaromatic" as used herein alone or as part of another group denotes optionally substituted aromatic groups having at least one heteroatom in at least one ring, and having in the range of 2 up to 12 carbon atoms, or preferably 5 or 6 atoms in each ring. The heteroaromatic group preferably has 1 or 2 oxygen atoms and/or 1 to 4 nitrogen atoms in the ring, and is bonded to the remainder of the molecule through a carbon. Exemplary groups include furyl, benzofuryl, oxazolyl, isoxazolyl, oxadiazolyl, benzoxazolyl, benzoxadiazolyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, indolyl, isoindolyl, indolizynyl, benzimidazolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl, carbazolyl, purinyl, quinolinyl, isoquinolinyl, imidazopyridyl, and the like. Exemplary substituents include one or more of the following groups: hydrocarbyl, substituted hydrocarbyl, alkyl, alkoxy, acyl, acyloxy, alkenyl, alkenoxy, aryl, aryloxy, amino, amido, acetal, carbamyl, carbocyclo, cyano, ester, ether, halogen, heterocyclo, hydroxyl, keto, ketal, phospho, nitro, and thiol.

[0146] The terms "heterocyclo" or "heterocyclic" as used herein alone or as part of another group denote optionally substituted, fully saturated or unsaturated, monocyclic or bicyclic, aromatic or non-aromatic groups having at least one heteroatom

in at least one ring, and preferably 5 or 6 atoms in each ring. The heterocyclo group preferably has 1 or 2 oxygen atoms and/or 1 to 4 nitrogen atoms in the ring, and is bonded to the remainder of the molecule through a carbon or heteroatom. Exemplary heterocyclo groups include heteroaromatics as described above. Exemplary substituents include one or more of the following groups: hydrocarbyl, substituted hydrocarbyl, alkyl, alkoxy, acyl, acyloxy, alkenyl, alkenoxy, aryl, aryloxy, amino, amido, acetal, carbamyl, carbocyclo, cyano, ester, ether, halogen, heterocyclo, hydroxyl, keto, ketal, phospho, nitro, and thio.

[0147] The terms "hydrocarbon" and "hydrocarbyl" as used herein describe organic compounds or radicals consisting exclusively of the elements carbon and hydrogen. These moieties include alkyl, alkenyl, alkynyl, and aryl moieties. These moieties also include alkyl, alkenyl, alkynyl, and aryl moieties substituted with other aliphatic or cyclic hydrocarbon groups, such as alkaryl, alkenaryl and alkynaryl. Unless otherwise indicated, these moieties preferably comprise 1 to 20 carbon atoms.

[0148] The "substituted hydrocarbyl" moieties described herein are hydrocarbyl moieties which are substituted with at least one atom other than carbon, including moieties in which a carbon chain atom is substituted with a heteroatom such as nitrogen, oxygen, silicon, phosphorous, boron, or a halogen atom, and moieties in which the carbon chain comprises additional substituents. These substituents include alkyl, alkoxy, acyl, acyloxy, alkenyl, alkenoxy, aryl, aryloxy, amino, amido, acetal, carbamyl, carbamate, carbocyclo, cyano, ester, ether, halogen, heterocyclo, hydroxyl, keto, ketal, phospho, nitro, thio, trifluoromethyl, sulfonyl, sulfonamide, and the like.

EXAMPLES

Example 1: Synthesis of (E)-3-(benzo[b]thiophen-2-yl)-2-(3,4,5-trimethoxyphenyl) acrylonitrile

[0149] A mixture of benzo[b]thiophene-2-carbaldehyde (1.62 g; 0.01 mol) and 2-(3,4,5-trimethoxyphenyl) acetonitrile (2.07 g; 0.01 mol), sodium methoxide (2.5 gm) in methanol (50 ml) were stirred at reflux temperature for 3 hours. The reaction mass was cooled to room temperature, and crushed ice was added to get solid product. The crude solid was separated by filtration and washed several times with cold methanol (3

X 5 ml). The isolated yellow solid recrystallized from methanol gave (*Z*)-3-(benzo[*b*]thiophen-2-yl)-2-(3,4,5-trimethoxyphenyl) acrylonitrile as a yellow crystalline product.

[0150] The compound (*Z*)-3-(benzo[*b*]thiophen-2-yl)-2-(3,4,5-trimethoxyphenyl) acrylonitrile was dissolved in methanol under reflux conditions and stirred for 48 hours under the UV light. The colorless solution was cooled to room temperature, and allowed to crystallize from methanol as white crystalline product, (*E*)-3-(benzo[*b*]thiophen-2-yl)-2-(3,4,5-trimethoxyphenyl)acrylonitrile, MF: C₂₀H₁₇NO₃S, mp: 201-203°C, ¹H NMR (DMSO-d₆): 3.76 (s, 3H), 3.78 (s, 6H), 6.81 (s, 2H), 7.36- 7.37 (t, 2H), 7.85-7.89 (m, 3H), 8.05 (s, 1H) ppm; ¹³C NMR (DMSO-d₆): 56.45, 61.32, 106.53, 112.34, 120.10, 122.42, 124.65, 125.13, 126.85, 127.01, 131.71, 136.93, 137.94, 138.10, 139.64, 141.94, 154.15 ppm.

Example 2: Synthesis of (*Z*)-2-(3,5-dimethoxyphenyl)-3-(1*H*-indol-3-yl)acrylonitrile

[0151] A mixture of 1*H*-indole-3-carbaldehyde (1.45 g; 0.01 mol) and 2-(3,5-dimethoxyphenyl)acetonitrile (1.77 g; 0.01 mol), sodium methoxide (2.5 gm) in methanol (50 ml) were stirred at reflux temperature for 4 hrs. The reaction mass was cooled to room temperature, and crushed ice was added to get solid product, the crude solid was separated by filtration and washed several times with cold methanol (3 X 5 ml). The isolated yellow solid recrystallized from methanol gave (*Z*)-2-(3,5-dimethoxyphenyl)-3-(1*H*-indol-3-yl)acrylonitrile as a yellow crystalline product; MF: C₁₉H₁₆N₂O₂, mp: 170-172 °C, ¹H NMR (CDCl₃): δ3.86 (s, 6H), 6.45 (s, 1H), 6.82 (s, 2H), 7.25-7.29 (m, 2H), 7.44-7.46 (d, *J*=8 Hz, 1H), 7.75-7.77 (d, *J*=7.2 Hz, 1H), 7.87 (s, 1H); 8.44 (s, 1H), 8.83 (brs, 1H, NH) ppm; ¹³C NMR (CDCl₃): 55.52, 100.10, 103.67, 111.79, 118.00, 119.95, 121.38, 123.50, 126.40, 127.28, 133.78, 135.45, 136.84, 161.21 ppm.

Example 3: Synthesis of (*E*)-2-(3,4,5-trimethoxystyryl)benzofuran

[0152] A mixture of benzofuran-2-carbaldehyde (0.146 g; 0.001 mol) and triphenyl(3,4,5-trimethoxybenzyl)phosphonium bromide (0.523 g; 0.001 mol), sodium methoxide (2.5 gm) in methanol (50 ml) were stirred at room temperature for 4 hours. Crushed ice was added to get solid product, and the crude solid was separated by

filtration and washed several times with cold methanol (3 X 5 ml). The isolated pale yellow solid recrystallized from methanol gave (*E*)-2-(3,4,5-trimethoxystyryl)benzofuran as a pale yellow crystalline product; MF: C₁₉H₁₈O₄, mp:124-126 °C, ¹H NMR (CDCl₃): δ 3.87 (s, 3H), 3.91 (s, 6H), 6.66 (s, 1H), 6.75 (s, 2H), 6.88-6.92 (d, *J*=16Hz, 1H), 7.20-7.26 (m, 3H), 7.44-7.46 (d, *J*=8.4 Hz, 1H), 7.51-7.53 (d, *J*=7.6Hz, 1H) *ppm*; ¹³C NMR (CDCl₃): 56.11, 60.98, 103.72, 105.04, 110.82, 115.88, 120.79, 122.90, 124.60, 129.11, 130.21, 132.25, 138.36, 153.44, 154.83, 154.94 *ppm*.

Example 4: Synthesis of (*E*)-2-(3,4,5-trimethoxystyryl)benzo[d]thiazole

[0153] A mixture of benzo[d]thiazole-2-carbaldehyde (0.163 g; 0.001 mol) and triphenyl(3,4,5-trimethoxybenzyl)phosphonium bromide (0.523 g; 0.001 mol), sodium methoxide (2.5 gm) in methanol (50 ml) were stirred at room temperature for 4 hours. Crushed ice was added to get a solid product, and the crude solid was separated by filtration and washed several times with cold methanol (3 X 5 ml). The isolated pale yellow solid recrystallized from methanol gave (*E*)-2-(3,4,5-trimethoxystyryl)benzo[d]thiazole as a pale yellow crystalline product; MF: C₁₈H₁₇NO₃S, mp: 125-127°C, ¹H NMR (CDCl₃): δ 3.91 (s, 3H), 3.93 (s, 6H), 6.83 (s, 2H), 7.33-7.48 (m, 4H), 7.87 (s, 1H), 8.0 (s, 1H) *ppm*; ¹³C NMR (CDCl₃): δ 56.12, 60.96, 104.47, 121.48, 122.89, 125.32, 126.33, 130.95, 134.26, 137.47, 153.5, 153.8, 166.78 *ppm*.

Example 5: *In vitro* growth inhibition and cytotoxicity Formula (I)

[0154] In a primary screen, all synthesized compounds were evaluated for their cytotoxic potency at the National Cancer Institute (NCI). The compounds were considered to be active if they reduced the growth of any of the cancer cell lines to 60% or more in at least eight of the cell lines screened. They were then passed on for evaluation in a full panel of 60 different cancer cell lines. From the preliminary 60 cell screen the compounds which showed ≥60% growth inhibition in at least eight of the cancer cell lines screened were selected for further five dose studies. From all these compounds the three most active compounds were subsequently evaluated in five dose-response studies for their *in vitro* cytotoxic effects on growth parameters against each of the 60 human tumor cell lines. These three analogues exhibited good growth

inhibition even at nanomolar levels in five dose screening against all the cancer cell lines. Cytotoxic effects of each compound were determined as GI₅₀ and LC₅₀ values, which represent the molar drug concentration required to cause 50% growth inhibition, and the concentration that kills 50% of the cells, respectively. The results are presented in **TABLE 1**.

TABLE 1: Growth Inhibition and Cytotoxicity Studies N-benzoyl indole analogs (Formula (I))

Panel/cell Line	Formula (I)(a)		Formula (I)(b)		Formula (I)(c)		Formula (I)(d)	
	GI ₅₀ (nM)	LC ₅₀ (μM)	GI ₅₀ (nM)	LC ₅₀ (μM)	GI ₅₀ (nM)	LC ₅₀ (μM)	GI ₅₀ (nM)	LC ₅₀ (μM)
<u>Leukemia</u> CCEF-CEM	<10.0	>100	42.4	>100	0.42	>100	0.13	>100
HL-60(TM)	<10.0	>100	31.2	>100	0.35	>100	0.037	>100
K-562	<10.0	>100	43.2	>100	0.26	>100	0.041	>100
MOLT-4	<10.0	>100	49.1	>100	0.85	>100	1.28	>100
RPMI-8226	<10.0	>100	65.5	>100	0.70	>100	0.15	>100
SR	<10.0	>100	33.4	>100	0.09	>100	0.036	>100
<u>Lung Cancer</u> A549/ATCC	<10.0	>100	61.8	>100	0.61	>100	0.11	>100
HOP-62	<10.0	>100	>100	>100	0.77	>100	0.39	81.5
HOP-92	<10.0	>100	68.4	>100	0.17	>100	0.036	77.4
NCI-H226	17.9	>100	>100	>100	1.1	>100	0.24	88.5
NCI-H23	<10.0	>100	>100	>100	3.09	>100	0.72	>100
NCI-H322M	18.3	>100	na	>100	15.9	>100	na	>100
NCI-H460	<10.0	>100	39.2	>100	0.41	>100	0.11	>100
NCIH522	Na	na	27.1	>100	0.43	>100	0.16	47.9
<u>Colon Cancer</u> COLO 205	<10.0	0.25	47.7	15.2	0.40	19.5	0.049	24.6
HCC-2998	19.2	>100	>100	>100	3.34	>100	2.23	63.5
HCT-116	<10.0	>100	42.5	>100	0.522	77.0	0.0072	>100

HCT-15	<10.0	>100	53.5	>100	0.40	>100	0.063	>100
HT29	<10.0	>100	38.4	>100	0.37	>100	0.038	>100
KM12	<10.0	>100	40.9	>100	0.50	>100	0.072	41.6
SW-620	<10.0	>100	44.1	>100	0.44	>100	0.43	>100
<u>CNS</u> <u>Cancer</u> SF268	<10.0	>100	78.3	>100	0.86	>100	0.56	>100
SF-2395	Na	na	45.3	>100	0.35	>100	0.070	>100
SF-539	<10.0	>100	52.2	90.2	0.27	>100	0.076	56.2
SNB-19	39.1	>100	62.1	>100	0.58	>100	0.095	>100
SNB-75	<10.0	>100	34.8	>100	0.47	>100	0.16	>100
U251	<10.0	>100	45.4	>100	0.66	81.2	0.88	>100
<u>Melanoma</u> LOX IM VI	<10.0	>100	78.4	>100	0.89	60.4	1.9	67.9
MALMW-3M	<10.0	>100	na	>100	0.41	86.3	0.07	51.6
M14	<10.0	>100	42.4	>100	0.47	88.4	0.063	48.5
MDA-MB-435	<10.0	>100	20.3	>100	0.078	>100	0.024	44.6
SK-MEL-2	<10.0	>100	51.2	>100	0.76	>100	0.064	64.2
SK-MEL-28	<10.0	>100	81.1	>100	0.83	>100	0.31	50.5
SK-MEL-5	<10.0	>100	48.6	>100	0.34	42.0	0.047	34.0
UACC-257	<10.0	>100	48.7	>100	16.4	>100	15.0	>100
UACC-62	<10.0	>100	49.3	>100	0.50	>100	0.05	55.9
<u>Ovarian</u> <u>Cancer</u> IGROVI	<10.0	>100	>100	>100	0.80	>100	0.24	94.2
OVCAR-3	<10.0	>100	31.2	>100	0.42	48.1	0.069	>100
OVCAR-4	<10.0	>100	>100	>100	1.15	>100	1.81	>100
OVCAR-5	<10.0	>100	>100	>100	2.94	>100	0.93	>100
OVCAR-8	<10.0	>100	>100	>100	2.05	>100	0.39	>100
NCI/ADR-RES	<10.0	>100	33.3	>100	0.51	>100	0.10	>100
SK-OV-3	<10.0	>100	>100	>100	0.65	>100	0.16	>100

<u>Renal Cancer</u> 786-0	<10.0	>100	77.3	>100	0.85	79.8	1.32	>100
A498	<10.0	>100	35.3	>100	0.40	48.4	0.041	35.8
ACHN	<10.0	>100	>100	>100	0.86	>100	1.22	>100
CAKL-1	37.8	>100	35.0	>100	0.58	>100	0.14	>100
RXF 393	<10.0	>100	83.7	>100	0.32	>100	0.14	97.6
SNI2C	<10.0	>100	77.9	>100	4.09	>100	9.37	>100
TK-10	<10.0	>100	>100	>100	8.4	>100	11.1	>100
UO-31	<10.0	>100	>100	>100	1.15	>100	0.37	>100
<u>Prostate Cancer</u> PC-3	<10.0	>100	75.5	>100	.52	>100	0.13	>100
DU-145	<10.0	>100	>100	>100	1.86	>100	0.27	>100
<u>Breast Cancer</u> MCF7	<10.0	>100	41.4	>100	0.37	>100	0.31	51.5
MDA-MB-231/ATCC	<10.0	>100	>100	>100	1.17	>100	0.71	>100
HS 578T	<10.0	>100	>100	>100	0.49	>100	0.17	>100
BT-549	<10.0	>100	>100	>100	1.09	79.5	3.7	58.8
T-47D	<10.0	>100	>100	>100	0.69	>100	0.96	>100
MDA-MB-468	<10.0	>100	>100	>100	0.66	>100	0.82	>100

Example 6: Synthesis of (Z)-3-(quinolin-2-yl)-2-(3,4,5-trimethoxyphenyl) acrylonitrile

[0155] A mixture of quinoline-2-carboxaldehyde (1.57 g; 0.01 mol) and 2-(3,4,5-trimethoxyphenyl) acetonitrile (2.07 g; 0.01 mol), sodium methoxide (1.0 gm) in methanol (50 ml) were stirred at reflux temperature for 3 hours. The reaction mass was cooled to room temperature, and crushed ice was added to get a solid product. The crude solid was separated by filtration and washed several times with cold methanol (3x5 ml). The isolated yellow solid was recrystallized from methanol and gave (Z)-3-

(quinolin-2-yl)-2-(3,4,5-trimethoxyphenyl)acrylonitrile as a yellow fluffy product. MF: $C_{21}H_{18}N_2O_3$, mp: 106-108°C, 1H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 3H), 3.96 (s, 6H), 7.02 (s, 2H), 7.61 (t, 1H, $J_1=7.6$ Hz, $J_2=14.8$ Hz), 7.78-7.79 (d, 1H, $J=7.2$ Hz), 7.86 (s, 1H), 7.86-7.88 (d, 1H, $J=8.40$ Hz), 8.14-8.20 (m, 2H), 8.27-8.29 (d, 1H, $J=8.8$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.29, 60.96, 103.74, 115.91, 117.44, 120.54, 127.55, 127.64, 127.73, 127.86, 129.43, 129.60, 130.35, 137.00, 139.73, 140.74, 140.87, 148.10, 152.21, 153.59 ppm.

Example 7: Synthesis of (Z)-2-(3,5-dimethoxyphenyl)-3-(quinolin-2-yl) acrylonitrile

[0156] A mixture of quinolone-2-carboxaldehyde (1.57 g; 0.01 mol) and 2-(3,5-dimethoxyphenyl)acetonitrile (1.77 g; 0.01 mol), sodium methoxide (1.0 gm) in methanol (50 ml) was stirred at reflux temperature for 4 hours. The reaction mass was cooled to room temperature, crushed ice was added to get a solid product. The crude solid was separated by filtration and washed several times with cold methanol (3x5 ml). The isolated light yellow solid was recrystallized from methanol and gave (Z)-2-(3,5-dimethoxyphenyl)-3-(quinolin-2-yl)acrylonitrile as a light yellow crystalline product; MF: $C_{20}H_{16}N_2O_2$, mp: 106°C -108°C, 1H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 6H), 6.52 (s, 1H), 6.92 (s, 2H), 7.56-7.60 (t, 1H, $J_1=7.2$ Hz, $J_2=15.2$ Hz), 7.73-7.77 (t, 1H, $J_1=8.0$ Hz, $J_2=15.2$ Hz), 7.81 (s, 1H), 7.83-7.85 (d, 1H, $J=8.8$ Hz), 8.11-8.15 (t, 2H, $J_1=9.6$ Hz, $J_2=18$ Hz), 8.26 (d, 1H, $J=8.8$ Hz) ppm; ^{13}C NMR (100MHz, $CDCl_3$) 55.52, 101.63, 104.33, 113.92, 117.59, 126.69, 127.37, 127.49, 127.62, 128.78, 129.29, 129.36, 131.16, 135.16, 135.23, 135.84, 138.33, 148.40, 151.26, 161.31 ppm.

Example 8: Synthesis of (Z)-3-(3,5-dimethoxyphenyl)-3-(quinolin-2-yl)acrylonitrile

[0157] A mixture of quinolone-3-carboxaldehyde (1.57 g; 0.01 mol) and 2-(3,5-dimethoxyphenyl)acetonitrile (1.77 g; 0.01 mol), sodium methoxide (1.0 gm) in methanol (50 ml) were stirred at reflux temperature for 4 hours. The reaction mass was cooled to room temperature, crushed ice was added to get a solid product. The crude solid was separated by filtration and was washed several times with cold methanol (3 X 5 ml). The isolated light yellow solid was recrystallized from methanol and gave (Z)-3-(3,5-dimethoxyphenyl)-3-(quinolin-2-yl)acrylonitrile as a light yellow crystalline product;

MF: C₂₀H₁₆N₂O₂, mp: 150-152°C, ¹H NMR (400 MHz, CDCl₃): δ 3.85 (s, 6H), 6.52 (s, 1H), 6.85 (s, 2H), 7.58-7.62 (t, 1H, *J*=8.0 Hz, *J*₂=15.2 Hz), 7.66 (s, 1H), 7.76-7.80 (t, 1H, *J*₁=8.0 Hz, *J*₂=15.6 Hz), 7.92-7.94 (d, 1H, *J*=8.0 Hz), 8.10-8.12 (d, 1H, *J*=8.8 Hz), 8.93 (s, 1H), 9.09 (d, 1H, 1.6 Hz) *ppm*; ¹³C NMR (100 MHz, CDCl₃): 55.52, 101.63, 104.33, 113.92, 117.59, 126.69, 127.37, 127.49, 127.62, 128.78, 129.29, 129.36, 131.16, 135.23, 135.84, 138.33, 148.40, 151.26, 161.31 *ppm*.

Example 9: *In vitro* growth inhibition and cytotoxicity Formula (II)

[0158] In a primary *screen*, all synthesized compounds were evaluated for their cytotoxic potency at the National Cancer Institute (NCI). The compounds were considered to be active if they reduced the growth of any of the cancer cell lines to 60% or more in at least eight of the cell lines screened. They were then passed on for evaluation in a full panel of 60 different cancer cell lines at five different doses. The analogues exhibited good growth inhibition even at nanomolar levels in five dose screening against all the cancer cell lines. Cytotoxic effects of each compound were determined as GI₅₀ and LC₅₀ values, which represent the molar drug concentration required to cause 50% growth inhibition, and the concentration that kills 50% of the cells, respectively. The results are presented in **TABLE 2**.

[0159] The substitution of 3,4,5-trimethoxyphenyl acrylonitrile moiety on the second position of quinoline (NSC:D-76345211; PNR-4-90) (*Z*-3-(quinolin-2-yl)-2-(3,4,5-trimethoxyphenyl)acrylonitrile] exhibited potent growth inhibition on 91% of the cancer cell lines with GI₅₀ ranging from 0.033 to 0.943 μM and the average GI₅₀ value of this compound on all the cancer cell lines is 0.40 μM. This compound exhibited potent growth inhibition on MDA-MB-435 melanoma cancer cell lines with GI₅₀ of 0.033 μM (**TABLE 2**).

[0160] The substitution of 3,5-dimethoxyphenyl acrylonitrile moiety on the second position of quinoline (NSC:D-763448/1 PNR-4-84) [(*Z*-3-(quinolin-2-yl)-2-(3,5-dimethoxyphenyl)acrylonitrile] exhibited potent growth inhibition on 86% of the cancer cell lines with GI₅₀ ranging from 0.094 to 0.983 μM and the average GI₅₀ value of this compound on all the cancer cell lines is 0.49 μM. This compound exhibited potent growth inhibition on NCI-11522 lung cancer cell lines with GI₅₀ of 0.094 μM (**TABLE 2**).

[0161] The substitution of 3,4,5-trimethoxyphenyl acrylonitrile moiety on the third position of quinoline (NSC:D-764126/1; PNR-5-10) [(Z)-3-(quinolin-3-yl)-2-(3,4,5-trimethoxy phenyl) acrylonitrile] exhibited potent growth inhibition on 47% of the cancer cell lines with G_{150} ranging from 0.227 to 0.911 μM and the average G_{150} value of this compound on all the cancer cell lines is 2.49 μM . This compound exhibited potent growth inhibition on MDA-MB-435 melanoma cancer cell lines with G_{150} of 0.227 μM (TABLE 2).

[0162] The substitution of 3,5-dimethoxyphenyl acrylonitrile moiety on the third position of quinoline (NSC:D-763449/1 PNR-4-85) [(Z)-3-(quinolin-3-yl)-2-(3,5-dimethoxy phenyl) acrylonitrile] exhibited potent growth inhibition on 81% of the cancer cell lines with G_{150} ranging from 0.053 to 0.903 μM and the average G_{150} value of this compound on all the cancer cell lines is 2.21 μM . This compound exhibited potent growth inhibition on MDA-MB-435 melanoma cancer cell lines with G_{150} of 0.053 μM (TABLE 2).

TABLE 2: Growth Inhibition Concentration and Cytotoxicity Formula (II)

Panel/cell-line	PNR-4-90 NSC:D-763452/1 Formula (II)(a)		PNR-4-84 NSC:D-763448/1 Formula (II)(b)		PNR-4-85 NSC:D-763449/1 Formula (II)(c)		PNR-5-10 NSC:D-764126/1 Formula (II)(d)	
	G_{150} (μM)	LC_{50} (μM)	G_{150} (μM)	LC_{50} (μM)	G_{150} (μM)	LC_{50} (μM)	G_{150} (μM)	LC_{50} (μM)
Leukemia CCRF-CEM	0.248	>100	0.332	>100	0.332	>100	1.38	>100
HL-60(TB)	0.223	>100	0.27	>100	0.234	>100	329	>100
K-562	0.080	>100	0.353	>100	0.243	>100	0.444	>100
MOLT-4	0.488	>100	0.419	>100	0.378	>100	3.20	>100
RPM1-8226	0.297	>100	0.433	>100	0.332	>100	2.06	>100
SR	NA	NA	NA	NA	NA	NA	0.569	>100
Lung Cancer A549/ATCC	0.375	>100	0.649	>100	0.556	>100	0.680	>100

HOP-62	0.567	>100	0.959	>100	0.793	>100	10.3	>100
HOP-92	0.736	>100	0.542	>100	3.09	>100	0.403	>100
NCI-H226	4.78	>100	10.8	>100	62.2	>100	>100	>100
NCI-H23	0.751	>100	0.983	>100	0.747	>100	2.93	>100
NCI-H322M	0.718	>100	3.02	>100	0.903	>100	27 , 4	>100
NCI-H460	0.361	>100	0.339	>100	0.362	>100	2.05	>100
NCI-H522	0.0372	>100	0.094	>100	0.069	>100	0.299	>100
<u>Colon Cancer</u> COLO 205	0.198	32.7	0.374	>100	0.398	89.9		9.44
HCC-2998	0.61	>100	1.42	>100	1.45	>100	2.01	>100
HCT-116	0.234	>100	0.416	47.3	0.420	>100	0.464	>100
HCT-15	0.319	>100	0.409	>100	0.455	>100	1.08	>100
HT29	0.24	>100	0.367	>100	0.362	>100	0.421	>100
KM12	0.35	>100	0.425	>100	0.409	>100	0.436	>100
SW-620	0.164	>100	0.357	>100	0.352	>100	0.420	>100
<u>CNS Cancer</u> SF-268	0.835	>100	0.476	>100	0.654	>100	9.17	>100
SF-295	0.277	>100	0.341	>100	0.243	>100	0.556	>100
SF539	0.197	14.9	0.286	8.03	0.289	>100	0.361	>100
SNB-19	0.578	>100	0.728	>100	0.614	>100	5.23	>100
SNB-75	0.182	98.8	0.311	>100	0.224	>100	1.49	>100
U251	0.355	90.5	0.425	>100	0.374	>100	1.70	>100
<u>Melanoma</u> LOX-IMVI	0.766	>100	0.61	>100	0.672	>100	0.645	>100
MALME-3M	na	na	0.348	>100	0.635	>100	0.691	>100

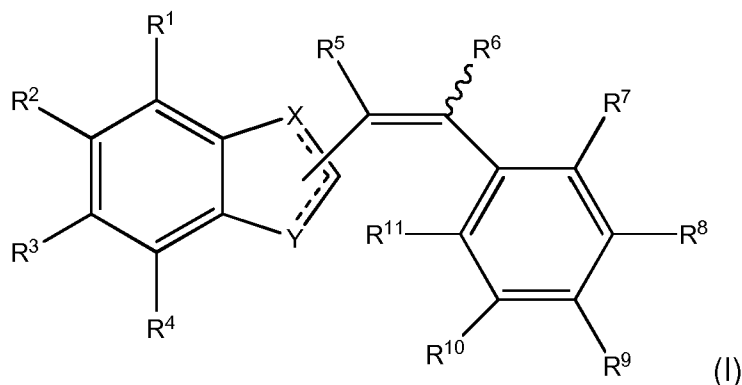
M14	0.173	>100	0.36	>100	0.310	>100	0.540	>100
MDA-MB-435	0.033	60.0	0.147	>100	0.053	>100	0.227	>100
SK-MEL-2	0.483	>100	0.522	>100	0.709	>100	1.05	>100
SK-MEL-28	0.518	>100	0.896	>100	1.40	>100	3.27	>100
SK-MEL-5	0.243	>100	0.406	>100	0.249	>100	0.410	>100
UACC-257	0.761	>100	Nd	>100	12.8	>100	Nd	>100
UACC-62	0.092	>100	0.449	>100	0.357	>100	0.478	>100
<u>Ovarian Cancer</u> IGROV1	0.846	>100	0.958	>100	3.50	>100	3.15	>100
OVCAR-3	0.163	54.9	0.309	34.0	0.279	>100	0.263	>100
OVCAR-4	1.43	>100	0.788	>100	1.73	>100	13.8	>100
OVCAR-5	0.580	>100	0.716	42.8	0.587	>100	3.94	>100
OVCAR-8	0.446	>100	0.659	>100	0.584	>100	3.41	>100
NCI/ADR-RES	0.112	>100	0.283	>100	0.224	>100	0.343	>100
SK-OV-3	0.524	>100	0.804	>100	0.576	>100	1.34	>100
<u>Renal Cancer</u> 786-0	0.445	>100	0.501	>100	0.484	>100	6.29	>100
A498	0.295	>100	0.275	>100	0.333	>100	0.678	>100
ACHN	1.04	>100	0.773	>100	1.19	>100	0.911	>100
CAKI-1	0.068	>100	0.318	>100	0.223	>100	0.346	>100
RXF 393	0.271	>100	0.334	>100	0.297	>100	0.579	>100
SN12C	0.627	>100	0.661	>100	0.661	>100	1.94	>100
TK-10	4.69	>100	3.28	>100	17.7	>100	2.55	>100
UO-31	0.762	>100	0.573	>100	ad	>100	0.580	>100

<u>Prostate Cancer</u> PC-3	0.348	>100	0.584	>100	0.506	>100	1.08	>100
DU-145	0.446	>100	0.801	>100	0.505	>100	1.51	>100
<u>Breast Cancer</u> MCF7	0.275	>100	0.537	>100	0.333	>100	0.429	>100
MDA-MB-231/ATCC	0.943	>100	1.02	>100	1.15	>100	2.83	>100
HS-578T	0.689	>100	0.70	>100	0.715	>100	1.31	>100
BT-549	0.315	>100	0.342	80.6	0.388	>100	1.43	>100
T-47D	4.76	>100	1.23	>100	0.628	>100	9.54	>100
MDA-MB-468	0.243	>100	1.50	>100	0.217	>100	0.870	>100

CLAIMS

What is claimed is:

1. A compound comprising Formula (I):



wherein:

R^1 , R^2 , R^3 , R^4 , R^7 , R^8 , R^9 , R^{10} , R^{11} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro;

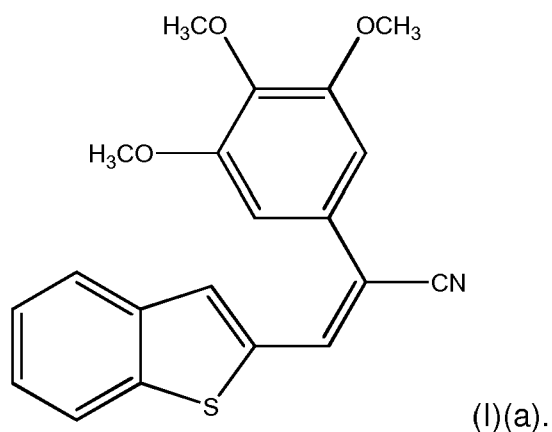
R^5 and R^6 are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, carboxyl, ester, and cyano;

X and Y are independently chosen from O, C, CR^{12} , $CR^{12}R^{13}$, S, SR^{14} N, or NR^{15} ; and

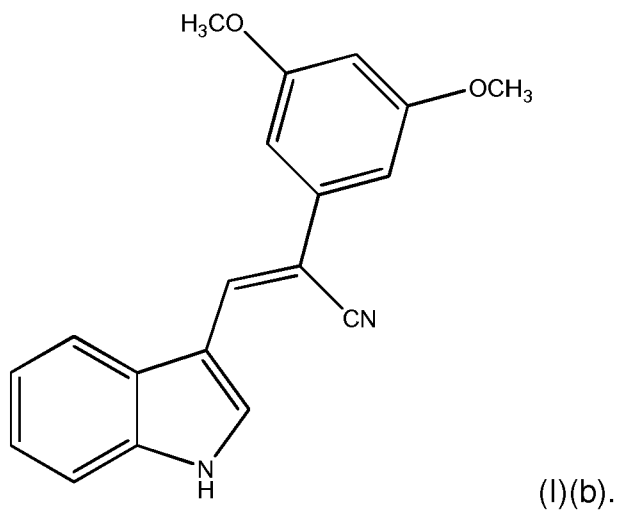
R^{12} , R^{13} , R^{14} , and R^{15} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro.

2. The compound of claim 1, wherein R^1 , R^4 , R^7 , and R^{11} are hydrogen.
3. The compound of claim 1, wherein R^6 is chosen from hydrogen, cyano, and carboxyl, and R^5 is hydrogen.
4. The compound of claim 1, wherein R^8 , R^9 , and R^{10} are independently chosen from hydrogen, methoxy, ethoxy, benzyloxy, substituted benzyloxy, hydroxyl, and lower alkyl groups.

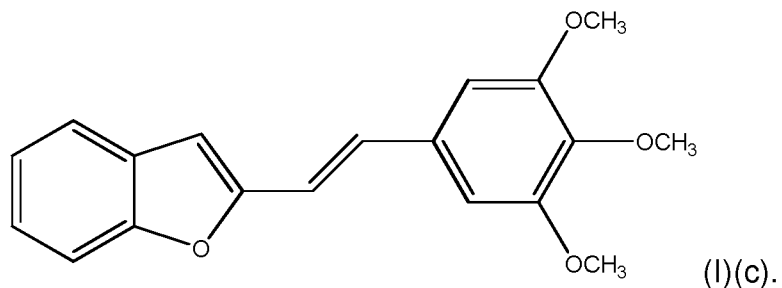
5. The compound of claim 1, wherein R^8 , R^9 , and R^{10} are independently chosen from hydrogen, hydroxyl, and methoxy.
6. The compound of claim 1, wherein X is chosen from C or S.
7. The compound of claim 1, wherein Y is chosen from O, S, and NR^{15} .
8. The compound of claim 1, wherein the compound comprises Formula (I)(a):



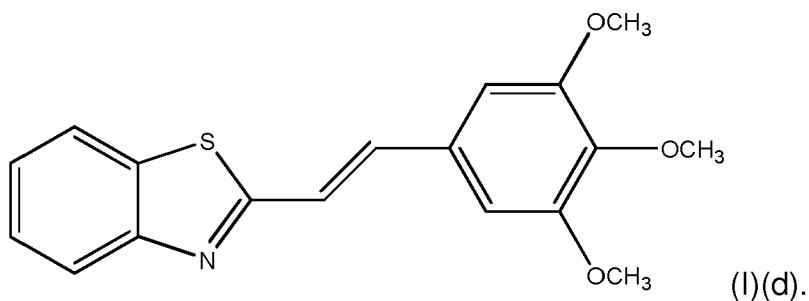
9. The compound of claim 1, wherein the compound comprises Formula (I)(b):



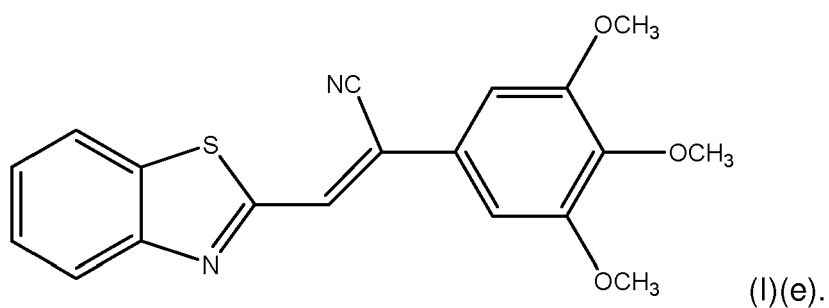
10. The compound of claim 1, wherein the compound comprises Formula (I)(c):



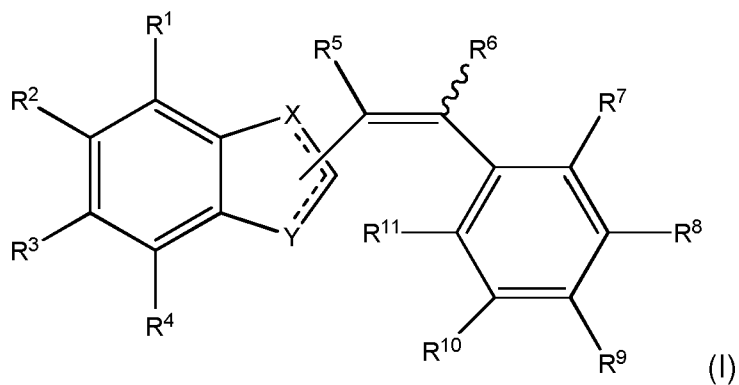
11. The compound of claim 1, wherein the compound comprises Formula (I)(d):



12. The compound of claim 1, wherein the compound comprises Formula (I)(e):



13. A pharmaceutical composition comprising a compound of Formula (I):



wherein:

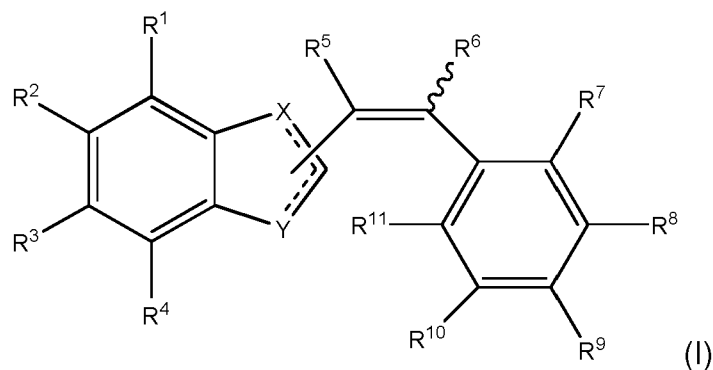
R^1 , R^2 , R^3 , R^4 , R^7 , R^8 , R^9 , R^{10} , R^{11} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro;

R^5 and R^6 are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, carboxyl, ester, and cyano;

X and Y are independently chosen from O, C, CR^{12} , $CR^{12}R^{13}$, S, SR^{14} N, or NR^{15} ;

R^{12} , R^{13} , R^{14} , and R^{15} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro; and
at least one pharmaceutically acceptable excipient.

14. A process for producing a compound comprising Formula (I):



wherein:

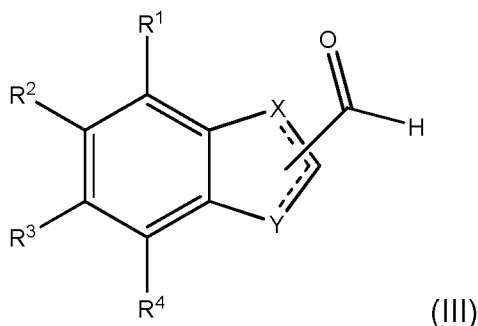
R^1 , R^2 , R^3 , R^4 , R^7 , R^8 , R^9 , R^{10} , R^{11} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro;

R^5 and R^6 are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, carboxyl, ester, and cyano;

X and Y are independently chosen from O, C, CR^{12} , $CR^{12}R^{13}$, S, SR^{14} N, or NR^{15} ;

R^{12} , R^{13} , R^{14} , and R^{15} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro; and

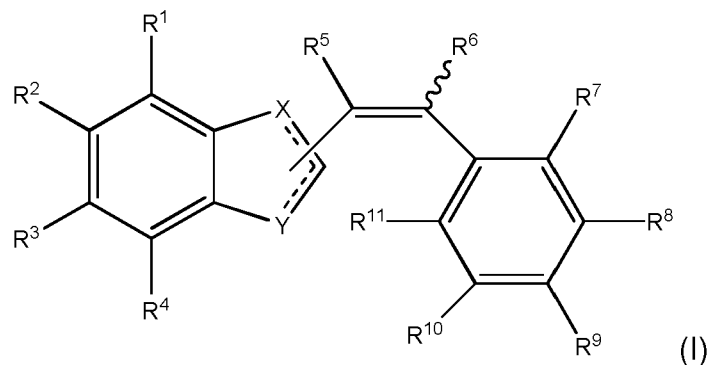
the processes comprises contacting a compound of Formula (III):



with a phenyl acetonitrile or a phenyl triphenyl phosphine and a proton acceptor.

15. The process of claim 14, wherein the compound comprising Formula (III) is chosen from benzo[b]thiophene-2-carbaldehydes, benzo[b]thiophene-3-carbaldehydes, benzofuran-2-carboxaldehydes, benzofuran-3-carboxaldehydes, indole-2-carboxaldehydes, indole-3-carboxaldehydes, and benzthiazole-2-carboxaldehydes.
16. The process of claim 14, wherein the phenyl acetonitrile is chosen from 3,4,5-trimethoxy phenylacetonitrile, 3,4-dimethoxyphenylacetonitrile, and 4-hydroxy, 3,5-trimethoxyphenylacetonitrile.
17. The process of claim 14, wherein the phenyl triphenyl phosphine is chosen from 3,4,5 trimethoxy phenyltriphenyl phosphine bromide, 3,4-dimethoxy phenyltriphenyl phosphine bromide, 4-hydroxy, and 3,5-dimethoxyphenyltriphenyl phosphine bromide.
18. The process of claim 14, wherein the base is a methoxide base.

19. A method of inhibiting tubulin polymerization in a subject, the method comprising administering to the subject a compound comprising Formula (I):



wherein:

R^1 , R^2 , R^3 , R^4 , R^7 , R^8 , R^9 , R^{10} , R^{11} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro;

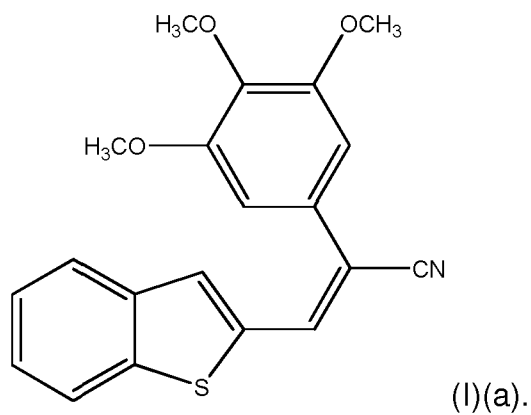
R^5 and R^6 are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, carboxyl, ester, and cyano;

X and Y are independently chosen from O, C, CR^{12} , $CR^{12}R^{13}$, S, SR^{14} N, or NR^{15} ; and

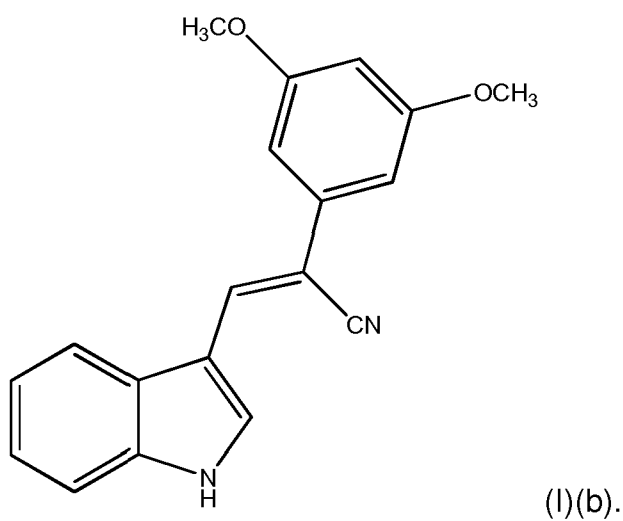
R^{12} , R^{13} , R^{14} , and R^{15} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro.

20. The method of claim 19, wherein the compound comprising Formula (I) is administered with at least one pharmaceutically acceptable excipient.

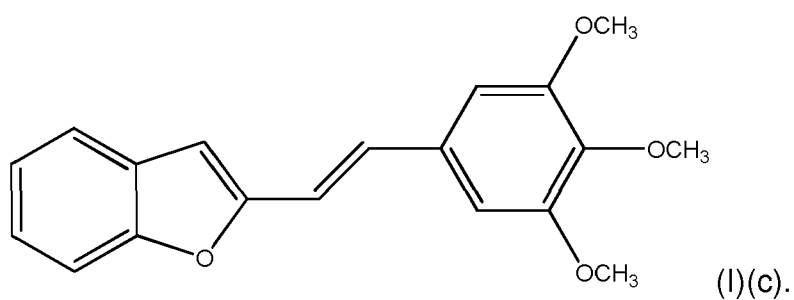
21. The method of claim 19, wherein the compound comprising Formula (I) is Formula (I)(a):



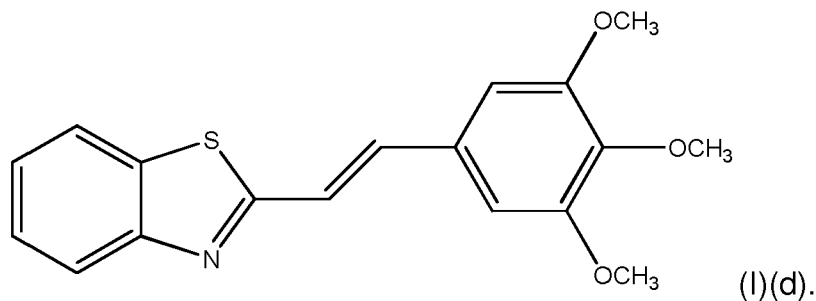
22. The method of claim 19, wherein the compound comprising Formula (I) is Formula (I)(b):



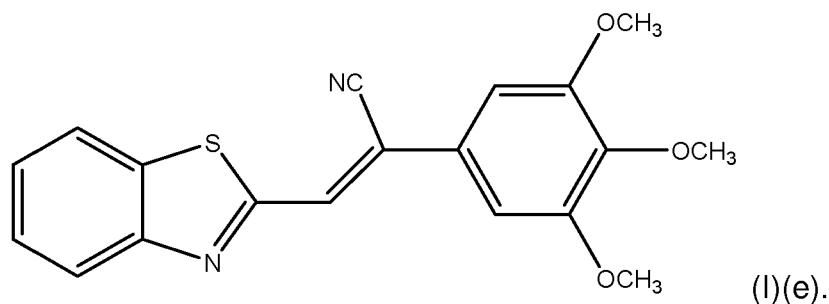
23. The method of claim 19, wherein the compound comprising Formula (I) is Formula (I)(c):



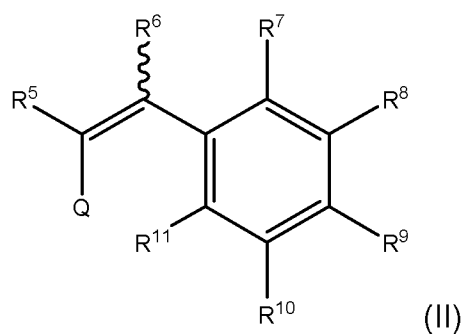
24. The method of claim 19, wherein the compound comprising Formula (I) is Formula (I)(d):



25. The method of claim 19, wherein the compound comprising Formula (I) is Formula (I)(e):



26. A compound comprising Formula (II):



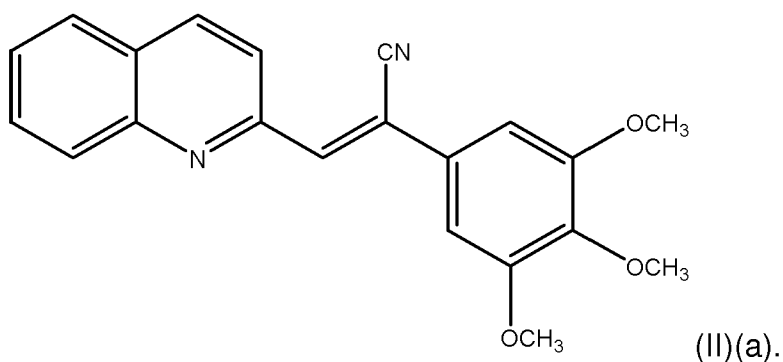
wherein:

R^7 , R^8 , R^9 , R^{10} , R^{11} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkoxy, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro;

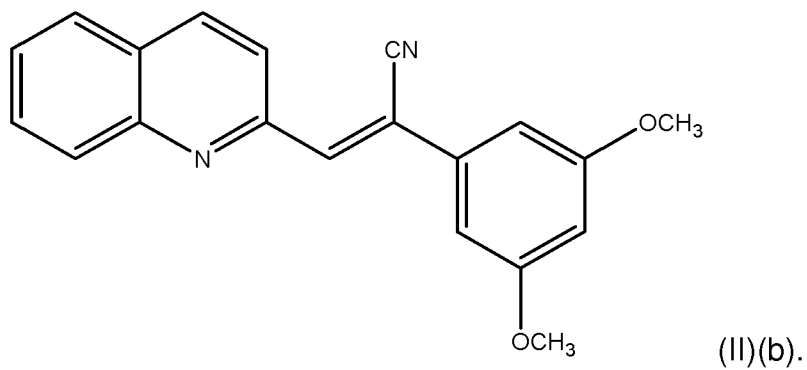
R^5 and R^6 are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, carboxyl, ester, and cyano; and

Q is a quinolinyl moiety,
with the proviso that where R⁶ is cyano, R⁸ and R⁹ are not each OCH₃.

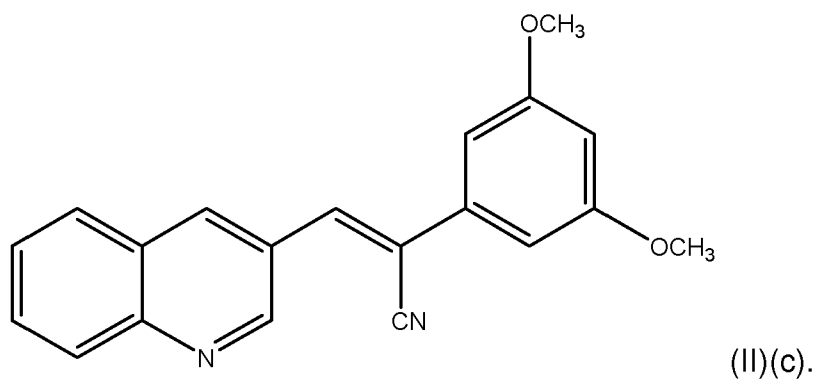
27. The compound of claim 26, wherein R⁵ is hydrogen and R⁶ is cyano.
28. The compound of claim 26, wherein Q is chosen from 2-quinolinyl and 3-quinolinyl.
29. The compound of claim 26, wherein R⁷, R⁸, R⁹, R¹⁰, R¹¹ are independently chosen from hydrogen and hydroxyl.
30. The compound of claim 26, wherein R⁷ and R¹¹ are hydrogen.
31. The compound of claim 26, wherein R⁸, R⁹, and R¹⁰ are independently chosen from hydrogen and hydroxyl.
32. The compound of claim 26, wherein R⁸, R⁹, and R¹⁰ are hydroxyl.
33. The compound of claim 26, wherein R⁸ and R¹⁰ are hydroxyl.
34. The compound of claim 26, wherein the compound comprises Formula (II)(a):



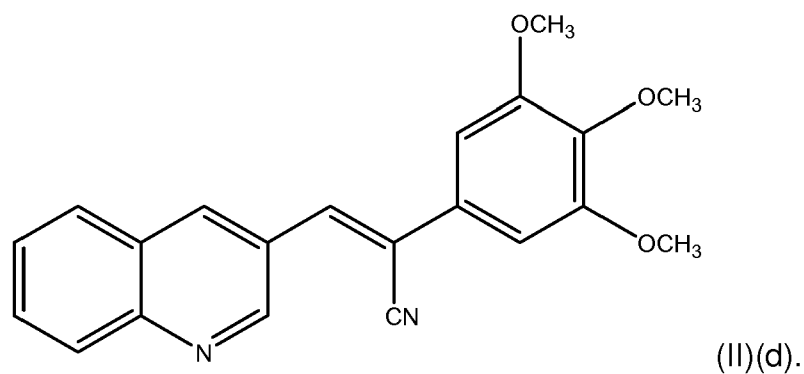
35. The compound of claim 1, wherein the compound comprises Formula (II)(b):



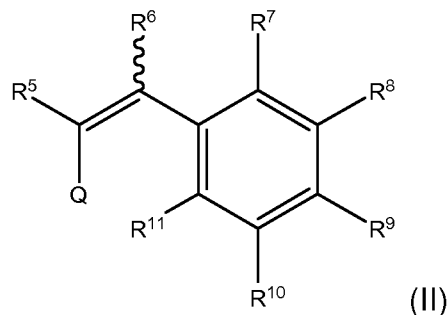
36. The compound of claim 1, wherein the compound comprises Formula (II)(c):



37. The compound of claim 1, wherein the compound comprises Formula (II)(d):



38. A pharmaceutical composition comprising a compound of Formula (II):



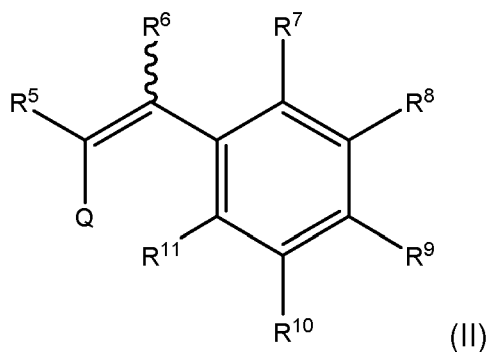
wherein:

R⁷, R⁸, R⁹, R¹⁰, R¹¹ are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkoxy, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro;

R⁵ and R⁶ are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, carboxyl, ester, and cyano; and

Q is a quinolinyl moiety.

39. A process for producing a compound comprising Formula (II):



wherein:

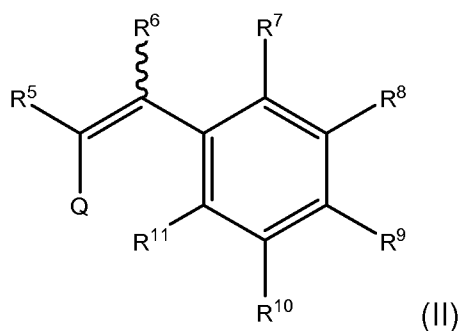
R⁷, R⁸, R⁹, R¹⁰, R¹¹ are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkoxy, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro;

R⁵ and R⁶ are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, carboxyl, ester, and cyano; and

Q is a quinolinyl moiety;

the processes comprises contacting a quinolinyl carboxaldehyde with a phenyl acetonitrile or a phenyl triphenyl phosphine and a proton acceptor.

40. The process of claim 39, wherein the quinolinyl carboxaldehyde is chosen from quinolinyl-2-carboxaldehyde, quinolinyl-3-carboxaldehyde, and quinolinyl-4-carboxaldehyde.
41. The process of claim 39, wherein the phenyl acetonitrile is chosen from 3,4,5-trimethoxy phenylacetonitrile, 3,4-dimethoxyphenylacetonitrile, and 4-hydroxy, 3,5-trimethoxyphenylacetonitrile.
42. The process of claim 39, wherein the base is a methoxide base.
43. The process of claim 39, wherein the phenyl triphenyl phosphine is chosen from 3,4,5 trimethoxyphenyl triphenyl phosphine bromide, 3,4-dimethoxyphenyl triphenyl phosphine bromide, 4-hydroxy, and 3,5-dimethoxyphenyl triphenyl phosphine bromide.
44. A method of inhibiting tubulin polymerization in a subject, the method comprising administering to the subject a compound comprising Formula (II):



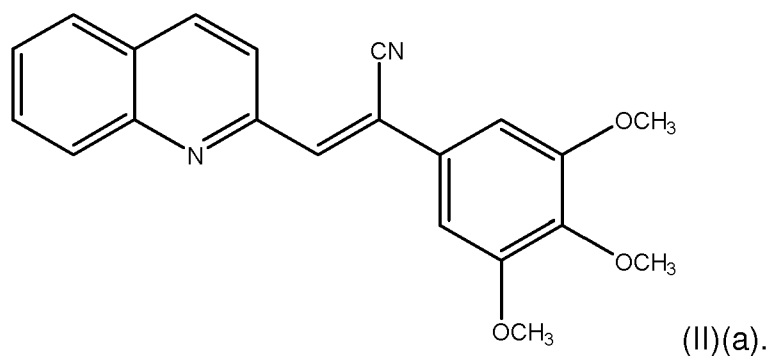
wherein:

R⁷, R⁸, R⁹, R¹⁰, R¹¹ are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkoxy, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro;

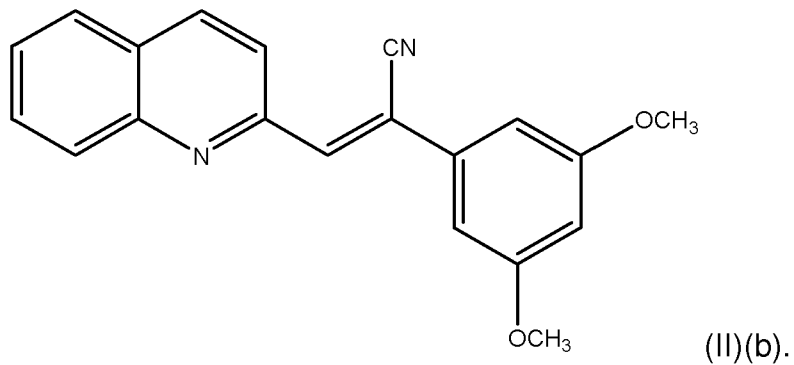
R⁵ and R⁶ are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, carboxyl, ester, and cyano; and

Q is a quinolinyl moiety.

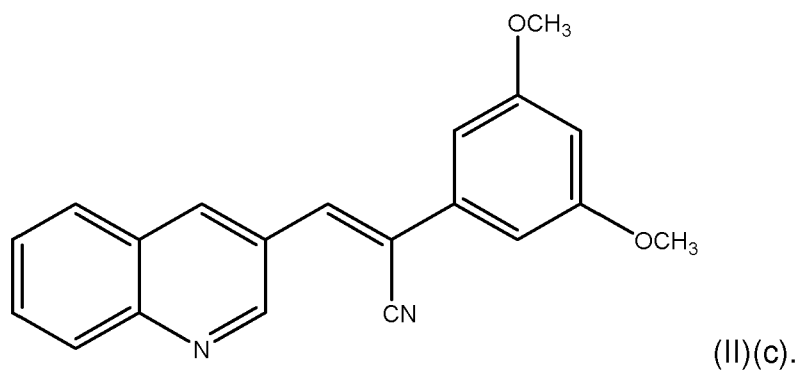
45. The method of claim 44, wherein the compound comprising Formula (II) is administered with at least one pharmaceutically acceptable excipient.
46. The method of claim 44, wherein the compound comprising Formula (II) is Formula (II)(a):



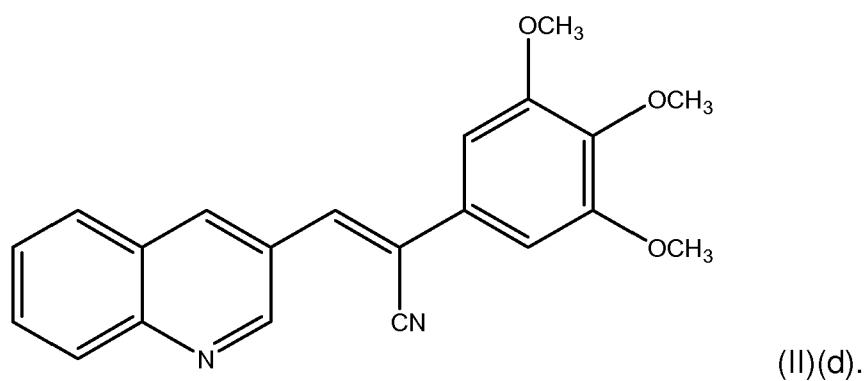
47. The method of claim 44, wherein the compound comprising Formula (II) is Formula (II)(b):



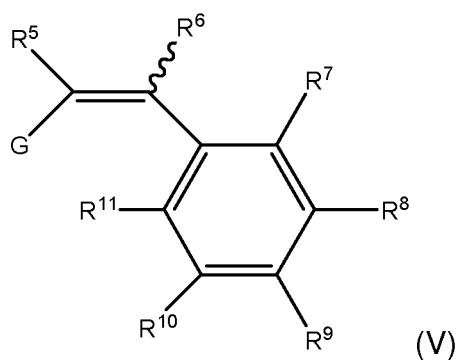
48. The method of claim 44, wherein the compound comprising Formula (II) is Formula (II)(c):



49. The method of claim 44, wherein the compound comprising Formula (II) is Formula (II)(d):

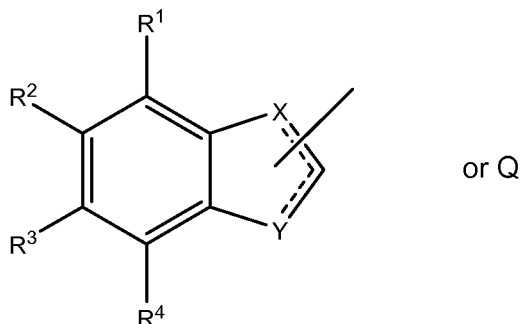


50. A compound comprising Formula (V):



wherein:

G is chosen from



Q is a quinolinyl moiety;

R^1 , R^2 , R^3 , R^4 , R^7 , R^8 , R^9 , R^{10} , R^{11} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro;

R^5 and R^6 are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, carboxyl, ester, and cyano;

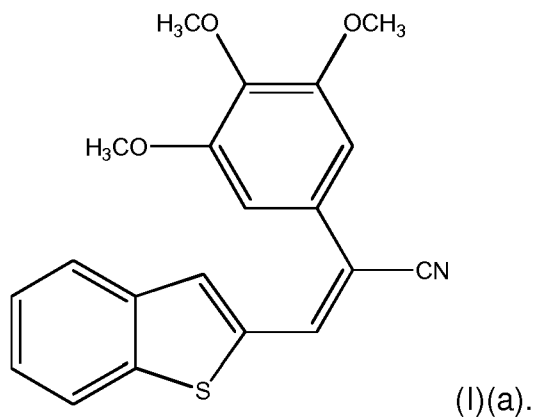
X and Y are independently chosen from O, C, CR^{12} , $CR^{12}R^{13}$, S, SR^{14} N, or NR^{15} ; and

R^{12} , R^{13} , R^{14} , and R^{15} are independently chosen from hydrogen, hydrocarbyl, substituted hydrocarbyl, alkylalkylamino, amidine, amino, carboxyl, cyano, ester, halogen, hydroxyl, and nitro.

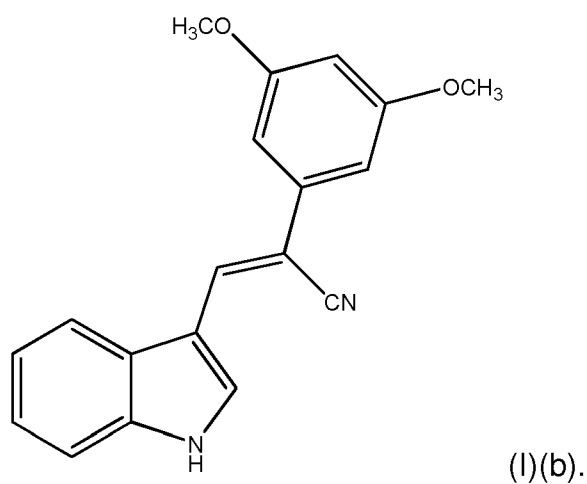
51. The compound of claim 50, wherein R^1 , R^4 , R^7 , and R^{11} are hydrogen.
52. The compound of claim 50 or 51, wherein R^6 is chosen from hydrogen, cyano, and carboxyl, and R^5 is hydrogen.
53. The compound of any one of claims 50 to 52, wherein R^8 , R^9 , and R^{10} are independently chosen from hydrogen, methoxy, ethoxy, benzyloxy, substituted benzyloxy, hydroxyl, and lower alkyl groups.
54. The compound of any one of claims 50 to 53, wherein R^8 , R^9 , and R^{10} are independently chosen from hydrogen, hydroxyl, and methoxy.
55. The compound of any one of claims 50 to 54, wherein X is chosen from C or S.

56. The compound of any one of claims 50 to 55, wherein Y is chosen from O, S, and NR¹⁵.

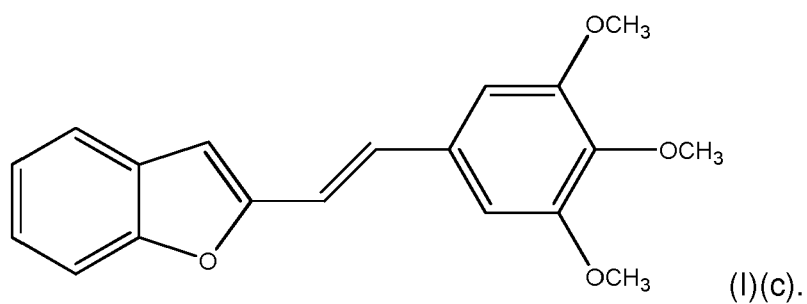
57. The compound of claim 50, wherein the compound comprises Formula (I)(a):



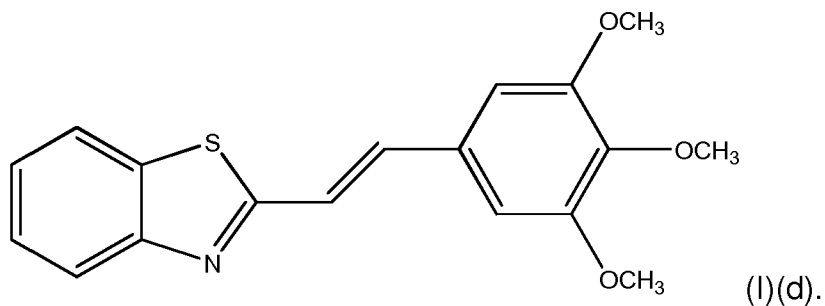
58. The compound of claim 50, wherein the compound comprises Formula (I)(b):



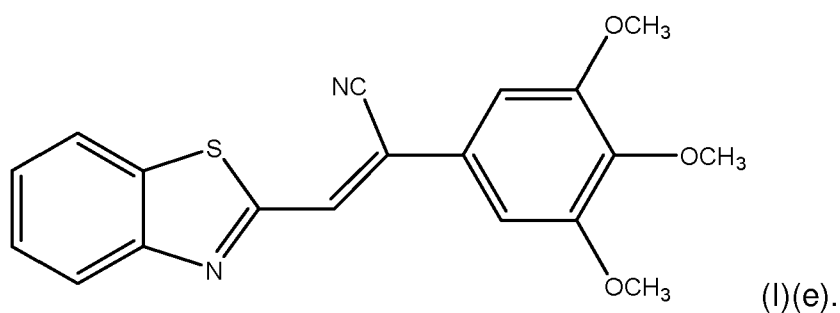
59. The compound of claim 50, wherein the compound comprises Formula (I)(c):



60. The compound of claim 50, wherein the compound comprises Formula (I)(d):



61. The compound of claim 50, wherein the compound comprises Formula (I)(e):



62. The compound of any one of claims 50 to 61 in combination with at least one pharmaceutically acceptable excipient.