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(54) BICYCLIC AND TRICYCLIC PYRIMIDINE TYROSINE KINASE INHIBITORS WITH ANTITUBULIN ACTIVITY AND METHODS OF TREATING A PATIENT

BICYCLISCHE UND TRICYCLISCHE PYRIMIDINTYROSIN-KINASEHEMMER MIT ANTITUBULINWIRKUNG UND VERFAHREN ZUR BEHANDLUNG EINES PATIENTEN

INHIBITEURS PYRIMIDINES BICYCLIQUES ET TRICYCLIQUES DE TYROSINE KINASE AYANT UNE ACTIVITÉ ANTITUBULINE, ET MÉTHODES DE TRAITEMENT D'UN PATIENT

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(73) Proprietor: **Duquesne University of The Holy Spirit**
Pittsburgh, PA 15282 (US)

(72) Inventor: **GANGJEE, Aleem**
Allison Park
Pennsylvania 15101 (US)

(74) Representative: **Grünecker Patent- und Rechtsanwälte**
PartG mbB
Leopoldstraße 4
80802 München (DE)

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Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0001] The present invention relates to bicyclic and tricyclic pyrimidine tyrosine kinase inhibitors with antitubulin activity. The compositions of this invention have dual activity of potent vascular endothelial growth factor receptor inhibitory activity along with cytotoxic activity in a single agent. The compositions of this invention may be made into salts that are water soluble for providing orally active antiangiogenic agents. These compositions for use in treating a patient are also provided.

2. Description of the Background Art

[0002] Antitubulin agents are some of the most successful cancer chemotherapeutic agents and are clinically used in a variety of cancers. Three distinct classes of antitubulin binding agents have been identified depending on their binding on tubulin.

[0003] The taxanes, including paclitaxel and docetaxel, are highly successful agents in cancer chemotherapy, both as monotherapy and in combination in solid tumors, particularly in breast, lung, ovarian, head and neck, and bladder cancers, among several others. The binding site of the taxanes (including epothilones) lies on the inside surface of the β-subunit of the alpha beta (αβ)-heterodimer that make up the microtubule. These compounds increase microtubule polymerization and are referred to as microtubule stabilizing agents.

[0004] The second class of antitubulin binding agents is the Vinca alkaloids, including vincristine, vinblastine, vinorelbine, and vindesine. These compounds are clinically used in leukemias, lymphomas, small cell lung cancer, and other cancers, and also bind to the β-subunit of tubulin, but at a distinctly different site than the taxanes. Further, unlike the taxanes, the Vincas are microtubule polymerization inhibitors.

[0005] The colchicine site binding agents comprise a third class of antitubulin binding agents which includes colchicine and a variety of small molecules that bind to β-tubulin at the interface with α-tubulin. The colchicine binding agents inhibit the polymerization of tubulin. Combretastatins (CA) are a class of colchicine site binding agents of which the water soluble analog CA4P (Zybrestat7) has been approved by the FDA for metastatic anaplastic thyroid cancer (ATC) and ovarian cancer, and has been accorded fast track status for other types of cancer. Several colchicine site binding agents are currently in clinical trials, and the FDA approval of CA4P has established the viability of colchicine site binding agents for the treatment of cancer.

[0006] Though antimitotic agents have unprecedented success in the chemotherapy of cancer both as monotherapy and in combination, failure rate of cancer chemotherapy with antimitotics is high. This failure is very often due to multidrug resistance (MDR) that is traced to the overexpression of P-glycoprotein (Pgp) that pumps the chemotherapeutic agent out of the tumor cell. Pgp overexpression has been reported in a number of tumors in the clinical setting and hence attests to its clinical importance, particularly after patients have received chemotherapy. Overexpression of Pgp appears to be more important in clinical tumor resistance than elevation of MRP1 levels. Thus the clinical success of new microtubule targeting drugs will depend, to a significant extent, on the drugs not being subject to Pgp resistance.

[0007] βIII-tubulin is an isoform of the β-tubulin to which the taxanes and Vinca alkaloids bind. βIII-tubulin plays a major role in clinical resistance to the taxanes and Vincas in lung, breast, ovarian, and gastric tumors, among others. The importance of βIII-tubulin in chemotherapy resistance has been published and is known by those skilled in the art. It has been shown that tumor resistance due to βIII-tubulin can be circumvented with colchicine site binding agents and highlights the critical importance developing new agents that bind to the colchicine site on tubulin as clinically important alternatives to tumors resistant to the taxanes and Vincas.

[0008] The compositions of the present invention bind to the colchicine site and are believed to circumvent βIII-tubulin resistance. The recent FDA approval of ixabepilone attests to the need to overcome βIII-tubulin resistance. Clinical evidence implicates both Pgp and βIII-tubulin as the most important mechanisms of treatment failure for the taxanes and Vincas. Thus, there is an urgent need for new drugs that circumvent Pgp and/or βIII-tubulin mediated tumor resistance that would be useful for the large number of patients that either do not respond to or have developed resistance to the taxanes and/or the Vincas. The compounds of the present invention are believed to overcome both resistance mechanisms and fill an unmet need for patients resistant to taxanes and Vinca alkaloids.

[0009] Poor water solubility has plagued the clinical use of taxanes and is an important drawback of ixabepilone as well. Enormous effort continues to be expended to develop soluble formulations of antimitotics. For example, Abraxane (paclitaxel with albumin) reduces the administration time from 3 hrs (for cremophore solvent) to about 1 hour. However, water soluble antimitotics are highly coveted. The compositions of the present invention are highly water soluble as their HCl (or other acid) salts and circumvent the solubility issues associated with other antimitotics.

[0010] The combination of two or more antimitotics that act at different or overlapping sites on tubulin often results in synergistic or additive effects. Discodermolide and paclitaxel, vinblastine and paclitaxel, the colchicine analog CI-980 and docetaxel, paclitaxel plus vinorelbine or docetaxel plus vinorelbine and estramastine with either vinblastine or paxlitaxe are all superior in combination than either drug alone. CA4P, the colchicine site binding agent, is in multiple clinical trials with paclitaxel and the Vinca alkaloids, as is a derivative of CA4P termed AVE8063 (clinicaltrials.gov) (Omrabulin). Thus, analogs that act at the colchicine site as distinct from the taxane or Vinca site are highly desirable to use as monotherapy and in particular in combination chemotherapy with other antimitotics. The compositions of the present invention are believed to act at the colchicine site.

[0011] Angiogenesis is the formation of new blood vessels from preexisting ones. Angiogenesis occurs in adults during wound healing, menstrual cycle, and during pregnancy. Except for these instances, normal adults do not need angiogenesis. Tumor cells, once beyond the 1-2 mm size, are in a state of angiogenesis to provide nutrients needed to grow as well as to metastasize. Angiogenesis is thus a critical factor in the development and metastasis of a variety of tumor types and is an important hallmark of malignant disease. The principal mediator of angiogenesis is vascular endothelial growth factor (VEGF) and its receptor VEGFR2. Other growth factors, such as platelet-derived growth factor (PDGF), are also involved in angiogenesis. Antiangiogenic agents (AA) that inhibit tumor growth defined a new paradigm for cancer treatment. Bevacizumab, an anti-VEGF antibody and the first FDA approved AA significantly increases overall survival (OS) or progression free survival (PFS) of patients with metastatic colorectal cancer, non-small cell lung cancer, and breast cancer in combination with conventional chemotherapeutic agents. More recently, bevacizumab was approved for glioblastoma. Sunitinib and sorafenib, two small molecule VEGFR2 inhibitors (along with other receptor tyrosine kinase (RTK) inhibitors) are approved for advanced renal cell carcinoma, hepatocellular cancer (sorafenib), and gastrointestinal stromal tumor (GIST). Several RTK inhibitors, both approved and in development, including VEGFR2 inhibitors, are currently in clinical trials with the numbers of trials in the several hundred (see clinicaltrials.gov). Although RTK inhibitors in the form of AAs afford a new set of targets for the treatment of a variety of cancers, it is now generally accepted that, with very few exceptions, when used alone, AAs (including multikinase targeting agents) are highly unlikely to afford growth or metastatic control of tumors in the long run in most patients. The heterogeneity of solid tumors and their ability to escape single mechanism targets (like angiogenesis) and the ability to metastasize are two of the reasons for the lack of success of AAs alone. In addition, it is well established that most AAs (with very few exceptions) are cytostatic, in that they arrest tumor growth but do not eradicate the tumor. Thus, it has been determined that the utility of AAs lies in the combination of cytostatic AAs with cytotoxic conventional chemotherapeutic agents and/or radiation to afford the most viable cancer treatment options.

[0012] The realization that AAs are cytostatic and that their main utility in treating cancer would be in combination with cytotoxic agents has led to a plethora of combinatorial clinical trials that involve FDA approved AAs as well as those in development, and cytotoxic chemotherapeutic agents (see clinicaltrials.gov). Some of these combinations have been highly successful and were in fact the basis of the approval of bevacizumab, which in combination afforded overall improved or overall and/or progression free survival in colorectal lung and breast cancer. The vast number of clinical trials with AAs and in particular with VEGFR2 inhibitors and antitubulin agents currently ongoing, such as for example, but not limited to, paclitaxel with sorafenib, docetaxal with sorafenib, paclitaxel with sunitinib, docetaxel with sunitinib, paclitaxel with bevacizumab, docetaxel with bevacizumab, paclitaxel with anitinib, docetaxel with axitinib, vincristine with bevacizumab, and vinblastine with bevacizumab, provides strong evidence for the importance of these two types of agents in combination chemotherapy protocols with and without radiation. In addition, a vast number of successful preclinical studies of VEGFR2 inhibitors and antitubulin agents also supports this combination. The two mechanisms that attempt to explain this combination therapy rationale are that chemotherapy when delivered at close regular intervals using relatively low doses with no prolonged drug-free intervals (metronomic therapy) preferentially damages endothelial cells in tumor blood vessels. The antiangiogenic therapy has already destroyed or inhibited much of these endothelial cells, thus the combined effect, like a one-two punch, is amplified on the endothelial cells leading to improved subsequent killing of the tumor cells with the conventional chemotherapeutic agent or radiation. The second mechanism, proposed by Jain and that is widely accepted, is that AAs cause an inhibition of new vessel formation and also prime and kill immature tumor vessels and afford a transient normalization of the remaining tumor vasculature by decrease in macromolecular permeability and consequently the interstitial fluid pressure (IFP) and hypoxia resulting in a transient improvement in blood perfusion to the tumor. It is during this transient window of improved blood perfusion that the cytotoxic agent of the combination is able to penetrate the tumor much more efficiently than in the absence of the AA. Thus, the combination of the cytostatic AA with a cytotoxic agent provides potent additive or synergistic effects that are absent with either drug alone. The details of the preclinical and clinical evidence for normalization of tumor vasculature and the benefit in combination chemotherapy with and without radiation is surfeit in the literature.

[0013] Eugene L. Piatnitski Chekler et al., Medicinal Chemistry Letters, 1 (9), 2010, 488-492 discloses compounds as dual VEGFR-2 and tubulin inhibitors for the treatment of cancer.

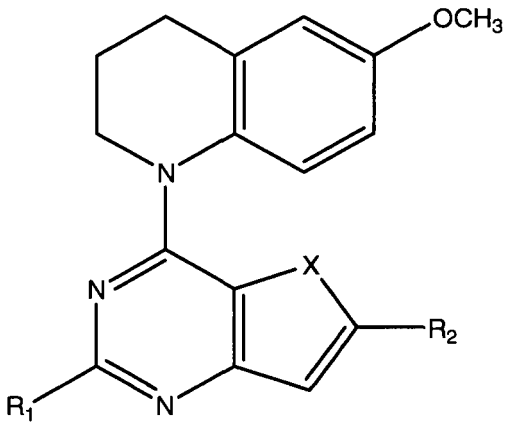
[0014] There is a need for a composition having dual activity of potent vascular endothelial growth factor receptor inhibitory activity along with cytotoxic activity in a single agent. The present invention provides such single agent com-

positions.

SUMMARY OF THE INVENTION

[0015] The present invention meets the above described need by providing bicyclic and tricyclic pyrimidine compositions that have dual (combined) activity, namely, vascular endothelial growth factor receptor inhibitory activity and antitubulin activity.

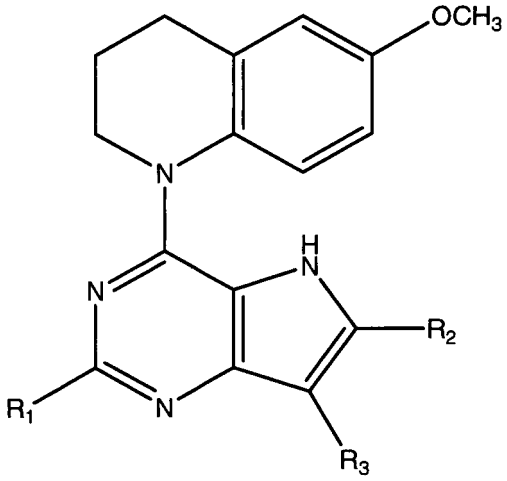
[0016] The present invention provides a compound of the Formula 5:



5

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein X is selected from the group consisting of NH, NCH_3, O, and S; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 5 are set forth in Series XIII, Figure 6, identified by Compositions 98-100, and Series XIV, Figure 7, identified by Compositions 101-103, and Series XVa, Figure 7, Composition 104. Composition 104 is also referred to herein as "RP249" and/or "RP/AG/159-249".

[0017] Disclosed herein is a composition of Formula 7:

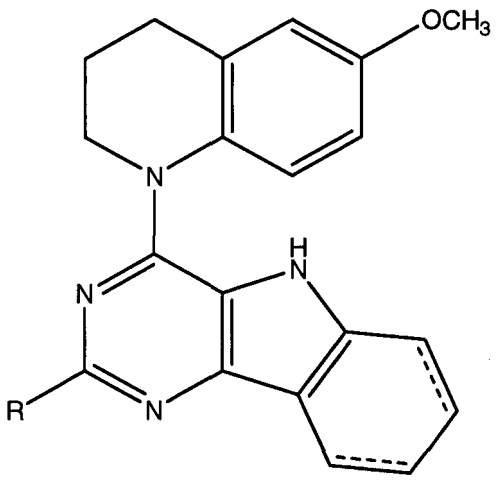


7

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting

of H, a phenyl group, a substituted phenyl group, a benzyl group, a substituted benzyl group, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms, and wherein said alkyl group is optionally substituted with one or more of a phenyl group or a substituted phenyl group, or combinations thereof; and wherein each of said substituents of any said substituted group is the same or different and are selected from the group consisting of an electron withdrawing group and an electron donating group, and combinations thereof; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 7 are set forth in Series XIV, Compositions 101-103, Figure 7, and Series XVa, Compositions 104-105, Figure 7.

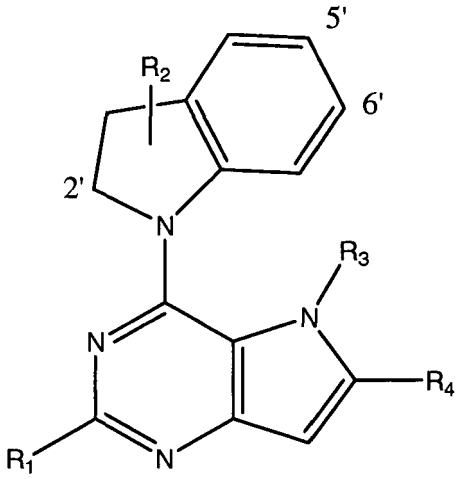
[0018] Further disclosed herein is a composition of the Formula 8:



8

comprising wherein R is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the composition embodied by Formula 8 is set forth in Series XVb, Figure 8, identified by Composition 106. The HCl salt of Composition 106 is also referred to herein as "RP248" and/or "RP/AG/159-248". It will be appreciated that the lower far right ring of the chemical structure set forth in Formula 8 (and in Formula 21 herein) may be completely unsaturated, partially unsaturated, or partially saturated as indicated by the broken double lines in the ring.

[0019] Further disclosed herein is a composition of the Formula 9:

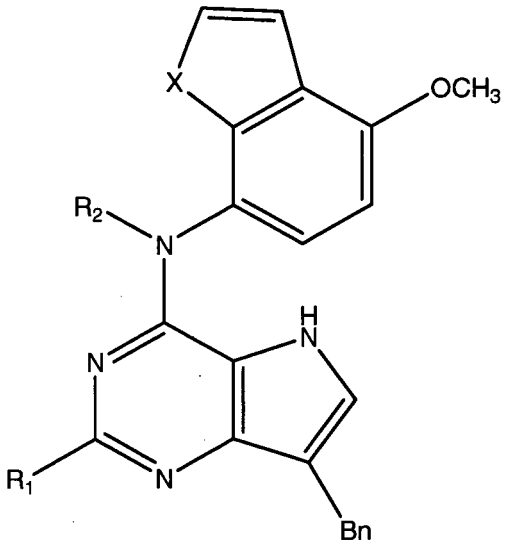


9

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl

group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of (a) 2'-CH_3, 5'-OCH_3, (b) 6'-OCH_3, 5'-OCH_3, (c) 5'-OCH_2CH_3, and (d) 5'-OCH_3; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_4 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 9 are set forth in Series XVIa, Figure 8, identified by Compositions 107-111. It will be appreciated that R_2 may be positioned at one of the 2', 5', and 6' positions of one of the two upper rings, and that R2 may be preferably positioned at one or more (multiple) locations of one or both of the two upper rings at positions 2', 5', and 6', and combinations thereof.

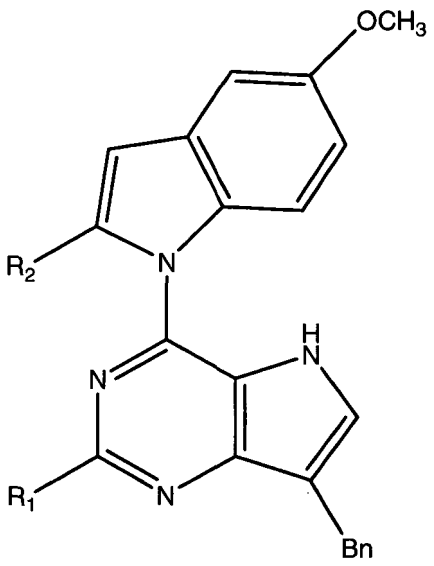
[0020] Further disclosed herein is a composition of Formula 17:



17

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein X is selected from the group consisting of (a) CH=CH, (b) NH, (c) NCH_3, (d) O, and (e) S; wherein Bn is selected from the group consisting of H, a phenyl group, a substituted phenyl group, a benzyl group, a substituted benzyl group, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms, and wherein said alkyl group is optionally substituted with one or more of a phenyl group or a substituted phenyl group, or combinations thereof; and wherein each of said substituents of any said substituted group is the same or different and are selected from the group consisting of an electron withdrawing group and an electron donating group, and combinations thereof; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 17 are set forth in Series I, Figure 1, identified by Compositions 4-8.

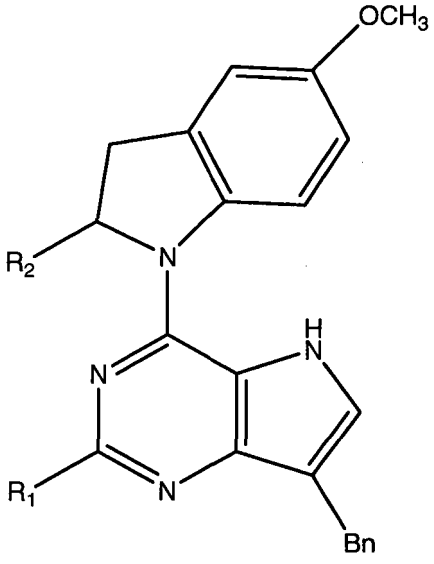
[0021] Further disclosed herein is a composition of Formula 1:



1

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; wherein Bn is selected from the group consisting of H, a phenyl group, a substituted phenyl group, a benzyl group, a substituted benzyl group, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms, and wherein said alkyl group is optionally substituted with one or more of a phenyl group or a substituted phenyl group, or combinations thereof; and wherein each of said substituents of any said substituted group is the same or different and are selected from the group consisting of an electron withdrawing group and an electron donating group, and combinations thereof; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 1 are set forth in Series IIa, Figure 1, identified by Compositions 15 and 16.

[0022] Further disclosed herein is a composition of Formula 2 :

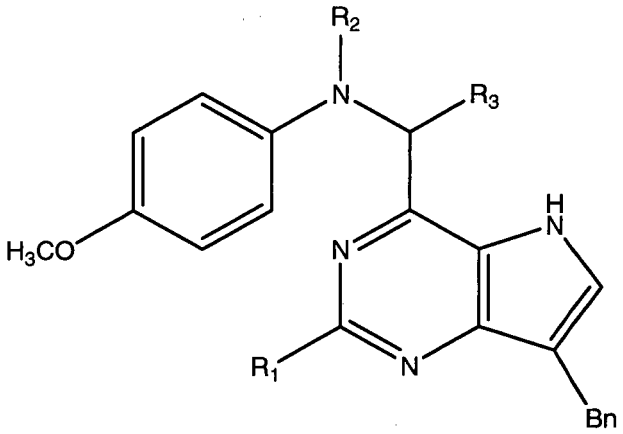


2

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; wherein Bn is selected from the group consisting of H, a phenyl group, a substituted phenyl group, a benzyl group, a substituted benzyl group, and a straight chain or

branched chain alkyl group having from 1 to 10 carbon atoms, and wherein said alkyl group is optionally substituted with one or more of a phenyl group or a substituted phenyl group, or combinations thereof; and wherein each of said substituents of any said substituted group is the same or different and are selected from the group consisting of an electron withdrawing group and an electron donating group, and combinations thereof; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 2 are set forth in Series IIb, Figure 2, identified by Compositions 17 and 18.

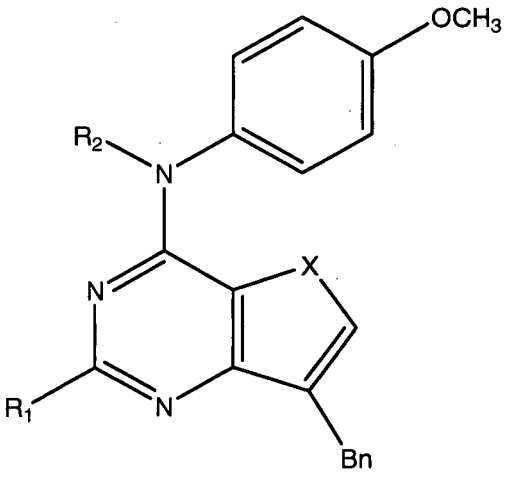
[0023] Further disclosed herein is a composition of the Formula 18:



18

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein Bn is selected from the group consisting of H, a phenyl group, a substituted phenyl group, a benzyl group, a substituted benzyl group, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms, and wherein said alkyl group is optionally substituted with one or more of a phenyl group or a substituted phenyl group, or combinations thereof; and wherein each of said substituents of any said substituted group is the same or different and are selected from the group consisting of an electron withdrawing group and an electron donating group, and combinations thereof; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 18 are set forth in Series III, Figure 2, identified by Compositions 22-24.

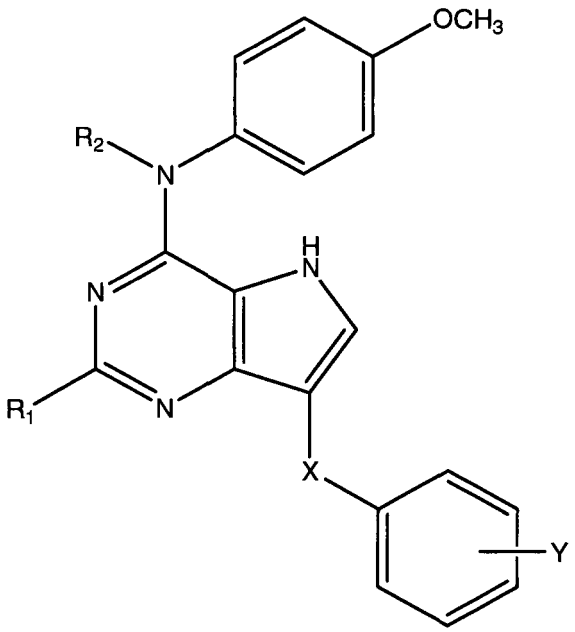
[0024] Further disclosed herein is a composition of Formula 24:



24

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein X is S; and wherein Bn is selected from the group consisting of H, a phenyl group, a substituted phenyl group, a benzyl group, a substituted benzyl group, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms, and wherein said alkyl group is optionally substituted with one or more of a phenyl group or a substituted phenyl group, or combinations thereof; and wherein each of said substituents of any said substituted group is the same or different and are selected from the group consisting of an electron withdrawing group and an electron donating group, and combinations thereof; optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. A preferred embodiment of the compositions embodied by Formula 24 is set forth in Series IV, Figure 3, identified by Composition 27.

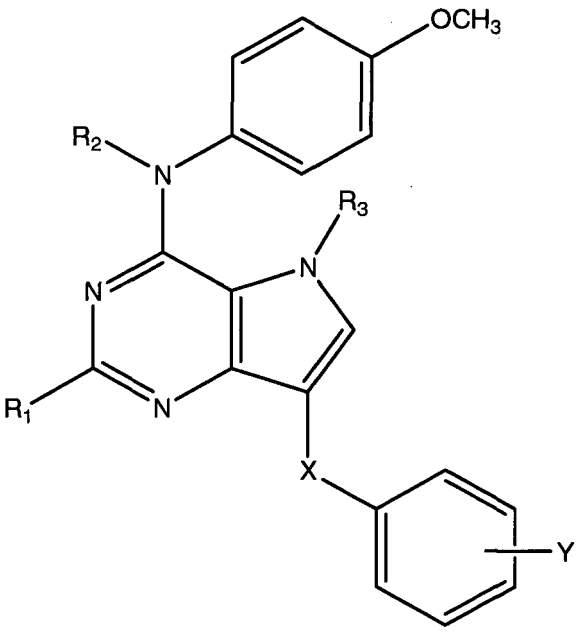
[0025] Further disclosed herein is a composition of the Formula 19:



19

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein X is selected from the group consisting of (a) NH, (b) NCH_3, (c) O, and (d) S; and wherein Y is selected from the group consisting of H, CH_3, $(CH)_4$,Cl, and OCH_3, and wherein Y may be attached at one or more positions of the ring and may be the same or different; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 19 are set forth in Series VIIIa, Figure 3, identified by Compositions 50-57.

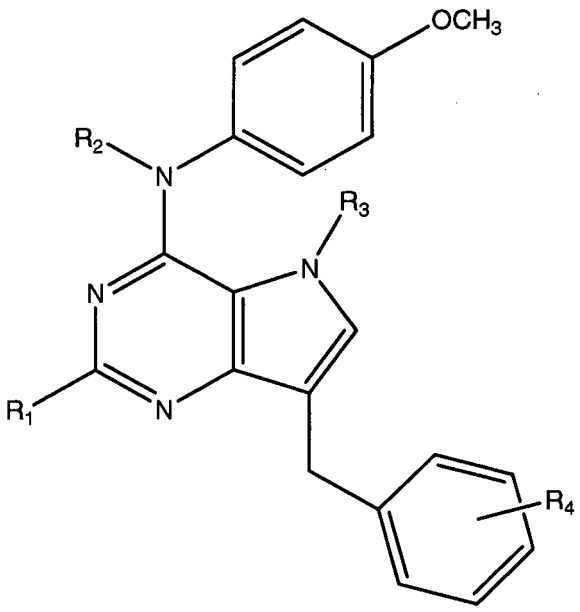
[0026] Further disclosed herein is a composition of the Formula 20:



20

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein X is selected from the group consisting of (a) NH, (b) NCH_3, (d) O, and (e) S; and wherein Y is selected from the group consisting of H, CH_3, $(CH)_4$, Cl, and OCH_3, and wherein Y may be at one or more positions of the ring and may be the same or different; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 20 are set forth in Series VIIIb, Figure 4, identified by Compositions 58-65.

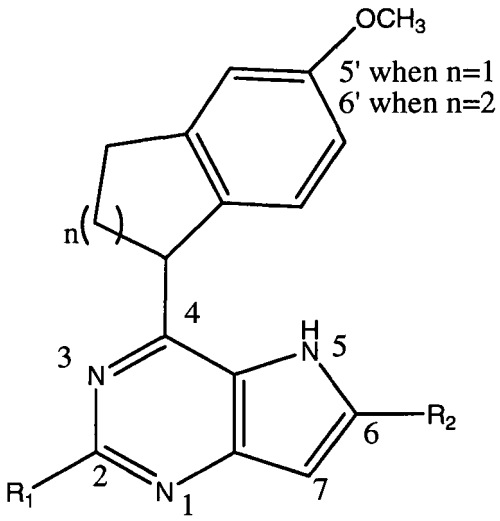
[0027] Further disclosed herein is a composition of Formula 32:



32

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R3 is selected from the group consisting of H and a straight or barnched chain alkyl group having from 1 to 10 carbon atoms, and wherein R_4 is selected from the group consisting of (a) 2',6'-diCH_3, (b) 2',5'-diOCH_3, (c) 2',4'-diCl, (d) 3',4'-diCl, (e) 2',3'-$(CH)_4$, (f) 3',4'-$(CH)_4$, and (g) 3',4',5'-triOCH_3; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 32 are set forth in Series X(a), Figure 4, identified by Compositions 74, and 77-82, and in Series X(b), Figure 5, identified by Compositions 83, and 86-91. It will be appreciated that R_4 may be positioned at one or more locations of the phenyl ring as set forth in Formula 32.

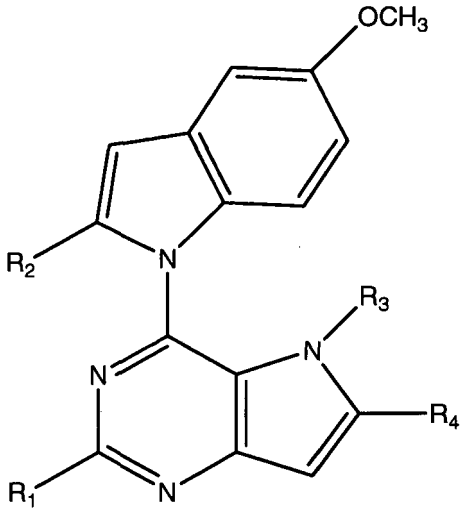
[0028] Further disclosed herein is a composition of the Formula 3:



3

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein n is 1 or 2; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 3 are set forth in Series XI, Figure 5, identified by Composition 92 (where n=1) and Composition 93 (where n=2).

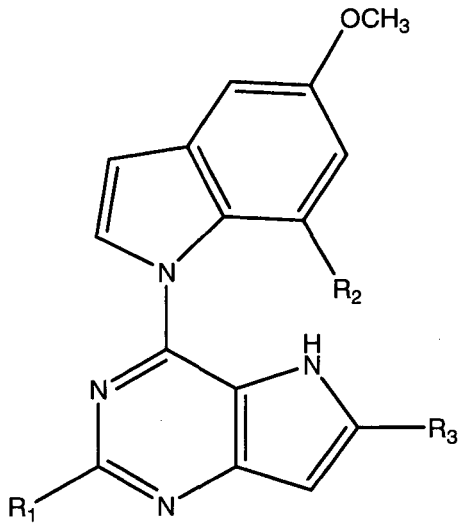
[0029] Further disclosed herein is a composition of Formula 4:



4

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_4 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 4 are set forth in Series XII, Figure 6, identified by Compositions 94-97.

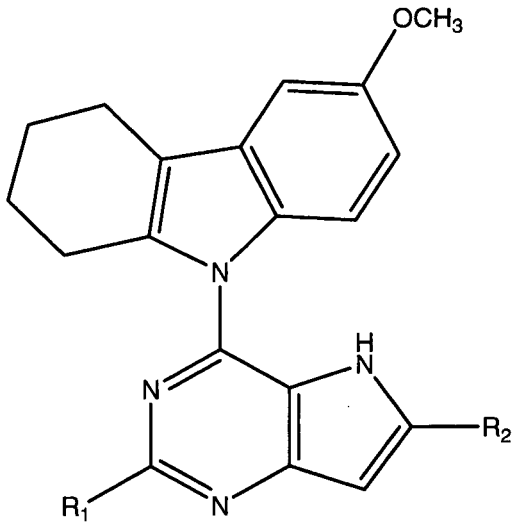
[0030] Further disclosed herein is a composition of the Formula 10:



10

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. A preferred embodiment of the compositions embodied by Formula 10 is set forth in Series XVI(b), Figure 9, identified by Composition 112.

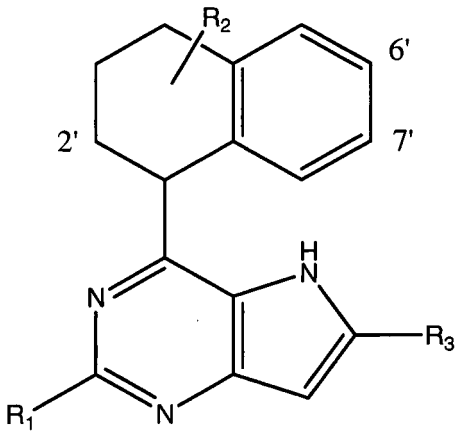
[0031] Further disclosed herein is a composition of the Formula 11:



11

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable thereof. A preferred embodiment of the compositions embodied by Formula 11 is set forth in Series XVI(c), Figure 9, identified by Composition 113.

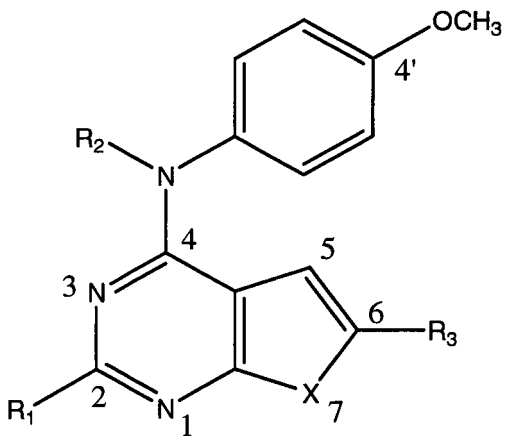
[0032] Further disclosed herein is a composition of the Formula 12:



12

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of (a) 2'-CH_3, 6'-OCH_3, (b) 7'-OCH_3, 6'-OCH_3, (c) 7'-OH, 6'-OCH_3, (d) 2'-CH_3, 6'-OH, and (e) 6'-OCF_3; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 12 are set forth in Series XVII, Figure 10, identified by Compositions 114-118. It will be appreciated that R_2 may be positioned at one of the 2', 6', and 7' positions of one of the two upper rings, and that R2 may be positioned at one or more (multiple) locations of one or both of the two upper rings at positions 2', 6', and 7', and combinations thereof.

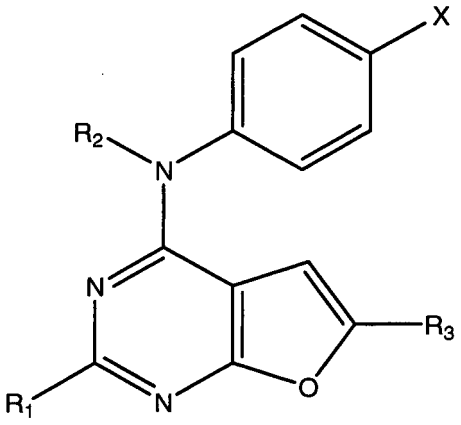
[0033] Further disclosed herein is a composition of the Formula 33:



33

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein X is S; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. A preferred embodiment of the compositions embodied by Formula 33 is set forth in Series XVIII, Figure 10, identified by Composition 121.

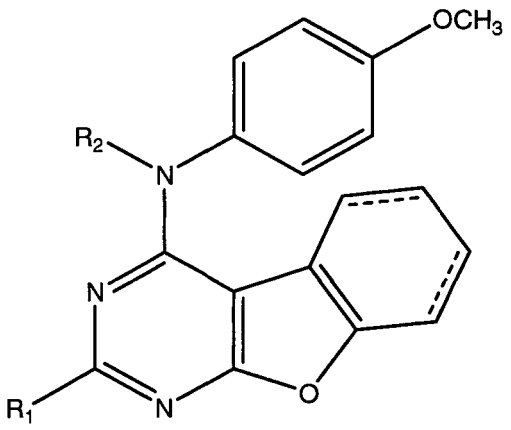
[0034] Further disclosed herein is a composition of Formula 35:



35

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein X is SCH_3; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable thereof. A preferred embodiment of the compositions embodied by Formula 35 is set forth in Series XX, Figure 11, identified by Composition 125.

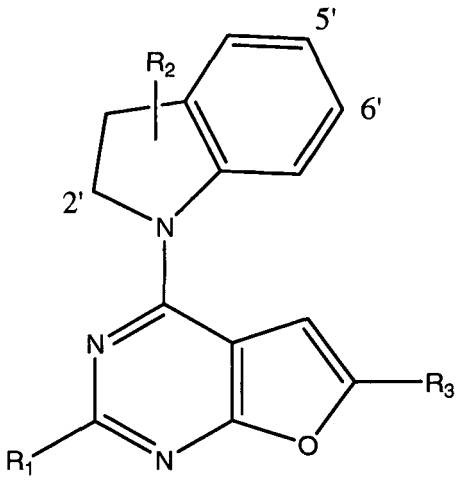
[0035] Further disclosed herein is a composition of Formula 21:



21

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable thereof. A preferred embodiment of the compositions embodied by Formula 21 is set forth in Series XXII, Figure 11, identified by Composition 138.

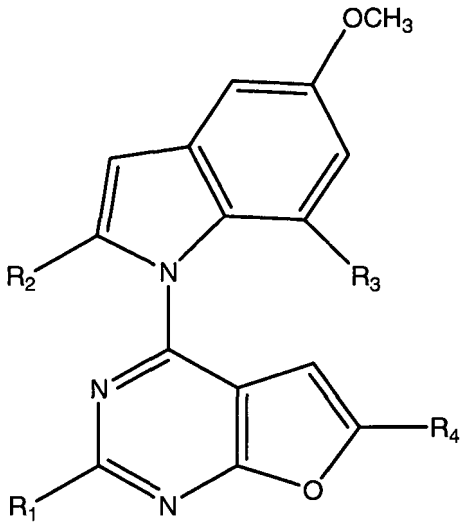
[0036] Further disclosed herein is a composition of the Formula 13:



13

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of (a) 2'-CH_3, 5'-OCH_3, (b) 6'-OCH_3, 5'-OCH3, and (c) 5'-OCH_2CH_3; and wherein R3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 13 are set forth in Series XXIII(a), Figure 12, identified by Compositions 139-141. It will be appreciated that R_2 may be positioned at one of the 2', 5', and 6' positions of one of the two upper rings, and that R2 may be positioned at one or more (multiple) locations of one or both of the two upper rings at positions 2', 5', and 6', and combinations thereof.

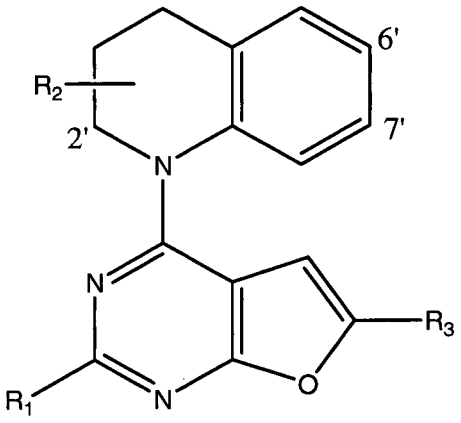
[0037] Further disclosed herein is a composition of the Formula 14:



14

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_4 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 14 are set forth in Series XXIII(b), Figure 12, identified by Compositions 142-144.

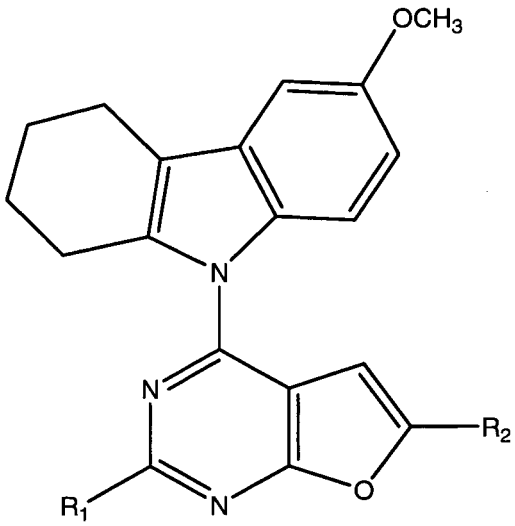
[0038] Further disclosed herein is a composition of the Formula 15:



15

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of (a) 2'-CH_3, 6'-OCH_3, (b) 7'-OCH_3, 6'-OCH_3, (c) 7'-OH, 6'-OCH_3, (d) 2'-CH_3, 6'-OH, and (e) 6'-OCF_3; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 15 are set forth in Series XXIV, Figure 13, identified by Compositions 146-150. It will be appreciated that R_2 may be positioned at one of the 2', 6', and 7' positions of one of the two upper rings, and that R2 may be positioned at one or more (multiple) locations of one or both of the two upper rings at positions 2', 6', and 7', and combinations thereof.

[0039] Further disclosed herein is a composition of the Formula 16:



16

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. A preferred embodiment of the compositions embodied by Formula 16 is set forth in Series XXIII(c), Figure 12, identified by Composition 145.

[0040] Water soluble salts, such as for example HCL salts (or other acids), of the compositions of Formulae 1-5, 7-21, 24, 32, 33 and 35 of the present invention (as set forth in Figures 1-13) are also provided herein.

[0041] A method of treating a patient having cancer is disclosed herein comprising administering to a patient an effective amount of a composition selected from the group consisting of compositions of Formulae 1-5, 7-21, 24, 32, 33, and 35, and salts thereof, for treating the patient. Further, a method of treating a patient with macular degeneration or arthritis is disclosed herein comprising administering to a patient an effective amount of a composition of the present invention as identified by Formulae 1-5, 7-21, 24, 32, and 35, and salts thereof, for treating the patient having macular degeneration or arthritis. Further, a method of treating a patient having cancer comprising inhibiting VEGFR2 receptors and tubulin assembly by administering a therapeutically effective amount of at least one composition of Formulae 1-5, 7-21, 24, 32,33, and 35, and salts thereof, to the patient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0042] A full description of the invention may be gained from the following description of the preferred embodiments of the invention when read in conjunction with the accompanying drawings in which:

Figures 1-13 show the chemical structures of the preferred compositions of the present invention. Figure 7 shows the chemical structure of a more preferred embodiment of the present invention, namely, the chemical structure of chemical Composition No. 104 which is also identified herein as sample identification number RP/AG/159-249 (or "RP 249"). Figure 8 shows the chemical structure of another preferred embodiment of the present invention, namely, the chemical structure of chemical Composition No. 106. The HCl salt of chemical Composition No. 106 is identified herein as sample identification number RP/ AG/159-248 (or "RP 248"). As used herein, the term "benzyl" means $-CH_2$-phenyl. Figure 4, Series Xa, Composition No. 80 shows that the R group 2',3'-$(CH)_4$ is attached to the lower right ring to form a composition having a 1-naphthyl moiety, and that Composition 81 shows that the R group 3',4'-$(CH)_4$ is attached to the lower right ring to form a composition having a 2-naphthyl moiety. Figure 5, Series Xb, Composition No. 89 shows that the R group 2',3'-$(CH)_4$ is attached to the lower right ring to form a composition having a 1-naphthyl moiety, and that Composition 90 shows that the R group 3',4'-$(CH)_4$ is attached to the lower right ring to form a composition having a 2-naphthyl moiety. It will be understood by those persons skilled in the art that many of the other compositions of the present invention recite a R group that is -$(CH)_4$ and that is attached to a ring for forming a composition having a naphthyl moiety. The compositions shown in Figures 1 through Figures 13 have VEGFR2 inhibition, antitubulin activity, and cytotoxic activity against tumor cells.

Figure 14 shows National Cancer Institute data on 60 tumor cell lines for Composition 104 (RP 249).

Figure 15 shows RP 249 as inhibiting tubulin assembly having an IC_{50} of 1.2 μM.

Figure 16 shows a comparison of RP 249 against VEGFR2 (Flk-1) with known VEGFR2 inhibitors such as SU5416, Sunitinib.

Figure 17 shows U251 flank animal weight change (animal has flank xenograft implant) with treatment with Composition 104 (RP249) of the present invention.

Figure 18 shows the synthesis scheme for Composition 104 (RP249) of the present invention.

Figure 19 shows the kinase inhibition and A431 cytotoxicity of Composition 106 as the HCl salt formulation as compared to commercially available compositions cisplatin, sunitinib, and erlotinib.

Figure 20 shows the National Cancer Institute data on 60 tumor cell lines for Composition 106 as the HCl (hydrochloride) salt formulation.

Figure 21 shows the National Cancer Institute Developmental Therapeutics Program One Dose Mean Graph data for Composition 106 as the HCl salt formulation for 58 tumor cell lines.

Figures 22A, 22B, and 22C show the National Cancer Institute Developmental Therapeutics program Dose Response Curves for Composition 106 as the HCl salt formulation concerning 57 tumor cell lines.

Figure 23 shows the National cancer Institute Developmental Therapeutics Program Mean Graph data for Composition 106 as the HCl salt formulation against 57 tumor cell lines.

Figures 24-30 provide synthesis schematics of the compositions of this invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

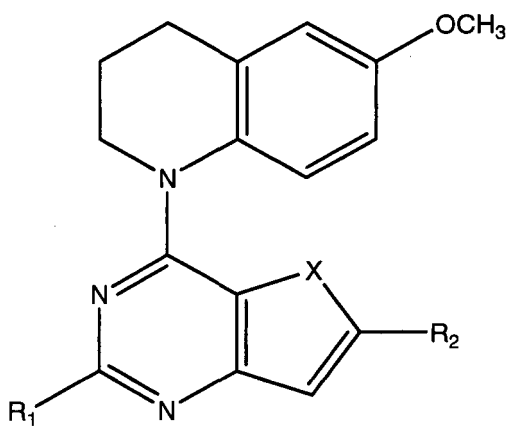
[0043] As used herein, the term "patient" means members of the animal kingdom, including but not limited to, human beings.

[0044] As used herein, the term "an effective amount" or "therapeutically effective amount" refers to that amount of any of the present compositions or salts thereof required to bring about a desired effect in a patient. The desired effect will vary depending on the illness being treated. For example, the desired effect may be reducing the tumor size, destroying cancerous cells, and/or preventing metastasis, any one of which may be the desired therapeutic response. On its most basic level, a therapeutically effective amount is that amount of a substance needed to inhibit mitosis of a cancerous cell.

[0045] The remarkable clinical success and the hundreds of ongoing clinical trials of antiangiogenic agents (AAs), particularly VEGFR2 inhibitors, and in combination with antitubulins, attests to the clinical importance of this combination in cancer chemotherapy. Combination chemotherapy with the use of two separate agents is not a new idea, however, the present invention provides compositions that have the attributes of VEGFR2 inhibition along with antitubulin activity in a single molecule and thus are novel over the background art. In addition, the compositions of the present invention are highly water soluble and are not subject to Pgp efflux, and thus the present compositions overcome some of the important drawbacks of taxanes and the Vinca alkaloids. In addition, the present compositions inhibit almost all the tumor cells in the NCI 60 tumor panel with GI_{50} values of 10^{-7} - 10^{-8} M, including those that were taxol resistant and demonstrated potent in vivo antitumor activity and antiangiogenic activity against triple negative breast cancer mouse models better than paclitaxel alone or sunitinib alone, without toxicity.

[0046] The present invention meets the above described need by providing bicyclic and tricyclic pyrimidine compositions that have dual (combined) activity, namely, vascular endothelial growth factor receptor inhibitory activity and antitubulin activity.

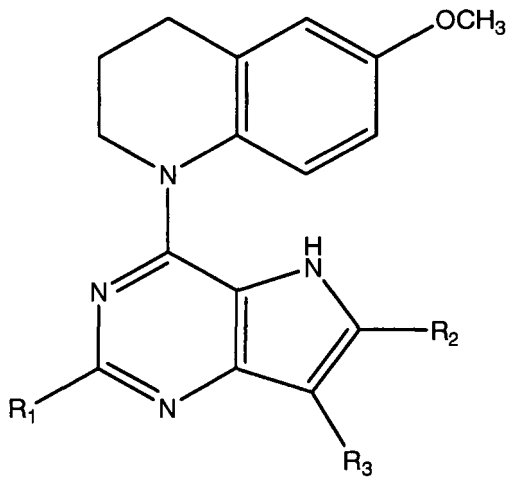
[0047] The present invention provides a compound of the Formula 5:



5

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein X is selected from the group consisting of NH, NCH_3, O, and S; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 5 are set forth in Series XIII, Figure 6, identified by Compositions 98-100, and Series XIV, Figure 7, identified by Compositions 101-103, and Series XVa, Figure 7, Composition 104. Composition 104 is also referred to herein as "RP249" and/or "RP/AG/159-249".

[0048] Further disclosed herein is a composition of Formula 7:



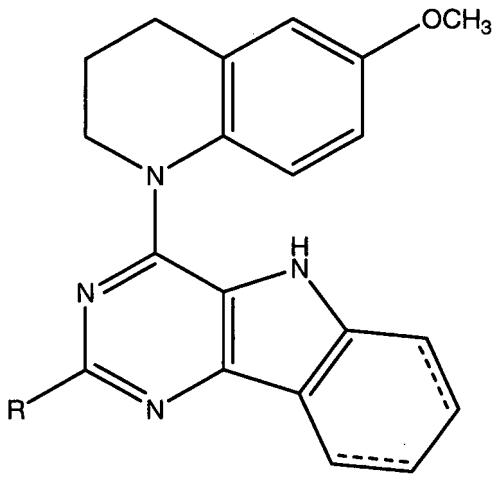
7

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting of H, a phenyl group, a substituted phenyl group, a benzyl group, a substituted benzyl group, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms, and wherein the alkyl group is optionally substituted with one or more of a phenyl group or a substituted phenyl group, or combinations thereof; and wherein each of the substituents of any of the substituted groups is the same or different and are selected from the group consisting of an electron withdrawing group and an electron donating group, and combinations thereof; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 7 are set forth in Series XIV, Compositions 101-103, Figure 7, and Series XVa, Compositions 104-105, Figure 7.

[0049] As used herein, the term "electron withdrawing group" or "EWG" is a functional group that draws electrons away from a reaction center. For example, but not limited to, an electron withdrawing group is a halogen (for example, but not limited to Cl and F), a nitrile (CN), a carbonyl (CO), a trihalide (for example but not limited to, $-CF_3$, and $-CCl_3$), $-OCF_3$, and a nitro group (NO_2). As used herein, the term "electron donating group" or EDG" is a functional group that releases electrons into a reaction center. For example, but not limited to, an electron donating group is an alkyl group having from 1 to 10 carbon atoms (for example, but not limited to CH_3 , CH_2CH_3, and $CH_2CH_2CH_3$), alcohol groups, alkoxy groups (for example, OCH_3), and amino groups.

[0050] The polar effect or electronic effect in chemistry is the effect exerted by a substituent on modifying electrostatic forces operating on a nearby reaction center. The total substituent effect is the combination of the polar effect and the combined steric effects. In electrophilic aromatic substitution and nucleophilic aromatic substitution, substituents are divided into activating groups and deactivating groups where the direction of activation or deactivation is also taken into account. A functional group is an activating group (or electron donating group), for example, if a benzene molecule to which it is attached more readily participates in electrophilic substitution reactions. A deactivating group (or electron withdrawing group), for example, is a functional group attached to a benzene molecule that removes electron density from the benzene ring, making electrophilic aromatic substitution reactions slower.

[0051] Further disclosed herein is a composition of the Formula 8:



8

comprising wherein R is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the composition embodied by Formula 8 is set forth in Series XVb, Figure 8, identified by Composition 106. The hydrochloride salt formulation of Composition 106 is also referred to herein as "RP248" and/or "RP/AG/159-248". It will be appreciated that the lower far right ring of the chemical structure set forth in Formula 8 (and in Formula 21 herein) may be completely unsaturated, partially unsaturated, or partially saturated as indicated by the broken double lines in the ring.

[0052] The compositions of the present invention as described hereinabove and herein below remarkably possess all the attributes described above and also inhibit tubulin assembly, bind to the colchicine site on tubulin (as distinct from taxane and Vincas), inhibit VEGFR2 at levels similar to sunitinib and semaxinib, and afford antiangiogenic activity in the CAM assay. It will be appreciated by those persons skilled in the art that the present compositions combine the cytostatic activity of VEGFR2 inhibitors along with the cytotoxic activity of antitubulin agents in a single agent and thus have all the advantages of combination chemotherapy when two separate agents, VEGFR2 inhibitors and antitubulins, delay or prevent tumor resistance. A further advantage of the present compositions is that they do not suffer from the pharmacokinetic disadvantages of drug-drug interactions, overlapping toxicities, lack of patient compliance, and the high cost associated with use of two separate drugs in combination. Most importantly, the single agent compositions of the present invention provide the antitubulin cytotoxic effect in the same molecule as the antiangiogenic VEGFR2 inhibitory effect such that the cytotoxic effect is manifested at the same time in the same place where the VEGFR2 antiangiogenic effect is operable. Since the tumor is usually heterogeneous, a separately dosed cytotoxic antitubulin (as discussed in the background art section) may miss the transient windows of tumor vasculature normalization via VEGFR2 inhibition (unless the antitubulin is administered metronomically) and thus precludes the intent of combination therapy. Antitubulin activity along with VEGFR2 activity in single agents manifest tumor cytotoxicity at the time dictated by the antiangiogenic effects. The single agent compositions of the present invention are on the spot for uptake into the tumor for the cytotoxic action as soon as or even during vasculature normalization due to the angiogenic effects. Such on the spot agents are much more efficient in getting into the tumor and do not need to be as potent as conventional separately dosed cytotoxic agents, thus reducing one of the major obstacles to combination chemotherapy--dose related toxicity. The present compositions having antimitotic and antiangiogenic activities are in keeping with the two mechanisms, metronomic dosing, and transient vascular normalization, that explain the clinical success of VEGFR2 inhibitors and antitubulin agents in combination chemotherapy. Thus, the compositions of the present invention afford cancer treatment options alone and in combination and for the vast majority of patients that become resistant to other antitumor agents and antitubulins.

[0053] In additional embodiments of the present invention, additional compositions having the structures set forth below are provided. These additional compositions of the present invention set forth below and in Figures 1-13, for convenience of this Application, are placed in the following optimized structural Series I, II, III, IV, VIII, X through XVIII, XX, and XXII through XXIV. These additional compositions of the present invention each have VEGFR2 inhibition, antitubulin activity and cytotoxic activity against tumor cells. The applicant realizes that the structural requirements for each of the compositions of the different Series set forth herein for VEGFR2, tubulin and tumor cell inhibition may be different (i.e. structural features for compositions of Series I, for example, for VEGFR2 inhibition, may be different than that for tubulin inhibition and different for tumor cell inhibition). Thus, "optimization" of the structures as set forth in the

various Series (see Figures 1-13) of compositions of this invention will provide chemical structural features that afford the best balance of potency against all three primary evaluations (VEGFR2, tubulin and tumor cell inhibition). It is also important to note that the HCl or other acid salts of all of the structures of the chemical compositions set forth in this Application (except perhaps for compositions of Series XI) can be easily synthesized by those persons skilled in the art.

[0054] For each of the compositions in the above mentioned Series (except Series XI) it has been determined that for antitubulin activity, the 4-position needs to have a N+CH_3-4-OMe-aniline or some variation that includes all three aspects (NCH_3, 4-OMe, C_6H_4), thus all of the compositions of the Series of the present invention contain this structural requirement.

[0055] Series I-II compositions address the bulk and conformational restriction of the 4-anilino moiety.

[0056] Series III compositions extends the chain length between the 4-OMePh and the 4-position to determine optimum distance.

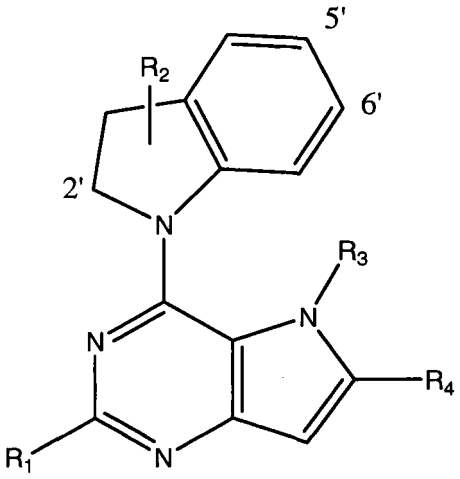
[0057] Series IV compositions show the importance to activity of the pyrrole NH and its intra-and intermolecular H-bonding ability.

[0058] Series VIII compositions show the optimum distance and bond angle or the benzylic atom of the pyrrolo[3,2-*d*]pyrimidine and the 7-benzyl group. In addition, the R_1, R_2, and R_3 restrict conformational rotation of the 7-benzyl group to determine optimal conformation(s) for activity of the 7-benzyl moiety relative to the pyrrolo[3,2-*d*]pyrimidine. In the N5-CH_3 analogs in Series VIII, the nature of the N5-H and its ability to H-bond and restrict conformational rotation and the effect on biological activity are set forth.

[0059] Series XIII, XIV, XV, XVII, and XXIV compositions all address the size and conformation of the 4-(6'-OMe) tetrahydroquinoline.

[0060] The compositions of Series XVI and XVII show conformational restriction at the 4-position. The 4-position substitution of Composition 104 is a tetrahydroquinoline. Figure 14 shows National Cancer Institute data on 60 tumor cell lines for Composition 104, a dual acting antitubulin/VEGFR2 inhibitor of the present invention, also identified herein as RP 249 and RP/AG/159-249. Figure 15 shows RP 249 as inhibiting tubulin assembly having an IC_{50} of 1.2 μM. Figure 16 shows a comparison of Composition 104 of the present invention, namely RP 249, against VEGFR2 (Flk-1) with known VEGFR2 inhibitors such as SU5416, Sunitinib. RP 249 is 30.6 μM against VEGFR2 comparable to the current standards at 12.9 and 18.9 μM. Figure 17 shows U251 flank animal weight change with treatment with Composition 104 of the present invention.

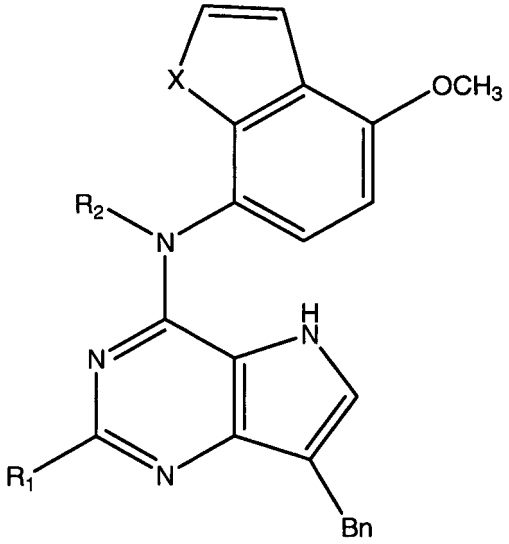
[0061] Further disclosed herein is a composition of the Formula 9:



9

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of (a) 2'-CH_3, 5'-OCH_3, (b) 6'-OCH_3, 5'-OCH_3, (c) 5'-OCH_2CH_3, and (d) 5'-OCH_3; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_4 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 9 are set forth in Series XVIa, Figure 8, identified by Compositions 107-111. It will be will be understood that R_2 may be positioned at one of the 2', 5', and 6' positions of one of the two upper rings, and that R_2 may be positioned at one or more (multiple) locations of one or both of the two upper rings at positions 2', 6', and 7', and combinations thereof.

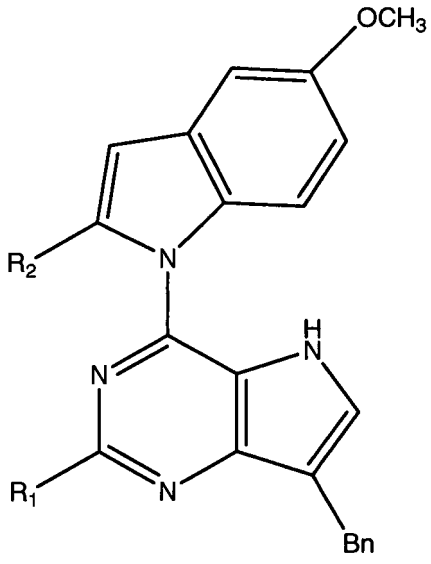
[0062] Further disclosed herein is a composition of Formula 17:



17

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein X is selected from the group consisting of (a) CH=CH, (b) NH, (c) NCH_3, (d) O, and (e) S; wherein Bn is selected from the group consisting of H, a phenyl group, a substituted phenyl group, a benzyl group, a substituted benzyl group, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms, and wherein said alkyl group is optionally substituted with one or more of a phenyl group or a substituted phenyl group, or combinations thereof; and wherein each of said substituents of any said substituted group is the same or different and are selected from the group consisting of an electron withdrawing group and an electron donating group, and combinations thereof; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 17 are set forth in Series I, Figure 1, identified by Compositions 4-8.

[0063] Further disclosed herein is a composition of Formula 1:

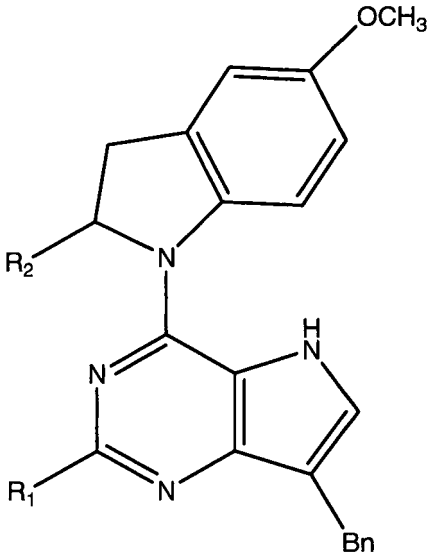


1

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl

group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; wherein Bn is selected from the group consisting of H, a phenyl group, a substituted phenyl group, a benzyl group, a substituted benzyl group, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms, and wherein said alkyl group is optionally substituted with one or more of a phenyl group or a substituted phenyl group, or combinations thereof; and wherein each of said substituents of any said substituted group is the same or different and are selected from the group consisting of an electron withdrawing group and an electron donating group, and combinations thereof; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 1 are set forth in Series IIa, Figure 1, identified by Compositions 15 and 16.

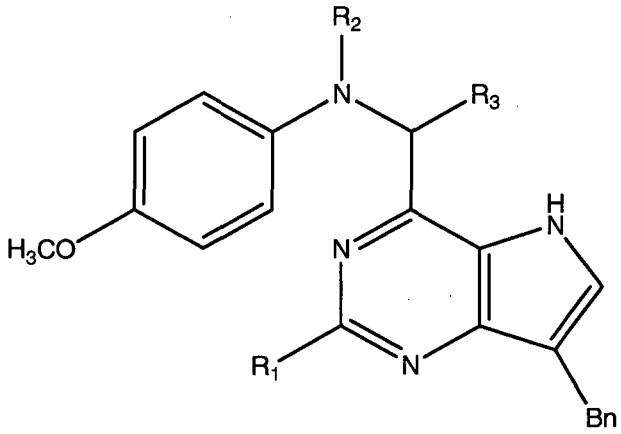
[0064] Further disclosed herein is a composition of Formula 2 :



2

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; wherein Bn is selected from the group consisting of H, a phenyl group, a substituted phenyl group, a benzyl group, a substituted benzyl group, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms, and wherein said alkyl group is optionally substituted with one or more of a phenyl group or a substituted phenyl group, or combinations thereof; and wherein each of said substituents of any said substituted group is the same or different and are selected from the group consisting of an electron withdrawing group and an electron donating group, and combinations thereof; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 2 are set forth in Series IIb, Figure 2, identified by Compositions 17 and 18.

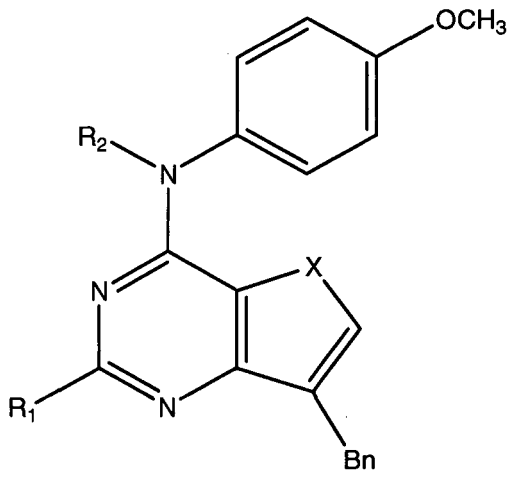
[0065] Further disclosed herein is a composition of the Formula 18:



18

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein Bn is selected from the group consisting of H, a phenyl group, a substituted phenyl group, a benzyl group, a substituted benzyl group, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms, and wherein said alkyl group is optionally substituted with one or more of a phenyl group or a substituted phenyl group, or combinations thereof; and wherein each of said substituents of any said substituted group is the same or different and are selected from the group consisting of an electron withdrawing group and an electron donating group, and combinations thereof; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 18 are set forth in Series III, Figure 2, identified by Compositions 22-24.

[0066] Further disclosed herein is a composition of Formula 24:

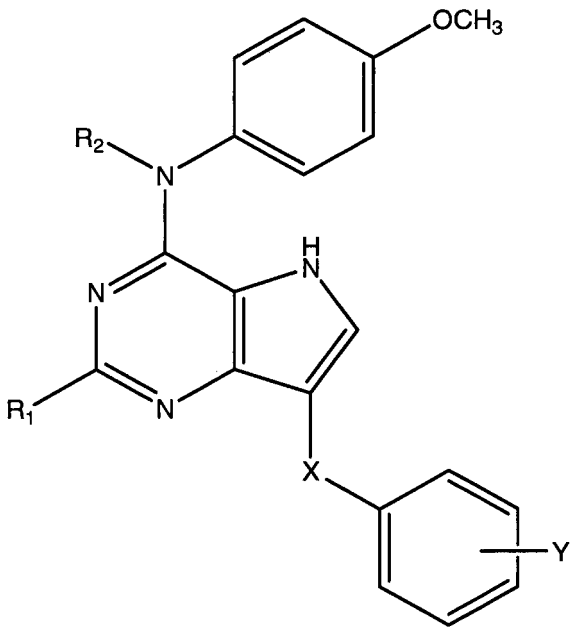


24

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein X is S; and wherein Bn is selected from the group consisting of H, a phenyl group, a substituted phenyl group, a benzyl group, a substituted benzyl group, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms, and wherein said alkyl group is optionally substituted with one or more of a phenyl group or a substituted phenyl group, or combinations thereof; and wherein each of said substituents of any said substituted group is the same or different and are selected from the group consisting of

an electron withdrawing group and an electron donating group, and combinations thereof; optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. A preferred embodiment of the compositions embodied by Formula 24 is set forth in Series IV, Figure 3, identified by Composition 27.

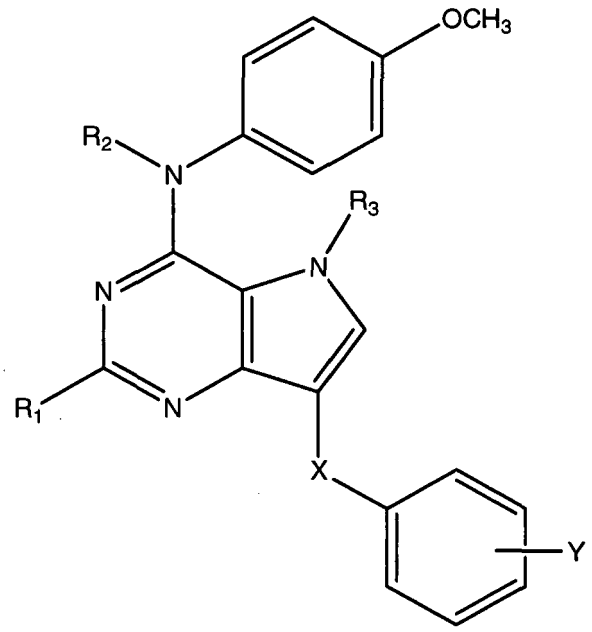
[0067] Further disclosed herein is a composition of the Formula 19:



19

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein X is selected from the group consisting of (a) NH, (b) NCH_3, (c) O, and (d) S; and wherein Y is selected from the group consisting of H, CH_3, $(CH)_4$, Cl, and OCH_3, wherein Y may be attached to the ring at one or more positions and may be the same or different; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 19 are set forth in Series VIIIa, Figure 3, identified by Compositions 50-57.

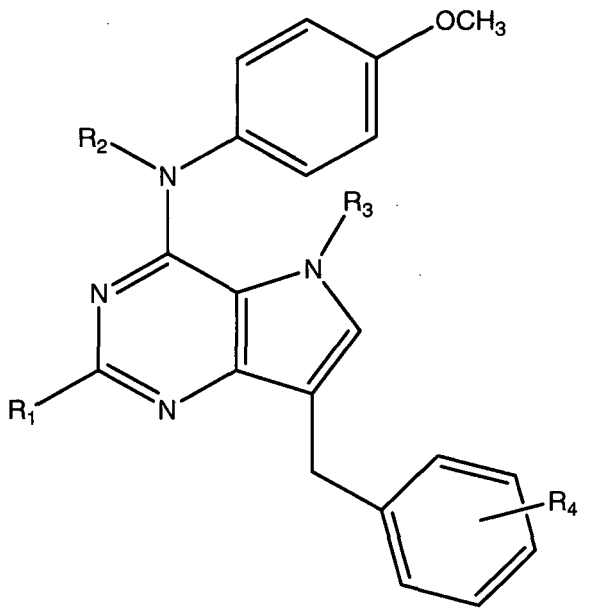
[0068] Further disclosed herein is a composition of the Formula 20:



20

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein X is selected from the group consisting of (a) NH, (b) NCH_3, (d) O, and (e) S; and wherein Y is selected from the group consisting of H, CH_3, $(CH)_4$, Cl, and OCH_3 , and wherein Y may be attached to the ring at one or more positions and may be the same or different; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 20 are set forth in Series VIIIb, Figure 4, identified by Compositions 58-65.

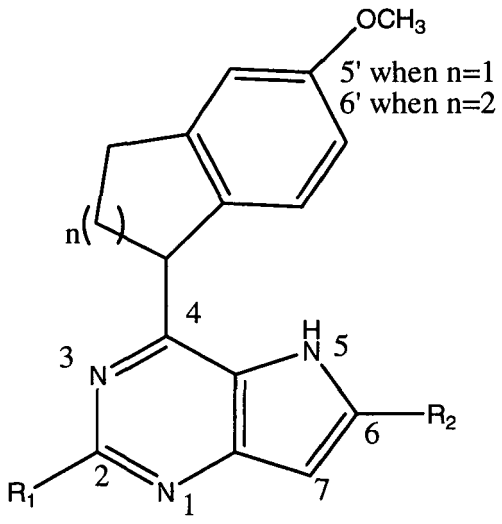
[0069] Further disclosed herein is a composition of Formula 32:



32

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R3 is selected from the group consisting of H and a straight or barnched chain alkyl group having from 1 to 10 carbon atoms, and wherein R_4 is selected from the group consisting of (a) 2',6'-diCH_3, (b) 2',5'-diOCH_3, (c) 2',4'-diCl, (d) 3',4'-diCl, (e) 2',3'-$(CH)_4$, (f) 3',4'-$(CH)_4$, and (g) 3',4',5'-triOCH_3; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 32 are set forth in Series X(a), Figure 4, identified by Compositions 74, and 77-82, and in Series X(b), Figure 5, identified by Compositions 83, and 86-91. It will be appreciated from the structure of Formula 32 that R_4 may be attached to the phenyl ring at one or more positions (i.e. at multiple positions of the phenyl ring).

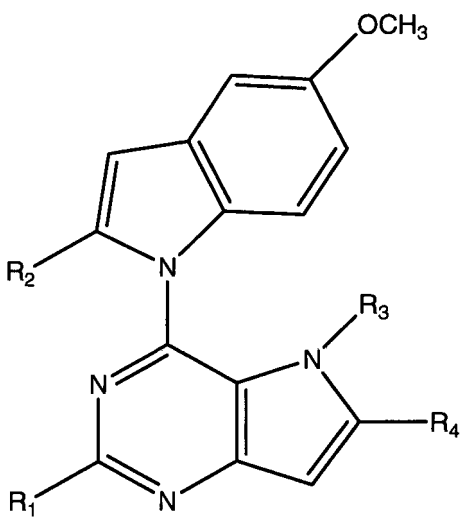
[0070] Further disclosed herein is a composition of the Formula 3:



3

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein n is 1 or 2; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 3 are set forth in Series XI, Figure 5, identified by Composition 92 (where n=1) and Composition 93 (where n=2).

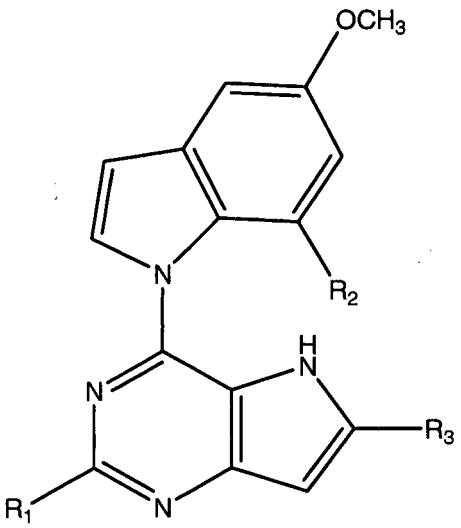
[0071] Further disclosed herein is a composition of Formula 4:



4

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_4 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 4 are set forth in Series XII, Figure 6, identified by Compositions 94-97.

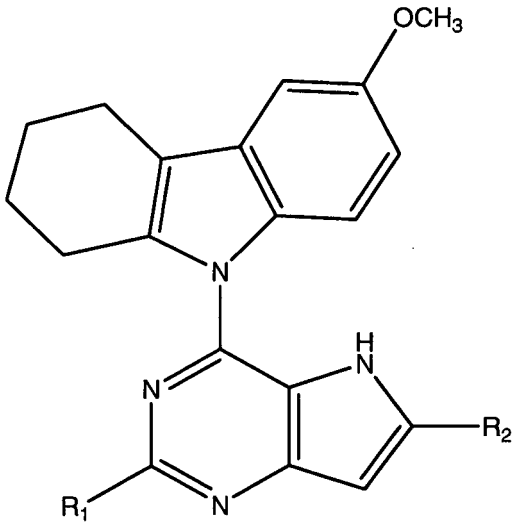
[0072] Further disclosed herein is a composition of the Formula 10:



10

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. A preferred embodiment of the compositions embodied by Formula 10 is set forth in Series XVI(b), Figure 9, identified by Composition 112.

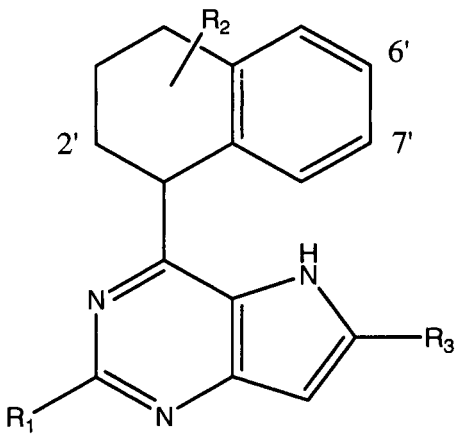
[0073] Further disclosed herein is a composition of the Formula 11:



11

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable thereof. A preferred embodiment of the compositions embodied by Formula 11 is set forth in Series XVI(c), Figure 9, identified by Composition 113.

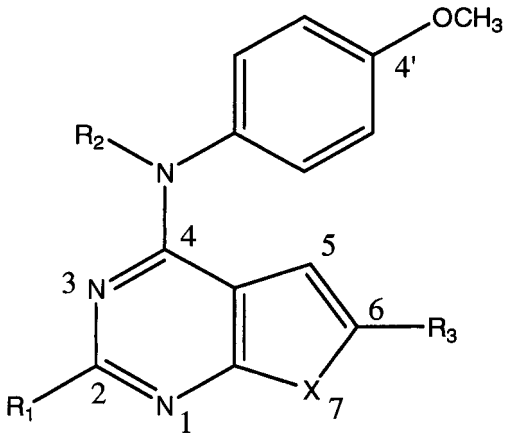
[0074] Further disclosed herein is a composition of the Formula 12:



12

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of (a) 2'-CH_3, 6'-OCH_3, (b) 7'-OCH_3, 6'-OCH_3, (c) 7'-OH, 6'-OCH_3, (d) 2'-CH_3, 6'-OH, and (e) 6'-OCF_3; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 12 are set forth in Series XVII, Figure 10, identified by Compositions 114-118. It will be appreciated that R_2 may be positioned at one of the 2', 6', and 7' positions of one of the two upper rings, and that R2 may be positioned at one or more (multiple) locations of one or both of the two upper rings at positions 2', 6', and 7', and combinations thereof.

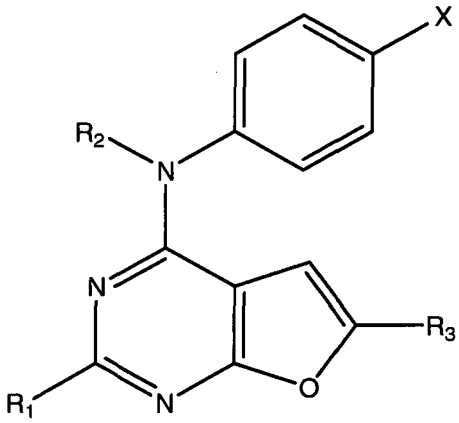
[0075] Further disclosed herein is a composition of the Formula 33:



33

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein X is S; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. A preferred embodiment of the compositions embodied by Formula 33 is set forth in Series XVIII, Figure 10, identified by Composition 121.

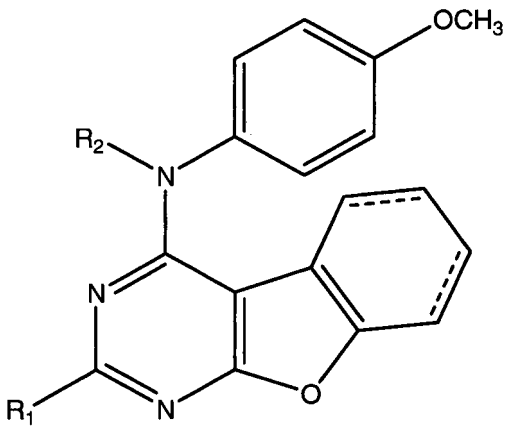
[0076] Further disclosed herein is a composition of Formula 35:



35

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein X is SCH_3; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable thereof. A preferred embodiment of the compositions embodied by Formula 35 is set forth in Series XX, Figure 11, identified by Composition 125.

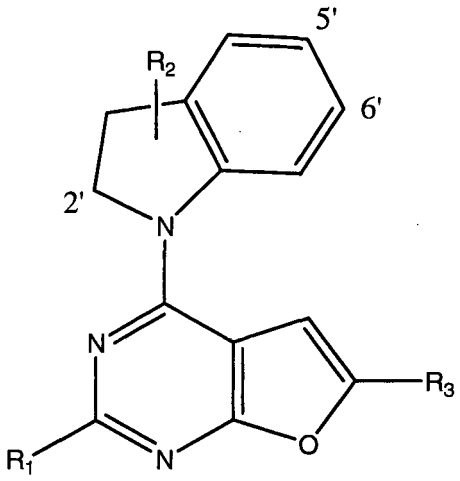
[0077] Further disclosed herein is a composition of Formula 21:



21

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable thereof. A preferred embodiment of the compositions embodied by Formula 21 is set forth in Series XXII, Figure 11, identified by Composition 138. It will be appreciated that the lower far right ring of the chemical structure set forth in Formula 21 may be completely unsaturated, partially unsaturated, or partially saturated as indicated by the broken double lines in the ring.

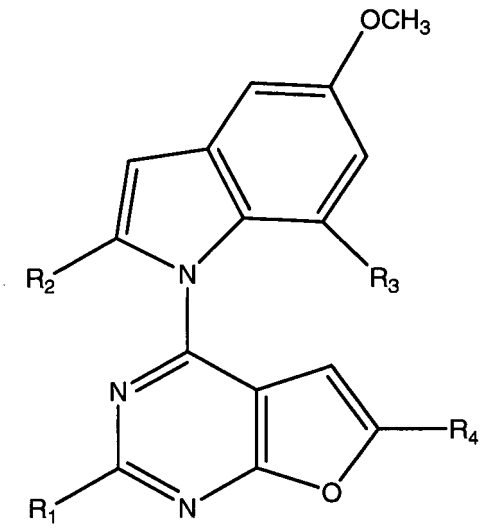
[0078] Further disclosed herein is a composition of the Formula 13:



13

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of (a) 2'-CH_3, 5'-OCH_3, (b) 6'-OCH_3, 5'-OCH3, and (c) 5'-OCH_2CH_3; and wherein R3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 13 are set forth in Series XXIII(a), Figure 12, identified by Compositions 139-141. It will be appreciated that R_2 may be positioned at one of the 2', 5', and 6' positions of one of the two upper rings, and that R2 may be positioned at one or more (multiple) locations of one or both of the two upper rings at positions 2', 5', and 6', and combinations thereof.

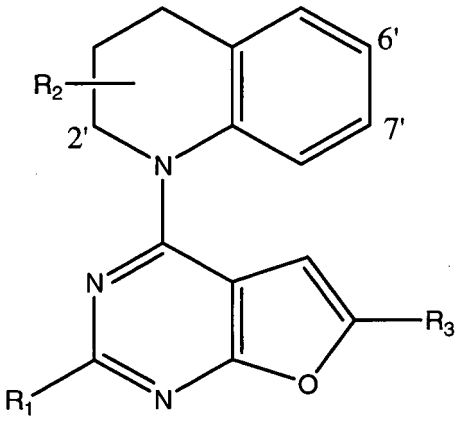
[0079] Further disclosed herein is a composition of the Formula 14:



14

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_4 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 14 are set forth in Series XXIII(b), Figure 12, identified by Compositions 142-144.

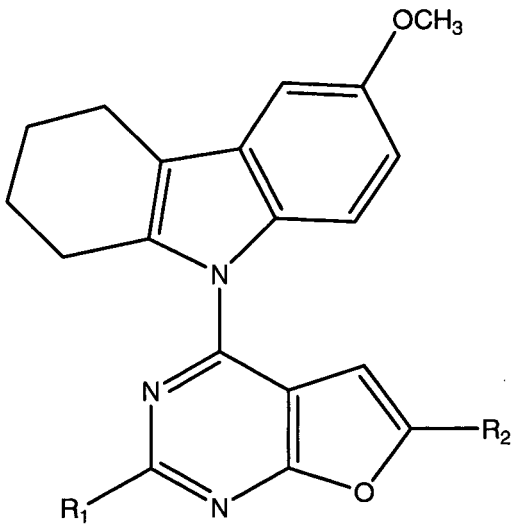
[0080] Further disclosed herein is a composition of the Formula 15:



15

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of (a) 2'-CH_3, 6'-OCH_3, (b) 7'-OCH_3, 6'-OCH_3, (c) 7'-OH, 6'-OCH_3, (d) 2'-CH_3, 6'-OH, and (e) 6'-OCF_3; and wherein R_3 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. Preferred embodiments of the compositions embodied by Formula 15 are set forth in Series XXIV, Figure 13, identified by Compositions 146-150. It will be appreciated that R_2 may be positioned at one of the 2', 6', and 7' positions of one of the two upper rings, and that R2 may be positioned at one or more (multiple) locations of one or both of the two upper rings at positions 2', 6', and 7', and combinations thereof.

[0081] Further disclosed herein is a composition of the Formula 16:



16

comprising wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and optionally comprising stereochemical conformations thereof; and optionally comprising a pharmaceutically acceptable salt thereof. A preferred embodiment of the compositions embodied by Formula 16 is set forth in Series XXIII(c), Figure 12, identified by Composition 145.

[0082] Water soluble salts, such as for example HCL salts (or other acids), of the compositions of Formulae 1-5, 7-21, 24, 32, 33and 35 of the present invention (as set forth in Figures 1-13) are also provided herein.

[0083] A composition of the present invention as identified by any one or more of the compositions of the present invention, for example, the compositions of Formula 5, and salts thereof, for use in treating a patient having cancer. In another embodiment of this invention, a composition of the present invention as identified by Formula 5, and salts thereof, are provided for use in treating the patient having macular degeneration or arthritis. In another embodiment of the present invention at least one composition of Formula 5 is provided for use in treating a patient having cancer comprising inhibiting VEGFR2 receptors and tubulin assembly.

SYNTHESIS OF COMPOSITIONS

[0084] Compound E (Figure 18) was synthesized from benzaldehyde using a reported procedure known by those persons skilled in the art. Compound E (Figure 18), when treated with acetonitrile, afforded the bicyclic Compound F which was chlorinated with $POCl_3$ to yield Compound G. Nucleophilic displacement of the 4-Cl group with commercially available compound H and formation of the HCl salt afforded the HCl salt formulation of Composition 104 (RP249).

[0085] All intermediates and final compounds were analyzed by melting point, TLC, NMR, HRMS and/or elemental analysis and chromatography for purity and characterization. The intermediate and final compounds may be used to synthesize the analog compositions.

[0086] Highly water soluble salts of the compositions of the present invention are easily obtained by those persons skilled in the art. Compositions of the present invention in all Series (except Series XI), all contain basic nitrogens and can easily form acids salts as shown in Schemes A-C (Figure 18) for the compositions of the present invention..

[0087] The synthesis of the compositions in Series I, II, III, IV, VIII, X through XVIII, XX, and XXII through XXIV (structures presented in Figures 1-13) as their HCl salts may be conducted using modified methods outlined in Scheme A for the present compositions of Series I, II, III, IV, VIII, and X, Scheme B for the present compositions of Series XII through XVII, and Scheme C for the present compositions of Series XVIII, XX, and XXII through XXIV. Generally the synthetic methods involve the synthesis of the parent scaffold with a 4-oxo functionality that is easily converted to the 4-chloro with $POCl_3$. The parent scaffolds for all the Series compositions set forth in Figures 1-13 are either in Schemes A-C or commercially available or available directly from literature methods. Suitable method modifications of Schemes A, B, and C as are known by those persons skilled in the art and obtainable from available literature references provide for the structures of the compositions of Figures 1-13. Displacement of the 4-chloro derivative with appropriate anilines as in Schemes A-C should afford most of the 4-substituted compounds. In addition, alternate Pd or Cu catalyzed cross coupling reactions of the Buchwald type with the aniline and the 4-halo derivative can also be employed for this reaction. Water soluble HCl or other acid salts made by methods outlined in Schemes A-C for the HCl salt are also simple and

easily obtained. These synthesis methods are routine as well as well documented in the literature. Bulk synthesis of the compositions of the present invention as set forth in Figures 1-13 selected for animal studies will follow routine synthetic methods.

Synthesis of Composition 106 (C ring aromatic) **as the HCl salt**

Referring to Figure 24, Scheme A:

[0088] **2-methyl-3*H*-pyrimido[5,4-*b*]indol-4(5*H*)-one (E)** is shown in Figure 24, Scheme A. HCl gas was bubbled through a stirred solution of **A** (1g, 4.9mmol) in acetonitrile (20mL) for 3 h. Most of the solvent was removed in vaccuo. The residue was dissolved in 10mL distilled water and the pH was adjusted to 8 with aq. ammonia solution to generate a yellow suspension which was filtered. The collected solid was dried in vacuum using P_2O_5 to afford 730 mg (75%) of **E** as a light yellow powder. ^{1}H NMR (DMSO-d_6): δ 2.43(s, 3H), 7.19(t, 1H), 7.43(t, 1H), 7.50(d, 1H), 7.959(d, 1H), 11.90(s, 1H), 12.268(s, 1H)

[0089] **4-chloro-2-methyl-5*H*-pyrimido[5,4-*b*]indole (F).** To a 50mL flask was added **E** (600mg, 3.01mmol) and 15mL $POCl_3$. The resulting mixture was heated to reflux for 4h, and the solvent was removed under reduced pressure, pH adjusted to 8 using aq. ammonia solution to afford a light brown suspension. The precipitate was collected by filtration to afford 480mg (73%) of **F** as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 2.75(s, 3H), 7.34(t, 1H), 7.67(m, 2H), 8.22(d, 1H), 12.201(s, 1H)

[0090] **4-(6-methoxy-3,4-dihydroquinolin-1(2*H*)-yl)-2-methyl-5H-pyrimido[5,4-*b*]indole hydrochloride (Composition No. 106. HCl).** To a 50mL flask was added F (100mg, 459.44μmol), **H** (90mg, 551.33μmol) and 10mL isopropanol. The mixture was heated to reflux for 24h and the solvent was removed under reduced pressure. To the residue obtained was added silica gel and MeOH and the solvent removed. The resulting plug was loaded on to a silica gel column with 1 % MeOH in $CHCl_3$ as the eluent. Fractions that showed the desired spot (TLC R_f = 0.5 in 1:10 MeOH: $CHCl_3$) were pooled, and the solvent evaporated to dryness to afford a residue. To this residue was added ethylacetate (1 mL) and diethylether (10 mL), and HCl gas was bubbled at room temperature for 5 mins to afford 134mg (76.6%) of Composition No. 106. HCl. ^{1}H NMR (DMSO-d_6): δ 2.075(m, 2H), 2.80(s, 3H), 2.87(t, 2H), 3.82(t, 2H) 4.2(s, 3H), 6.78(d, 1H), 7.0(d, 1H), 7.11(s, 1H), 7.35(t, 1H), 7.63(m, 2H), 8.46(d, 1H), 10.85(s, 1H), 15.96(s, 1H) Anal. Calcd. for $C_{21}H_{21}ClN_4O$. 0.3 H_2O: C, 65.30; H, 5.64; N, 14.50, Cl, 19.18. Found C, 65.37; H, 5.50; N,14.48, Cl, 9.06.

Synthesis of Composition No. 125

Referring to Figure 24, Scheme C:

[0091] **2-Methyl-5-prop-2-yn-1-ylpyrimidine-4,6-diol** (**K**). 50 mL anhydrous MeOH was added to a 250 mL flask, **I** (3.96 g, 2 mmol) and **J** (1.85 g, 2 mmol) were dissolved in this solution. After 800 mg (2 mmol) Na was added to the solution, yellow precipitate was observed. The resulting mixture was refluxed overnight. The yellow precipitate was collected by filtration and then dissolved in 10 mL H_2O. The pH of the resulting solution was adjusted to 6.5 by adding 2 N HCl to afford a yellow precipitate, which was collected by filtration and dried over P_2O_5 to afford 1.21 g (37%) **K**; mp >300°C; R_f 0.11 ($CHCl_3$/MeOH 6:1); ^{1}H NMR (DMSO-d_6) δ 2.23 (s, 3 H), 3.05 (s, 2 H), 3.32 (s, 1 H), 11.92 (s, 2 H).

[0092] **2,6-Dimethylfuro[2,3-*d*]pyrimidin-4(3*H*)-one (L).** 1.64 g (1 mmol) **K** was added to 15 mL H_2SO_4 (conc.) The solution was stirred overnight and poured in to 100 mL distilled water and extracted by 3X30 mL $CHCl_3$. The organic layer was pooled and concentrated to afford 1.36 (83%) **L** as a yellow powder; mp >300°C; R_f 0.35 ($CHCl_3$/MeOH 6:1); ^{1}H NMR (DMSO-d_6) δ 2.42 (s, 3 H), 2.44 (s, 3 H), 6.63 (s, 1 H), 12.50 (s, 1 H).

[0093] **4-Chloro-2,6-dimethylfuro[2,3-*d*]pyrimidine** (**M**). To a 50 mL flask was added 1.64 g (1 mmol) L and 10 mL $POCl_3$. The resulting mixture was refluxed for 2 h, and the solvent was removed under reduced pressure to afford a dark residue. To this was added 30 mL of $CHCl_3$ and 3 g of silica gel. The solvent was evaporated to afford a plug. Column chromatography of the plug with hexane: acetyl acetate=20:1 as eluent afford 1.55 g (85%) **M** as a yellow solid; R_f 0.26 (Hexane/EtOAC 15:1); ^{1}H NMR (DMSO-d_6) δ 2.48 (s, 3 H), 2.63 (s, 3 H), 6.77 (s, 1 H).

[0094] **2,6-Dimethyl-N-[4-(methylsulfanyl)phenyl]furo[2,3-*d*]pyrimidin-4-amine (N).** To a 50 mL flask was added **M** (91 mg, 0.5 mmol), 4-(methylsulfanyl)aniline (76 mg, 0.55 mmol) and *i*-PrOH (5 mL). To this solution was added 2 drops of concentrated HCl solution and the mixture was refluxed. TLC indicated the disappearance of starting material **5**, the solvent was removed under reduced pressure. To the residue obtained was added silica gel and MeOH and the solvent removed to make a plug. This plug was separated by column chromatography to give 97 mg (68%) of **7** as a yellow powder; R_f 0.4 (Hexane/EtOAC 3:1); ^{1}H NMR (DMSO-d_6) δ 2.43 (s, 3 H), 2.48 (s, 3 H), 2.49 (sq, 3 H), 6.70 (s, 1 H), 7.28-7.30 (d, 2H), 7.78-7.80 (d, 2H), 9.51 (s, 1H); Anal. Calcd. for $C_{15}H_{15}N_3OS$: C, 63.13; H, 5.30; N, 14.73, S, 11.24. Found C, 62.99; H, 5.27; N,14.56, S, 11.10.

[0095] ***N*,2,6-Trimethyl-*N*-[4-(methylsulfanyl)phenyl]furo[2,3-*d*]pyrimidin-4-amine (Composition No. 125)** To a

25 mL round bottom flask was weighed **N** (143 mg, 0.5 mmol) and was added DMF (2 mL) to afford a solution. The flask was purged with argon for five min followed by cooling down to 0 °C using ice bath. Sodium hydride (36 mg, 1.5 mmol) was added to the solution at 0 °C. The solution was stirred for 30 min at 0 °C under argon atmosphere. Dimethyl sulfate (150 mg, 1.2 mmol) was introduced to the reaction mixture with the help of a syringe and the flask was warmed to room temperature. The mixture was stirred at room temperature for another 3h at the end of which 1 N hydrochloric acid (5 mL) was added carefully to quench the reaction. The reaction solvent was removed under reduced pressure and the residue was suspended in water (20 mL). The suspension was extracted using ethyl acetate (10 mL x 2). Combined organic extracts were washed with brine (10 mL) dried (anhydrous sodium sulfate) and concentrated under reduced pressure. Silica gel (200 mg) was added and solvent evaporated to afford a plug. Column chromatography by elution with hexane: ethyl acetate (5:1) afforded 78 mg (52%) of Composition No. **125** as a light yellow solid: R_f 0.5 (AcOEt/Hexane, 1:3); ^{1}H NMR (DMSO-d_6) δ 2.18 (s, 3H), 2.49 (s, 3H), 2.54 (s, 3H), 3.47 (s, 3H), 4.73 (s, 1H), 7.30-7.32 (d, 2H,), 7.38-7.39 (d, 2H); Anal. Calcd. for $C_{16}H_{17}N_3OS$: C, 64.19; H, 5.72; N, 14.04, S, 10.71. Found C, 64.26; H, 5.68; N,13.90, S, 10.80.

Prophetic Synthesis of Compositions of the Present Invention

Referring to Figure 25, Scheme 1:

[0096] 4-Chloro group on the pyrimidine heterocycles can be displaced by appropriate nucleophiles under various conditions. The typical reaction procedure for the displacement of 4-Cl by substituted anilines is to dissolve the two reaction partners in *i*PrOH, add 1-2 drops of HCl (conc.) and then heat the reaction solution to reflux for 24h. For certain reactions, the conditions can further be optimized. Such variations include the changes from *i*PrOH to BuOH, from HCl (conc.) to H_2SO_4 (conc.) or the changes from bench-top reactions to microwave assisted conditions. For the displacement of 4-Cl by heterocyclic nucleophiles, similar displacement reactions as well as some Pd- or Cu-catalyzed coupling reactions can be adopted. See, for example, Xi, Z.; Liu, F.; Zhou, Y.; Chen, W. CuI/L (L=Pyridine-functionalized 1,3-Diketones) Catalyzed C-N Coupling Reactions of Aryl Halides with NH-containing Heterocycles. Tetrahedron 2008, 64, 4254-4259; and Lagisetty, P.; Russon, L. M.; Lakshman, M. K. A General Synthesis of C6-azolyl Purine Nucleosides. Angew. Chem. Int. Ed. 2006, 45, 3660-3663.

Referring to Figure 25, Scheme 2:

[0097] Commercially available **158** (Scheme 2, Figure 25) can be converted to **159** by reductive amination which on treatment with **C** (Scheme A) should afford **4.** See, for example, Baxter, E. W.; Reitz, A. B. Reductive Aminations of Carbonyl Compounds with Borohydride and Borane Reducing Agents. In Organic Reactions; Overman, L. E., Eds., Wiley & Sons: New York, 2002; Vol. 59, pp 1-170; and Gangjee, A.; Zhao, Y.; Lin, L.; Raghavan, S.; Roberts, E. G.; Risinger, A. L.; Hamel, E.; Mooberry, S. L. Synthesis and Discovery of Water-soluble Microtubule Targeting Agents that Bind to the Colchicine Site on Tubulin and Circumvent Pgp Mediated Resistance. J. Med. Chem. 2010, 53, 8116-8128.

Referring to Figure 25, Scheme 3:

[0098] Methylation of commercially available **160** (Scheme 3, Figure 25) with methyl iodide will afford **161.** Compounds **160** and **161** on catalytic hydrogenation will afford **162** and **163** respectively. Compounds **162, 163** and commercially available **164** can be converted to **165-167** respectively which on treatment with **C** (Scheme A, Figure 24) should afford Composition Nos. **5-7** respectively. Treatment of **C** with ammonia should afford **168** which on Pd-catalyzed coupling with **169** will afford Composition No. **8**. See for example, Johansen, M. B.; Kerr, M. A. Direct Functionalization of Indoles: Copper-catalyzed Malonyl Carbenoid Insertions. Org. Lett. 2010, 12, 4956-4959; Makuc, D.; Triyanti; Albrecht, M.; Plavec, J.; Rissanen, K.; Valkonen, A.; Schalley, C. A. The Halide Binding Behavior of 2-Carbamoyl-7-ureido-1H-indoles: Conformational Aspects. Eur. J. Org. Chem. 2009, 28, 4854-4866; Gangjee, A.; Zaware, N.; Raghavan, S.; Ihnat, M.; Shenoy, S.; Kisluik, R. L. Single Agents with Designed Combination Chemotherapy Potential: Synthesis and Evaluation of Substituted Pyrimido[4,5-b]indoles as Receptor Tyrosine Kinase and Thymidylate Synthase Inhibitors and as Antitumor Agents. J. Med. Chem. 2010, 53, 1563-1578; and Ngassa, F. N.; DeKorver, K. A.; Melistas, T. S.; Yeh, E. A.-H.; Lakshman, M. K. Pd-xantphos-catalyzed Direct Arylation of Nucleosides. Org. Lett. 2006, 8, 4613-4616.

Referring to Figure 26, Scheme 5:

[0099] Commercially available indoles **183** and **184** (Scheme 5, Figure 26) can be treated with NaH and C (Scheme A) to afford Composition Nos. **15** and **16** respectively. See for example, Dunn, J. P.; Goldstein, D. M.; Gong, L.; Hogg, J. H.; Michoud, C.; Palmer, W. S.; Sidduri, A.; Silva, T.; Tivitmahaisoon, P.; Trejo-Martin, T. A. Preparation of Pyrimidines

as c-Jun N-Terminal Kinase (JNK) Modulators. PCT Int. Appl. 068171, 2008.
Compound **C** (Scheme A, Figure 24) can be treated with commercially available **185-(±)186** to afford Composition Nos. **17-(±)18** respectively.

Referring to Figure 26, Scheme 26:

[0100] Stille coupling of **C** (Scheme A, figure 24) with **190** (Scheme 6, Figure 26) and commercially available **192** should afford **191** and **193** respectively. Reductive amination of **191** and **193** with **D** (Scheme A, Preliminary Studies) should afford **22** and (±)**23** respectively. Reductive amination of **191** with *p*-anisidine should afford (±)**24**. See for example, Bender, J. A.; Yang, Z.; Kadow, J. F.; Meanwell, N. A. Diazaindole-dicarbonyl-piperazinyl Antiviral Agents. U.S. Pat. Appl. 0124623, 2005; and Baker, S. J.; Goldsmith, P. J.; Hancox, T. C.; Pegg, N. A.; Shuttleworth, S. J.; Dechaux, E. A.; Krintel, S. L.; Price, S.; Large, J. M.; McDonald, E. 2-(Morpholin-4-yl)pyrimidine Derivatives as PI3K Inhibitors and their Preparation, Pharmaceutical Compositions and use in the Treatment of Diseases. PCT Int. Appl. 125833, 2008.

Referring to Figure 26, Scheme 7:

[0101] Analogous to **A** (Scheme A, Figure 24), compounds **195** (Scheme 7, Figure 26) can be converted to **27.** See for example, Morris Jr., P. E.; Elliott, A. J.; Montgomery, J. A. New Syntheses of 7-Substituted-2-aminothieno- and Furo[3,2-d]pyrimidines. J. Heterocycl. Chem. 1999, 36, 423-427.

Referring to Figure 27, Scheme 12:

[0102] Compound **213** (Scheme 12, Figure 27) can be reacted with commercially available **215-222** (Scheme 13, Figure 27) to afford compositions with general structure of Composition No. **223** analogous to **E** (Scheme A, Figure 24) which can be converted to Composition Nos. **50-57.** Composition Nos. **50-57** can be methylated to afford Composition Nos. **58-65.**

Referring to Figure 28, Scheme 15:

[0103] Using a reported methodology of Elliott, A. J.; Morris Jr., P. E.; Petty, S. L.; Williams, C. H. An Improved Synthesis of 7-Substituted Pyrrolo[3,2-d]pyrimidines. J. Org. Chem. 1997, 62, 8071-8075, commercially available compositions **231,234-239** (Scheme 15, Figure 28) can be converted to compounds with general structure of composition **240** analogous to **A** (Scheme A, Figure 24) which can be treated with acetonitrile and HCl to afford the corresponding bicyclics which on chlorination and subsequent displacement with **D** (Scheme A, figure 24) will afford Composition Nos. **74,77-82.** Composition Nos. **74, 77-82** can be methylated to afford Composition Nos. **83, 86-91.**

Referring to Figure 28, Scheme 16:

[0104] Compounds **244** and **245** (Scheme 16, Figure 28) can be prepared from commercially available compositions **241** and **242** by palladium-catalyzed benzylic C-H borylation. See for example, Giroux, A. Synthesis of Benzylic Boronates via Palladium-Catalyzed Cross-Coupling Reaction of Bis(pinacolato)diboron with Benzylic Halides. Tetrahedron Lett. 2002, 44, 233-235. Compounds **244** and **245** on Suzuki coupling (see Havelková, M.; Dvorak, D.; Hocek, M. The Suzuki-Miyaura Cross-coupling Reactions of 2-, 6- or 8-Halopurines with Boronic Acids Leading to 2-, 6- or 8-Aryl- and -Alkenylpurine Derivatives. Synthesis 2001, 1704-1710) with **G** (Scheme A, Figure 24) affords Composition Nos. (±)**92** and (±)**93** respectively. Commercially available **246** and **247** (Scheme 17, Figure 28) can be deprotonated using sodium hydride and treated with **G** (Scheme A, Figure 24) to afford **Composition Nos. 94-95** which on methylation affords Composition Nos. **96-97.** Composition 104 (RP 249) can be methylated using sodium hydride and methyl iodide to afford Composition **98.**

Referring to Figure 29, Scheme 18:

[0105] Analogous to **A** (Scheme A, Figure 24) commercially available **248** (Scheme 18, Figure 29) can be treated with acetonitrile and HCl to afford the corresponding bicyclic which on chlorination and subsequent displacement with **H** will afford Composition **99.** Analogous to **E** (Scheme A, Figure 24), compound **249** (see for example, Ren, W.-Y.; Rao, K. V. B.; Klein, R. S. Convenient Synthesis of Substituted 3-Aminothiophene-2-carbonitriles from α-Acetylenic Nitriles and their conversion to thieno[3,2-d]pyrimidines. J. Heterocycl. Chem. 1986, 23, 1757-1763) on chlorination and subsequent displacement with **H** (Scheme A, Figure 24) will afford Composition No. **100.**

[0106] Compounds **253-255** (Scheme 18, Figure 29) can be prepared from **250-252** by a known methodology (see, Gangjee, A.; Li, W.; Yang, J.; Kisliuk, R. L. Design, Synthesis, and Biological Evaluation of Classical and Nonclassical 2-Amino-4-oxo-5-substituted-6-methylpyrrolo[3,2-d]pyrimidines as Dual Thymidylate Synthase and Dihydrofolate Reductase Inhibitors. J. Med. Chem. 2008, 51, 68-76). Analogous to **A** (Scheme A, Figure 24), compounds **253-255** can be converted to Composition Nos. **101-103.**

Referring to Figure 29, Schemes 19, 20, and 21:

[0107] Compounds **213** and **214** (Scheme 12, Figure 27) can be reacted with $Al(CH_3)_3$ to afford **256** and **257** (Scheme 19, Figure 29) which on chlorination and subsequent displacement with **H** will afford Composition Nos. **104-105.** See for example, Hocek, M.; Pohl, R.; Cisarová, I. Highly Methylated Purines and Purinium Salts as Analogs of Heteromines. Eur. J. Org. Chem. 2005, 3026-3030.

[0108] Commercially available **258** (Scheme 20, Figure 29) on chlorination with phosphorous oxychloride will afford **259** which on treatment with the carbanion of cyclohexanone will afford **260.** See for example, Thurkauf, A.; Hutchison, A. Certain Aryl Fused Pyrrolopyrimidines; a new Class of GABA Brain Receptor Ligands, U.S. Pat. 5326868, 1994. Compound **260** on cyclization affords **261.** See for example, US Patent 5326868. On treatment with **H** (Scheme A, Figure 24), **261** affords Composition No. **106.**

[0109] Treatment of **G** (Scheme A, Figure 24) with commercially available (±)**186** (Scheme 5, Figure 26), **263-264, 185** (Scheme 5, Figure 26), **265-268,** easily accessible **269, 270** (see Yamada, K.; Somei, M. Photo-induced Rearrangement of 1-Ethoxy-2-phenylindole. Heterocycles 1998, 48, 2481-2484) affords Composition Nos. (±)**107, 108-109, 110,** 112-115, **116** (after silyl deprotection) and **118** respectively. Composition No. **110** on methylation will afford Composition No. **111.** The *O*-demethylation of Composition No. (±)**114** using BBr_3 yields Composition No. (±)**117**. See for example, McOmie, J. F. W.; Watts, M. L.; West, D. E. Demethylation of Aryl Methyl Ethers by Boron Tribromide. Tetrahedron 1968, 24, 2289-2292.

[0110] Analogous to **A** (Scheme A, Figure 24), compound **272** can be treated with acetonitrile and HCl to afford the corresponding bicyclic which on chlorination and subsequent displacement with **D** (Scheme A, Figure 24) will afford Composition Nos. **119** and **121** respectively. Composition No. **119** on methylation affords Composition No. **120.**

Referring to Figure 30, Scheme 22:

[0111] Treatment of **303** (Scheme 22, Figure 30) with malononitrile will afford **276,** which can be treated with acetonitrile and HCl to yield **279.** See for example, Matsuda, T.; Yamagata, K.; Yukihiko, T.; Yamazaki, M. Studies on Heterocyclic Enaminonitriles. VI. Synthesis of 2-Amino-3-cyano-4,5-dihydrofurans. Chem. Pharm. Bull. 1985, 33, 937-943. Coupling between **279** and 4-methoxy iodobenzene using copper (I) iodide and *L*-proline as a chelating ligand in the presence of potassium carbonate affords **282.** See for example Guo, X.; Rao, H.; Fu, H.; Jiang, Y.; Zhoa, Y. An Inexpensive and Efficient Copper Catalyst for N-Arylation of Amines, Amides and Nitrogen-containing Heterocycles. Adv. Synth. Catal. 2006, 348, 2197-2202. Reductive amination of **282** will afford Composition No. **138** (C ring saturated). Composition No. **138** (C ring saturated) can be treated with 10% Palladium on carbon or manganese dioxide to provide Composition No. **138** (C ring aromatic). See for example, Nakamichi, N.; Kawashita, Y.; Hayashi, M. Oxidative Aromatization of 1,3,5-Trisubstituted Pyrazolines and Hantzsch 1,4-Dihydropyridines by Pd/C in Acetic Acid. Org. Lett. 2002, 4, 3955-3957.

[0112] Treatment **of M** (Scheme C, Figure 24) with commercially available (±)**186** (Scheme 5, Figure 26), **263-264** (Scheme 21, Figure 30), **246-247** (Scheme 17, Figure 28), **265-268** easily accessible **269, 270** (see for example, Yamada, K.; Somei, M. Photo-induced Rearrangement of 1-Ethoxy-2-phenylindole. Heterocycles 1998, 48, 2481-2484) (Scheme 21, Figure 30) affords Composition Nos. (±)**139, 140-141, 142-143, 144-147, 148** (after silyl deprotection) and **150** respectively. The *O*-demethylation of Composition No. (±)**148** using BBr_3 yields Composition No. (±)**150**. See for example, McOmie, J. F. W.; Watts, M. L.; West, D. E. Demethylation of Aryl Methyl Ethers by Boron Tribromide. Tetrahedron 1968, 24, 2289-2292.

Biological Evaluation

[0113]

Table 1. Tumor cell inhibitory activity (NCI) GI_{50} (nM) of Composition No. 104.

Panel/ Cell line	GI_{50} (nM) Composition	Panel/ Cell line	GI_{50} (nM) Composition	Panel/ Cell line	GI_{50} (nM) Compound	Panel/ Cell line	GI_{50} (nM) Compound
Leukemia	**104**	**Colon Cancer**	**104**	**Melanoma**	**104**	**Renal Cancer**	**104**
CCRF-CEM	35.1	COLO 205	27.4	LOX IMVI	72.5	786-0	63.1
HL-60(TB)	26.2	HCC-2998	86.0	M14	29.4	A498	24.3
K-562	41.5	HCT-116	39.2	MDA-MB-435	17.0	ACHN	70.1
MOLT-4	98.3	HCT-15	42.1	SK-MEL-2	56.5	CAKI-1	42.3
RPMI-8226	42.9	HT29	37.7	SK-MEL-28	74.9	RXF 393	28.9
SR	30.9	KM12	35.6	SK-MEL-5	48.6	SN12C	84.9
NSCLC		SW-620	39.8	UACC-62	48.4	TK10	
A549/ATCC	40.1	**CNS Cancer**		**Ovarian cancer**		UO-31	54.3
EKVX	99.6	SF-268	62.6	IGROVI	47.0	**Prostate Cancer**	
HOP-62	45.3	SF-295	16.6	OVCAR-3	22.7	PC-3	50.4
HOP-92	59.5	SF-539	25.4	OVCAR-4	96.6	DU-145	34.9
NCI-H226	82.3	SNB-19	50.3	OVCAR-5	60.7	**Breast Cancer**	
NCI-H23	71.0	SNB-75	38.0	OVCAR-8	43.9	MCF7	38.0
NCI-H322M	44.2	U251	39.9	NCI/ADR-RES	29.4	MDA-MB-231/ATCC	101
NCI-H460	36.9			SK-OV-3	33.9	HS 578T	30.2
NCI-H522						BT-549	218
						MDA-MB-468	23.4

[0114] NCI (National Cancer Institute) 60 tumor panel (Table 1). Composition 104 of the present invention shows a remarkable 2- digit nanomolar GI_{50} in all the NCI 60 tumor cell lines.

Table 2. Inhibition of tubulin assembly, ^{3}H-colchicine binding and kinase inhibition IC_{50} (μM) for Composition No. 104

COMPOSITION	Inhibition of			kinase inhibition IC_{50}(μM)		
	tubulin assembly IC_{50}(μM)	colchicine binding		EGFR	VEGFR2	PDGFRβ
		(1μM)	(5μM)			
	5					
104	1.2±0.007	76±0.5		20.2±3.8	30.6±4.5	82.3±10.3
CA[a]	1.2±0.01	98±0.3				
PD153035				0.21±0.002		
Semaxinib					12.9	
DOX						
cisplatin						
sunitinib				172.1±19.4μM	18.9±2.7	83.1±10.1
erlotinib				1.2±0.2μM	124.7±18.2	12.2±1.9
DMBI						3.75
[a]CA = combretastatin ; DOX=doxirubicin; DMBI= inhibitor of PDGRβ						

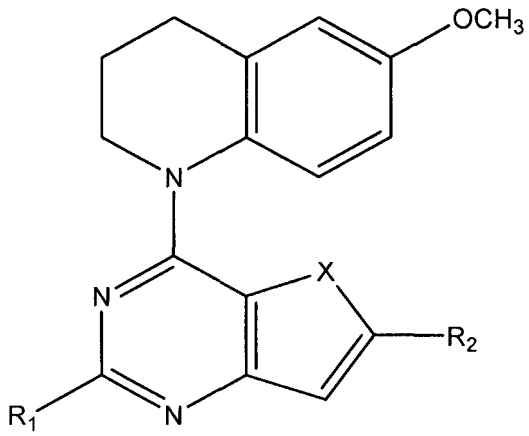
[0115] Compositions of the present invention are effective and potent inhibitors of bovine tubulin assembly (Composition 104, Table 2). This provides direct evidence of interaction of Composition 104 with tubulin. Composition 104 of the present invention is comparable to combretastatin (CA). In addition, Composition 104 is also a potent inhibitors of [^{3}H] colchicine binding (Table 2), thus, indicating that the compositions of the present invention bind at the colchicine binding site on tubulin similar to CA. Composition 104 was also evaluated against epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR2) and platelet derived growth factor preceptor-β (PDGFR-β) (Table 2). The tyrosine kinase inhibitory values (Table 2) are compared with standards sunitinib and semaxinib (VEGFR2), erlotinib (PDGFR-β and EGFR), DMBI (PDGFR-β) and PD153035 (EGFR). DMBI is a potent inhibitor of tyrosine kinase activities of the PDGFβ-receptor. DMBI (commercially available from EMD Chemicals, Inc., Gibbstown 08027, USA) does not inhibit EGFR even at concentrations greater than 100μM. Composition 104 of the present invention has comparable potency as sunitinib and semaxinib against VEGFR2 (Table 2). However, Composition 104 is a relatively poor inhibitor of EGFR and PDGFR-β, compared to standards. In order to rule out off target toxicity, Composition 104 was evaluated in a kinase profiling service (Luceome Biotechnologies) against 50 other kinases and found no activity at 10 μM. Composition 104 is unlikely to be Pgp or MRP substrates, and it possesses relative selectivity of kill on tumor versus normal cell types.

[0116] Figure 16 shows that Compositions No. 104 and 106 of the present invention are potent inhibitors of EGFR kinase, Flk-1 (VEGR2) kinase, and PDGFR kinase, and that each are comparable to sunitinib.

[0117] Molecular Modeling and Computational Studies. The structural basis of the inhibition of tubulin at the colchicine binding site of Composition 104 was determined. The X-ray crystal structure of αβ-tubulin at 3.58 Δ resolution (PDB ID 1SAO) complexed with DAMA colchicine, was used. Pharmacophores of the various small molecule colchicine-site binders have been determined. Docking of Composition 104 and its respective analog compositions having the structural formulae set forth in Figures 1-13 for scaffold analogs Series I, II, III, IV, VIII, X-XVIII, XX, and XXII-XXIV into the colchicine binding site have been accomplished. In addition, using the VEGFR2 X-ray crystal structure, we have docked Composition 104 and analogs thereof in VEGFR2. In addition, pharmacophore models using SYBYL have been determined from IC_{50} values for antitubulin and for other antitumor agents. We employ programs implemented in MOE and SYBYL 8.2 along with docking programs from MOE, SYBYL Glide, Gold among others. These programs allow the generation of pharmacophores and COMFA and COMISA. The relation of tumor cell inhibition data and the pharmacophore generation employs literature methods that have been successfully used for antitubulins as well as other antitumor agents using SYBYL.

Claims

1. A compound of Formula 5:



(5)

wherein R_1 is selected from the group consisting of H, NH_2, and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and
wherein R_2 is selected from the group consisting of H and a straight chain or branched chain alkyl group having from 1 to 10 carbon atoms; and
wherein X is selected from the group consisting of NH, NCH_3, O, and S; and stereochemical conformations thereof; and
a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 wherein R_1 and R_2 are each CH_3 and wherein X is NH.

3. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 or 2, or a pharmaceutically acceptable hydrate of any one of said compounds.

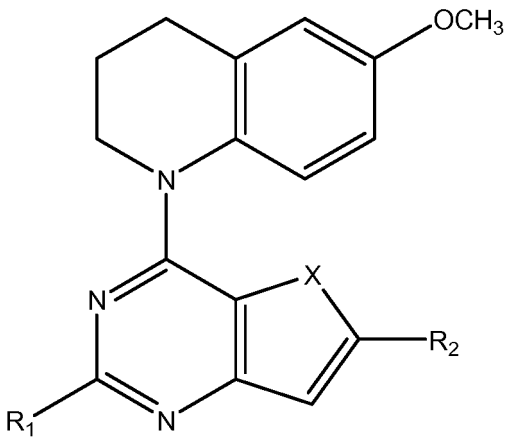
4. The pharmaceutical composition of Claim 3 comprising at least one pharmaceutically acceptable carrier.

5. The compounds of any claim 1 or 2 or any one of the pharmaceutical compositions of Claims 3 and 4 for use in treating a patient diagnosed with cancer, macular degeneration, or arthritis.

6. The compounds of claim 1 or 2 or any one of the pharmaceutical composition of claims 3 and 4 for use in treating a patient having cancer by targeting cancerous cells by inhibiting VEGFR2 receptors and tubulin assembly comprising providing a compound of claim 1 or 2 or pharmaceutical composition of claims 3 and 4 and administering to the patient a therapeutically effective amount of at least one compound of claim 1 or 2 or any one of said pharmaceutical compositions of claims 3 and 4.

Patentansprüche

1. Eine Verbindung der Formel 5:



(5)

worin R_1 ausgewählt ist aus der Gruppe bestehend aus H, NH_2 und einer geradkettigen oder verzweigtkettigen Alkylgruppe mit 1 bis 10 Kohlenstoffatomen; und
worin R_2 ausgewählt ist aus der Gruppe bestehend aus H und einer geradkettigen oder verzweigtkettigen Alkylgruppe mit 1 bis 10 Kohlenstoffatomen; und
worin X ausgewählt ist aus der Gruppe bestehend aus NH, NCH_3, O und S; und stereochemischen Konformationen davon; und
einem pharmazeutisch verträglichen Salz davon.

2. Die Verbindung nach Anspruch 1, worin R_1 und R_2 jeweils CH_3 sind und worin X NH ist.

3. Eine pharmazeutische Zusammensetzung, die eine therapeutisch wirksame Menge einer Verbindung nach Anspruch 1 oder 2, oder a pharmazeutisch verträgliches Hydrat von einer der Verbindungen umfasst.

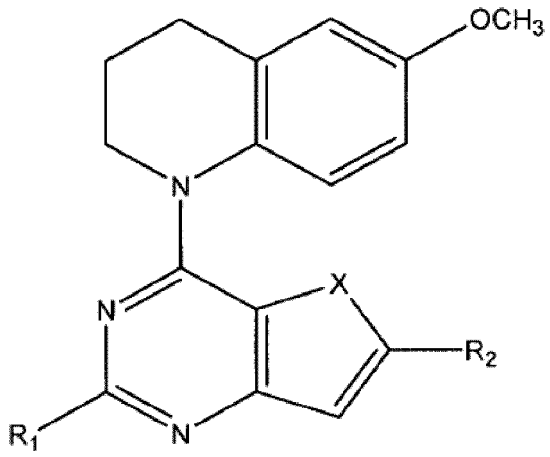
4. Die pharmazeutische Zusammensetzung nach Anspruch 3, die mindestens einen pharmazeutisch verträglichen Träger umfasst.

5. Die Verbindung nach einem der Ansprüche 1 oder 2, oder eine der pharmazeutischen Zusammensetzungen nach Anspruch 3 und 4 zur Verwendung bei der Behandlung eines Patienten, bei dem Krebs, Makuladegeneration oder Arthritis diagnostiziert wurde.

6. Die Verbindung nach Anspruch 1 oder 2, oder eine der pharmazeutischen Zusammensetzungen nach Anspruch 3 und 4 zur Verwendung bei der Behandlung eines Krebspatienten, wobei die Krebszellen durch Inhibierung von VEGFR2-Rezeptoren und Tubulin-Assemblierung anvisiert werden, umfassend der Bereitstellung einer Verbindung nach Anspruch 1 oder 2; oder einer pharmazeutischen Zusammensetzung nach Anspruch 3 und 4, und Verabreichen einer therapeutisch wirksamen Menge mindestens einer Verbindung nach Anspruch 1 oder 2, oder einer der pharmazeutischen Zusammensetzungen nach Anspruch 3 und 4.

Revendications

1. Composé de Formule 5 :



(5)

dans laquelle R_1 est sélectionné dans le groupe constitué de H, NH_2, et d'un groupe alkyle à chaîne linéaire ou à chaîne ramifiée ayant de 1 à 10 atomes de carbone ; et
R_2 étant sélectionné dans le groupe constitué de H et d'un groupe alkyle à chaîne linéaire ou à chaîne ramifiée ayant de 1 à 10 atomes de carbone ; et
X étant sélectionné dans le groupe constitué de NH, NCH_3, 0, et S ; et
leurs conformations stéréochimiques ; et
son sel pharmaceutiquement acceptable.

2. Composé selon la revendication 1, R_1 et R_2 étant chacun le groupe CH_3 et X étant NH.

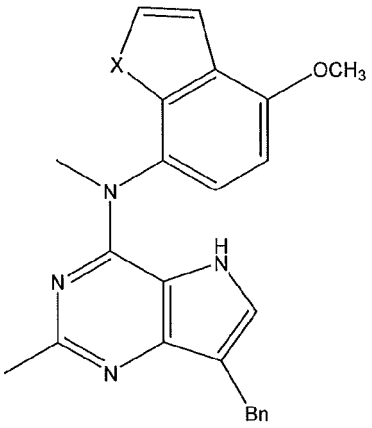
3. Composition pharmaceutique comprenant une quantité thérapeutiquement efficace d'un composé selon la revendication 1 ou 2, ou un hydrate pharmaceutiquement acceptable de l'un quelconque desdits composés.

4. Composition pharmaceutique selon la revendication 3 comprenant au moins un support pharmaceutiquement acceptable.

5. Composés selon l'une quelconque des revendications 1 ou 2 ou n'importe lesquelles des compositions pharmaceutiques selon les revendications 3 et 4 destinés à une utilisation dans le traitement de patient ayant reçu un diagnostic de cancer, de dégénérescence maculaire, ou d'arthrite.

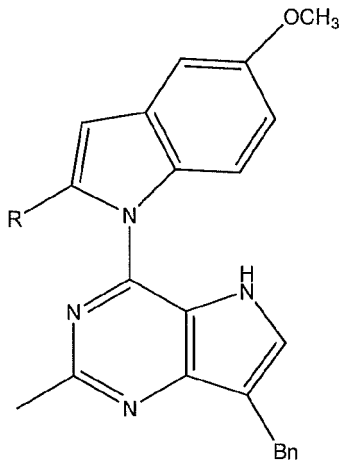
6. Composés selon la revendication 1 ou 2 ou l'une quelconque de la composition pharmaceutique selon les revendications 3 et 4 destinés à une utilisation dans le traitement d'un patient présentant un cancer en ciblant les cellules cancéreuses par inhibition des récepteurs du VEGFR2 et de l'ensemble tubuline comprenant la préparation d'un composé selon la revendication 1 ou 2 ou d'une composition pharmaceutique selon les revendications 3 et 4 et l'administration au patient d'une quantité thérapeutiquement efficace d'au moins un composé selon la revendication 1 ou 2 ou de l'une quelconque desdites compositions pharmaceutiques selon les revendications 3 et 4.

Series I:



COMPOSITION NUMBER	X	Bn
4	CH=CH	benzyl
5	NH	benzyl
6	NCH_3	benzyl
7	O	benzyl
8	S	benzyl

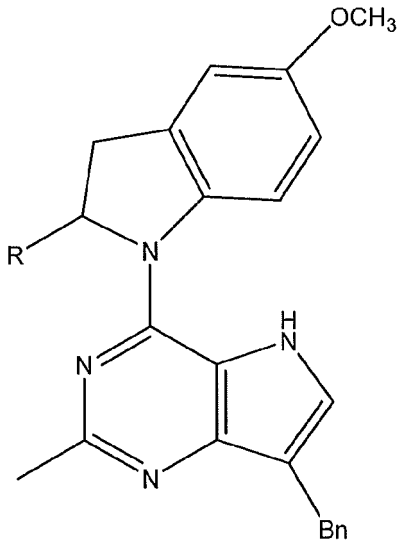
Series IIa:



COMPOSITION NUMBER	R	Bn
15	H	benzyl
16	CH_3	benzyl

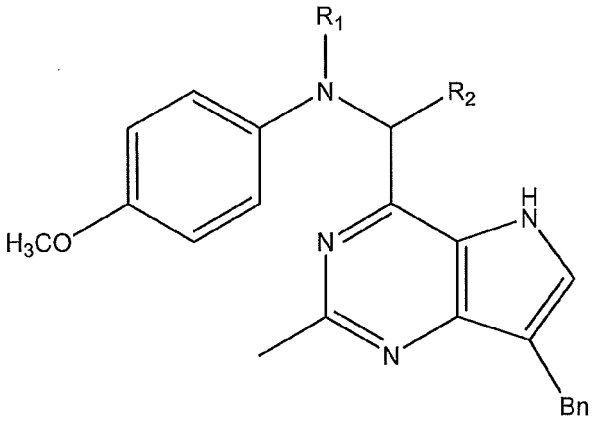
Figure 1

Series IIb:



COMPOSITION NUMBER	R	Bn
17	H	benzyl
18	CH_3	benzyl

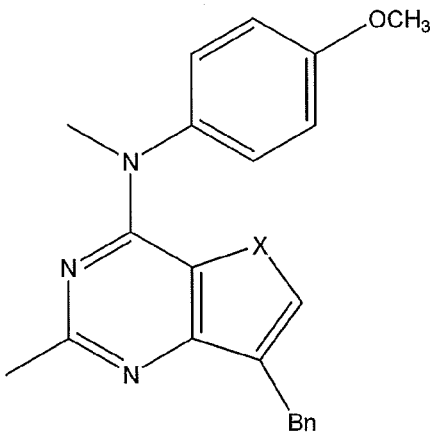
Series III:



COMPOSITION NUMBER	R_1	R_2	Bn
22	CH_3	H	benzyl
23	CH_3	CH_3	benzyl
24	H	CH_3	benzyl

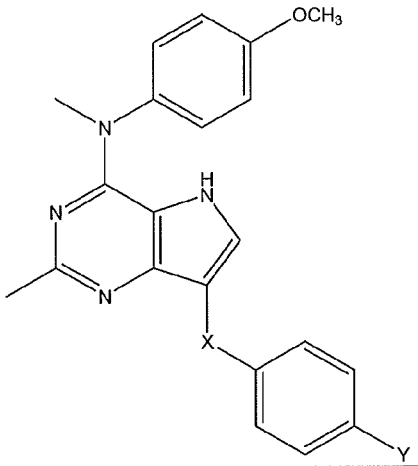
Figure 2

Series IV:



COMPOSITION NUMBER	X	Bn
27	S	benzyl

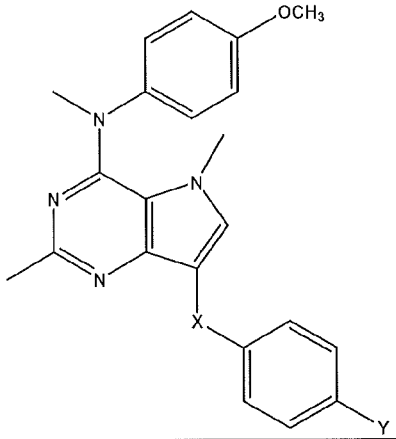
Series VIIIa:



COMPOUND NUMBER	X	Y
50	NH	H
51	NCH_3	H
52	O	H
53	S	H
54	NH	OCH_3
55	NCH_3	OCH_3
56	O	OCH_3
57	S	OCH_3

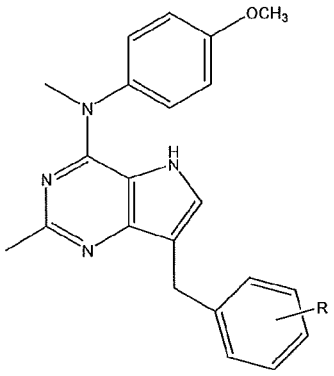
Figure 3

Series VIIIb:



COMPOSITION NUMBER	X	Y
58	NH	H
59	NCH_3	H
60	O	H
61	S	H
62	NH	OCH_3
63	NCH_3	OCH_3
64	O	OCH_3
65	S	OCH_3

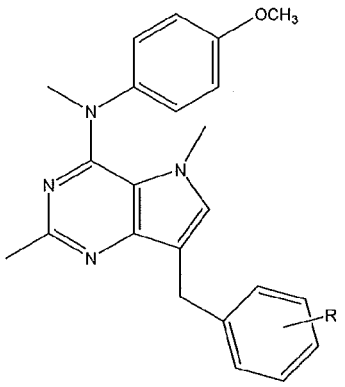
Series Xa:



COMPOSITION NUMBER	R
74	2',6'-diCH_3
77	2',5'-diOCH_3
78	2',4'-diCl
79	3',4'-diCl
80	2',3'-$(CH)_4$
81	3',4'-$(CH)_4$
82	3',4',5'-triOCH_3

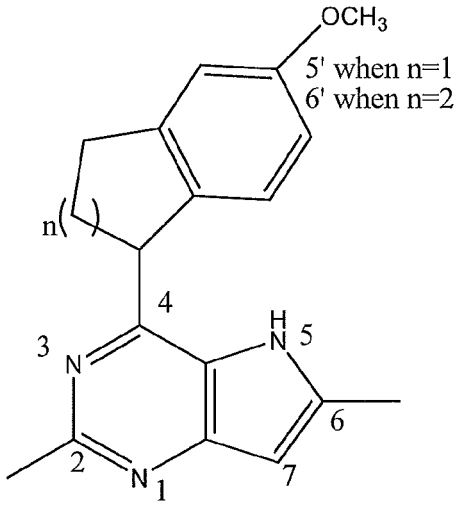
Figure 4

Series Xb:



COMPOSITION NUMBER	R
83	2',6'-diCH_3
86	2',5'-diOCH_3
87	2',4'-diCl
88	3',4'-diCl
89	2',3'-$(CH)_4$
90	3',4'-$(CH)_4$
91	3',4',5'-triOCH_3

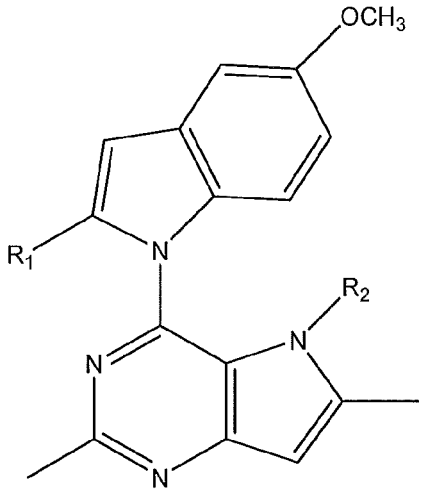
Series XI:



COMPOSITION NUMBER	n
92	1
93	2

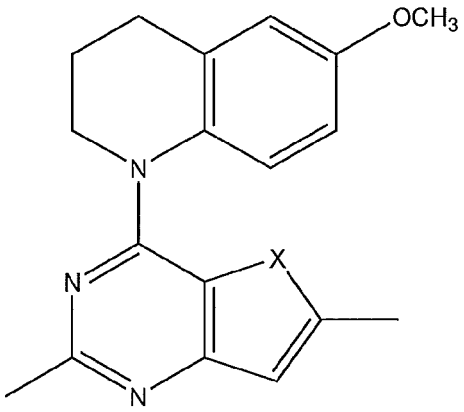
Figure 5

Series XII:



COMPOSITION NUMBER	R_1	R_2
94	H	H
95	CH_3	H
96	H	CH_3
97	CH_3	CH_3

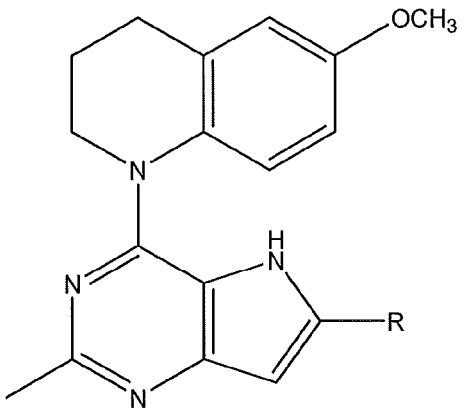
Series XIII:



COMPOSITION NUMBER	X
98	NCH_3
99	O
100	S

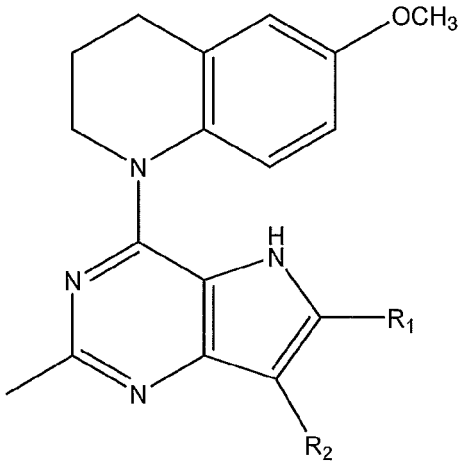
Figure 6

Series XIV:



COMPOSITION NUMBER	R
101	CH_2CH_3
102	$(CH_2)_2CH_3$
103	$CH(CH_3)_2$

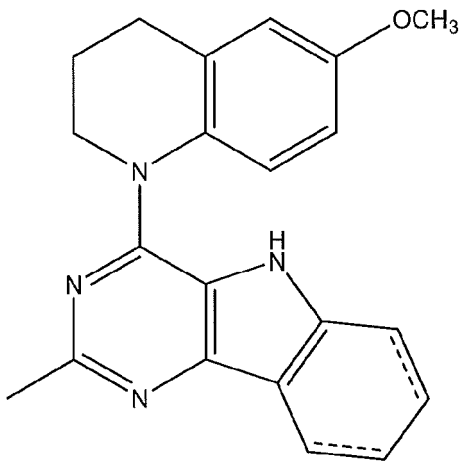
Series XVa:



COMPOSITION NUMBER	R_1	R_2
104 ("RP249")	CH_3	H
105	CH_3	CH_3

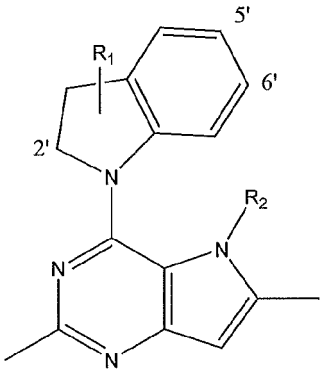
Figure 7

Series XVb:



Composition No. 106

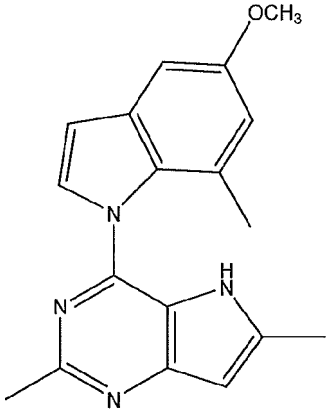
Series XVIa:



COMPOSITION NUMBER	R_1	R_2
107	2'-CH_3, 5'-OCH_3	H
108	6'-OCH_3, 5'-OCH_3	H
109	5'-OCH_2CH_3	H
110	5'-OCH_3	H
111	5'OCH_3	CH_3

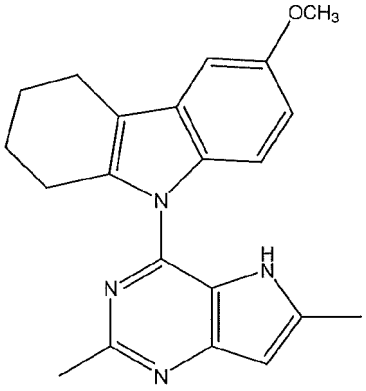
Figure 8

Series XVIb:



Composition No. 112

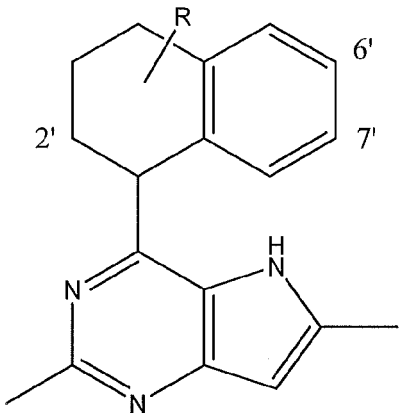
Series XVIc:



Composition No. 113

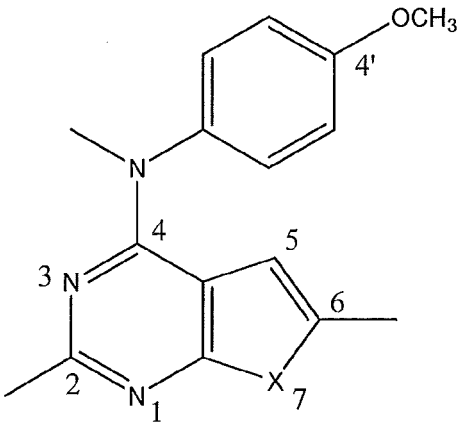
Figure 9

Series XVII:



COMPOSITION NUMBER	R
114	2'-CH_3, 6'-OCH_3
115	7'-OCH_3, 6'-OCH_3
116	7'-OH, 6'-OCH_3
117	2'-CH_3, 6'-OH
118	6'-OCF_3

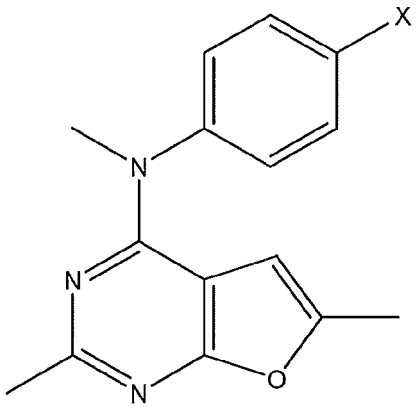
Series XVIII:



COMPOSITION NUMBER	X
121	S

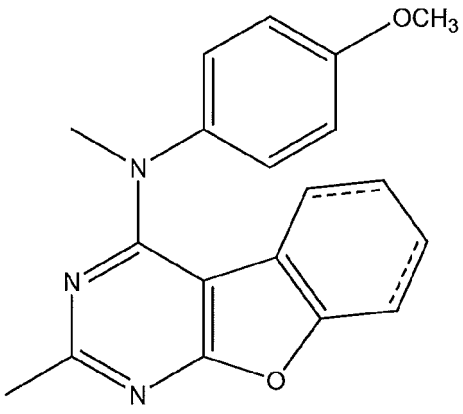
Figure 10

Series XX:



COMPOSITION NUMBER	X
125	SCH_3

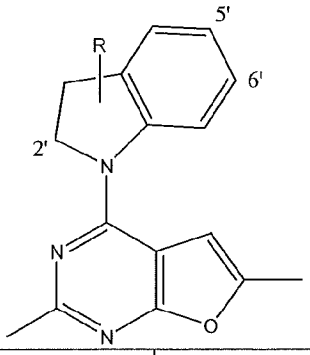
Series XXII:



Composition No. 138

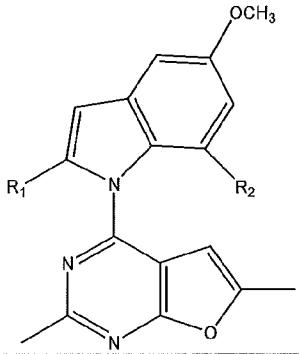
Figure 11

Series XXIIIa:



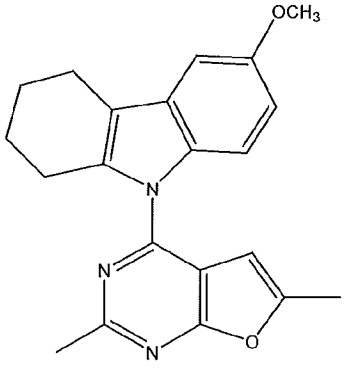
COMPOSITION NUMBER	R
139	2'-CH_3, 5'-OCH_3
140	6'-OCH_3, 5'-OCH_3
141	5'-OCH_2CH_3

Series XXIIIb:



COMPOSITION NUMBER	R_1	R_2
142	H	H
143	CH_3	H
144	H	CH_3

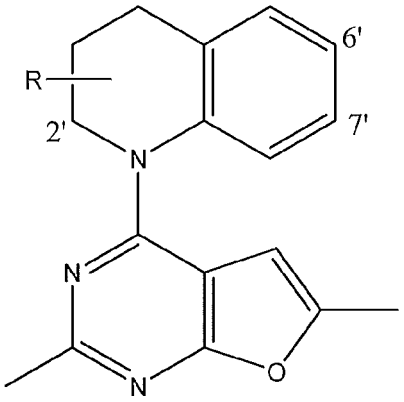
Series XXIIIc:



Composition No. 145

Figure 12

Series XXIV:



COMPOSITION NUMBER	R
146	2'-CH_3, 6'-OCH_3
147	7'-OCH_3, 6'-OCH_3
148	7'-OH, 6'-OCH_3
149	2'-CH_3, 6'-OH
150	6'-OCF_3

Figure 13

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 754268 / 1	Experiment ID : 1009NS24	Test Type : 08	Units : Molar
Composition No. 104		QNS :	MC :
COMI : RP/AG/159-249 (98554)	Stain Reagent : SRB Dual-Pass Related	SSPL : 0D4H	

			Log10 Concentration												
	Time		Mean Optical Densities					Percent Growth							
Panel/Cell Line	Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.218	1.011	0.975	0.314	0.296	0.293	0.244	95	12	10	9	3	3.61E-8	> 1.00E-4	> 1.00E-4
HL-60(TB)	0.654	2.252	2.237	0.536	0.510	0.506	0.522	99	-18	-22	-23	-20	2.62E-8	7.01E-8	> 1.00E-4
K-562	0.131	1.028	1.072	0.276	0.222	0.190	0.161	105	16	10	7	3	4.15E-8	> 1.00E-4	> 1.00E-4
MOLT-4	0.437	1.706	1.800	1.066	0.673	0.660	0.630	107	50	19	18	15	9.83E-8	> 1.00E-4	> 1.00E-4
RPMI-8226	0.500	2.211	2.131	0.906	1.063	0.982	0.695	95	24	33	28	11	4.29E-8	> 1.00E-4	> 1.00E-4
SR	0.352	1.673	1.773	0.426	0.341	0.316	0.369	93	5	-3	-11	1	3.09E-8		> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.362	1.404	1.399	0.543	0.416	0.437	0.341	100	17	5	7	-6	4.01E-8	3.58E-5	> 1.00E-4
EKVX	0.629	1.368	1.366	0.998	0.837	0.964	0.774	100	50	28	45	20	9.96E-8	> 1.00E-4	> 1.00E-4
HOP-62	0.485	1.170	1.134	0.667	0.637	0.598	0.470	95	27	22	16	-3	4.53E-8	6.87E-5	> 1.00E-4
HOP-92	0.808	1.525	1.463	1.308	1.324	1.121	1.048	91	70	72	44	33	5.95E-6	> 1.00E-4	> 1.00E-4
NCI-H226	0.586	1.257	1.180	0.886	0.694	0.671	0.622	89	46	19	15	8	8.23E-8	> 1.00E-4	> 1.00E-4
NCI-H23	0.535	1.043	1.070	0.987	0.835	0.736	0.641	103	41	27	18	10	7.10E-8	> 1.00E-4	> 1.00E-4
NCI-H322M	0.679	1.151	1.102	0.813	0.774	0.805	0.751	90	28	20	27	16	4.42E-8	> 1.00E-4	> 1.00E-4
NCI-H460	0.330	2.330	2.444	0.476	0.356	0.327	0.267	106	7	1	-1	-19	3.69E-8	3.84E-6	> 1.00E-4
Colon Cancer															
COLO 205	0.241	0.915	0.930	0.200	0.076	0.022	0.012	102	-17	-68	-91	-95	2.74E-8	7.20E-8	4.38E-7
HCC-2998	0.656	2.506	2.424	1.522	0.849	0.690	0.552	96	47	10	2	-16	8.60E-8	1.27E-5	> 1.00E-4
HCT-116	0.175	1.643	1.627	0.417	0.247	0.210	0.236	99	16	5	2	4	3.92E-8	> 1.00E-4	> 1.00E-4
HCT-15	0.199	1.160	1.138	0.396	0.314	0.242	0.230	99	21	12	4	3	4.21E-8	> 1.00E-4	> 1.00E-4
HT29	0.167	1.066	1.116	0.252	0.219	0.191	0.180	105	9	6	3	1	3.77E-8	> 1.00E-4	> 1.00E-4
KM12	0.218	0.926	0.924	0.286	0.161	0.121	0.067	100	10	-26	-45	-69	3.56E-8	1.84E-7	1.64E-5
SW-620	0.271	1.433	1.403	0.484	0.407	0.448	0.432	97	18	19	15	14	3.98E-8	> 1.00E-4	> 1.00E-4
CNS Cancer															
SF-268	0.469	1.350	1.261	0.827	0.668	0.654	0.474	92	39	21	19	-3	6.26E-8	7.21E-5	> 1.00E-4
SF-295	0.630	1.539	1.379	0.439	0.388	0.389	0.324	77	-47	-53	-53	-61	1.66E-8	4.19E-8	2.96E-7
SF-539	0.550	1.405	1.374	0.460	0.490	0.478	0.432	96	-18	-11	-13	-22	2.54E-8	6.93E-8	> 1.00E-4
SNB-19	0.440	1.393	1.366	0.730	0.752	0.677	0.671	97	30	32	24	24	5.03E-8	> 1.00E-4	> 1.00E-4
SNB-75	0.567	1.133	1.067	0.693	0.811	0.697	0.587	88	22	43	23	4	3.80E-8	> 1.00E-4	> 1.00E-4
U251	0.232	0.966	0.966	0.374	0.317	0.291	0.273	97	19	11	8	5	3.99E-8	> 1.00E-4	> 1.00E-4
Melanoma															
LOX IMVI	0.251	1.851	1.787	0.932	0.576	0.503	0.379	96	43	20	16	8	7.25E-8	> 1.00E-4	> 1.00E-4
MALME-3M	0.679	1.142	1.075	0.791	0.798	0.827	0.760	86	24	26	32	18	3.80E-8	> 1.00E-4	> 1.00E-4
M14	0.323	1.447	1.360	0.344	0.396	0.402	0.353	92	2	6	7	3	2.94E-8	> 1.00E-4	> 1.00E-4
MDA-MB-435	0.460	1.516	1.396	0.108	0.107	0.110	0.241	88	-78	-78	-77	-50	1.70E-8	3.41E-8	
SK-MEL-2	0.616	1.055	1.042	0.827	0.887	0.903	0.747	98	58	69	72	43	5.65E-8	> 1.00E-4	> 1.00E-4
SK-MEL-28	0.458	1.183	1.120	0.778	0.818	0.808	0.709	91	44	50	48	34	7.49E-8	> 1.00E-4	> 1.00E-4
SK-MEL-5	0.436	2.683	2.609	1.080	0.277	0.196	0.187	97	29	-36	-55	-57	4.88E-8	2.75E-7	6.30E-6
UACC-257	0.595	1.074	1.034	0.630	0.629	0.647	0.624	92	49	49	53	6		> 1.00E-4	> 1.00E-4
UACC-62	0.598	1.958	1.929	0.979	1.001	0.933	0.629	98	28	30	25	2	4.84E-8	> 1.00E-4	> 1.00E-4
Ovarian Cancer															
IGROV1	0.491	1.420	1.427	0.726	0.451	0.458	0.346	101	25	-8	-7	-30	4.70E-8	5.67E-7	> 1.00E-4
OVCAR-3	0.302	0.823	0.859	0.148	0.146	0.174	0.164	106	-51	-52	-43	-46	2.27E-8	4.73E-8	
OVCAR-4	0.460	1.108	1.083	0.820	0.779	0.680	0.568	96	56	50	35	18	9.66E-7	> 1.00E-4	> 1.00E-4
OVCAR-5	0.434	1.061	1.037	0.667	0.651	0.638	0.540	96	37	35	32	17	6.07E-8	> 1.00E-4	> 1.00E-4
OVCAR-8	0.597	1.924	1.902	0.903	0.688	0.677	0.590	98	23	7	6	-1	4.39E-8	6.87E-5	> 1.00E-4
NCI/ADR-RES	0.577	1.865	1.836	0.553	0.506	0.546	0.556	98	-4	-12	-5	-4	2.94E-8	9.09E-8	> 1.00E-4
SK-OV-3	0.562	1.386	1.373	0.620	0.677	0.535	0.509	98	7	2	-5	-9	3.39E-8	1.87E-6	> 1.00E-4
Renal Cancer															
786-0	0.562	2.098	2.030	1.165	0.905	0.819	0.699	96	39	22	17	9	6.31E-8	> 1.00E-4	> 1.00E-4
A498	1.159	1.783	1.673	1.141	1.028	1.007	0.933	82	-2	-11	-13	-20	2.43E-8	9.57E-8	> 1.00E-4
ACHN	0.332	1.287	1.278	0.724	0.611	0.527	0.416	99	41	29	20	9	7.01E-8	> 1.00E-4	> 1.00E-4
CAKI-1	0.736	2.065	2.004	1.041	0.953	0.977	0.833	95	23	16	18	7	4.23E-8	> 1.00E-4	> 1.00E-4
RXF 393	0.620	1.178	1.116	0.645	0.835	0.856	0.784	89	4	39	42	29	2.89E-8	> 1.00E-4	> 1.00E-4
SN12C	0.476	1.530	1.470	0.967	0.759	0.706	0.640	94	47	27	22	16	8.49E-8	> 1.00E-4	> 1.00E-4
TK-10	0.433	1.034	1.015	0.708	0.774	0.802	0.661	97	46	57	61	38		> 1.00E-4	> 1.00E-4
UO-31	0.590	1.118	1.053	0.782	0.734	0.607	0.409	88	36	27	3	-31	5.43E-8	1.24E-5	> 1.00E-4
Prostate Cancer															
PC-3	0.487	1.632	1.591	0.835	0.805	0.768	0.734	96	30	28	26	22	5.04E-8	> 1.00E-4	> 1.00E-4
DU-145	0.409	1.323	1.343	0.464	0.267	0.304	0.331	102	6	-35	-26	-19	3.49E-8	1.40E-7	> 1.00E-4
Breast Cancer															
MCF7	0.239	1.234	1.180	0.416	0.390	0.338	0.274	95	18	15	10	4	3.80E-8	> 1.00E-4	> 1.00E-4
MDA-MB-231/ATCC	0.681	1.324	1.391	1.004	0.687	0.723	0.676	110	50	1	6	-1	1.01E-7	7.74E-5	> 1.00E-4
HS 578T	0.533	0.933	0.929	0.617	0.538	0.515	0.479	99	-3	1	-3	-10	3.02E-8		> 1.00E-4
BT-549	0.732	1.652	1.602	1.271	1.038	1.080	0.967	95	59	33	38	25	2.18E-7	> 1.00E-4	> 1.00E-4
T-47D	0.543	1.191	1.192	0.826	0.823	0.858	0.674	100	44	43	49	20	7.74E-8	> 1.00E-4	> 1.00E-4
MDA-MB-468	0.470	1.220	1.170	0.357	0.303	0.282	0.433	93	-24	-36	-40	-8	2.34E-8	6.23E-8	> 1.00E-4

Figure 14

Compound	Inhibition of tubulin assembly	Inhibition of colchicine binding	
	IC_{50} (μM) ± SD	% Inhibition ± SD	
		5 μM inhibitor	1 μM inhibitor
CSA4	1.2 ± 0.01	98 ± 0.3	84 ± 3
RP/AG/159-249	1.2 ± 0.007	76 ± 0.5	

Figure 15

Composition	MW	EGFR Kinase Inhibitor μM	Flk-1 (VEGR2) Kinase Inhibition μM	Flt-1 Kinase Inhibition	PDGFR Kinase Inhibition μM	A431 Cytotoxicity μM
RP/AG/159-249 (Composition No. 104)	362.856	20.2sd3.8	30.6sd4.5	> 300	82.3sd.10.3	10.1sd1.8
RP/AG/159-248 (Composition No. 106)	386.277	29.3sd4.1	55.2sd8.3	> 300	110.2sd18.0	183.2sd19
Positive Controls						
PD153035		0.21sd0.002	124.7sd18.2		12.2sd1.9	
PD168393		0.13				
SU5416			12.9			
Doxirubicin (DOX)						1.35sd0.03
Cisplatin						16.2sd3.1
VEGF Kinase Inhibitor II				17.6sd3.1		
Sunitinib		172.1sd19.4	18.9sd2.7		83.1sd10.1	
Erlotinib		1.2sd0.2	124.7sd18.2		12.2sd1.9	
DMBI					3.75	

Figure 16

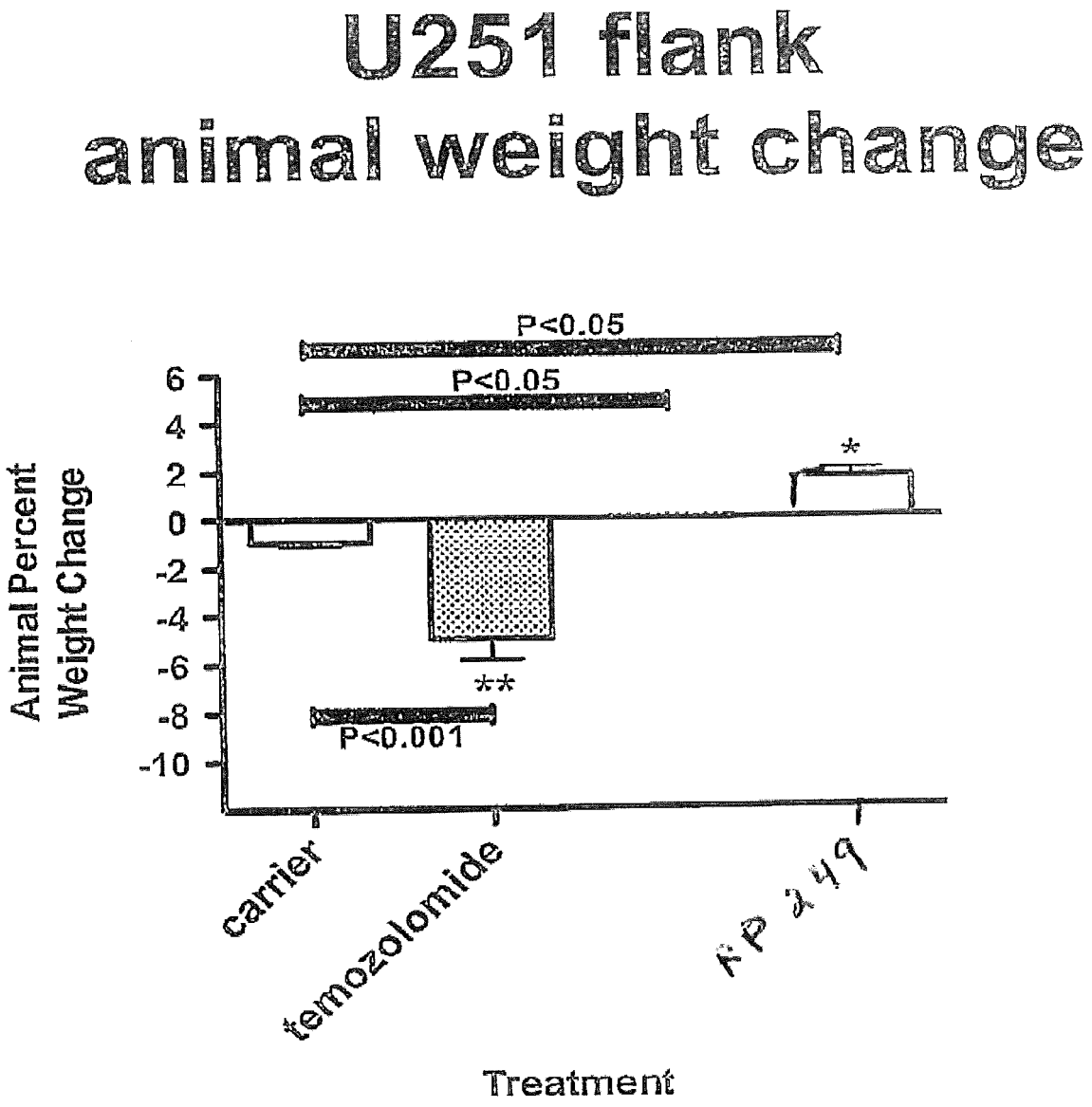
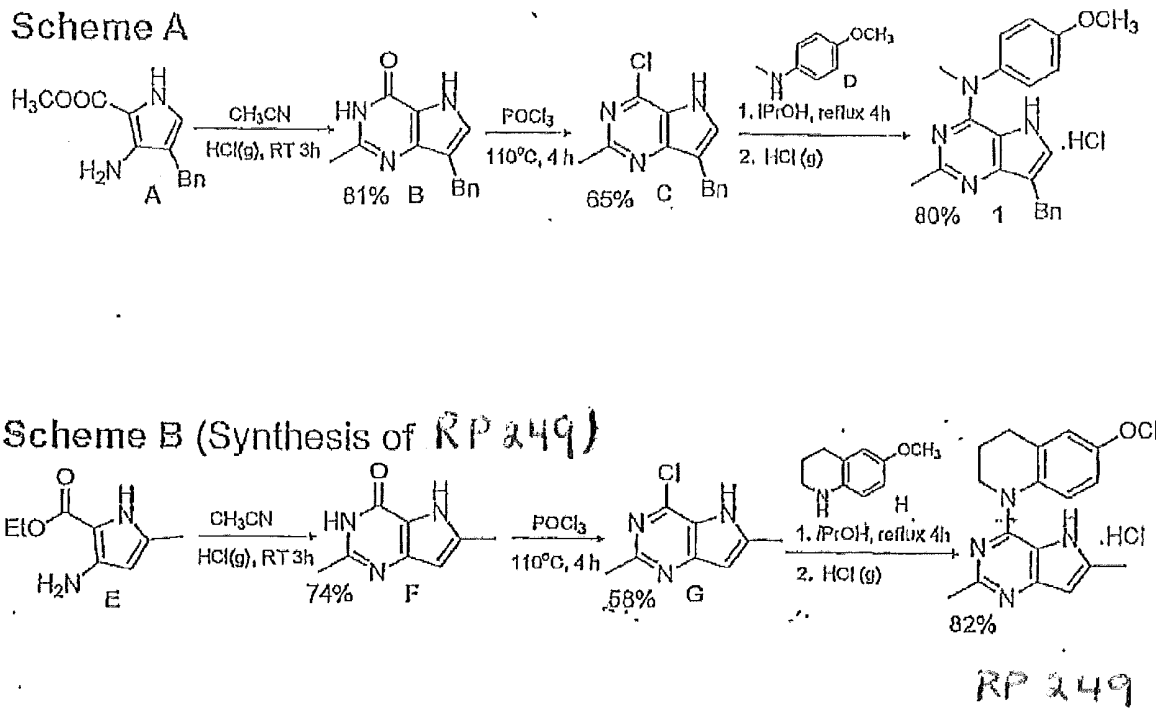

U251 flank
animal weight change
P<0.05
P<0.05
*
**
P<0.001
6
4
2
0
-2
-4
-6
-8
-10
Animal Percent
Weight Change
carrier
temozolomide
RP 249
Treatment

Figure 17


Scheme A
CH3CN
HCl(g), RT 3h
POCl3
110°C, 4 h
1. IPrOH, reflux 4h
2. HCl (g)
.HCl
A
81% B
65% C
80% 1
Bn
Scheme B (Synthesis of RP 249)
CH3CN
HCl(g), RT 3h
POCl3
110°C, 4 h
1. IPrOH, reflux 4h
2. HCl (g)
.HCl
E
74% F
58% G
82%
RP 249

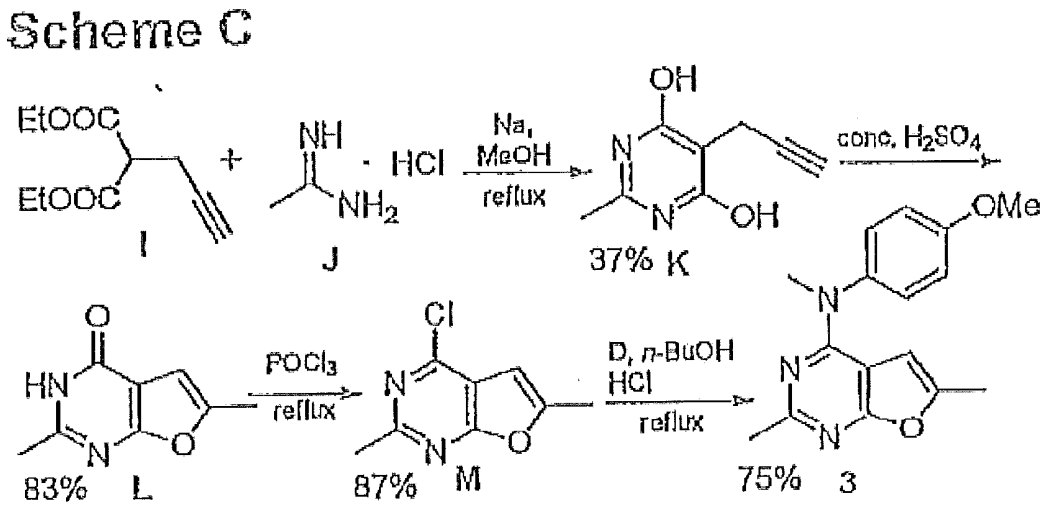

Scheme C
Na,
MeOH
reflux
conc. H2SO4
I
J
37% K
POCl3
reflux
D, n-BuOH
HCl
reflux
83% L
87% M
75% 3
OMe

Figure 18

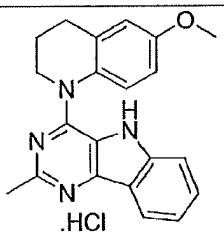
COMPOUND		kinase inhibition			A431cytotoxicity
		EGFR	VEGFR2	PDGFR	
		(μM)	(μM)	(μM)	(μM)
106. HCl		29.3±4.1	55.2±8.3	110.2±18.0	183.2±19
PD153035		0.21±0.002	124.7±18.2	12.2±1.9	
SU5416			12.9		
DOX					1.35±0.03
cisplatin					16.2±3.1
sunitinib		172.1±19.4	18.9±2.7	83.1±10.1	
erlotinib		1.2±0.2	124.7±18.2	12.2±1.9	
DMBI				3.75	

Figure 19

National Cancer Institute Developmental Therapeutics Program
In-Vitro Testing Results

NSC : D - 764121 / 1	Experiment ID : 1012RS67	Test Type : 08	Units : Molar
Report Date : January 24, 2012	Composition No. 106 HCl Salt	QNS :	MC :
COMI : RPIAGI159-248 (98287)	Stain Reagent : SRB Dual-Pass Related	SSPL : 004H	

			Log10 Concentration											
	Time		Mean Optical Densities					Percent Growth						
Panel/Cell Line	Zero	Ctrl	-8.0	-7.0	-6.0	-5.0	-4.0	-8.0	-7.0	-6.0	-5.0	-4.0	GI50	TGI	LC50
Leukemia															
CCRF-CEM	0.329	1.020	0.956	0.593	0.481	0.373	0.301	95	56	22	5	-9	4.19E-7	2.55E-5	> 1.00E-4
HL-60(TB)	0.736	2.900	2.919	2.997	1.312	0.895	0.628	101	105	11	5	-20	3.61E-7	1.69E-5	> 1.00E-4
K-562	0.239	1.578	1.734	1.721	0.464	0.364	0.175	107	103	16	9	-27	4.04E-7	1.69E-5	> 1.00E-4
MOLT-4	0.626	2.209	2.234	2.258	1.120	0.768	0.543	102	104	31	9	-13	5.83E-7	3.52E-5	> 1.00E-4
RPMI-8226	0.559	1.502	1.516	1.409	0.592	0.505	0.300	102	90	34	-11	-47	5.11E-7	5.63E-6	> 1.00E-4
SR	0.555	2.413	2.454	2.484	0.954	0.684	0.410	102	104	16	6	-27	4.08E-7	1.85E-5	> 1.00E-4
Non-Small Cell Lung Cancer															
A549/ATCC	0.280	1.366	1.405	1.432	0.953	0.461	0.309	102	104	52	15	3	1.13E-5	> 1.00E-4	> 1.00E-4
EKVX	0.539	1.259	1.312	1.317	1.020	0.897	0.561	102	89	61	43	-5	4.17E-5	7.42E-5	> 1.00E-4
HOP-62	0.479	1.527	1.531	1.529	0.979	0.831	0.509	100	100	48	34	3	9.04E-7	> 1.00E-4	> 1.00E-4
HOP-92	1.213	1.562	1.600	1.615	1.413	1.413	1.023	93	96	43	44	-16	6.75E-7	5.45E-5	> 1.00E-4
NCI-H226	0.599	1.258	1.311	1.247	1.172	0.921	0.591	102	93	62	46	-1	7.77E-6	9.37E-5	> 1.00E-4
NCI-H23	0.545	1.367	1.936	1.652	1.356	0.789	0.545	104	100	63	19	.	1.93E-6	> 1.00E-4	> 1.00E-4
NCI-H322M	0.732	1.205	1.227	1.290	1.251	0.968	0.645	104	116	112	53	-12	9.67E-6	6.41E-5	> 1.00E-4
NCI-H460	0.192	1.469	1.556	1.548	0.669	0.191	0.109	105	105	37	-1	-43	6.37E-7	9.24E-6	> 1.00E-4
NCI-H522	0.748	2.037	1.949	1.696	1.251	0.843	0.591	93	89	39	7	-21	6.03E-7	1.61E-5	> 1.00E-4
Colon Cancer															
COLO 205	0.350	0.350	0.945	0.697	0.591	0.165	0.075	119	101	53	-34	-70	1.03E-5	4.05E-6	2.79E-5
HCC-2998	0.579	2.121	2.235	2.248	1.316	0.632	0.428	107	108	60	3	-25	2.47E-5	1.30E-5	> 1.00E-4
HCT-116	0.226	2.063	2.059	1.684	0.733	0.439	0.216	100	91	28	12	-5	2.43E-7	5.18E-5	> 1.00E-4
HCT-15	0.270	1.705	1.641	1.625	0.843	0.570	0.404	96	94	43	21	9	6.82E-7	> 1.00E-4	> 1.00E-4
KM12	0.302	1.351	1.371	1.401	0.679	0.414	0.178	102	105	36	11	-41	6.25E-7	1.61E-5	> 1.00E-4
SW-620	0.175	1.033	1.031	1.012	0.340	0.361	0.149	99	97	19	22	-15	4.01E-7	3.91E-5	> 1.00E-4
CNS Cancer															
SF-268	0.306	1.233	1.214	1.224	0.756	0.523	0.324	98	99	50	35	2	9.82E-7	> 1.00E-4	> 1.00E-4
SF-295	0.583	1.877	1.834	1.822	0.749	0.503	0.218	101	96	13	-14	-63	3.88E-7	3.04E-6	5.52E-5
SF-539	0.774	2.278	2.249	2.136	1.165	0.825	0.763	98	91	25	3	-1	4.25E-7	5.07E-5	> 1.00E-4
SNB-19	0.486	1.644	1.562	1.604	1.099	0.914	0.725	93	97	53	37	21	1.51E-5	> 1.00E-4	> 1.00E-4
SNB-75	0.686	1.237	1.147	1.051	0.737	0.684	0.517	84	66	9	-1	-25	2.01E-7	6.55E-6	> 1.00E-4
U251	0.241	1.037	1.047	1.051	0.506	0.393	0.146	101	102	33	19	-40	5.69E-7	2.11E-5	> 1.00E-4
Melanoma															
LOX IMVI	0.336	2.216	2.192	2.177	1.164	1.043	0.415	98	96	44	35	4	7.75E-7	> 1.00E-4	> 1.00E-4
MALME-3M	0.505	0.800	0.796	0.794	0.626	0.692	0.303	99	96	41	63	-35	.	4.33E-5	> 1.00E-4
M14	0.364	1.443	1.476	1.364	0.740	0.445	0.361	103	93	35	9	2	5.48E-7	> 1.00E-4	> 1.00E-4
MDA-MB-435	0.464	1.705	1.636	1.606	0.414	0.360	0.336	98	92	-11	-19	-28	2.58E-7	7.63E-7	> 1.00E-4
SK-MEL-28	0.394	1.018	0.999	0.970	0.643	0.615	0.363	95	92	40	35	-3	6.41E-7	6.45E-5	> 1.00E-4
SK-MEL-5	0.602	2.415	2.456	2.440	0.952	0.588	0.029	102	101	23	-2	-95	4.27E-7	7.65E-6	3.26E-5
UACC-257	0.610	1.305	1.293	1.379	0.926	0.963	0.392	97	96	48	51	-36	.	3.66E-5	> 1.00E-4
UACC-62	0.796	1.961	2.027	2.069	1.283	1.114	0.463	107	110	42	27	-40	7.62E-7	2.95E-5	> 1.00E-4
Ovarian Cancer															
IGROV1	0.555	1.310	1.439	1.428	0.908	0.686	0.519	117	116	46	15	-6	8.76E-7	4.60E-5	> 1.00E-4
OVCAR-3	0.370	1.233	1.220	1.275	0.469	0.283	0.127	100	106	14	-24	-66	4.06E-7	3.36E-6	4.25E-5
OVCAR-4	0.612	1.525	1.518	1.479	1.254	0.795	0.602	99	95	72	30	-2	2.63E-6	8.41E-5	> 1.00E-4
OVCAR-5	0.635	1.572	1.522	1.532	1.384	1.019	0.855	95	96	80	41	24	5.65E-6	> 1.00E-4	> 1.00E-4
OVCAR-8	0.359	1.423	1.414	1.452	1.076	0.661	0.326	99	106	68	30	-9	2.95E-6	6.84E-5	> 1.00E-4
NCI/ADR-RES	0.416	1.603	1.648	1.631	0.975	0.566	0.433	104	100	39	13	1	6.52E-7	> 1.00E-4	> 1.00E-4
SK-OV-3	0.551	1.214	1.220	1.247	0.956	0.655	0.539	101	106	46	16	-2	8.57E-7	7.55E-5	> 1.00E-4
Renal Cancer															
786-0	0.667	2.395	2.440	2.416	1.349	1.325	0.761	103	101	68	39	7	4.05E-6	> 1.00E-4	> 1.00E-4
A498	0.993	1.384	1.341	1.360	0.979	0.803	0.615	89	94	-1	-19	-38	2.88E-7	9.66E-7	> 1.00E-4
ACHN	0.371	1.725	1.722	1.618	1.087	0.823	0.473	100	92	53	34	8	1.42E-6	> 1.00E-4	> 1.00E-4
CAKI-1	0.531	1.532	1.531	1.526	1.155	0.785	0.449	91	92	45	23	-16	3.81E-7	3.97E-5	> 1.00E-4
RXF 393	0.613	0.943	0.957	0.978	0.751	0.538	0.461	104	110	42	-12	-25	7.63E-7	5.92E-6	> 1.00E-4
SN12C	0.444	1.647	1.675	1.721	1.263	0.874	0.569	102	106	78	36	12	4.45E-5	> 1.00E-4	> 1.00E-4
TK-10	0.476	1.141	1.136	1.166	0.899	0.811	0.537	108	104	73	50	9	1.02E-5	> 1.00E-4	> 1.00E-4
UO-31	0.707	1.365	1.252	1.177	1.039	0.869	0.463	93	71	53	29	-32	1.05E-5	2.92E-5	> 1.00E-4
Prostate Cancer															
PC-3	0.366	1.097	1.104	1.088	0.816	0.359	0.277	101	99	65	11	1	1.97E-5	> 1.00E-4	> 1.00E-4
Breast Cancer															
MCF7	0.319	1.110	1.072	1.026	0.413	0.393	0.231	96	91	22	23	.	3.83E-7	> 1.00E-4	> 1.00E-4
MDA-MB-231/ATCC	0.643	1.268	1.245	1.334	1.078	0.719	0.405	94	106	72	24	-25	2.83E-5	3.04E-5	> 1.00E-4
HS 578T	0.666	1.467	1.474	1.481	1.011	0.923	0.763	101	99	24	13	-13	4.48E-7	3.71E-5	> 1.00E-4
BT-549	0.751	1.768	1.661	1.692	1.266	1.121	0.741	89	92	53	35	-1	1.48E-6	9.22E-5	> 1.00E-4
T-47D	0.481	1.132	1.118	1.133	0.960	0.747	0.424	98	100	74	41	-12	5.25E-6	6.55E-5	> 1.00E-4
MDA-MB-468	0.653	1.047	1.024	1.051	0.697	0.527	0.432	96	103	29	-5	-32	5.23E-7	7.26E-6	> 1.00E-4

Figure 20

Developmental Therapeutics Program	NSC: D-754121 / 1	Conc: 1.00E-5 Molar	Composition No. 106 HCl
One Dose Mean Graph	Experiment ID: 1008OS11		Report Date: Jan 24, 2012

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	16.59
K-562	10.34
MOLT-4	14.99
RPMI-8226	35.98
SR	9.45
Non-Small Cell Lung Cancer	
A549/ATCC	21.92
EKVX	34.64
HOP-62	37.26
HOP-92	45.62
NCI-H226	35.64
NCI-H23	21.17
NCI-H322M	18.36
NCI-H460	-7.24
NCI-H522	4.05
Colon Cancer	
COLO 205	-34.35
HCC-2998	2.80
HCT-116	12.88
HCT-15	19.46
HT29	3.18
KM12	9.04
SW-620	24.44
CNS Cancer	
SF-268	28.06
SF-295	-16.57
SF-539	-23.65
SNB-19	32.53
SNB-75	-5.44
U251	18.25
Melanoma	
LOX IMVI	35.86
M14	2.96
MDA-MB-435	-61.20
SK-MEL-2	20.21
SK-MEL-28	32.32
SK-MEL-5	21.37
UACC-257	61.18
UACC-62	38.40
Ovarian Cancer	
IGROV1	10.64
OVCAR-3	-62.86
OVCAR-4	48.61
OVCAR-5	42.56
OVCAR-8	25.32
NCI/ADR-RES	-18.45
SK-OV-3	-5.51
Renal Cancer	
786-0	25.07
A498	-20.87
ACHN	40.99
CAKI-1	17.86
RXF 393	-4.46
SN12C	40.38
TK-10	54.31
UO-31	-1.31
Prostate Cancer	
PC-3	28.41
DU-145	3.11
Breast Cancer	
MCF7	23.35
MDA-MB-231/ATCC	33.98
HS 578T	-18.10
BT-549	21.03
T-47D	42.46
MDA-MB-468	-12.58
Mean	14.39
Delta	77.25
Range	124.04

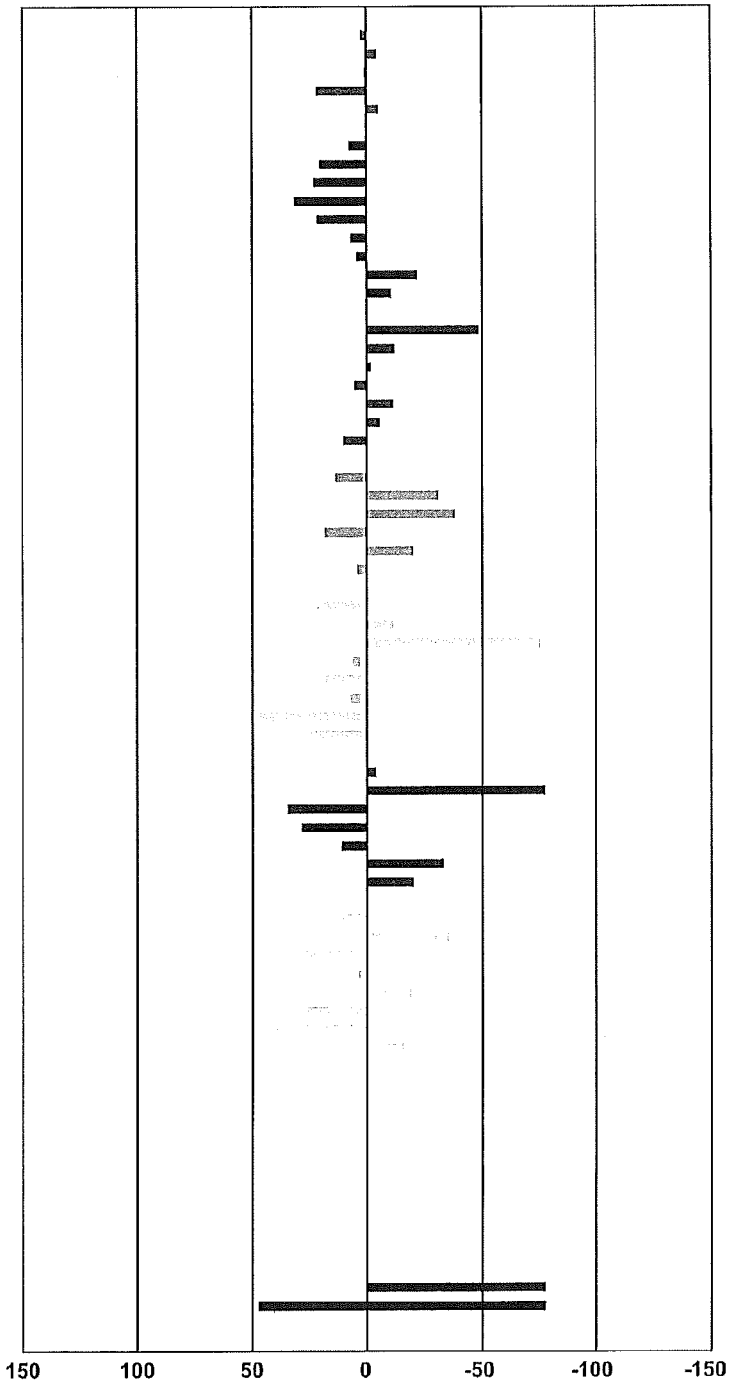


Figure 21

National Cancer Institute Developmental Therapeutics Program Dose Response Curves	NSC: D - 754121 / 1	SSPL: 0D4H	EXP. ID: 1012RS67
	Report Date: January 24, 2012	Composition No. 106 HCl Salt	

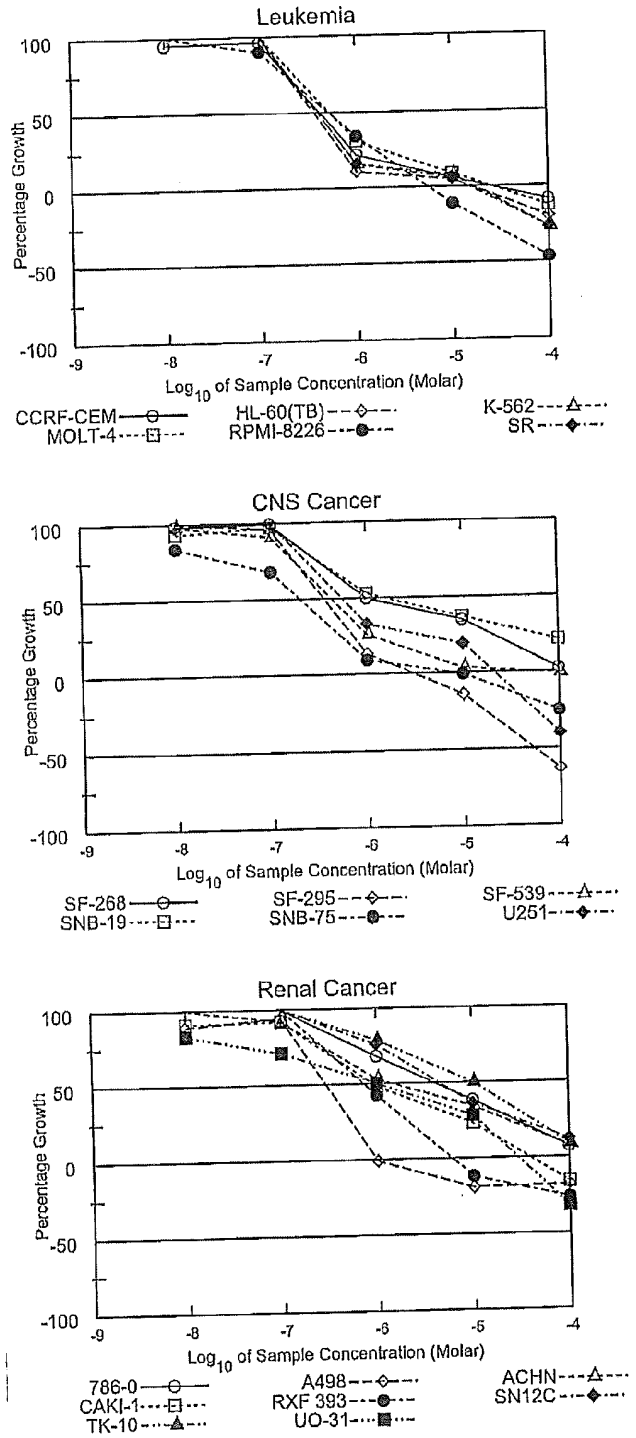


Figure 22a

National Cancer Institute Developmental Therapeutics Program Dose Response Curves	NSC: D - 754121 / 1	SSPL: 0D4H	EXP. ID: 1012RS67
	Report Date: January 24, 2012	Composition No. 106 HCl Salt	

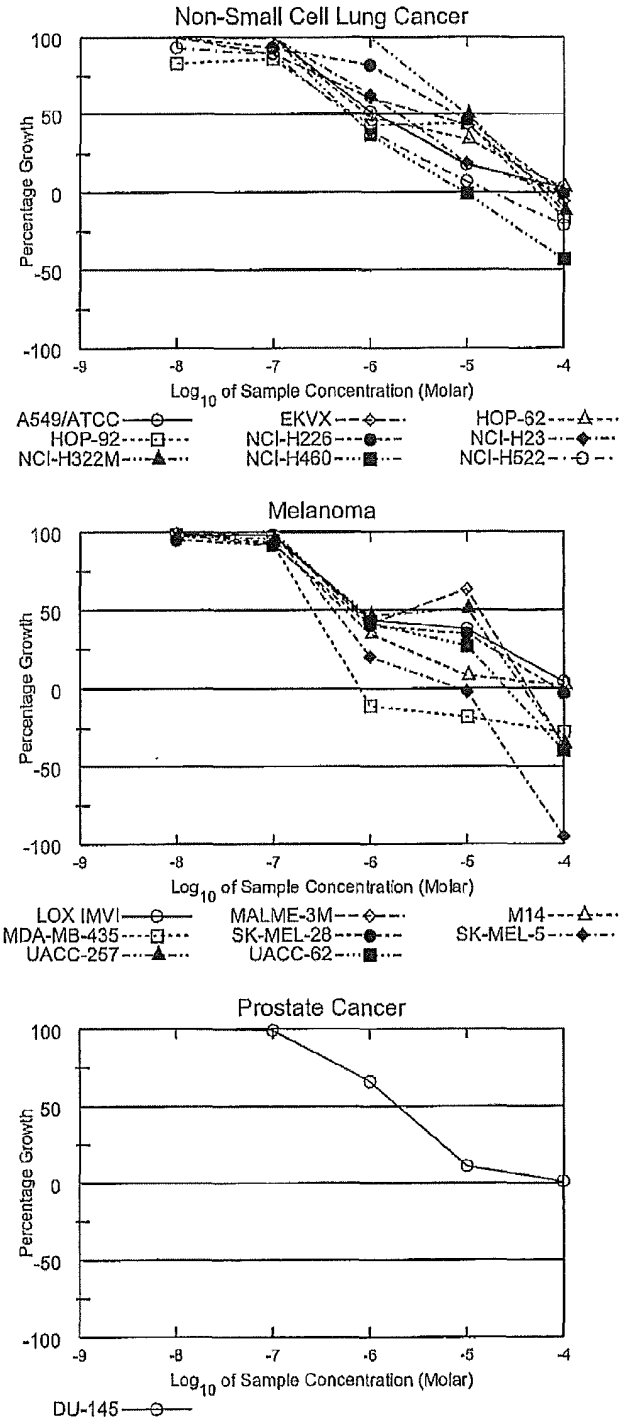


Figure 22b

National Cancer Institute Developmental Therapeutics Program Dose Response Curves	NSC: D - 754121 / 1	SSPL: 0D4H	EXP. ID: 1012RS67
	Report Date: January 24, 2012	Composition No. 106 HCl Salt	

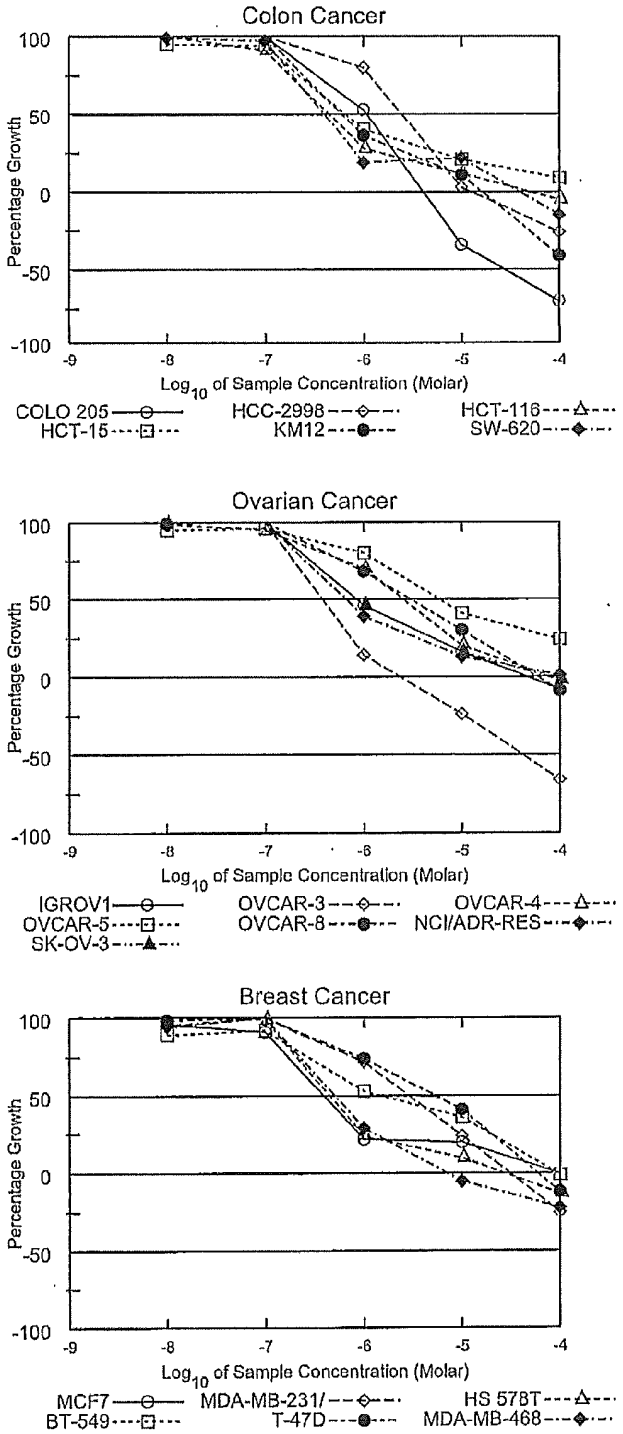


Figure 22c

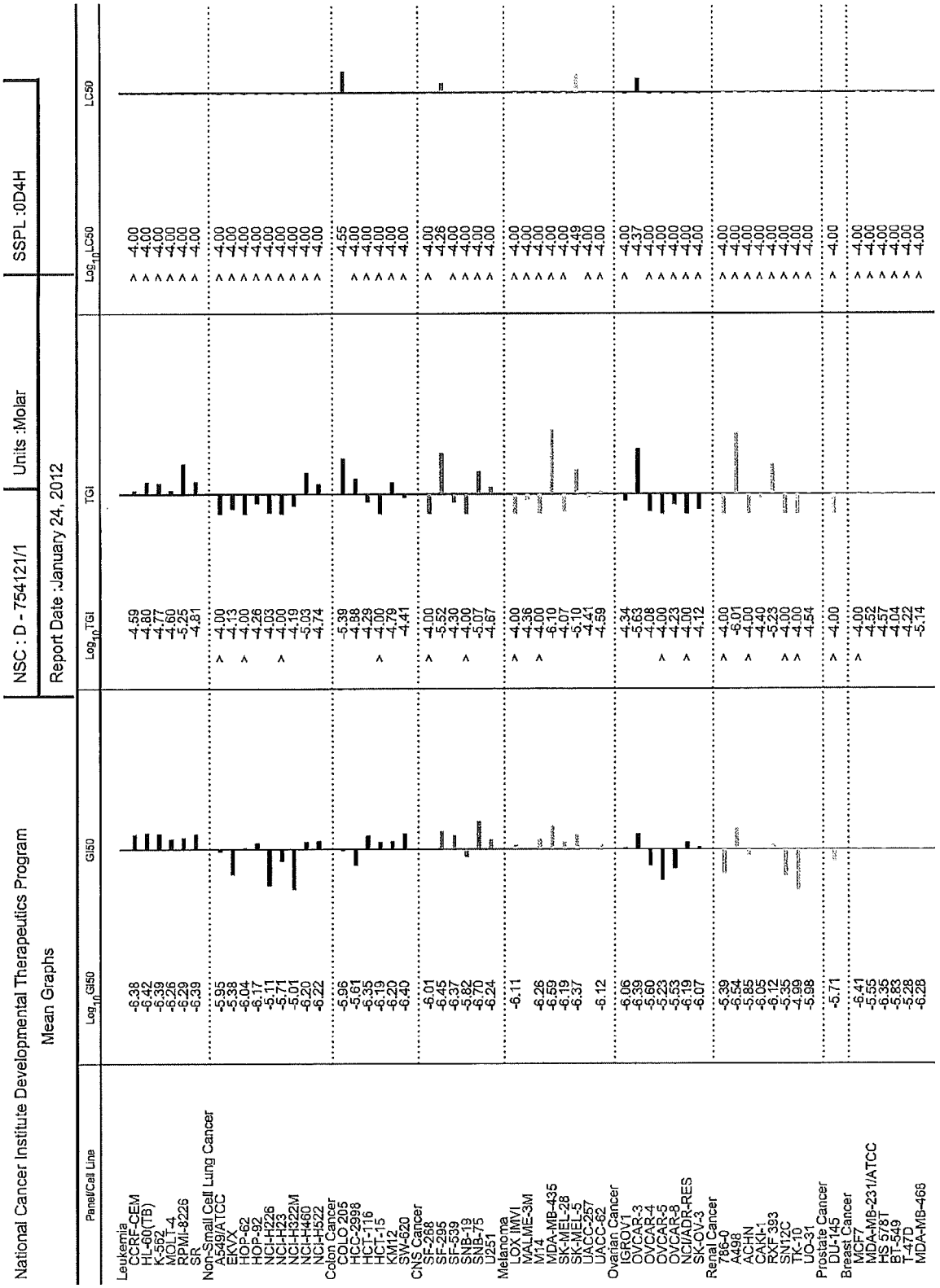
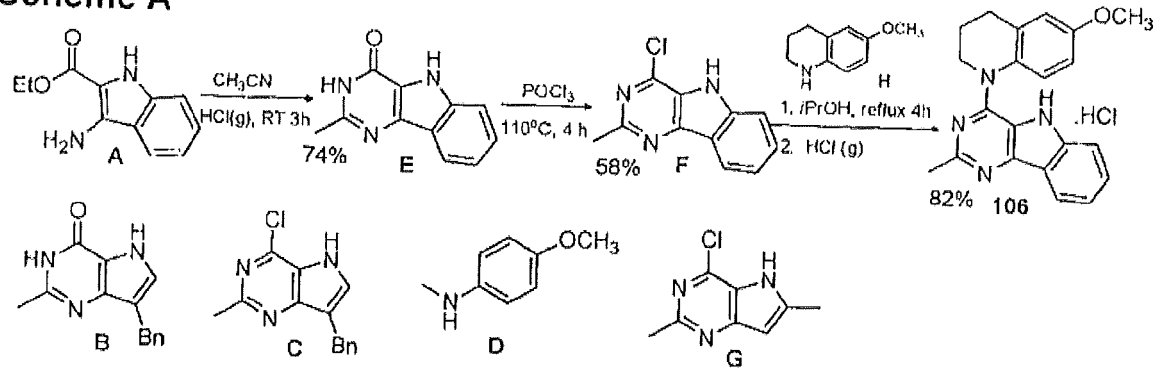

National Cancer Institute Developmental Therapeutics Program
Mean Graphs
NSC : D - 754121/1
Units :Molar
SSPL :0D4H
Report Date :January 24, 2012
Panel/Cell Line
Log10 GI50
GI50
Log10 TGI
TGI
Log10 LC50
LC50
Leukemia
CCRF-CEM -6.38 -4.59 -4.00
HL-60(TB) -6.42 -4.80 -4.00
K-562 -6.39 -4.77 -4.00
MOLT-4 -6.26 -4.60 -4.00
RPMI-8226 -6.29 -5.25 -4.00
SR -6.39 -4.81 -4.00
Non-Small Cell Lung Cancer
A549/ATCC -5.95 > -4.00 > -4.00
EKVX -5.38 -4.13 -4.00
HOP-62 -6.04 > -4.00 > -4.00
HOP-92 -6.17 -4.26 -4.00
NCI-H226 -5.11 -4.03 -4.00
NCI-H23 -5.71 > -4.00 > -4.00
NCI-H322M -5.01 -4.19 -4.00
NCI-H460 -6.20 -5.03 -4.00
NCI-H522 -6.22 -4.74 -4.00
Colon Cancer
COLO 205 -5.96 -5.39 -4.55
HCC-2998 -5.61 -4.88 -4.00
HCT-116 -6.35 -4.29 -4.00
HCT-15 -6.19 > -4.00 > -4.00
KM12 -6.20 -4.79 -4.00
SW-620 -6.40 -4.41 -4.00
CNS Cancer
SF-268 -6.01 > -4.00 > -4.00
SF-295 -6.45 -5.52 -4.26
SF-539 -6.37 -4.30 -4.00
SNB-19 -5.82 > -4.00 > -4.00
SNB-75 -6.70 -5.07 -4.00
U251 -6.24 -4.67 -4.00
Melanoma
LOX IMVI -6.11 > -4.00 > -4.00
MALME-3M -4.36 -4.00
M14 -6.26 > -4.00 > -4.00
MDA-MB-435 -6.59 -6.10 -4.00
SK-MEL-28 -6.19 -4.07 -4.00
SK-MEL-5 -6.37 -5.10 -4.49
UACC-257 -4.41 -4.00
UACC-62 -6.12 -4.59 -4.00
Ovarian Cancer
IGROV1 -6.06 > -4.34 > -4.00
OVCAR-3 -6.39 -5.63 -4.37
OVCAR-4 -5.60 -4.08 -4.00
OVCAR-5 -5.23 > -4.00 > -4.00
OVCAR-8 -5.53 > -4.23 > -4.00
NCI/ADR-RES -6.19 -4.00 -4.00
SK-OV-3 -6.07 -4.12 -4.00
Renal Cancer
786-0 -5.39 > -4.00 > -4.00
A498 -5.54 -6.01 -4.00
ACHN -5.65 > -4.00 > -4.00
CAKI-1 -6.05 -4.40 -4.00
RXF 393 -6.12 -5.23 -4.00
SN12C -5.35 > -4.00 > -4.00
TK-10 -4.99 -4.00 -4.00
UO-31 -5.98 -4.54 -4.00
Prostate Cancer
DU-145 -5.71 > -4.00 > -4.00
Breast Cancer
MCF7 -6.41 > -4.00 > -4.00
MDA-MB-231/ATCC -5.55 -4.52 -4.00
HS 578T -6.35 -4.57 -4.00
BT-549 -5.83 -4.04 -4.00
T-47D -5.28 -4.22 -4.00
MDA-MB-468 -6.28 -5.14 -4.00

Figure 23

Scheme A



Scheme C

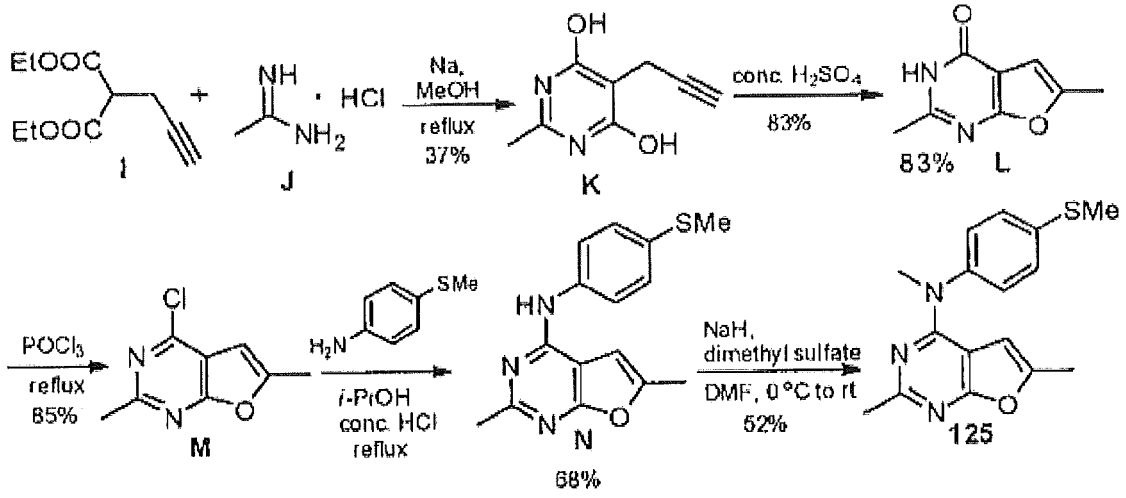
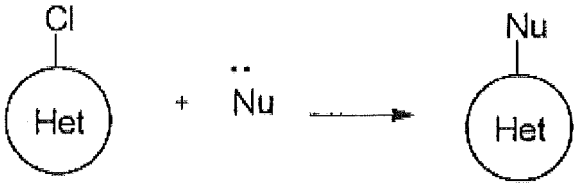
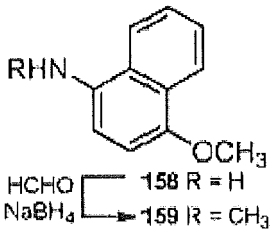


Figure 24

Scheme 1: General method for 4-Chloro displacement



Scheme 2
(Series I)



Scheme 3 (Series I)

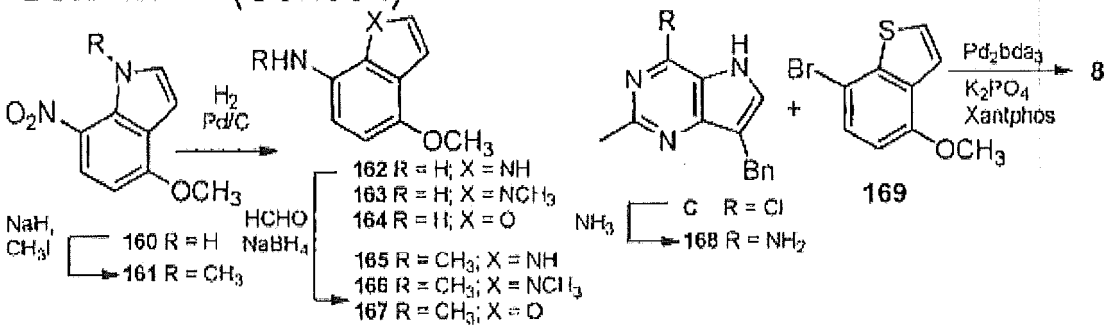
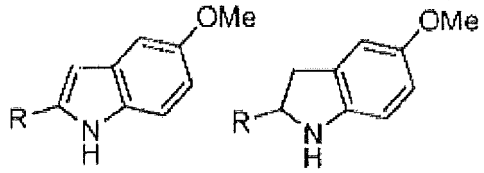


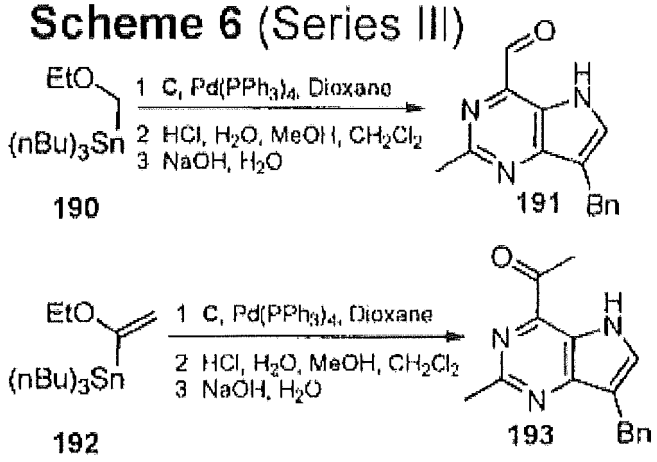
Figure 25

Scheme 5 (Series II, III)



183 R = H
184 R = CH_3
185 R = H
(±)-**186** R = CH_3

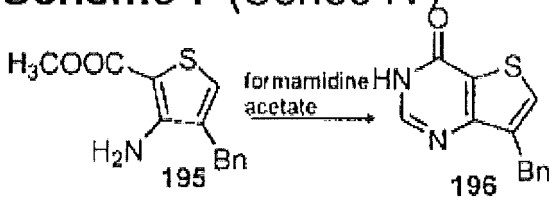
Scheme 6 (Series III)



190 **191**

192 **193**

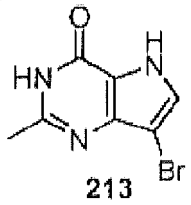
Scheme 7 (Series IV)



195 **196**

Figure 26

Scheme 12
(Series VII)



213

Scheme 13 (Series VIII)

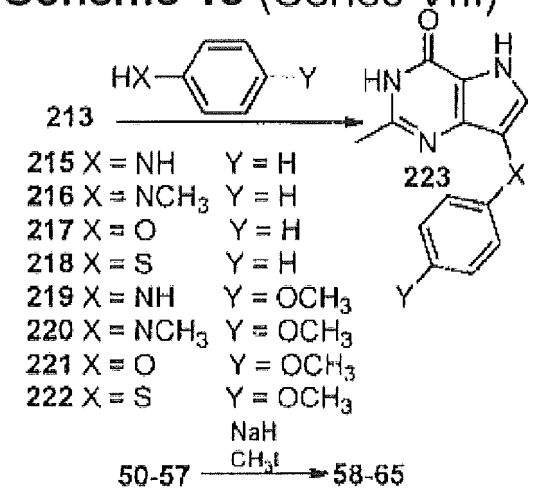
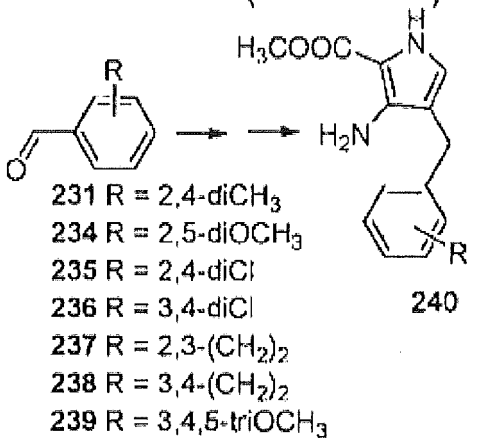


Figure 27

Scheme 15 (Series X)

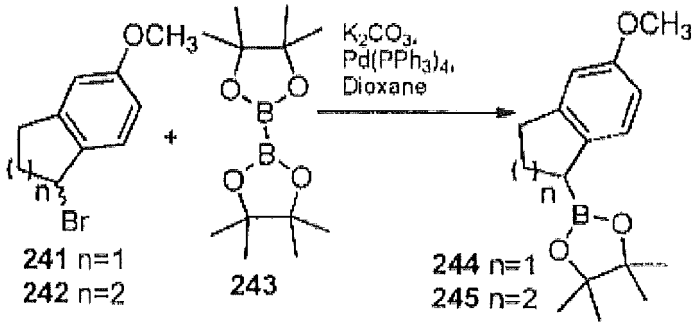


231 R = 2,4-diCH$_3$
234 R = 2,5-diOCH$_3$
235 R = 2,4-diCl
236 R = 3,4-diCl
237 R = 2,3-(CH$_2$)$_2$
238 R = 3,4-(CH$_2$)$_2$
239 R = 3,4,5-triOCH$_3$

240

74, 77-82 —(NaH, CH$_3$I)→ 83,86-91

Scheme 16 (Series XI)

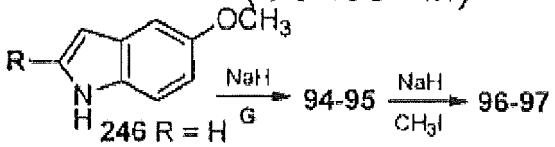


241 n=1
242 n=2

243

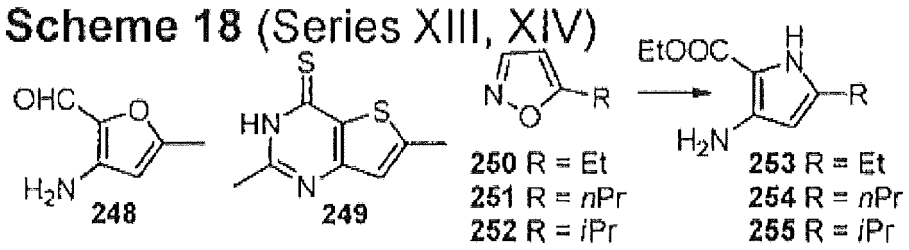
244 n=1
245 n=2

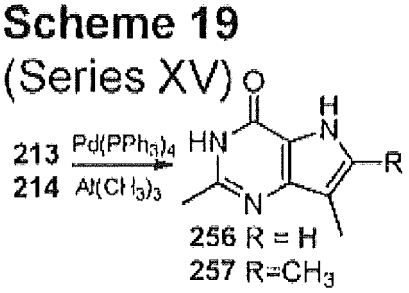
Scheme 17 (Series XII)



246 R = H
247 R = CH$_3$

Figure 28


Scheme 18 (Series XIII, XIV)
OHC
O
H2N
248
S
HN
S
N
249
N
O
R
250 R = Et
251 R = nPr
252 R = iPr
EtOOC
H
N
R
H2N
253 R = Et
254 R = nPr
255 R = iPr


Scheme 19
(Series XV)
O
213
214
Pd(PPh3)4
Al(CH3)3
HN
H
N
R
N
256 R = H
257 R=CH3

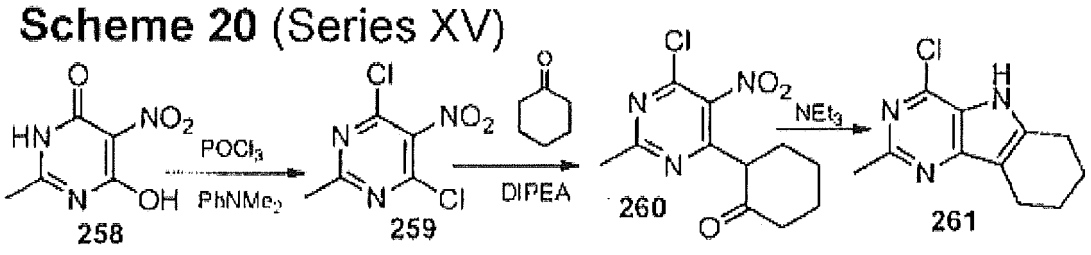
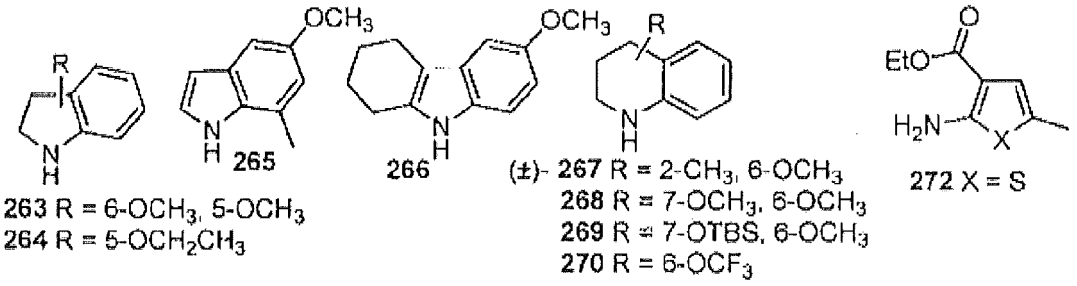

Scheme 20 (Series XV)
O
HN
NO2
N
OH
258
POCl3
PhNMe2
Cl
NO2
N
N
Cl
259
O
DIPEA
Cl
NO2
N
N
260
O
NEt3
Cl
H
N
N
261

Figure 29

Scheme 21 (Series XVI, XVII, XVIII, XXIII, XXIV)



Scheme 22 (Series XIX)

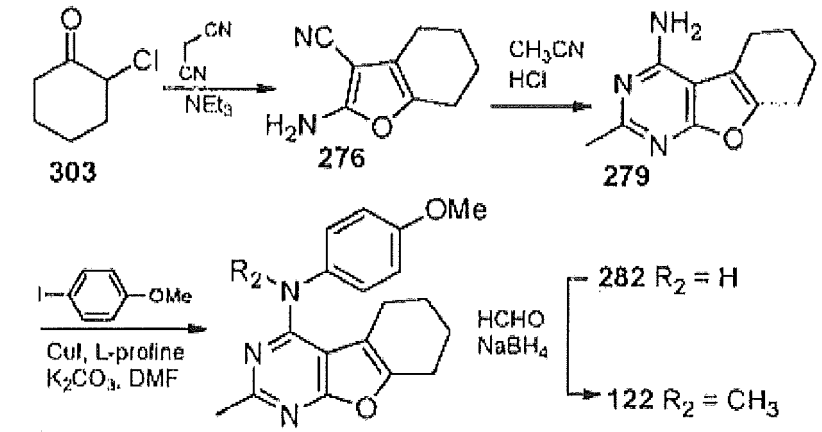


Figure 30

REFERENCES CITED IN THE DESCRIPTION

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