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(54) Title: METHODS AND COMPOSITIONS FOR THE TREATMENT OF CANCER, TUMORS, AND TUMOR-RELATED DISORDERS

(57) Abstract: Described herein are compositions and methods for using these compositions in the treatment of cancer, tumors, and tumor-related disorders in a subject.

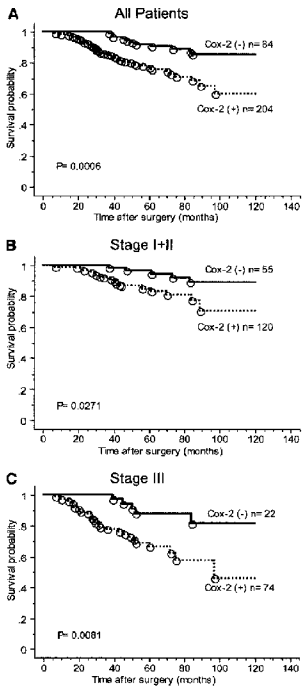

Fig. 1 Expression Levels Correlate with Survival in Colorectal Cancer. The overall 10-year survival curves of patients with Cox-2 negative and Cox-2 positive are shown for the entire cohort, $P = 0.0006$ (*A*), as well as for patients with stage I/II, $P = 0.0271$ (*B*), or stage III, $P = 0.0081$ (*C*) disease.

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METHODS AND COMPOSITIONS FOR THE TREATMENT OF CANCER, TUMORS, AND TUMOR-RELATED DISORDERS

CROSS-REFERENCE

[0001] This application claims the benefit of U. S. Provisional Application No. 60/949,483, filed July 12, 2007; U.S. Provisional Application No. 60/990,900, filed November 28, 2007; and U.S. Provisional Application No. 61/044,425, filed April 11, 2008, the contents of which are incorporated herein by reference in their entirety.

FIELD

[0002] The present invention relates to combination compositions and the use of such combinations for the treatment of cancer, tumors, and tumor-related disorders.

BACKGROUND

[0003] Cancer, tumors, tumor-related disorders, and neoplastic disease states are serious and often times life-threatening conditions. These diseases and disorders, which are characterized by rapidly-proliferating cell growth, continue to be the subject of research efforts directed toward the identification of therapeutic agents which are effective in the treatment thereof. Such agents prolong the survival of the patient, inhibit the rapidly-proliferating cell growth associated with the neoplasm, or effect a regression of the neoplasm.

[0004] Generally, surgery and radiation therapy are the first modalities considered for the treatment of cancer that is considered locally confined, and offer the best prognosis. Chemotherapy treatment of certain cancers typically results in disappointing survival rates but still offer a survival benefit. For example, in patients with non-small cell lung cancer, platinum-based chemotherapy regimens, such as the use of either cisplatin or carboplatin plus one of either paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, vinblastine, or bevacizumab is employed. If patients cannot tolerate this therapy, a single agent, such as *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine, commonly known as erlotinib (Tarceva®), can be used. Erlotinib targets the epidermal growth factor receptor tyrosine kinase which is highly expressed and occasionally mutated in various forms of cancer. If patients fail to respond to an erlotinib treatment, additional conventional treatment offers limited benefit.

[0005] Despite erlotinib's approval for the treatment of stage IIIB and IV non-small cell lung cancer, as with most therapeutic agents, side-effects result from its use. For example, common side effects, occurring in greater than 30% of patients taking erlotinib, include, rash, diarrhea, poor appetite, fatigue, shortness of breath, cough, nausea and vomiting. Additionally, less common side effects include infection, mouth sores, itching, dry skin, eye irritation, pulmonary fibrosis, and abdominal pain. Of greater concern, is the growing view that, while utilization of erlotinib for the treatment of tumors may initially shrink the size of the tumor, the tumor may eventually enlarge in size, indicating, among other things, the development of resistance. Erlotinib may be representative of the types of

therapeutic agents being used for cancer treatment; in that its use has an effect on cancer, but because of other factors, which are not entirely known, the tumor develops resistance and progresses.

[0006] What is needed, therefore, are compositions and/or methods of treatment for cancer which take advantage of the synergy found in a therapeutic combination that could increase the effectiveness of the agents and reduce and/or eliminate the side effects typically associated with conventional treatments.

SUMMARY OF THE INVENTION

[0007] The present invention is based at least in part on a synergistic effect obtained in treating conditions such as cancer by a combination comprising a COX-2 selective inhibitor and an EGFR inhibitor. Some of the possible favorable outcomes for synergism include 1) increasing the efficacy of the therapeutic effect, 2) decreasing the dosage but increasing or maintaining the same efficacy to avoid toxicity, 3) minimizing or slowing down the development of drug resistance, and 4) providing selective synergism against target (or efficacy synergism) versus host (or toxicity antagonism).

[0008] While some embodiments of the invention are illustrated through a fixed dose combination comprising a COX-2 inhibitor and an EGFR inhibitor, the embodiments of the invention cover compositions and methods wherein the COX-2 inhibitor and the EGFR inhibitor are provided in separate dosage forms.

[0009] The present invention is based, at least in part on the discovery that combinations of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor provide numerous advantages in the treatment of cancer, tumors, and tumor-related disorders. These combinations may allow for lesser amounts of each particular agent to be delivered and may produce the same or better effect as a greater amount of each particular agent. For example, a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor (provided in one fixed dose or in two separate dosage forms) will increase therapeutic efficacy, reduce side effects, reduce resistance, and when a fixed dose is used reduce the pill burden, enhance patient compliance, and thus, support a more favorable treatment setting and outcome. Such combinations can further increase the benefit of each particular agent which otherwise would be only marginally effective. As such, this synergistic or enhancement effect can be employed in the treatment of cancer, tumors, and tumor-related disorders, and may overcome resistance of tumors to drugs at conventional doses.

Methods of Use

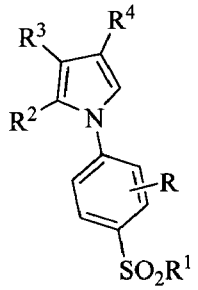
[0010] The present invention provides a method for treating cancer, tumors, and tumor-related disorders. For example, the method comprises administering to a subject in a combination therapy an amount of a COX-2 selective inhibitor and an EGFR inhibitor, wherein the COX-2 selective inhibitor and the EGFR inhibitor combine to give a therapy suitable for treating a cancer, tumor, and tumor-related disorders.

[0011] The invention further provides combinations of COX-2 selective inhibitors and EGFR inhibitors for antineoplastic, anti-tumor, anti-cancer combination therapy. In one embodiment the

invention provides compositions comprising a combination of a COX-2 selective inhibitor and an EGFR inhibitor. The invention also provides for the use of combinations of 1,2-diphenylpyrrole derivatives and an EGFR inhibitor and/or their pharmaceutically acceptable salt, solvate, or prodrug, as antineoplastic, anti-tumor, or anti-cancer combination therapy.

[0012] In one embodiment, the invention provides a method for treating a subject having cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor or their respective pharmaceutically acceptable salt, solvate or prodrug.

[0013] In one embodiment, the 1,2-diphenylpyrrole derivative of the combination composition has the following formula:



wherein:

R is a hydrogen atom, a halogen atom or an alkyl group having from 1 to 6 carbon atoms;

R^1 is an alkyl group having from 1 to 6 carbon atoms or an amino group;

R^2 is a phenyl group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents α and substituents β;

R^3 is a hydrogen atom, a halogen atom or an alkyl group which has from 1 to 6 carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6 carbon atoms and an alkylthio group having from 1 to 6 carbon atoms;

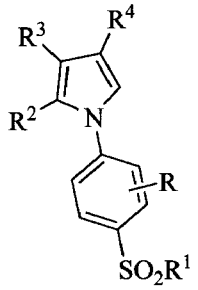
R^4 is a hydrogen atom; an alkyl group which has from 1 to 6 carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6 carbon atoms and an alkylthio group having from 1 to 6 carbon atoms; a cycloalkyl group having from 3 to 8 carbon atoms, an aryl group; or an aralkyl group; said aryl group having from 6 to 14 ring carbon atoms in a carbocyclic ring and are unsubstituted or are substituted by at least one substituent selected from the group consisting of substituents α and substituents β;

said aralkyl group are an alkyl group having from 1 to 6 carbon atoms and which are substituted by at least one aryl group as defined above;

said substituents α are selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6 carbon atoms and an alkylthio group having from 1 to 6 carbon atoms;

said substituents β are selected from the group consisting of an alkyl group which has from 1 to 6 carbon atoms and which is unsubstituted or are substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6 carbon atoms and an alkylthio group having from 1 to 6 carbon atoms; an alkanoyloxy group having from 1 to 6 carbon atoms; a mercapto group; an alkanoylthio group having from 1 to 6 carbon atoms; an alkylsulfinyl group having from 1 to 6 carbon atoms; a cycloalkloxy group having from 3 to 8 carbon atoms; a haloalkoxy group having from 1 to 6 carbon atoms; and an alkylenedioxy group having from 1 to 6 carbon atoms; or a pharmaceutically acceptable salt, solvate, or prodrug.

[0014] In another embodiment, a 1,2-diphenylpyrrole derivative of the combination composition has the following formula:



R is a hydrogen atom, a halogen atom or an alkyl group having from 1 to 4 carbon atoms;

R^1 is a methyl group or an amino group;

R^2 is an unsubstituted phenyl group or a phenyl group which is substituted by at least one substituent selected from the group consisting of a halogen atom; an alkoxy group having from 1 to 4 carbon atoms; an alkylthio group having from 1 to 4 carbon atoms; an unsubstituted alkyl group having from 1 to 4 carbon atoms; an alkyl group having from 1 to 4 carbon atoms and which is substituted by at least one substituent selected from the group consisting of a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to 4 carbon atoms; a haloalkoxy group having from 1 to 4 carbon atoms; and an alkylenedioxy group having from 1 to 4 carbon atoms;

R^3 is a hydrogen atom, a halogen atom, an unsubstituted alkyl group having from 1 to 4 carbon atoms or a substituted alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to 4 carbon atoms;

R^4 is a hydrogen atom; an unsubstituted alkyl group having from 1 to 4 carbon atoms; a substituted alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to carbon atoms; a cycloalkyl group having from 3 to 6 carbon atoms; an aryl group which has from 6 to 10 ring carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a halogen atom; an alkoxy group having from 1 to 4 carbon atoms; an alkylthio group having from 1 to

4 carbon atoms; an unsubstituted alkyl group having from 1 to 4 carbon atoms; an alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to 4 carbon atoms; and a cycloalkyloxy group having from 3 to 7 carbon atoms; an aralkyl group having from 1 to 4 carbon atoms in the alkyl part and containing at least one said aryl group; or a pharmaceutically acceptable salt, solvate, or prodrug.

[0015] In a further embodiment, the invention provides a 1,2-diphenylpyrrole derivative of the combination composition wherein:

R is a hydrogen atom;

R^1 is an amino group;

R^2 is an unsubstituted phenyl group or a phenyl group which is substituted by at least one substituent selected from the group consisting of a halogen atom, an alkoxy group having from 1 to 4 carbon atoms, an alkylthio group having from 1 to 4 carbon atoms, an alkyl group having from 1 to 4 carbon atoms, a haloalkyl group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 4 carbon atoms and a alkylenedioxy group having from 1 to 4 carbon atoms;

R^3 is a hydrogen atom, a halogen atom, an alkyl group having from 1 to 4 carbon atoms or a haloalkyl group having from 1 to 4 carbon atoms;

R^4 is a hydrogen atom; an unsubstituted alkyl group having from 1 to 4 carbon atoms; a substituted alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a hydroxy group and an alkoxy group having from 1 to 4 carbon atoms; a cycloalkyl group having from 3 to 6 carbon atoms; an aryl group which has from 6 to 10 ring carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a hydroxy group; a halogen atom; an alkoxy group having from 1 to 4 carbon atoms; an unsubstituted alkyl group having from 1 to 4 carbon atoms; an alkyl group having from 1 to 4 carbon atoms and which is unsubstituted or substituted by at least one halogen atom; and a cycloalkyloxy group having from 3 to 7 carbon atoms; and an aralkyl group having from 1 to 4 carbon atoms in the alkyl part and containing at least one said aryl group; or a pharmaceutically acceptable salt, solvate, or prodrug.

[0016] In yet a further embodiment, the 1,2-diphenylpyrrole derivative is selected from the group consisting of: 4-methyl-2-(4-methylphenyl)-1-(4-sulfamoylphenyl)pyrrole; 2-(4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(4-chlorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 4-methyl-2-(4-methylthiophenyl)-1-(4-sulfamoylphenyl)pyrrole; 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(4-methoxy-3-methylphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(3-fluoro-4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 4-methyl-1-(4-methylthiophenyl)-2-(4-sulfamoylphenyl)pyrrole; 1-(4-acetylaminosulfonylphenyl)-4-methyl-2-(4-methoxyphenyl)pyrrole; and 1-(4-acetylaminosulfonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole.

[0017] In one embodiment the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole.

[0018] In another embodiment the EGFR inhibitor is erlotinib.

[0019] In a further embodiment, the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

[0020] In yet a further embodiment the 1,2-diphenylpyrrole derivative and the EGFR inhibitor are administered sequentially in either order or simultaneously.

[0021] In one embodiment the 1,2-diphenylpyrrole derivative is administered first.

[0022] In another embodiment the EGFR inhibitor is administered first.

[0023] In one embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders, comprising administering the combination by a mode of administration comprising oral, parenteral, buccal, intranasal, epidural, sublingual, pulmonary, local, rectal, or transdermal administration.

[0024] In one embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the combination is orally administered as a single dosage form.

[0025] In another embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the single dosage form enhances patient compliance and/or reduces pill burden.

[0026] In a further embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the single dosage form is a single capsule or a single tablet.

[0027] In yet a further embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the composition is provided as a single tablet.

[0028] In a further embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders, comprising administering the combination by a mode of parenteral administration selected from intravenous, subcutaneous, intrathecal, and intramuscular administration.

Dosages

[0029] In one embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders comprising administering the combination in a single tablet wherein the single tablet comprises from about 1 mg to about 1200 mg of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and from about 25 mg to about 450 mg of erlotinib.

[0030] In another embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 25 mg of erlotinib.

[0031] In a further embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 100 mg of erlotinib.

[0032] In yet a further embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 150 mg of erlotinib.

[0033] In another embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 200 mg of erlotinib.

[0034] In yet another embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 300 mg of erlotinib.

[0035] In a further embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 450 mg of erlotinib.

[0036] In one embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the single tablet comprises about 1 mg, about 5 mg, about 10 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 600 mg, about 800 mg, about 1000 mg, or about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 25 mg of erlotinib.

[0037] In one embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the single tablet comprises about 1 mg, about 5 mg, about 10 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 600 mg, about 800 mg, about 1000 mg, or about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 100 mg of erlotinib.

[0038] In another embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the single tablet comprises about 1 mg, about 5 mg, about 10 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 600 mg, about 800 mg, about 1000 mg, or about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 150 mg of erlotinib.

[0039] In one embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the single tablet comprises about 1 mg, about 5 mg, about 10 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 600 mg, about 800 mg, about 1000 mg, or about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 200 mg of erlotinib.

[0040] In another embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the single tablet comprises about 1 mg, about 5 mg, about 10 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 600 mg, about 800 mg, about 1000 mg, or about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 300 mg of erlotinib.

[0041] In a further embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders wherein the single tablet comprises about 1 mg, about 5 mg, about 10 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 600 mg, about 800 mg, about 1000 mg, or about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 450 mg of erlotinib.

[0042] In one embodiment, the invention provides a method of treating cancer, tumors, and tumor-related disorders comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the composition is suitable for once-daily administration.

[0043] In a further embodiment, the invention provides a method wherein administering the combination enhances treatment of the subject compared to administering one component of the combination alone.

Types of Cancer

[0044] In yet a further embodiment, the invention provides a method wherein administering the combination reduces the side effects of treatment for a cancer, tumor, and tumor-related disorders.

[0045] In one embodiment the cancer is selected from the group consisting of: oral cancer, prostate cancer, rectal cancer, non-small cell lung cancer, lip and oral cavity cancer, liver cancer, lung cancer, anal cancer, kidney cancer, vulvar cancer, breast cancer, oropharyngeal cancer, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, urethra cancer, small intestine cancer, bile duct cancer, bladder cancer, ovarian cancer, laryngeal cancer, hypopharyngeal cancer, gallbladder cancer, colon cancer, colorectal cancer, head and neck cancer, glioma; parathyroid cancer, penile cancer, vaginal cancer, thyroid cancer, pancreatic cancer, esophageal cancer, Hodgkin's lymphoma, leukemia-related disorders, mycosis fungoides, and myelodysplastic syndrome.

[0046] In another embodiment the cancer is non-small cell lung cancer, pancreatic cancer, breast cancer, ovarian cancer, colorectal cancer, or head and neck cancer.

[0047] In yet another embodiment the cancer is a carcinoma, a tumor, a neoplasm, a lymphoma, a melanoma, a glioma, a sarcoma, or a blastoma.

[0048] In one embodiment the carcinoma is selected from the group consisting of: carcinoma, adenocarcinoma, adenoid cystic carcinoma, adenosquamous carcinoma, adrenocortical carcinoma, well differentiated carcinoma, squamous cell carcinoma, serous carcinoma, small cell carcinoma, invasive squamous cell carcinoma, large cell carcinoma, islet cell carcinoma, oat cell carcinoma, squamous carcinoma, undifferentiatied carcinoma, verrucous carcinoma, renal cell carcinoma, papillary serous adenocarcinoma, merkel cell carcinoma, hepatocellular carcinoma, soft tissue carcinomas, bronchial gland carcinomas, capillary carcinoma, bartholin gland carcinoma, basal cell carcinoma, carcinosarcoma, papilloma/carcinoma, clear cell carcinoma, endometrioid adenocarcinoma, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, cholangiocarcinoma, actinic keratoses, cystadenoma, and hepatic adenomatosis.

[0049] In another embodiment the tumor is selected from the group consisting of: astrocytic tumors, malignant mesothelial tumors, ovarian germ cell tumors, supratentorial primitive neuroectodermal tumors, Wilm's tumors, pituitary tumors, extragonadal germ cell tumors, gastrinoma, germ cell tumors, gestational trophoblastic tumors, brain tumors, pineal and supratentorial primitive neuroectodermal tumors, pituitary tumors, somatostatin-secreting tumors, endodermal sinus tumors, carcinoids, central cerebral astrocytoma, glucagonoma, hepatic adenoma, insulinoma, medulloepithelioma, plasmacytoma, vipoma, and pheochromocytoma.

[0050] In yet another embodiment the neoplasm is selected from the group consisting of: intraepithelial neoplasia, multiple myeloma/plasma cell neoplasm, plasma cell neoplasm, interepithelial squamous cell neoplasia, endometrial hyperplasia, focal nodular hyperplasia, hemangioendothelioma, and malignant thymoma.

[0051] In a further embodiment the lymphoma is selected from the group consisting of: nervous system lymphoma, AIDS-related lymphoma, cutaneous T-cell lymphoma, non-Hodgkin's lymphoma, lymphoma, and Waldenstrom's macroglobulinemia.

[0052] In another embodiment the melanoma is selected from the group consisting of: acral lentiginous melanoma, superficial spreading melanoma, uveal melanoma, lentigo maligna melanomas, melanoma, intraocular melanoma, adenocarcinoma nodular melanoma, and hemangioma.

[0053] In yet another embodiment the sarcoma is selected from the group consisting of: adenomas, adenosarcoma, chondosarcoma, endometrial stromal sarcoma, Ewing's sarcoma, Kaposi's sarcoma, leiomyosarcoma, rhabdomyosarcoma, sarcoma, uterine sarcoma, osteosarcoma, and pseudosarcoma.

[0054] In one embodiment the glioma is selected from the group consisting of: glioma, brain stem glioma, and hypothalamic and visual pathway glioma.

[0055] In another embodiment the blastoma is selected from the group consisting of: pulmonary blastoma, pleuropulmonary blastoma, retinoblastoma, neuroblastoma, medulloblastoma, glioblastoma, and hemangiblastomas.

EGFR Inhibitors

[0056] In a further embodiment, the invention provides a method wherein the EGFR inhibitor is a small molecule compound or an antibody.

[0057] In one embodiment, the invention provides a method wherein the small molecule compound is selected from the group consisting of: ZM-254530, BIBX-1382, reveromycin A, gefitinib, CGP-57148, CGP-59326, 4-(3-chloro)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine, tyrphostin, PKI-166, PD 153035, EKB-569, and 4-(phenylamino)quinazolines, or their pharmaceutically acceptable salts, solvates, or prodrugs.

[0058] In another embodiment the invention provides a method wherein the antibody is selected from the group consisting of: EGF receptor antibody, MR1scFvPE38KDEL MDX-447, MDX-210, MD-72000, MDX-260, wayne anti-EGFR Mabs, anti-EGFr Mab, anti-EGFr MAb, Genen anti-EGFR Mab, MAb DC-101, trastuzumab, anti-VEGF monoclonal, anti-EGFR-DM1 Ab, MAb 4D5, BAB-447,

EMD-55900, EMD-6200, -82633, anti-EGFR Mab, MAb 4D5, cetuximab, anti-EGFr MAb, anti-flk-1, CCX, CCZ, anti-flk-1, AG-514, AG-568, nti-EGFR-DM1 Ab, MDX-447, TgDCC-E1A and C225, matuzumab, panitumumab, DWP-408, and RC-3940II.

[0059] In another embodiment the EGFR inhibitor is selected from the group consisting of: muellerian-inhibiting hormone, TNP-470, tecogalan sodium, EGF receptor antisense, PI-88, oligonucleotide, bromelain molecules, amphiregulin, EGF fusion toxin, EGF fusion protein, Amphiregulin hbEGF-toxin, hbEGF-toxin, and EGF fusion protein.

Further Methods of Use

[0060] In one embodiment, the invention provides a method of inducing differentiation of tumor cells, the method comprising contacting the cells with an effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor whereby the combination induces differentiation of tumor cells.

[0061] In one embodiment, the invention provides a method of inhibiting proliferation of cancer cells, the method comprising contacting a cancer cell with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor whereby the combination inhibits proliferation of cancer cells.

[0062] In another embodiment, the invention provides a method for reducing proliferation of cancer cells, the method comprising delivering to the cells a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor, whereby the reduction of cell proliferation is greater than a reduction caused by either a 1,2-diphenylpyrrole derivative alone or an EGFR inhibitor alone.

[0063] In one embodiment, the invention provides a method of modulating autophosphorylation with a molecule of ATP, the method comprising delivering to a cancer cell an effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination inhibits autophosphorylation with a molecule of ATP.

[0064] In a further embodiment, the invention provides a method of inhibiting metastases of tumor cells, the method comprising administering an effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor such that the combination inhibits metastatic activity of tumor cells.

[0065] In one embodiment, the invention provides a method for inducing apoptosis in cancer cells, the method comprising contacting the cancer cells with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR kinase sufficient to induce apoptosis.

[0066] In another embodiment, the invention provides a method for sensitizing EGFR-inhibitor resistant cancer cells to an EGFR inhibitor, the method comprising administering a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination sensitizes the cancer cells to the EGFR inhibitor.

[0067] In one embodiment, the invention provides a method of treating EGFR resistance in a cancer cell, the method comprising, administering a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor

[0068] In a further embodiment, the invention provides a method of modulating prostaglandin synthesis in a cancer cell, the method comprising contacting the cell with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination inhibits prostaglandin synthesis in a cancer cell.

[0069] In one embodiment, the invention provides a method of modulating cyclooxygenase expression in a cancer cell, the method comprising delivering to the cell a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination inhibits cyclooxygenase expression in a cancer cell.

[0070] In one embodiment, the invention provides a method of modulating angiogenesis in a cancer cell, the method comprising contacting the cell with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination inhibits angiogenesis in a cancer cell.

[0071] In another embodiment, the invention provides a method of reducing the dosage in conventional treatment for neoplasia and/or neoplasia related disorders in a subject, the method comprising administering to a subject a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination reduces the dosage in conventional treatment for neoplasia and/or neoplasia-related disorders.

[0072] In one embodiment, the invention provides a method of treating neoplasia and/or neoplasia related disorders, the method comprising administering a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor

[0073] In one embodiment, the invention provides a composition for treating cancer comprising, a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor or their respective pharmaceutically acceptable salt, solvate or prodrug.

[0074] In one embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole.

[0075] In another embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor, wherein the EGFR inhibitor is erlotinib.

[0076] In yet another embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

[0077] In one embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the composition is a single dosage form.

[0078] In a further embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein a single dosage form enhances patient compliance and/or reduces pill burden.

[0079] In one embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders, comprising administering a combination according to the invention by a mode of administration comprising oral, parenteral, buccal, intranasal, epidural, sublingual, pulmonary, local, rectal, or transdermal administration.

[0080] In a further embodiment, the invention provides a method for treating cancer, tumors, and tumor-related disorders, comprising a combination according to the invention by parenteral administration selected from intravenous, subcutaneous, intrathecal, and intramuscular administration.

[0081] In one embodiment, the invention provides a method comprising administering the combination in a single dosage form.

[0082] In yet a further embodiment, the invention provides a method of treatment comprising administering a composition comprising a single tablet combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein a single dosage form is a single capsule or a single tablet.

[0083] In one embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the composition is in the form of a single tablet.

[0084] In another embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the single tablet comprises from about 1 mg to about 1200 mg of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and from about 25 mg to about 450 mg of erlotinib.

[0085] In yet another embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 25 mg of erlotinib.

[0086] In one embodiment, the invention provides a method of treatment comprising administering a single tablet composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 100 mg of erlotinib.

[0087] In another embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 150 mg of erlotinib.

[0088] In another embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an

EGFR inhibitor wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 200 mg of erlotinib.

[0089] In another embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 300 mg of erlotinib.

[0090] In another embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 450 mg of erlotinib.

[0091] In a further embodiment, the invention provides a method of treatment comprising administering a single tablet composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the single tablet comprises from about 1 mg, about 5 mg, about 10 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 600 mg, about 800 mg, about 1000 mg, or about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 25 mg of erlotinib.

[0092] In a further embodiment, the invention provides a method of treatment comprising administering a single tablet composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the single tablet comprises from about 1 mg, about 5 mg, about 10 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 600 mg, about 800 mg, about 1000 mg, or about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 100 mg of erlotinib.

[0093] In a further embodiment, the invention provides a method of treatment comprising administering a single tablet composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the single tablet comprises from about 1 mg, about 5 mg, about 10 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 600 mg, about 800 mg, about 1000 mg, or about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 150 mg of erlotinib.

[0094] In a further embodiment, the invention provides a method of treatment comprising administering a single tablet composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the single tablet comprises from about 1 mg, about 5 mg, about 10 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 600 mg, about 800 mg, about 1000 mg, or about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 200 mg of erlotinib.

[0095] In a further embodiment, the invention provides a method of treatment comprising administering a single tablet composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the single tablet comprises from about 1 mg, about 5 mg,

about 10 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 600 mg, about 800 mg, about 1000 mg, or about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 300 mg of erlotinib.

[0096] In a further embodiment, the invention provides a method of treatment comprising administering a single tablet composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the single tablet comprises from about 1 mg, about 5 mg, about 10 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 600 mg, about 800 mg, about 1000 mg, or about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 450 mg of erlotinib.

[0097] In one embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the composition is suitable for once-daily administration.

[0098] In another embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the EGFR inhibitor is a small molecule compound or an antibody.

[0099] In a further embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and a small molecule wherein the small molecule compound is selected from the group consisting of: ZM-254530, BIBX-1382, reveromycin A, gefitinib, CGP-57148, CGP-59326, 4-(3-chloro)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine, tyrphostin, PKI-166, PD 153035, EKB-569, and 4-(phenylamino)quinazolines, or their pharmaceutically acceptable salts, solvates, or prodrugs.

[00100] In another embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the EGFR inhibitor is an antibody selected from the group consisting of: EGF receptor antibody, MR1scFvPE38KDEL MDX-447, MDX-210, MD-72000, MDX-260, wayne anti-EGFR Mabs, anti-EGFr Mab, anti-EGFr MAb, Genen anti-EGFR Mab, MAb DC-101, trastuzumab, anti-VEGF monoclonal, anti-EGFR-DM1 Ab, MAb 4D5, BAB-447, EMD-55900, EMD-6200, -82633, anti-EGFR Mab, MAb 4D5, cetuximab, anti-EGFr MAb, anti-flk-1, CCX, CCZ, anti-flk-1, AG-514, AG-568, nti-EGFR-DM1 Ab, MDX-447, TgDCC-E1A, C225, matuzumab, panitumumab, DWP-408, and RC-3940II.

[00101] In yet another embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the composition contains a lower dose of an EGFR inhibitor than a conventional treatment for cancer.

[00102] In a further embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the composition reduces the side effects of cancer treatment.

[00103] In yet a further embodiment, the invention provides a method of treatment comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the composition enhances treatment of cancer.

Pharmaceutical Compositions

[00104] In one embodiment the invention provides a pharmaceutical composition for treating cancer comprising, a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor, and a pharmaceutically acceptable excipient or carrier.

[00105] In one embodiment, the invention provides a pharmaceutical composition for treating cancer wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole.

[00106] In another embodiment, the invention provides a pharmaceutical composition for treating cancer wherein the EGFR inhibitor is erlotinib.

[00107] In yet another embodiment, the invention provides a pharmaceutical composition for treating cancer wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

Kits/Articles of Manufacture

[00108] In one embodiment the invention provides a kit for treating cancer comprising a single dosage form comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor and instructions on administration.

[00109] In one embodiment the invention provides a kit for treating cancer having a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

INCORPORATION BY REFERENCE

[00110] All publications, patents, and patent applications described in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[00111] Figure 1 provides graphs illustrating COX-2 expression levels in colorectal cancer.

[00112] Figure 2 provides an illustration of the interactions between the EGFR and COX pathways.

[00113] Figure 3 provides a graph illustrating the results of a A431 squamous vulvar carcinoma xenograft study.

DETAILED DESCRIPTION

[00114] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below.

Definitions

[00115] As used herein, "abnormal cell growth," refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition), including the abnormal growth of normal cells and the growth of abnormal cells. This includes, but is not limited to, the abnormal growth of: (1) tumor cells (tumors), both benign and malignant, expressing an activated Ras oncogene; (2) tumor cells, both benign and malignant, in which the Ras protein is activated as a result of oncogenic mutation in another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs. Examples of such benign proliferative diseases are psoriasis, benign prostatic hypertrophy, human papilloma virus (HPV), and restenosis. Abnormal cell growth, also refers to and includes the abnormal growth of cells, both benign and malignant, resulting from activity of the enzymes farnesyl protein transferase, protein kinases, protein phosphatases, lipid kinases, lipid phosphatases, or activity of transcription factors, or intracellular or cell surface receptor proteins.

[00116] "Neoplasia" as described herein, is an abnormal, unregulated and disorganized proliferation of cells that is distinguished from normal cells by autonomous growth and somatic mutations. An accumulation of neoplastic cells is also known as a neoplasm, or tumor. As neoplastic cells grow and divide they pass on their genetic mutations and proliferative characteristics to progeny cells. In some embodiments, the neoplasm can be benign or malignant.

[00117] "Metastasis," as used herein, refers to the dissemination of tumor cells via lymphatics or blood vessels. Metastasis also refers to the migration of tumor cells by direct extension through serous cavities, or subarachnoid or other spaces. Through the process of metastasis, tumor cell migration to other areas of the body establishes neoplasms in areas away from the site of initial appearance.

[00118] As discussed herein, "angiogenesis" is prominent in tumor formation and metastasis. Angiogenic factors have been found associated with several solid tumors such as rhabdomyosarcomas, retinoblastoma, Ewing sarcoma, neuroblastoma, and osteosarcoma. A tumor cannot expand without a blood supply to provide nutrients and remove cellular wastes. Tumors in which angiogenesis is important include solid tumors such as renal cell carcinoma, hepatocellular carcinoma, and benign tumors such as acoustic neuroma, and neurofibroma, trachoma and pyogenic granulomas. Angiogenesis has been associated with blood-born tumors such as leukemias. It is believed that angiogenesis plays a role in the abnormalities in the bone marrow that give rise to leukemia. Prevention of angiogenesis could halt the growth of cancerous tumors and the resultant damage to the subject due to the presence of the tumor.

[00119] The term "subject" refers to an animal, including, but not limited to, a primate (e.g., human), cow, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject.

[00120] The terms "treat," "treating," and "treatment" are meant to include alleviating or abrogating a disorder, disease, or condition; or one or more of the symptoms associated with the disorder, disease, or condition; or alleviating or eradicating the cause(s) of the disorder, disease, or condition itself.

[00121] The term "therapeutically effective amount" refers to the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disorder, disease, or condition being treated. The term "therapeutically effective amount" also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a cell, tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor, or clinician.

[00122] The term "pharmaceutically acceptable carrier," "pharmaceutically acceptable excipient," "physiologically acceptable carrier," or "physiologically acceptable excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material. Each component must be "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation. It must also be suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. S*ee, Remington: The Science and Practice of Pharmacy*, 21st Edition; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients*, 5th Edition; Rowe et al., Eds., The Pharmaceutical Press and the American Pharmaceutical Association: 2005; and *Handbook of Pharmaceutical Additives*, 3rd Edition; Ash and Ash Eds., Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation*, Gibson Ed., CRC Press LLC: Boca Raton, FL, 2004).

[00123] The term "pharmaceutical composition" refers to a mixture of a compound disclosed herein with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to, oral, injection, aerosol, parenteral, and topical administration. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

Cyclooxygenase

[00124] Cyclooxygenase (COX) is an enzyme that is responsible for the formation of important biological mediators called prostanoids, including prostaglandins, prostacyclin and thromboxane. COX converts arachidonic acid, an ω-6 essential fatty acid, to prostaglandin H_2 (PGH_2), the precursor of the series-2 prostanoids. The enzyme contains two active sites: a heme with peroxidase activity, responsible for the reduction of PGG_2 to PGH_2, and a cyclooxygenase site, where arachidonic acid is converted into the hydroperoxy endoperoxide prostaglandin G_2 (PGG_2). The reaction proceeds through a hydrogen atom abstraction from arachidonic acid by a tyrosine radical generated by the peroxidase active site, then two oxygen molecules react with the arachidonic acid radical, giving PGG_2.

[00125] COX-1 is a constitutive enzyme responsible for biosynthesis of prostaglandins in the gastric mucosa and in the kidney among other sites. COX-2 is an enzyme that is produced by an inducible gene that is responsible for biosynthesis of prostaglandins in inflammatory cells. Inflammation causes induction of COX-2, leading to release of prostanoids (prostaglandin E2), which sensitize peripheral nociceptor terminals and produce localized pain hypersensitivity, inflammation and edema.

[00126] Historically, physicians have treated inflammation-related disorders with a regimen of NSAIDs such as, for example, aspirin and ibuprofen. Undesirably, however, some NSAIDs are known to cause gastrointestinal (GI) bleeding or ulcers in patients undergoing consistent long term regimens of NSAID therapy. Henry et al., *Lancet*, **1991**, 337, 730. A reduction of unwanted side effects of common NSAIDs was made possible by the discovery that the two cyclooxygenases involved in the transformation of arachidonic acid as the first step in the prostaglandin synthesis pathway were cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2).

[00127] Many common NSAIDs are now known to be inhibitors of both COX-1 and COX-2. Accordingly, when administered in sufficiently high levels, these NSAIDs not only alleviate the inflammatory consequences of COX-2 activity, but also inhibit the beneficial gastric maintenance activities of COX-1. Research into the area of arachidonic acid metabolism has resulted in the discovery of compounds that selectively inhibit the COX-2 enzyme to a greater extent than they inhibit COX-1. These COX-2 selective inhibitors are believed to offer advantages that include the capacity to prevent or reduce inflammation while avoiding harmful side effects associated with the inhibition of COX-1. Thus, COX-2 selective inhibitors have shown great promise for use in therapies, especially in therapies that require maintenance administration, such as for pain and inflammation control.

[00128] As described herein, the terms "cyclooxygenase-2 inhibitor" and "Cox-2 inhibitor", which can be used interchangeably herein, denote compounds which inhibit the cyclooxygenase-2 enzyme (COX-2) regardless of the degree of inhibition of the cyclooxygenase-1 enzyme (COX-1), and include pharmaceutically acceptable racemates, enantiomers, tautomers, salts, esters and prodrugs of those compounds. Thus, for purposes of the present disclosure, a compound is considered a COX-2 inhibitor although the compound inhibits COX-2 to an equal, greater, or lesser degree than it inhibits COX-1. COX-2 inhibitors herein therefore encompass many traditional non-selective NSAIDs.

COX-2 Selective Inhibitors

[00129] COX-2 inhibitors useful according to embodiments of the present disclosure are agents and compounds that selectively or preferentially inhibit COX-2 to a greater degree than they inhibit COX-1. Such agents and compounds are termed "COX-2 selective inhibitors" herein.

[00130] In practice, in a test for selectivity of a COX-2 selective inhibitor, the observed selectivity varies depending upon the conditions under which the test is performed and on the compound being tested. For example, selectivity of a COX-2 inhibitor can be measured as a ratio of the in vitro or in vivo IC_{50} value for inhibition of COX-1, divided by the corresponding IC_{50} value for inhibition of

COX-2 (COX-1 IC_{50}/COX-2 IC_{50}). A COX-2 selective inhibitor herein is thus any inhibitor for which COX-1 IC_{50}/COX-2 IC_{50} is greater than 1. In various embodiments, this ratio is greater than about 2, greater than about 5, greater than about 10, greater than about 50, or greater than about 100.

[00131] In one embodiment, the invention provides a composition, comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the ratio of selectivity of COX-2 over COX-1 inhibition is greater than about 1. In another embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the ratio of selectivity of COX-2 over COX-1 inhibition is greater than about 2. In a further embodiment, the invention provides a composition comprising combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the ratio of selectivity of COX-2 over COX-1 inhibition is greater than about 5. In another embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the ratio of selectivity of COX-2 over COX-1 inhibition is greater than about 7.8. In yet a further embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the ratio of selectivity of COX-2 over COX-1 inhibition is greater than about 10. In another embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the ratio of selectivity of COX-2 over COX-1 inhibition is greater than about 20. In a further embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the ratio of selectivity of COX-2 over COX-1 inhibition is greater than about 50. In yet a further embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the ratio of selectivity of COX-2 over COX-1 inhibition is greater than about 100. In one embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein 1-2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole. In another embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the EGFR inhibitor is erlotinib. In a further embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1-2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib and wherein the ratio of selectivity of COX-2 over COX-1 inhibition is greater than about 1, about 2, about 5, about 7.8, about 10, about 20, about 50, and about 100.

[00132] In one embodiment, the invention provides a method for treating a tumor and/or tumor related disease comprising administering a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the ratio of selectivity of COX-2 over COX-1 inhibition is greater than about 1. In one embodiment, the invention provides a method for treating a tumor and/or tumor related disease comprising administering a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor

wherein the ratio of selectivity of COX-2 over COX-1 inhibition is greater than about 2. In a further embodiment, the invention provides a method for treating a tumor and/or tumor related disease comprising administering a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the ratio of selectivity of COX-2 over COX-1 inhibition is greater than about 5. In yet a further embodiment, the invention provides a method for treating a tumor and/or tumor related disease comprising administering a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the ratio of selectivity of COX-2 over COX-1 inhibition is greater than about 10. In some embodiments, the invention provides methods for treating a tumor and/or tumor related disease comprising administering a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the ratio of selectivity of COX-2 over COX-1 inhibition is greater than about 20, than about 50, and about 100. In other embodiments, the invention provides methods for treating a tumor and/or tumor related disease comprising administering a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1-2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib wherein the ratio of selectivity of COX-2 over COX-1 inhibition is greater than about 1, about 2, about 5, about 7.8, about 10, about 20, about 50, and about 100.

[00133] As used herein, the term "IC_{50}" with respect to a COX-1 or COX-2 inhibitor refers to the concentration of a compound that is required to produce 50% inhibition of activity of COX-1 or COX-2. In one embodiment, 1,2-diphenylpyrrole derivatives useful in the present disclosure can have a COX-2 IC_{50} of less than about 3 μM. In another embodiment, the 1,2-diphenylpyrrole derivative has a COX-2 IC_{50} of less than about 2.8 μM. In yet another embodiment, the 1,2-diphenylpyrrole derivative has a COX-2 IC_{50} of less than about 2 μM. In some embodiments, 1,2-diphenylpyrrole derivative useful in the present disclosure can have a COX-2 IC_{50} of less than about 1 μM, less than about 0.5 μM, or less than about 0.2 μM. 1,2-diphenylpyrrole derivatives useful in the present disclosure can have a COX-1 IC_{50} of greater than about 1 μM, for example greater than about 20 μM. In one embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the IC_{50} is less than about 1 μM. In another embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the IC_{50} is less than about 0.5 μM. In a further embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the IC_{50} is less than about 0.2 μM. In one embodiment the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole. In another embodiment the EGFR inhibitor is erlotinib. In a further embodiment the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib wherein the IC_{50} is less than about 3 μM, about 2.8 μM, about 2 μM, about 1 μM, about 0.5 μM, and about 0.2 μM.

[00134] COX-2 inhibitors exhibiting a high degree of selectivity for COX-2 over COX-1 inhibition can indicate ability to reduce incidence of common NSAID-induced side effects. In one embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the NSAID-induced side effects are substantially diminished. For example, NSAID-induced side effects include, but are not limited to, nausea, vomiting, diarrhea, constipation, decreased appetite, rash, dizziness, headache, drowsiness, fluid retention, edema, kidney failure, liver failure, ulcers and prolonged bleeding after surgery. In another embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib and wherein the NSAID-induced side effects are substantially diminished.

[00135] A COX-2 selective inhibitor can be used in a form of a prodrug thereof. As described herein, a "COX-2 prodrug" is a compound that can be converted into an active COX-2 selective inhibitor by metabolic or simple chemical processes within the body of the subject. One example of a prodrug for a COX-2 selective inhibitor is parecoxib, for example in a form of a salt such as parecoxib sodium, which is a therapeutically effective prodrug of the tricyclic COX-2 selective inhibitor valdecoxib.

Overexpression of COX-2 and Cancer

[00136] The overexpression of COX-2 and also the upstream and downstream enzymes of the prostaglandin synthesis pathway has been demonstrated in multiple cancer types and some pre-neoplastic lesions. Direct interactions of prostaglandins with their receptors through autocrine or paracrine pathways to enhance cellular survival or stimulate angiogenesis have been proposed as molecular mechanisms underlying the pro-carcinogenic functions of COX enzymes. In this respect, preclinical studies suggest that COX-2 may be involved in the molecular pathogenesis of some types of lung cancer. Most of the studies point to its involvement in non-small cell lung cancer. Survival of patients with non-small cell lung cancer expressing high levels of COX-2 is markedly reduced. Treatment of humans with the selective COX-2 inhibitor celecoxib augments the antitumor effects of chemotherapy in patients with non-small cell lung cancer.

Studies indicate that prostaglandins synthesized by cyclooxygenase play a critical role in the initiation and promotion of cancer. Aberrant COX-2 expression was reported in colorectal carcinomas and adenomas, and has been detected in various human cancers, including those of the breast. Moreover, COX-2 is overexpressed in neoplastic lesions of the colon, breast, lung, prostate, esophagus, pancreas, intestine, cervix, ovaries, urinary bladder and head and neck (see Table 1 below).

Tumor Type	% Tissue expressing COX-2
Colorectal Cancer	70-95
Non-small Cell Lung Cancer	70-90
Gastric Cancer	45-75
Pancreatic Cancer	40-80

Glioblastoma Multiforme	40-70
Bladder Cancer	50-60
Esophageal Cancer	50-60
Breast Cancer	40-50
Ovarian Cancer	40-60
Prostate Cancer	40-60

Table 1. COX-2 Expression in Tumors

[00137] COX-2 overexpression in murine mammary glands is sufficient to cause tumor formation. In several in vitro and animal models, COX-2 inhibitors have inhibited tumor growth and metastasis.

[00138] In addition to cancers per se, COX-2 is also expressed in the angiogenic vasculature within and adjacent to hyperplastic and neoplastic lesions indicating that COX-2 plays a role in angiogenesis. In both the mouse and rat, COX-2 inhibitors markedly inhibited bFGF-induces neovascularization. The utility of COX-2 inhibitors as chemopreventive, antiangiogenic and chemotherapeutic agents is described in the literature. Koki et al., *Exp. Opin., Invest. Drugs*, **1999**, 8(10) 1623-38.

[00139] COX-2 has been shown to regulate some embodiments of tumor-associated angiogenesis. Angiogenesis is an attractive therapeutic target because it is a multi-step process that occurs in a specific sequence, thus providing several possible targets for drug action. Angiogenesis is important in two stages of tumor metastasis. The first stage where angiogenesis stimulation is important is in the vascularization of the tumor which allows the tumor cells to enter the blood stream and to circulate throughout the body. After the tumor cells have left the primary site and have settled into the secondary, metastasis site, angiogenesis must occur before the new tumor can grow and expand. Therefore, prevention of angiogenesis could lead to the prevention of metastasis of tumors and possibly contain the neoplastic growth at the primary site. Examples of agents that interfere with several of these steps include, angiostatin, endostatin, interferon alpha and COX-2 selective inhibitors that prevent the growth of cells that form new blood vessels; and protein-based compounds that simultaneously interfere with several of these targets.

[00140] Additionally, several studies have suggested that COX-2 expression is associated with parameters of aggressive breast cancer, including large tumor size, positive axillary lymph node metastases, and HER2-positive tumor status. Studies of mammary tumors in mice and rats have indicated that moderate to high COX-2 expression is related to the genesis of mammary tumors that are sensitive to treatment with nonspecific and specific COX-2 inhibitors. Further studies have shown that increased amounts of prostaglandins and COX-2 are commonly found in a wide range of premalignant tissues and malignant tumors including cervical dysplasia and cancer. Elevated prostaglandin and COX-2 levels substantially contribute to carcinogenesis by inhibiting apoptosis and stimulating angiogenesis. Tsujii and DuBois, *Cell*, **1995**, 83, 493-501.

[00141] Further, COX-2 is also highly expressed in prostate cancer, particularly in the epithelial cell of high-grade prostatic intraepithelial neoplasia and cancer. It was shown that treatment of human

prostate cancer cell lines with a selective COX-2 inhibitor induces apoptosis both in vitro and in vivo. The in vivo results also indicate that the COX-2 inhibitor decreases tumor microvessel density and angiogenesis. COX-2 inhibitors can prevent the hypnoxic upregulation of a potent angiogenic factor, vascular endothelial growth factor.

[00142] Overexpression of COX-2 has been documented in several premalignant and malignant tissues. Subbaramaiah et al., *Trends Pharmacol. Sci.*, **2003**, 24, 96-102. Without wishing to be bound by any particular theory, this increase in expression is thought to be a product of stimulation of PKC signaling, which stimulates activity of MAPK, enhancing transcription of COX-2 by nuclear factors. Additionally, enhanced stability of COX-2 mRNA transcripts in cancer cells due to augmented binding of the RNA-binding protein HuR, as well as activation of extracellular signal related kinase 1 and 2 (ERK 1 and 2) and p38, is thought to contribute to increased expression of COX-2.

[00143] These results indicate that COX-2 inhibitors may serve as effective chemopreventive and therapeutic agents in cancer of the prostate.

COX-2 Selective Inhibitors

[00144] It has recently been found that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with the prevention and treatment of several types of cancer. Thun et al., *J. National Cancer Inst.*, **2002**, 94(4), 252-66. COX-2 inhibitors have been utilized for the treatment of cancer and for the treatment of tumors. For example, celecoxib, a COX-2 selective inhibitor, exerted a potent inhibition of fibroblast growth factor-induced corneal angiogenesis in rats. Masferrer et al., *Proc. Am. Assoc. Cancer Research*, **1999**, 40, 396. Other COX-2 inhibitors have been described for the treatment of cancer, tumors and neoplasia. FR 27 71 005 describes compositions containing a COX-2 inhibitor and N-methyl-d-aspartate (NMDA) antagonist used to treat cancer and other diseases. Further, WO 99/18960 describes a combination comprising a COX-2 inhibitor that can be used to treat colorectal and breast cancer. Additionally, WO 97/36497 describes a combination comprising a COX-2 inhibitor and a 5-lipoxygenase inhibitor useful in treating cancer.

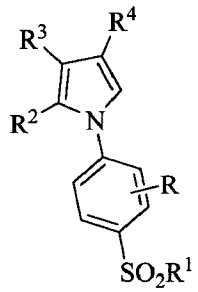
1,2-Diphenylpyrrole Derivatives

[00145] 1,2-Diphenylpyrrole derivatives and pharmaceutically acceptable salts, solvates, or prodrugs are known to have analgesic and antiphlogistic properties. Further, they have been shown to act as COX-2 selective inhibitors and are thus effective for the prophylaxis and therapy of diseases mediated by COX-2 and/or inflammatory cytokines. In addition, 1,2-diphenylpyrrole derivatives have been shown to treat diseases involving or resulting from the resorption of bone, such as osteoporosis, rheumatoid arthritis and osteoarthritis.

[00146] These types of analgesics, anti-inflammatory agents and/or antipyretics exhibit effects not only on inflammatory diseases, such as pain, pyrexia, and edema, but also on chronic inflammatory diseases, such as chronic rheumatoid arthritis and osteoarthritis, allergic inflammatory diseases, asthma, sepsis, psoriasis, various autoimmune diseases, systemic lupus erythematosus, juvenile onset

diabetes, autoimmune intestinal diseases (such as ulcerative colitis, Crohn's disease), viral infection, and glomerulonephritis.

[00147] 1,2-Diphenylpyrrole derivatives described herein have the general formula:



wherein:

R is a hydrogen atom, a halogen atom or an alkyl group having from 1 to 6 carbon atoms;

R^1 is an alkyl group having from 1 to 6 carbon atoms or an amino group;

R^2 is a phenyl group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents α and substituents β;

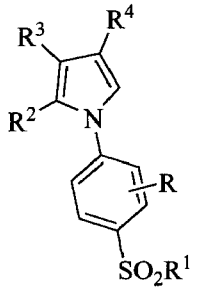
R^3 is a hydrogen atom, a halogen atom or an alkyl group which has from 1 to 6 carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6 carbon atoms and an alkylthio group having from 1 to 6 carbon atoms;

R^4 is a hydrogen atom; an alkyl group which has from 1 to 6 carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6 carbon atoms and an alkylthio group having from 1 to 6 carbon atoms; a cycloalkyl group having from 3 to 8 carbon atoms, an aryl group; or an aralkyl group; said aryl group having from 6 to 14 ring carbon atoms in a carbocyclic ring and are unsubstituted or are substituted by at least one substituent selected from the group consisting of substituents α and substituents β; said aralkyl group are an alkyl group having from 1 to 6 carbon atoms and which are substituted by at least one aryl group as defined above;

said substituents α are selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6 carbon atoms and an alkylthio group having from 1 to 6 carbon atoms;

said substituents β are selected from the group consisting of an alkyl group which has from 1 to 6 carbon atoms and which is unsubstituted or are substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6 carbon atoms and an alkylthio group having from 1 to 6 carbon atoms; an alkanoyloxy group having from 1 to 6 carbon atoms; a mercapto group; an alkanoylthio group having from 1 to 6 carbon atoms; an alkylsulfinyl group having from 1 to 6 carbon atoms; a cycloalkloxy group having from 3 to 8 carbon atoms; a haloalkoxy group having from 1 to 6 carbon atoms; and an alkylenedioxy group having from 1 to 6 carbon atoms; or a pharmaceutically acceptable salt, solvate, or prodrug.

[00148] In one embodiment, the invention provides a 1,2-diphenylpyrrole derivative having the formula:



wherein:

R is a hydrogen atom, a halogen atom or an alkyl group having from 1 to 4 carbon atoms;

R^1 is a methyl group or an amino group;

R^2 is an unsubstituted phenyl group or a phenyl group which is substituted by at least one substituent selected from the group consisting of a halogen atom; an alkoxy group having from 1 to 4 carbon atoms; an alkylthio group having from 1 to 4 carbon atoms; an unsubstituted alkyl group having from 1 to 4 carbon atoms; an alkyl group having from 1 to 4 carbon atoms and which is substituted by at least one substituent selected from the group consisting of a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to 4 carbon atoms; a haloalkoxy group having from 1 to 4 carbon atoms; and an alkylenedioxy group having from 1 to 4 carbon atoms;

R^3 is a hydrogen atom, a halogen atom, an unsubstituted alkyl group having from 1 to 4 carbon atoms or a substituted alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to 4 carbon atoms;

R^4 is a hydrogen atom; an unsubstituted alkyl group having from 1 to 4 carbon atoms; a substituted alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to carbon atoms; a cycloalkyl group having from 3 to 6 carbon atoms; an aryl group which has from 6 to 10 ring carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a halogen atom; an alkoxy group having from 1 to 4 carbon atoms; an alkylthio group having from 1 to 4 carbon atoms; an unsubstituted alkyl group having from 1 to 4 carbon atoms; an alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to 4 carbon atoms; and a cycloalkyloxy group having from 3 to 7 carbon atoms; an aralkyl group having from 1 to 4 carbon atoms in the alkyl part and containing at least one said aryl group; or a pharmaceutically acceptable salt, solvate, or prodrug.

[00149] In one embodiment, the invention provides a 1,2-diphenylpyrrole derivative wherein:

R is a hydrogen atom;

R^1 is an amino group;

R^2 is an unsubstituted phenyl group or a phenyl group which is substituted by at least one substituent selected from the group consisting of a halogen atom, an alkoxy group having from 1 to 4 carbon atoms, an alkylthio group having from 1 to 4 carbon atoms, an alkyl group having from 1 to 4 carbon atoms, a haloalkyl group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 4 carbon atoms and a alkylenedioxy group having from 1 to 4 carbon atoms;

R^3 is a hydrogen atom, a halogen atom, an alkyl group having from 1 to 4 carbon atoms or a haloalkyl group having from 1 to 4 carbon atoms;

R^4 is a hydrogen atom; an unsubstituted alkyl group having from 1 to 4 carbon atoms; a substituted alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a hydroxy group and an alkoxy group having from 1 to 4 carbon atoms; a cycloalkyl group having from 3 to 6 carbon atoms; an aryl group which has from 6 to 10 ring carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a hydroxy group; a halogen atom; an alkoxy group having from 1 to 4 carbon atoms; an unsubstituted alkyl group having from 1 to 4 carbon atoms; an alkyl group having from 1 to 4 carbon atoms and which is unsubstituted or substituted by at least one halogen atom; and a cycloalkyloxy group having from 3 to 7 carbon atoms; and an aralkyl group having from 1 to 4 carbon atoms in the alkyl part and containing at least one said aryl group; or a pharmaceutically acceptable salt, solvate, or prodrug.

[00150] In one embodiment, R is a hydrogen atom. In another embodiment, R is a fluorine atom. In a further embodiment, R is a chlorine atom. In yet a further embodiment, R is a methyl group.

[00151] In one embodiment, R^1 is a methyl group. In another embodiment, R^1 is an amino group.

[00152] In one embodiment, R^2 is a phenyl group.

[00153] In one embodiment, R^3 is a hydrogen atom. In another embodiment, R^3 is a halogen atom.

[00154] In one embodiment, R^4 is a hydrogen atom.

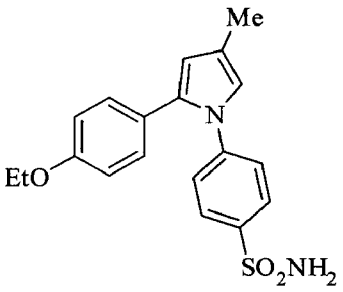
[00155] The term "aryl" refers to a carbocyclic aromatic hydrocarbon group having from 6 to 14 carbon atoms in one or more aromatic rings or such a group which is fused to a cycloalkyl group having from 3 to 10 carbon atoms, and the group is unsubstituted or it is substituted by at least one substituent selected from the group consisting of hydroxy groups, halogen atoms, lower alkoxy groups, lower alkylthio groups, lower alkyl groups, alkanoyloxy groups, mercapto groups, alknoylthio groups, lower alkylsulfinyl groups, lower alkyl groups having at least one substituent selected from the group consisting of cycloalkloxy groups, lower haloalkoxy groups, and lower alkylenedioxy groups.

[00156] In some embodiments, the 1,2-diphenylpyrrole derivative is selected from the group consisting of compounds **2-1 – 2-213** of Table 2 as disclosed in U.S. 6,887,893, which is herein incorporated in its entirety by reference.

[00157] In one embodiment, the 1,2-diphenylpyrrole derivative is selected from the group consisting of: 4-methyl-2-(4-methylphenyl)-1-(4-sulfamoylphenyl)pyrrole; 2-(4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(4-chlorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 4-methyl-2-(4-methylthiophenyl)-1-(4-sulfamoylphenyl)pyrrole; 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(4-methoxy-3-methylphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(3-fluoro-4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 4-methyl-1-(4-methylthiophenyl)-2-(4-sulfamoylphenyl)pyrrole; 1-(4-acetylaminosulfonylphenyl)-4-methyl-2-(4-methoxyphenyl)pyrrole; and 1-(4-acetylaminosulfonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole. In another embodiment, the invention provides a method wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole.

[00158] In another embodiment, the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole.

[00159] The methods for synthesizing 1,2-diphenylpyrrole derivatives, illustrated herein, are described in the Examples section and in U.S. RE39,420, which is incorporated herein by reference in its entirety.



2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole

[00160] 2-(4-Ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole has alternative chemical names, including 4-[2-(4-ethoxyphenyl)-4-methyl-1H-pyrrol-1-yl benzenesulfonamide, 4-[2-(4-ethoxyphenyl)-4-methyl-1H-pyrrol-1-yl]benzenesulfonamide, TG01, CS-706 and apricoxib. It has a molecular formula of $C_{19}H_{20}N_2O_3S$, a molecular weight of 356.4 and the CAS registry number is 197904-84-0.

Receptor Tyrosine Kinases

[00161] Protein tyrosine kinases are a class of enzymes that catalyze the transfer of a phosphate group from ATP or GTP to the tyrosine residue located on protein substrates. Protein tyrosine kinases clearly play a role in normal cell growth. Many of the growth factor receptor proteins function as tyrosine kinases and it is by this process that they effect signaling. The interaction of growth factors with these receptors is a necessary event in normal regulation of cell growth. Under certain conditions, however, as a result of either mutation or overexpression, these receptors can become deregulated; the result of which is uncontrolled cell proliferation which can lead to tumor growth and

ultimately to the disease known as cancer. Wilks, *Adv. Cancer Res.*, **1993**, 60, 43. Among the growth factor receptor kinases and their proto-oncogenes that have been identified and which are targets of the combinations presented herein are the epidermal growth factor receptor kinase (EGFR kinase, the protein product of the erbB oncogene), and the product produced by the erbB-2 (also referred to as the neu or HER2) oncogene. Since the phosphorylation event is a necessary signal for cell division to occur and since overexpressed or mutated kinases have been associated with cancer, an inhibitor of this event, a protein tyrosine inhibitor, will have therapeutic value for the treatment of cancer and other diseases characterized by uncontrolled or abnormal cell growth. For example, overexpression of the receptor kinase product of the erbB-2 oncogene has been associated with human breast and ovarian cancers. Slamon et. al., *Science*, **1989**, 244, 707. Deregulation of EGFR kinase has been associated with epidermoid tumors and tumors involving other major organs. Because of the importance of the role played by deregulated receptor kinases in the pathogenesis of cancer, many recent studies have dealt with the development of specific PTK inhibitors as potential anti-cancer therapeutic agents.

[00162] Receptor tyrosine kinases span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor (EGF), a transmembrane domain, and an intracellular portion which functions as a kinase to phosphorylate specific tyrosine kinase residues in proteins and hence to influence cell proliferation. The EGF receptor tyrosine kinase family has four members: EGFR (HER1, erbB1); HER2 (c-erbB2, erbB2, neu); HER3 (erbB3); and HER4 (erbB4). The ErbB receptors generally transduce signals through two pathways. It is known that such kinases are frequently and aberrantly expressed in common human cancers such as breast cancer, gastrointestinal cancer of colon, rectum or stomach, leukemia, and ovarian, bronchial or pancreatic cancer. As discussed previously, epidermal growth factor receptor (EGFR), is mutated and/or overexpressed in many human cancers such as brain, lung, squamous cell, bladder, gastric, breast, head and neck, oesophageal, gynecological and thyroid tumors.

Epidermal Growth Factor Receptors

[00163] Control of cell growth is regulated by the interaction of soluble growth factors and cell membrane receptors. The first step in the mitogenic stimulation of epidermal cells is the specific binding of epidermal growth factor (EGF) to a membrane glycoprotein known as the epidermal growth factor receptor (EGFR). The EGFR is composed of 1,186 amino acids which are divided into an extracellular portion of 621 residues and a cytoplasmic portion of 542 residues connected by a single hydrophobic transmembrane segment of 23 residues. Ullrich et al., *Nature*, **1986**, vol. 309, 418-25. The external portion of the EGFR can be subdivided into four domains. Recently, it has been demonstrated that domain III, residues 333 to 460 which is flanked by two cysteine domains is likely to contain the EGFR binding site of the receptor. Lax et al., *Mol. And Cell Biol.*, **1988**, vol. 8, 1831-34. The binding of EGF to domain III leads to the initiation of pleiotropic responses leading to DNA synthesis and cell proliferation.

[00164] EGFR has also been found in various types of human tumor cells and that those cells overexpress EGFR. For example, the cancerous cells of bladder tumors have been shown to have a relatively large population of EGF receptors. Neal et al., *Lancet*, **1985**, vol. 1, 366-67. Breast cancer cells exhibit a positive correlation between EGFR density and tumor size and a negative correlation with the extent of differentiation. Sainsbury et al., *Lancet*, **1985**, vol. 1, 364-66. The tumorigenicity of a series of human vulval epidermoid carcinoma (A431) clonal variants implanted into athymic mice having different levels of EGFR was found to correlate directly with the level of expression of the EGF receptor. Santon et al., *Cancer Res.*, **1986**, vol. 46, 4700-01. Thus, it has been proposed that overexpression of EGFRs play a role in the origin or tumorigenesis of cancer cells.

EGFR and COX Pathways

[00165] The relationship between the EGFR and COX pathways, to date, has not yet been fully elucidated. It has been submitted, however, that induction of COX-2 results in the production of increased levels of prostaglandins which then stimulate angiogenesis, cell proliferation and cell differentiation in an autocrine and/or paracrine manner. As described above, NSAIDs inhibit this process. Prostaglandins promote angiogenesis, along with cellular differention and proliferation. They also activate signaling through the EGFR. EGFR activation leads to phosphorylation on tyrosine residues by the receptor's tyrosine kinase domain, initiating a signaling pathway that includes the molecules Grb-2, SOS, the small G protein Raf. Raf activates Mitogen-Activated Protein Kinase Kinase (MAPKK) and group of nuclear transcription factors (c-myc, c-fos, c-jun); (see Figure 2). These factors initiate transcription of genes involved in the regulation of cell proliferation and differentiation. Additionally, these factors induce transcription of the COX-2. These effects may significantly amplify the original EGFR mediated signal and lead to pro-neoplastic effects. Inhibiting both signaling pathways could lead to a significant anti-neoplastic effect.

[00166] Studies have provided support that EGFR induces COX-2 in intestinal epithelial cells and anti-HER2 antibodies can inhibit COX-2 expression in colorectal cancer cells. In addition, overexpression of COX-1 or COX-2 in colon carcinoma cells has been shown to increase EGFR expression. Thus, COX and EGFR levels appear to be linked in a positive feedback cycle during colon cancer development. While the exact mechanism by which dysregulated EGF signaling promotes colon carcinogenesis is not clearly understood, it has been submitted that EGFR activation in a variety of cell types results in stimulation of cell proliferation and alterations in cell motility and/or adhesion to extra-cellular matrix. Studies have suggested that COX can positively influence tumor growth by promoting tumor associated angiogenesis.

[00167] It has also recently been proposed that the activation and overexpression of COX-2 in adenomatous polyps is due to activation of the EGFR. EGFR stimulation by one of its ligands, amphiregulin (AR), induces the nuclear targeting of COX-2, release of prostaglandins and subsequent mitogenesis, in polarized colonic epithelial cells. COX-2 inhibitors have been shown to prevent this series of events.

EGFR Inhibitors

[00168] Accordingly, it has been recognized that inhibitors of receptor tyrosine kinases are useful as selective inhibitors of the growth of mammalian cancer cells. For example, erbstatin, a tyrosine kinase inhibitor, selectively attenuates the growth in athymic nude mice of a transplanted human mammary carcinoma which expresses EGFR but is without effect on the growth of another carcinoma which does not express the EGFR.

[00169] Various other compounds, such as styrene derivatives, have also been shown to possess tyrosine kinase inhibitory properties. Others have disclosed that certain quinazoline derivatives possess anti-cancer properties which result from their tyrosine inhibitory properties.

[00170] As described herein, an "EGFR inhibitor" is a molecule which inhibits the kinase domain of the epidermal growth factor receptor. Compounds which are EGFR inhibitors can readily be identified by one skilled in the art using methods such as, for example, standard pharmacological test procedures which measure the inhibition of the phosphorylation of the tyrosine residue of a peptide substrate catalyzed by EGFR. Briefly, the peptide substrate (RR-SRC) has the sequence arg-arg-leu-ile-glu-asp-ala-glu-tyr-ala-ala-arg-gly. The enzyme is obtained as a membrane extract of A431 cells (American Type Culture Collection, Rockville, Md.). A431 cells are grown in T175 flasks to 80% confluency. The cells are washed twice with phosphate buffered saline (PBS) without Ca^{2+}. Flasks are rotated for 1.5 hours in 20 ml PBS with 1.0 mM ethylenediaminetetraacetic acid (EDTA) at room temperature and centrifuged at 600 g for 10 minutes. The cells are solubilized in 1 ml per $5x10^6$ cells of cold lysis buffer {10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), pH 7.6, 10 mM NaCl, 2 mM EDTA, 1 mM phenylmethylsulfonyl-fluoride (PMSF), 10 mg/ml aprotinin, 10 mg/ml leupeptin, 0.1 mM sodium orthovanadate} in a Dounce homogenizer with 10 strokes on ice. The lysate is centrifuged at 600 g for 10 minutes first to clear cell debris and the supernatant further centrifuged at 100,000 g for 30 min at 4.degree. C. The membrane pellet is suspended in 1.5 ml HNG buffer (50 mM HEPES, pH 7.6, 125 mM NaCl, 10% glycerol). The membrane extract is divided into aliquots, immediately frozen in liquid nitrogen and stored at -70 °C.

[00171] Compositions to be evaluated are made into 10 mg/ml stock solutions in 100% dimethylsulfoxide (DMSO). Stock solutions are diluted to 500 mM with buffer (30 mM Hepes pH 7.4) and then serially diluted to the desired concentration. An aliquot of the A431 membrane extract (10 mg/ml) is diluted in 30 mM HEPES (pH 7.4) to give a protein concentration of 50 μg/ml. To 4 μl of enzyme preparation, EGF (1 μl at 12 μg/ml) is added and incubated for 10 min on ice followed by 4 μl of the test compound or buffer; this mix is incubated on ice for 30 min. To this is added the ^{33}P-ATP (10 mCi/ml) diluted 1:10 in assay buffer along with the substrate peptide at a concentration of 0.5 mM (control reactions get no test compound) and the reaction is allowed to proceed for 30 min at 30°C. The reaction is stopped with 10% TCA and left on ice for at least 10 min after which tubes are microcentrifuged at full speed for 15 min. A portion of the supernatants are then spotted on P81 phosphocellulose discs and washed twice in 1% acetic acid then water for 5 min each followed by

scintillation counting. The results obtained can be expressed as an IC_{50}. The IC_{50} is the concentration of test compound needed to reduce the total amount of phosphorylated substrate by 50%. The % inhibition of the test compound is determined for at least three different concentrations and the IC_{50} value is evaluated from the dose response curve. The % inhibition is evaluated with the following formula:

$$\% \text{ inhibition} = 100\text{-}[\text{CPM(drug)}/\text{CPM(control)}]\text{x}100$$

where CPM(drug) is in units of counts per minute and is a number expressing the amount of radiolabeled ATP ($g\text{-}^{33}$ P) incorporated onto the RR-SRC peptide substrate by the enzyme after 30 minutes at 30 °C in the presence of test compound as measured by liquid scintillation counting. CPM(control) is in units of counts per minute and is a number expressing the amount of radiolabeled ATP ($g\text{-}^{33}$ P) incorporated into the RR-SRC peptide substrate by the enzyme after 30 minutes at 30 °C. in the absence of test compound as measured by liquid scintillation counting. The CPM values are corrected for the background counts produced by ATP in the absence of the enzymatic reaction. Compounds having an IC_{50} of about 200 nM or less are considered to be significantly active EGFR inhibitors.

[00172] The identification of EGFR as an oncogene has led to the development of anticancer therapeutics directed against EGFR, including gefitinib and cetuximab for colon cancer. Cetuximab is an example of a monoclonal antibody inhibitor, while gefitinib is a small molecule inhibitor.

Monoclonal Antibodies

[00173] The monoclonal antibodies block the extracellular ligand binding domain. With the binding site blocked, signal molecules can no longer attach there and activate the tyrosine kinase.

[00174] Cetuximab is a chimeric monoclonal antibody generated from fusion of the variable region of the murine anti-EGFR monoclonal antibody M225 and the human IgG1 constant region. The resulting antibody retains high affinity and specificity to EGFR and reduces immunogenicity. Preclinical studies have demonstrated that cetuximab effectively inhibits the proliferation of a variety of EGFR-expressing cancer cells in vitro and that it inhibits tumor growth in xenograft models. In an orthotopic pancreatic cancer model, cetuximab significantly suppressed the growth of orthotopically implanted pancreatic tumors, and this effect was enhanced by the addition of gemcitabine. Histologic analysis of tumor specimens revealed that cetuximab induced apoptosis and suppressed proliferation of tumor cells. Interestingly, cetuximab also induced apoptosis of endothelial cells, which are not believed to be direct targets of EGFR inhibition. Moreover, an antiangiogenic effect, characterized by decreased microvascular densities associated with reduced expression of tumor-related VEGF and interleukin-8, was observed. These data suggest that, in addition to direct antiproliferative activity, antiangiogenic activity contributes significantly to the antitumor effect of EGFR inhibitors.

[00175] Panitumumab (ABX-EGF) is a fully human monoclonal antibody specific to EGFR and is produced by immunization of transgenic mice, that are able to produce human immunoglobulin light

and heavy chains. Following immunization, a specific clone of B cells that produced the antibody against EGFR are selected and immortalized for the generation of the antibody.

[00176] Effective anti-EGFR monoclonal antibodies compete with endogenous ligands, primarily EGF and transforming growth factor a for receptor ligand-binding sites. Binding to EGFR blocks critical signaling pathways and interferes with the growth of tumors expressing EGFR. Anti-EGFR monoclonal antibodies that are currently under study include EMD 55900 and ICR 62.

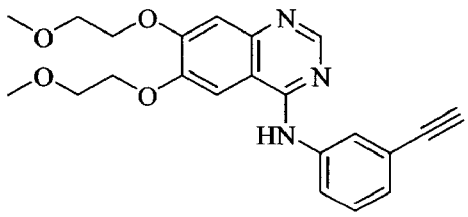
Small Molecules

[00177] Another method is using small molecules to inhibit the EGFR tyrosine kinase, which is on the cytoplasmic side of the receptor. Without kinase activity, EGFR is unable to activate itself, which is a prerequisite for binding of downstream adaptor proteins. Ostensibly by halting the signaling cascade in cells that rely on this pathway for growth, tumor proliferation and migration is diminished.

[00178] Gefitinib is currently only indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in patients who have previously received chemotherapy. While gefitinib has yet to be proven to be effective in other cancers, there is potential for its use in the treatment of other cancers where EGFR overexpression is involved.

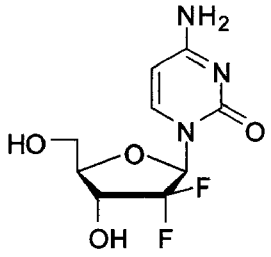
Erlotinib

[00179] *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine, also known as erlotinib (Tarceva®), is currently being used to help treat advanced non-small cell lung cancer, and in combination with gemcitabine in the treatment for advanced metastatic pancreatic cancer. U.S. 5,747,498 describes the preparation of erlotinib and other chemically-related compounds. Additionally, U.S. 6,900,221 describes the use of a stable polymorph of erlotinib as an inhibitor of the erbB family of oncogenic and protoncogenic protein kinases such as EGFR. Also, the patent illustrates methods for the treatment of non-small cell lung cancer, pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), melanoma, Barrett's esophagus (pre-malignant syndrome), adrenal and skin cancers and auto immune, neoplastic cutaneous diseases and atherosclerosis.



N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine

Gemcitabine



Gemcitabine

[00180] Gemcitabine is a nucleoside analog that exhibits antitumor activity. The chemical name for gemcitabine is β-2'-deoxy-2',2'-difluorocytidine and is administered as the hydrochloride salt. The cytotoxic effect of gemcitabine is attributed to two actions. First, gemcitabine diphosphate inhibits ribonucleotide reductase causing a reduction in deoxynucleotides available for DNA synthesis. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The two actions working in combination lead to high levels of gemcitabine nuceotide incorportion into growing DNA chains. This leads to inhibition of further DNA synthesis and chain termination.

[00181] Gemcitabine is indicated for use in the treatment of ovarian, breast, NSCL and pancreatic cancer. Gemcitabine hydrochloride is administered as an intravenous infusion of a 1000 mg/m^2 dose over 30 minutes once a week for up to 7 weeks. This is followed by one week of rest and then subsequent cycles of weekly infusions for 3 weeks of a 4 week cycle. Complete details are provided in the prescribing instructions for gemcitabine, which is included by reference in its entirety.

[00182] In one embodiment the invention provides a composition comprising a combination of a COX-2 selective inhibitor and an EGFR inhibitor disclosed herein for the treatment and prevention of cancer, tumors, and tumor-related disorders, and neoplastic disease states. In one embodiment, the EGFR inhibitor is a small molecule compound or an antibody.

[00183] In one embodiment, the EGFR inhibitor is selected from gefitinib, cetuximab, and erlotinib. In another embodiment, the EGFR inhibitor is erlotinib.

[00184] In another embodiment the small molecule compound is selected from the group consisting of: ZM-254530, BIBX-1382, reveromycin A, gefitinib, CGP-57148, CGP-59326, 4-(m-chloro)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine, tyrphostin, PKI-166, PD 153035, EKB-569, and 4-(phenylamino)quinazolines, or their pharmaceutically acceptable salts, solvates, or prodrugs. In another embodiment, the small molecule is selected from the compounds disclosed in PCT/US04/027574 which is herein incorporated by reference in its entirety.

[00185] In another embodiment, the antibody is selected from the group consisting of: EGF receptor antibody, MR1scFvPE38KDEL MDX-447, MDX-210, MD-72000, MDX-260, wayne anti-EGFR Mabs, anti-EGFr Mab, anti-EGFr MAb, Genen anti-EGFR Mab, MAb DC-101, trastuzumab, anti-VEGF monoclonal, anti-EGFR-DM1 Ab, MAb 4D5, BAB-447, EMD-55900, EMD-6200, -82633, anti-EGFR Mab, MAb 4D5, cetuximab, anti-EGFr MAb, anti-flk-1, CCX, CCZ, anti-flk-1, AG-514, AG-568, nti-EGFR-DM1 Ab, MDX-447, TgDCC-E1A, of: muellerian-inhibiting hormone, TNP-470, tecogalan sodium, C C225, matuzumab, panitumumab, DWP-408, and RC-3940II. In another

embodiment are provided compositions wherein the EGFR inhibitor is selected from the inhibitors disclosed in PCT/US04/027574 which is herein incorporated by reference in its entirety.

[00186] In a further embodiment the EGFR inhibitor is selected from the group consisting EGF receptor antisense, PI-88, oligonucleotide, bromelain molecules, amphiregulin, EGF fusion toxin, EGF fusion protein, Amphiregulin hbEGF-toxin, hbEGF-toxin, and EGF fusion protein.

[00187] As described herein "a selective EGFR inhibitory effect" is meant that the composition comprising a combination of a 1,2-diphenylpyrrole derivative with erlotinib displays selective inhibition against EGFR than other kinases. In some embodiments, combinations presently disclosed display selective inhibition against EGFR kinase than against other tyrosine kinases such as other erbBRs such as erbB2. For example in one embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative with erlotinib is at least 5 times or at least 10 times selective against EGFR than it is against erbB2, as determined from the relative IC_{50} values in suitable assays (for example by comparing the IC_{50} value from the KB cell assay with the IC_{50} value from the Clone 24 phospho-erbB2 cell assay for a given composition as described above). In another embodiment, the invention provides a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib wherein the combination is at least 5 times or at least 10 times selective against EGFR than it is against erbB2.

[00188] The compositions provided herein may be enantiomerically pure, such as a single enantiomer or a single diastereomer, or be stereoisomeric mixtures, such as a mixture of enantiomers, a racemic mixture, or a diastereomeric mixture, or a polymorph of the active agent, for example for erlotinib , polymorphs, including but not limited to polymorphs A, B, and E, and amorphous forms or solid amorphous dispersions as disclosed in US20060154941. As such, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (S) form. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate using, for example, chiral chromatography, recrystallization, resolution, diastereomeric salt formation, or derivatization into diastereomeric adducts followed by separation.

[00189] When the composition described herein contains an acidic or basic moiety, it may also be provided as a pharmaceutically acceptable salt (*See*, Berge et al., *J. Pharm. Sci.* **1977**, 66, 1-19; and "Handbook of Pharmaceutical Salts, Properties, and Use," Stah and Wermuth, Ed.; Wiley-VCH and VHCA, Zurich, 2002).

[00190] Suitable acids for use in the preparation of pharmaceutically acceptable salts include, but are not limited to, acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, boric acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid,

caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, cyclohexanesulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, α-oxo-glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, lauric acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, perchloric acid, phosphoric acid, L-pyroglutamic acid, saccharic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, undecylenic acid, and valeric acid.

[00191] Suitable bases for use in the preparation of pharmaceutically acceptable salts, including, but not limited to, inorganic bases, such as magnesium hydroxide, calcium hydroxide, potassium hydroxide, zinc hydroxide, or sodium hydroxide; and organic bases, such as primary, secondary, tertiary, and quaternary, aliphatic and aromatic amines, including L-arginine, benethamine, benzathine, choline, deanol, diethanolamine, diethylamine, dimethylamine, dipropylamine, diisopropylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylamine, ethylenediamine, isopropylamine, N-methyl-glucamine, hydrabamine, 1H-imidazole, L-lysine, morpholine, 4-(2-hydroxyethyl)-morpholine, methylamine, piperidine, piperazine, propylamine, pyrrolidine, 1-(2-hydroxyethyl)-pyrrolidine, pyridine, quinuclidine, quinoline, isoquinoline, secondary amines, triethanolamine, trimethylamine, triethylamine, N-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, and tromethamine.

[00192] The composition described herein may also be provided as a prodrug, which is a functional derivative of the 1,2-diphenylpyrrole derivative and/or the EGFR inhibitor and is readily convertible into the parent compound in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent compound. They may, for instance, be bioavailable by oral administration whereas the parent compound is not. The prodrug may also have enhanced solubility in pharmaceutical compositions over the parent compound. A prodrug may be converted into the parent drug by various mechanisms, including enzymatic processes and metabolic hydrolysis. See Harper, *Progress in Drug Research* **1962**, *4*, 221-294; Morozowich et al. in "Design of Biopharmaceutical Properties through Prodrugs and Analogs," Roche Ed., APHA Acad. Pharm. Sci. 1977; "Bioreversible Carriers in Drug in Drug Design, Theory and Application," Roche Ed., APHA Acad. Pharm. Sci. 1987; "Design of Prodrugs," Bundgaard, Elsevier, 1985; Wang et al., *Curr. Pharm. Design* 1999, *5*, 265-287; Pauletti et al., *Adv. Drug. Delivery Rev.* **1997**, *27*, 235-256; Mizen et al., *Pharm. Biotech.* **1998**, *11*, 345-365; Gaignault et al., *Pract. Med. Chem.* **1996**, 671-696; Asgharnejad in "Transport Processes in Pharmaceutical Systems," Amidon et al., Ed., Marcell Dekker, 185-218, 2000; Balant et al., *Eur. J. Drug Metab. Pharmacokinet.* **1990**, *15*, 143-53; Balimane and Sinko, *Adv. Drug Delivery*

Rev. **1999**, *39*, 183-209; Browne, *Clin. Neuropharmacol.* **1997**, *20*, 1-12; Bundgaard, *Arch. Pharm. Chem.* **1979**, *86*, 1-39; Bundgaard, *Controlled Drug Delivery* **1987**, *17*, 179-96; Bundgaard, *Adv. Drug Delivery Rev.* **1992**, *8*, 1-38; Fleisher et al., *Adv. Drug Delivery Rev.* **1996**, *19*, 115-130; Fleisher et al., *Methods Enzymol.* **1985**, *112*, 360-381; Farquhar et al., *J. Pharm. Sci.* **1983**, *72*, 324-325; Freeman et al., *J. Chem. Soc., Chem. Commun.* **1991**, 875-877; Friis and Bundgaard, *Eur. J. Pharm. Sci.* **1996**, *4*, 49-59; Gangwar et al., *Des. Biopharm. Prop. Prodrugs Analogs*, **1977**, 409-421; Nathwani and Wood, *Drugs* **1993**, *45*, 866-94; Sinhababu and Thakker, *Adv. Drug Delivery Rev.* **1996**, *19*, 241-273; Stella et al., *Drugs* **1985**, *29*, 455-73; Tan et al., *Adv. Drug Delivery Rev.* **1999**, *39*, 117-151; Taylor, *Adv. Drug Delivery Rev.* **1996**, *19*, 131-148; Valentino and Borchardt, *Drug Discovery Today* **1997**, *2*, 148-155; Wiebe and Knaus, *Adv. Drug Delivery Rev.* **1999**, *39*, 63-80; Waller et al., *Br. J. Clin. Pharmac.* **1989**, *28*, 497-507.

Methods of Use

[00193] The invention provides a method for treating a subject having tumors, tumor-related disorders, and/or cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib.

[00194] In one embodiment, the invention provides a method for treating a subject having tumors, tumor-related disorders, and/or cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole.

[00195] In another embodiment, the invention provides a method for treating a subject having tumors, tumor-related disorders, and/or cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the EGFR inhibitor is erlotinib.

[00196] In yet another embodiment, the invention provides a method for treating a subject having a tumors, tumor-related disorders, and/or cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor or their respective pharmaceutically acceptable salt, solvate or prodrug.

[00197] In one embodiment, the invention provides a method for treating a subject having tumors, tumor-related disorders, and/or cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is selected from the group consisting of: 4-methyl-2-(4-methylphenyl)-1-(4-sulfamoylphenyl)pyrrole; 2-(4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(4-chlorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 4-methyl-2-(4-methylthiophenyl)-1-(4-sulfamoylphenyl)pyrrole; 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(4-methoxy-3-methylphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(3-fluoro-4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(3,4-dimethylphenyl)-4-

methyl-1-(4-sulfamoylphenyl)pyrrole; 4-methyl-1-(4-methylthiophenyl)-2-(4-sulfamoylphenyl)pyrrole; 1-(4-acetylaminosulfonylphenyl)-4-methyl-2-(4-methoxyphenyl)pyrrole; and 1-(4-acetylaminosulfonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole.

[00198] In yet another embodiment, the invention provides a method for treating a subject having tumors, tumor-related disorders, and/or cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative and the EGFR inhibitor are administered sequentially in either order or simultaneously. In a further embodiment, the invention provides a method for treating a subject having tumors, tumor-related disorders, and/or cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is administered first. In one embodiment, the invention provides a method for treating a subject having tumors, tumor-related disorders, and/or cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the EGFR inhibitor is administered first. In another embodiment, the invention provides a method for treating a subject having tumors, tumor-related disorders, and/or cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein administering the combination enhances treatment of the subject in comparison to a treatment of either a 1,2-diphenylpyrrole derivative or an EGFR inhibitor alone. In yet another embodiment, the invention provides a method for treating a subject having tumors, tumor-related disorders, and/or cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein administering the combination reduces the side effects of the treatment of tumors, tumor-related disorders, and/or cancer.

[00199] In one embodiment, the invention provides a method for treating a subject having tumors, tumor-related disorders, and/or cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the cancer is selected from the group consisting of: oral cancer, prostate cancer, rectal cancer, non-small cell lung cancer, lip and oral cavity cancer, liver cancer, lung cancer, anal cancer, kidney cancer, vulvar cancer, breast cancer, oropharyngeal cancer, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, urethra cancer, small intestine cancer, bile duct cancer, bladder cancer, ovarian cancer, laryngeal cancer, hypopharyngeal cancer, gallbladder cancer, colon cancer, colorectal cancer, head and neck cancer, parathyroid cancer, penile cancer, vaginal cancer, thyroid cancer, pancreatic cancer, esophageal cancer, Hodgkin's lymphoma, leukemia-related disorders, mycosis fungoides, and myelodysplastic syndrome.

[00200] In another embodiment, the invention provides a method for treating a subject having tumors, tumor-related disorders, and/or cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the cancer is non-small cell lung cancer, pancreatic cancer, breast cancer, ovarian cancer, colorectal cancer, and head and neck cancer.

[00201] In one embodiment, the invention provides a method for treating a subject having tumors, tumor-related disorders, and/or cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the cancer is a carcinoma, a tumor, a neoplasm, a lymphoma, a melanoma, a glioma, a sarcoma, and a blastoma. In another embodiment, the invention provides a method for treating a subject having a carcinoma, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the carcinoma is selected from the group consisting of: carcinoma, adenocarcinoma, adenoid cystic carcinoma, adenosquamous carcinoma, adrenocortical carcinoma, well differentiated carcinoma, squamous cell carcinoma, serous carcinoma, small cell carcinoma, invasive squamous cell carcinoma, large cell carcinoma, islet cell carcinoma, oat cell carcinoma, squamous carcinoma, undifferentiatied carcinoma, verrucous carcinoma, renal cell carcinoma, papillary serous adenocarcinoma, merkel cell carcinoma, hepatocellular carcinoma, soft tissue carcinomas, bronchial gland carcinomas, capillary carcinoma, bartholin gland carcinoma, basal cell carcinoma, carcinosarcoma, papilloma/carcinoma, clear cell carcinoma, endometrioid adenocarcinoma, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, cholangiocarcinoma, actinic keratoses, cystadenoma, and hepatic adenomatosis. In a further embodiment the tumor is selected from the group consisting of: astrocytic tumors, malignant mesothelial tumors, ovarian germ cell tumor, supratentorial primitive neuroectodermal tumors, Wilm's tumor, pituitary tumors, extragonadal germ cell tumor, gastrinoma, germ cell tumors, gestational trophoblastic tumor, brain tumors, pineal and supratentorial primitive neuroectodermal tumors, pituitary tumor, somatostatin-secreting tumor, endodermal sinus tumor, carcinoids, central cerebral astrocytoma, glucagonoma, hepatic adenoma, insulinoma, medulloepithelioma, plasmacytoma, vipoma, and pheochromocytoma. In yet another embodiment, the invention provides a method for treating a subject having a neoplasm, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the neoplasm is selected from the group consisting of: intaepithelial neoplasia, multiple myeloma/plasma cell neoplasm, plasma cell neoplasm, interepithelial squamous cell neoplasia, endometrial hyperplasia, focal nodular hyperplasia, hemangioendothelioma, and malignant thymoma. In one embodiment the lymphoma is selected from the group consisting of: nervous system lymphoma, AIDS-related lymphoma, cutaneous T-cell lymphoma, non-Hodgkin's lymphoma, lymphoma, and Waldenstrom's macroglobulinemia. In another embodiment the melanoma is selected from the group consisting of: acral lentiginous melanoma, superficial spreading melanoma,

uveal melanoma, lentigo maligna melanomas, melanoma, intraocular melanoma, adenocarcinoma nodular melanoma, and hemangioma.

[00202] In a further embodiment, the invention provides a method for treating a subject having a sarcoma, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the sarcoma is selected from the group consisting of: adenomas, adenosarcoma, chondosarcoma, endometrial stromal sarcoma, Ewing's sarcoma, Kaposi's sarcoma, leiomyosarcoma, , rhabdomyosarcoma, sarcoma, uterine sarcoma, osteosarcoma, and pseudosarcoma. In one embodiment, the glioma is selected from the group consisting of: glioma, brain stem glioma, and hypothalamic and visual pathway glioma. In another embodiment, the invention provides a method for treating a subject having a blastoma, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the blastoma is selected from the group consisting of: pulmonary blastoma, pleuropulmonary blastoma, retinoblastoma, neuroblastoma, medulloblastoma, glioblastoma, and hemangiblastomas.

[00203] In one embodiment the EGFR inhibitor is a small molecule compound or an antibody. In another embodiment the EGFR inhibitor is a small molecule compound is selected from the group consisting of: ZM-254530, BIBX-1382, reveromycin A, gefitinib, CGP-57148, CGP-59326, 4-(m-chloro)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine, tyrphostin, PKI-166, PD 153035, EKB-569, and 4-(phenylamino)quinazolines, or their pharmaceutically acceptable salts, solvates, or prodrugs. In a further embodiment, the EGFR inhibitor is an antibody is selected from the group consisting of: EGF receptor antibody, MR1scFvPE38KDEL MDX-447, MDX-210, MD-72000, MDX-260, wayne anti-EGFR Mabs, anti-EGFr Mab, anti-EGFr MAb, Genen anti-EGFR Mab, MAb DC-101, trastuzumab, anti-VEGF monoclonal, anti-EGFR-DM1 Ab, MAb 4D5, BAB-447, EMD-55900, EMD-6200, -82633, anti-EGFR Mab, MAb 4D5, cetuximab, anti-EGFr MAb, anti-flk-1, CCX, CCZ, anti-flk-1, AG-514, AG-568, nti-EGFR-DM1 Ab, MDX-447, TgDCC-E1A, C225, matuzumab, panitumumab, DWP-408, and RC-3940II. In yet a further embodiment the EGFR inhibitor is selected from the group consisting of: muellerian-inhibiting hormone, TNP-470, tecogalan sodium, EGF receptor antisense, PI-88, oligonucleotide, bromelain molecules, amphiregulin, EGF fusion toxin, EGF fusion protein, Amphiregulin hbEGF-toxin, hbEGF-toxin, and EGF fusion protein.

[00204] In one embodiment the invention provides a method of inducing differentiation of tumor cells, the method comprising contacting the cells with an effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor whereby the combination induces differentiation of tumor cells. In one embodiment, the invention provides a method of inducing differentiation of tumor cells, the method comprising contacting the cells with an effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

[00205] In one embodiment the invention provides a method of inhibiting proliferation of cancer cells, the method comprising contacting a cancer cell with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor whereby the combination inhibits proliferation of cancer cells. In one embodiment, the invention provides a method of inhibiting proliferation of cancer cells, the method comprising contacting a cancer cell with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

[00206] In another embodiment the invention provides a method for reducing proliferation of cancer cells, the method comprising delivering to the cells a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor, whereby the reduction of cell proliferation is greater than a reduction caused by either a 1,2-diphenylpyrrole derivative alone or an EGFR inhibitor alone. In one embodiment, the invention provides a method for reducing proliferation of cancer cells, the method comprising delivering to the cells a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

[00207] In one embodiment the invention provides a method of modulating autophosphorylation with a molecule of ATP, the method comprising delivering to a cancer cell an effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination inhibits autophosphorylation with a molecule of ATP. In one embodiment, the invention provides a method of modulating autophosphorylation with a molecule of ATP, the method comprising delivering to a cancer cell an effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

[00208] In a further embodiment the invention provides a method of inhibiting metastases of tumor cells, the method comprising administering an effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor such that the combination inhibits metastatic activity of tumor cells. In one embodiment, the invention provides a method of inhibiting metastases of tumor cells, the method comprising administering an effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

[00209] In one embodiment the invention provides a method for inducing apoptosis in cancer cells, the method comprising contacting the cancer cells with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor sufficient to induce apoptosis. In one embodiment, the invention provides a method for inducing apoptosis in cancer cells, the method comprising contacting the cancer cells with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

[00210] In another embodiment the invention provides a method for sensitizing EGFR inhibitor resistant cancer cells to an EGFR inhibitor, the method comprising administering a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination sensitizes the cancer cells to the EGFR inhibitor. In one embodiment, the invention provides a method for sensitizing EGFR inhibitor resistant cancer cells to an EGFR inhibitor, the method comprising administering a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

[00211] In a further embodiment the invention provides a method of modulating prostaglandin synthesis in a cancer cell, the method comprising contacting the cell with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination inhibits prostaglandin synthesis in a cancer cell. In one embodiment, the invention provides a method of modulating prostaglandin synthesis in a cancer cell, the method comprising contacting the cell with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

[00212] In one embodiment the invention provides a method of modulating cyclooxygenase expression in a cancer cell, the method comprising delivering to the cell a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination inhibits cyclooxygenase expression in a cancer cell. In one embodiment, the invention provides a method of modulating cyclooxygenase expression in a cancer cell, the method comprising delivering to the cell a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

[00213] In one embodiment the invention provides a method of modulating angiogenesis in a cancer cell, the method comprising contacting the cell with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination inhibits angiogenesis in a cancer cell. In one embodiment the invention provides a method of modulating angiogenesis in a cancer cell, the method comprising contacting the cell with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib. In another embodiment the invention provides a method of reducing the dosage in conventional treatment for neoplasia and/or neoplasia related disorders in a subject, the method comprising administering to a subject a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination reduces the dosage in conventional treatment for neoplasia and/or neoplasia-related disorders. In one embodiment, the invention provides a method of reducing the dosage in conventional treatment for neoplasia and/or neoplasia related disorders in a subject, the method comprising administering to a

subject a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

[00214] In one embodiment the invention provides a method of treating neoplasia and/or neoplasia related disorders, the method comprising administering a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor. In one embodiment, embodiment the invention provides a method of treating neoplasia and/or neoplasia related disorders, the method comprising administering a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

[00215] The combinations presently described herein may also be useful in the treatment of additional disorders in which aberrant expression ligand/receptor interactions or activation or signalling events related to various protein tyrosine kinases are involved. Such disorders may include those of neuronal, glial, astrocytal, hypothalamic, glandular, macrophagal, epithelial, stromal, or blastocoelic nature in which aberrant function, expression, activation or signalling of the erbB tyrosine kinases are involved. In addition, the combinations presented herein may have therapeutic utility in inflammatory, angiogenic and immunologic disorders involving both identified and as yet unidentified tyrosine kinases that are inhibited by the combinations presented herein.

Combination Therapy

[00216] In some embodiments, the composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor described herein, has an effect that is additive of the effects of the 1,2-diphenylpyrrole derivative alone and the effects of the EGFR inhibitor alone. In another embodiment, the invention provides a composition comprising, a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib, wherein the combination has an effect that is additive of the effects of the 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole alone and the effects of erlotinib alone.

[00217] In some other embodiments, the composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor described herein, has an effect that is greater than the additive effects of the 1,2-diphenylpyrrole derivative alone and the effects of the EGFR inhibitor alone. In another embodiment, the invention provides a composition comprising, a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib, wherein the combination has an effect that is greater than the additive effects of the 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole alone and the effects of erlotinib alone.

[00218] In some embodiments, the composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor described herein, has an effect that is greater than the effects of the

1,2-diphenylpyrrole derivative alone (e.g., cyclooxygenase-2 inhibition alone). In another embodiment, the invention provides a composition comprising, a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib, wherein the combination has an effect that is greater than the effects of the 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole alone.

[00219] In other embodiments, the composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor described herein, has an effect that is greater than the effects of the EGFR inhibitor alone (epidermal growth factor receptor kinase inhibition alone). In another embodiment, the invention provides a composition comprising, a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib, wherein the combination has an effect that is greater than the effects of erlotinib alone.

[00220] In other embodiments, the invention provides a method for treating cancer, tumors, and tumor-related disorders comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor described herein, wherein the combination has an effect that is additive of the effects of the 1,2-diphenylpyrrole derivative alone and the effects of the EGFR inhibitor alone. In further embodiments, the invention provides a method for treating cancer, tumors, and tumor-related disorders comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib, wherein the combination has an effect that is additive of the effects of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole alone and the effects of erlotinib alone.

[00221] In some other embodiments, the invention provides a method for treating cancer, tumors, and tumor-related disorders, comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor described herein, wherein the combination has an effect that is greater than the additive effects of the effects of the 1,2-diphenylpyrrole derivative alone and the effects of the EGFR inhibitor alone. In other embodiments, the invention provides method for treating cancer, tumors, and tumor-related disorders, comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib, wherein the combination has an effect that is greater than the additive effects of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole alone and the effects of erlotinib alone.

[00222] In some embodiments, the invention provides a method for treating cancer, tumors, and tumor-related disorders comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor described herein, wherein the combination has an

effect that is greater than the effects of the 1,2-diphenylpyrrole derivative alone (e.g., cyclooxygenase-2 inhibition alone). In other embodiments, the invention provides a method for treating cancer, tumors, and tumor-related disorders comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib, wherein the combination has an effect that is greater than the effects of is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole alone.

[00223] In further embodiments, the invention provides a method for treating cancer, tumors, and tumor-related disorders comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor described herein, wherein the combination has an effect that is greater than the effects of the EGFR inhibitor alone (epidermal growth factor receptor kinase inhibition alone). In other embodiments, the invention provides a method for treating cancer, tumors, and tumor-related disorders comprising administering a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib, wherein the combination has an effect that is greater than the effects of erlotinib alone.

[00224] Synergism of the composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor, may be used to obtain the desired effect at doses to which side effects are minimal. For example, a patient may be treated for a disease, disorder, or condition which benefits from EGFR inhibition, such as tumors, tumor-related diseases, cancer, neoplasia, while concomitantly being treated for a side effect of the EGFR inhibition, such as inflammation, through the benefit of the 1,2-diphenylpyrrole derivative inhibitor. In one embodiment, the invention provides a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib which may be used to obtain the desired effect at doses to which side effects are minimal.

[00225] The composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor, may be applied as a sole therapy or may involve one or more other materials and treatment agents such as but not limited to a combination of inhibitors of MMP (matrix-metallo-proteinase), other tyrosine kinases including VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, $CTLA_4$ (cytotoxic T-lymphocyte antigen 4) and erbB2, as well as MAb to VEGFr, and other cancer-related antibodies including rhuMAb-VEGF, the erbB2 MAb, or avb3.

[00226] Thus, the composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor, may be applied with one or more other anti-tumor substances, for example, those selected from, mitotic inhibitors, for example vinblastine; alkylating agents, for example, cis-platin, carboplatin, and cyclophosphamide; anti-metabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea, or, for example, anti-metabolites such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2 -thenoyl)-L-glutamic acid; growth factor inhibitors; cell

cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example interferon; and anti-hormones, for example anti-estrogens such as Nolvadex® (tamoxifen) or, for example anti-androgens such as Casodex® (4'-cyano-3-(4-fluorophenyl sulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide). In one embodiment, the invention provides a combination a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib, may be applied with one or more other anti-tumor substances, for example, those selected from, mitotic inhibitors, for example vinblastine; alkylating agents, for example, cis-platin, carboplatin, and cyclophosphamide; anti-metabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea, or, for example, anti-metabolites such as N-(5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2 -thenoyl)-L-glutamic acid; growth factor inhibitors; cell cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example interferon; and anti-hormones, for example anti-estrogens such as Nolvadex® (tamoxifen) or, for example anti-androgens such as Casodex® (4'-cyano-3-(4-fluorophenyl sulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide).

[00227] For the combination therapies including combination therapies having pharmaceutical compositions described herein, the effective amounts of the compound presently described herein useful for inhibiting abnormal cell growth (e.g., other antiproliferative agent, anti-angiogenic, signal transduction inhibitor or immune-system enhancer) can be determined by those of ordinary skill in the art, based on the effective amounts for the compound described herein and those known or described for the chemotherapeutic or other agent. The formulations and routes of administration for such therapies and compositions can be based on the information described herein for compositions and therapies comprising the combinations presented herein as the sole active agent and on information provided for the chemotherapeutic or other agent in combination therewith.

[00228] In one embodiment, the invention provides a method for inhibiting abnormal cell growth in a subject comprising administering to the subject an effective amount of a composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor, or their pharmaceutically acceptable salt, solvate or prodrug thereof, in combination with radiation therapy effective in inhibiting abnormal cell growth in the subject. Techniques for administering radiation therapy are known to a person of skill in the art and these techniques can be used in the combination therapy described herein.

Additional Therapy

[00229] Available additional treatments for cancer that may be advantageously employed in combination with the therapies and compositions disclosed herein include, without limitation, surgery, radiation therapy, chemotherapy, high dose chemotherapy with stem cell transplant; hormone therapy, and monoclonal antibody therapy.

[00230] Surgical procedure are often used in the treatment of cancer.

[00231] Radiation therapy is a cancer treatment that uses high-energy x-rays or other types of radiation to kill cancer cells or keep them from growing.

[00232] Chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is placed directly into the spinal column, an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy). The way the chemotherapy is given depends on the type and stage of the cancer being treated.

[00233] Different chemotherapeutic agents are known in the art for treating cancer. Cytoxic agents used for treating cancer include doxorubicin, cyclophosphamide, methotrexate, 5-fluorouracil, mitomycin C, mitoxantrone, paclitaxel, taxane formulations such as by way of example only, Abraxane® (ABI-007), Paclitaxel-Cremophor EL, Paclitaxel poliglumex, and Paclitaxel injectable emulsion (PIE), gemcitabine, docetaxel, capecitabine and epirubicin.

[00234] Other chemotherapy against cancer includes treatment with one or more of bendamustine, carboplatin (for example, Paraplatin®), carmustine (for example, BCNU®), chlorambucil (for example, Leukeran®), cisplatin (for example, Platinol®), cyclophosphamide injection (for example, Cytoxan®), oral cyclophosphamide (for example, Cytoxan®), dacarbazine (for example, DTIC®), ifosfamide (for example, ifex®), lomustine (for example, CCNU®), mechlorethamine (for example, nitrogen mustard, Mustargen®), melphalan (for example, Alkeran®), procarbazine (for example, Matulane®), bleomycin (for example, Blenoxane®), doxorubicin (for example, Adriamycin®, Rubex®), epirubicin, Idarubicin (for example, Idamycin®), mitoxantrone (for example, Novantrone®), gemcitabine (for example, Gemzar®), oral mercaptopurine (for example, Purinethol®). methotrexate, pentostatin IV (for example, Nipent®), oral thioguanine (for example, Lanvis®), oral etoposide (for example, VP-16, VePesid®, Etopophos) - etoposide IV (for example, VP-16, VePesid®, Etopophos), vinblastine (for example, Velban®), vincristine (for example, Oncovin®), vinorelbine (for example, Navelbine®), dexamethasone (for example, Decadron®), methylprednisolone (for example, Medrol®), and prednisone (for example, Deltasone®). Erlotinib in combination with gemcitabine is indicated for the treatment of advanced pancreatic cancer.

[00235] Monoclonal antibody therapy is a cancer treatment that uses antibodies made in the laboratory, from a single type of immune system cell. These antibodies can identify substances on cancer cells or normal substances that may help cancer cells grow. The antibodies attach to the substances and kill the cancer cells, block their growth, or keep them from spreading. Monoclonal antibodies are given by infusion. They may be used alone or to carry drugs, toxins, or radioactive material directly to cancer cells. Monoclonal antibodies are also used in combination with chemotherapy as adjuvant therapy.

[00236] Trastuzumab (Herceptin®) is a monoclonal antibody that blocks the effects of the growth factor protein HER2, which transmits growth signals to breast cancer cells.

[00237] Trastuzumab leads to clinical responses as a single agent and improves survival when added to chemotherapy for advanced HER2-positive breast cancer. However, some patients do not respond to trastuzumab, and most eventually develop clinical resistance. Mechanisms of intrinsic and acquired trastuzumab resistance are poorly understood. One study which utilized a cell line-based approach to delineate genetic and protein alterations associated with resistance has been reported. (D. Tripathy et al Journal of Clinical Oncology, 2005 Vol 23, No 16S, 3121. These researchers studied two HER2-positive breast cancer cell lines (BT474 and SKBR3) that were serially passaged in the presence of trastuzumab until *in vitro* resistance was documented. Resistant cell lines emerged after 12 months and exhibited a 3-fold more rapid growth rate in the absence of trastuzumab. Following trastuzumab exposure, G_0/G_1 arrest was observed in sensitive compared to resistant cells (84 vs. 68%), with fewer cells in S-phase (3 vs. 14%). Resistant cell lines exhibited fewer changes in gene expression with trastuzumab as well as upregulation of the chemokine receptor CXCR4 and mitotic checkpoint regulators, and downregulation of PTEN compared to sensitive cells.

[00238] Additional, illustrative, treatments that may be advantageously combined with the compositions and therapies disclosed herein may include, without limitation, administration of agents including, but not limited to capecitabine, docetaxel, epirubicin, epothilone A, B or D, goserelin acetate, paclitaxel, pamidronate, bevacizumab, and trastuzumab.

EGFR Resistance

[00239] Studies have shown that after a period of about 8-12 months of EGFR-directed treatments, the cancer cells become resistant to the treatment, most commonly by 1) recruiting a mutated IGF-1 receptor to act as one of the EGFR partners in the homodimer, thus, forming a heterodimer (this allows the signal to be transmitted even in the presence of an EGFR inhibitor); 2) the presence of redundant tyrosine kinase receptors; 3) increased angiogenesis; 4) the constitutive activation of downstream mediators; and 5) the existence of specific EGFR mutations. Understanding the molecular mechanisms of resistance and sensitivity may lead to improvements in therapies that target EGFR.

[00240] IGF-1R activates many of the same downstream pathways as EGFR and can lead to tumorigenesis, increased proliferation, angiogenesis, and metastasis. PI-3K/Akt signaling is a critical component of the downstream mediation of EGFR and also plays a functional role in IGF-1R signaling. Without wishing to be bound by any particular theory, this redundancy may explain how the receptors can mimic the function of one another. Chakravarti et al., identified two glioblastoma cell lines that each overexpressed EGFR but exhibited very different responses to EGFR inhibitors. The resistant cell line significantly overexpressed IGF-1R and showed further increases in IGF-1R expression in response to EGFR inhibition by AG1478, an EGFR TKI. PI-3K/Akt signaling persisted in these resistant cell lines in response to AG1478 treatment, and these cells also maintained their invasive and antiapoptotic characteristics. These studies support the concept of redundant signaling through IGF-1R that maintains activation of critical pathways for survival in the presence of EGFR

inhibition. Inhibiting both IGF-1R and EGFR may significantly reduce the growth and invasiveness of cells that are resistant to EGFR inhibitors alone. Further evidence that IGF-1R activation may bypass inhibition of other tyrosine kinase receptors comes from a study by Lu et al., who showed that the degree of overexpression of IGF-1R was inversely related to the response of breast cancer cells to trastuzumab, an antibody directed against ErbB2. SKBR3 human breast cancer cells, which normally overexpress HER2/neu and minimally express IGF-1R, showed a 42% decrease in proliferation in response to trastuzumab. Unlike the parental cell line

[00241], SKBR3 cells that were engineered to overexpress IGF-1R showed no response to trastuzumab. When the IGF-1R was inhibited by IGF-binding protein-3 in the engineered cell lines, the response to trastuzumab returned to normal. These studies clearly indicate that activation of alternative tyrosine kinase receptors in tumor cells may override the effect of EGFR family inhibitors. These examples suggest that a combination may be able to overcome resistance to a single receptor inhibitor and thus more effectively inhibit pathways leading to cancer growth and survival. Recently, an enhanced response was shown in breast cancer cell lines treated with either recombinant bispecific antibodies to both EGFR and IGF-1R or a combination of single receptor antibodies compared with either antibody alone. Signaling pathways downstream of the receptors were also more effectively inhibited by the combination therapy. By combining therapies that attack multiple cell surface and intracellular signaling pathways, redundant receptor signaling might be blocked and greater clinical benefit achieved. Thus, identifying key downstream signaling molecules in which growth factor receptor signals converge may be important in the development of therapeutic agents that block signals from multiple activated growth factor receptors. Similarly, Jung et al. discloses the use of a combination of mAbs to EGFR and mAbs to VEGFR-2 to treat gastric cancer grown in nude mice. Both mAbs were modestly effective at inhibiting tumor growth, but the combination achieved significantly greater tumor growth inhibition that was also associated with decreased tumor vascularity and increased tumor cell apoptosis.

[00242] In one embodiment the invention provides a method for treating a subject having an EGFR inhibitor resistant cancer cell comprising administering to the subject a therapeutically effective amount of a composition comprising a 1,2-diphenylpyrrole derivative in combination with an EGFR inhibitor. In one embodiment, the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole. In another embodiment the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

[00243] In one embodiment the invention provides a method for sensitizing EGFR inhibitor resistant cancer cells to an EGFR inhibitor, the method comprising administering a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination sensitizes the cancer cells to the EGFR inhibitor. In one embodiment, the invention provides a method for sensitizing EGFR inhibitor resistant cancer cells to erlotinib, the method comprising administering a combination

comprising a 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib wherein the combination sensitizes the cancer cells erlotinib.

Lung Cancer

[00244] In many countries including Japan, Europe and America, the number of patients with lung cancer is fairly large and continues to increase year after year and is the most frequent cause of cancer death in both men and women. Although there are many potential causes for lung cancer, tobacco use, and particularly cigarette smoking, is the most important. Additionally, etiologic factors such as exposure to asbestos, especially in smokers, or radon are contributory factors. Also occupational hazards such as exposure to uranium have been identified as an important factor. Finally, genetic factors have also been identified as another factor that increases the risk of cancer.

[00245] Lung cancers can be histologically classified into non-small cell lung cancers (e.g. squamous cell carcinoma (epidermoid), adenocarcinoma, large cell carcinoma (large cell anaplastic), etc.) and small cell lung cancer (oat cell). Non-small cell lung cancer (NSCLC) has different biological properties and responses to chemotherapeutics from those of small cell lung cancer (SCLC). Thus, chemotherapeutic formulas and radiation therapy are different between these two types of lung cancer.

Non-Small Cell Lung Cancer

[00246] Where the location of the non-small cell lung cancer tumor can be easily excised (stage I and II disease) surgery is the first option of therapy and offers a relatively good chance for a cure. In more advanced disease (stage IIIa and greater), however, where the tumor has extended to tissue beyond the bronchopulmonary lymph nodes, surgery may not lead to complete excision of the tumor. In such cases, the patient's chance for a cure by surgery alone is greatly diminished. Where surgery will not provide complete removal of the NSCLC tumor, other types of therapies must be utilized. Today, chemoradiation therapy, is the standard treatment to control unresectable or inoperable NSCLC. Improved results have been seen when radiation therapy has been combined with chemotherapy, but gains have been modest and the search continues for improved methods of combining modalities.

[00247] Radiation therapy is based on the principle that high-dose radiation delivered to a target area will result in the death of reproductive cells in both tumor and normal tissues. The radiation dosage regimen is generally defined in terms of radiation absorbed dose (rad), time and fractionation, and must be carefully defined by the oncologist. The amount of radiation a patient receives will depend on various consideration but the two most important considerations are the location of the tumor in relation to other critical structures or organs of the body, and the extent to which the tumor has spread. One course of treatment for a patient undergoing radiation therapy for NSCLC will be a treatment schedule over a 5 to 6 week period, with a total dose of 50 to 60 Gy administered to the patient in a single daily fraction of 1.8 to 2.0 Gy, 5 days a week. A Gy is an abbreviation for Gray and refers to 100 rad of dose.

[00248] As NSCLC is a systemic disease, however, and radiation therapy is a local modality, radiation therapy as a single mode of therapy is unlikely to provide a cure for NSCLC, at least for those tumors

that have metastasized distantly outside the zone of treatment. Thus, the use of radiation therapy with other modality regimens has important beneficial effects for the treatment of NSCLC.

[00249] Generally, radiation therapy has been combined temporally with chemotherapy to improve the outcome of treatment. There are various terms to describe the temporal relationship of administering radiation therapy in combination with COX-2 inhibitors and chemotherapy, and the following examples are the treatment regimens and are provided for illustration only and are not intended to limit the use of other combinations. "Sequential" therapy refers to the administration of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib and/or radiation therapy separately in time in order to allow the separate administration of the composition, and/or radiation therapy. "Concomitant" therapy refers to the administration of the composition, and/or radiation therapy on the same day.

[00250] Finally, "alternating" therapy refers to the administration of radiation therapy on the days in which the composition would not have been administered if it was given alone. It is reported that advanced non-small cell lung cancers do not respond favorably to single-agent chemotherapy and useful therapies for advanced inoperable cancers have been limited. (Journal of Clinical Oncology, vol. 10, pp. 829-838 (1992)).

[00251] Japanese Patent Kokai 5-163293 refers to some specified antibiotics of 16-membered-ring macrolides as a drug delivery carrier capable of transporting anthracycline-type anticancer drugs into the lungs for the treatment of lung cancers. Thus, the use of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib and a macrolide as a drug delivery carrier is contemplated herein for the treatment of non-small cell lung cancer.

[00252] Several chemotherapeutic agents have been shown to be efficacious against NSCLC. Chemotherapeutic agents that can be used in the present disclosure against NSCLC include cisplatin, carboplatin, paclitaxel, docetaxel, taxane formulations such as by way of example only, Abraxane® (ABI-007), Paclitaxel-Cremophor EL, Paclitaxel poliglumex, and Paclitaxel injectable emulsion (PIE), gemcitabine, navelbine, pemetrexate, etoposide, methotrexate, 5-Fluorouracil, epirubicin, doxorubicin, vinblastine, cyclophosphamide, ifosfamide, mitomycin C, epirubicin, vindesine, camptothecins, fotemustine, and edatrexate.

[00253] In one embodiment, the invention provides a method of the treatment of NSCLC which utilizes a therapeutically effective amounts of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib. Further, therapy for the treatment of NSCLC utilizes a therapeutically effective amounts of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole with erlotinib, and one of the following antineoplastic agents: bevacizumab, docetaxel, gefitinib, gemcitabine, cisplatin, carboplatin, etoposide, paclitaxel, pemetrexate, vinorelbine, or radiation therapy.

Small Cell Lung Cancer

[00254] Approximately 15 to 20 percent of all cases of lung cancer reported worldwide are small cell lung cancer (SCLC). Ihde DC: Cancer 54:2722, 1984. Currently, treatment of SCLC incorporates multi-modal therapy, including chemotherapy and radiation therapy. Response rates of localized or disseminated SCLC remain high to systemic chemotherapy, however, persistence of the primary tumor and persistence of the tumor in the associated lymph nodes has led to the integration of several therapeutic modalities in the treatment of SCLC.

[00255] Therapy for the treatment of lung cancer according to one embodiment of the invention utilizes a combination of therapeutically effective amount of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib. In another embodiment, therapy for the treatment of lung cancer according to the invention utilizes a combination of therapeutically effective amount of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib and one of the following antineoplastic agents: vincristine, docetaxel, camptothecin, topotecan cisplatin, carboplatin, cyclophosphamide, epirubicin (high dose), etoposide (VP-16) I.V., etoposide (VP-16) oral, isofamide, teniposide (VM-26), doxorubicin, and amrubicin. Other preferred single-agents chemotherapeutic agents that may be used in the present disclosure include BCNU (carmustine), vindesine, hexamethylmelamine (altretamine), methotrexate, nitrogen mustard, and CCNU (lomustine). Other chemotherapeutic agents under investigation that have shown activity against SCLC include iroplatin, gemcitabine, Ionidamine, and taxol.

Glioma

[00256] A glioma is a type of primary central nervous system (CNS) tumor that arises from glial cells. The most common site of involvement of gliomas is the brain, but they can also affect the spinal cord or any other part of the CNS, such as the optic nerves. Treatment for brain gliomas depends on the location and the grade. Often, treatment is a combined approach, using surgery, radiation therapy, and chemotherapy. The radiation therapy is in the form of external beam radiation or the stereotactic approach using radiosurgery. Spinal cord tumors can be treated by surgery and radiation. Temozolomide is a chemotherapeutic drug that is able to cross the blood-brain barrier effectively and is being used in therapy.

[00257] EGFR is frequently amplified, overexpressed, or mutated in glioblastomas, but gnereally only 10 to 20 % of patients have a response to EGFR inhibitors. It has been shown that glioblastoma that overexpresses the EGFRvIII oncogene and are PTEN tumor suppressor wildtype are sensitive to erlotinib treatment.

[00258] Therapy for the treatment of glioma according to one embodiment of the invention utilizes a combination of therapeutically effective amount of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib. In another embodiment, therapy for the treatment of glioma according to the invention utilizes a combination of therapeutically

effective amount of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib and temozolomide.

Head and Neck Cancer

[00259] Head and neck cancer includes cancers of the mouth, nose, sinuses, salivary glands, throat and lymph nodes in the neck. Most begin in the moist tissues that line the mouth, nose and throat. Symptoms include a lump or sore that does not heal, a sore throat that does not go away, trouble swallowing and a change or hoarseness in the voice. Using tobacco or alcohol increases cancer risk. Treatments of head and neck cancer may include surgery, radiation therapy, chemotherapy or a combination. Treatments can affect eating, speaking or even breathing, so patients may need rehabilitation.

[00260] Head and neck cancer is often complex, with many different sites and staging systems. However, current therapy offers several alternatives, including surgery, radiation, and chemotherapy, either alone or in combination.

[00261] Combined modality therapy is becoming the principal method of treating patients with locally advanced head and neck cancers. Meanwhile, researchers are actively investigating new treatments such as gene therapy. Newer chemotherapy agents (e.g., paclitaxel [Taxol®], docetaxel [Taxotere®], gemcitabine [Gemzar®], doxorubicin [Doxil®]) may be combined with established chemotherapeutic agents (e.g., methotrexate [Trexall®, Methotrex®]) to improve results.

[00262] In March 2006, the Food and Drug Administration (FDA) approved cetuximab (Erbitux®), in combination with radiation, for patients with squamous cell carcinoma of the head and neck that cannot be treated surgically. Cetuximab also may be used alone (called monotherapy) in patients with head and neck cancer that has spread (metastasized) following standard chemotherapy.

[00263] Therapy for the treatment of head and neck cancer according to one embodiment of the invention utilizes a combination of therapeutically effective amount of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib. In another embodiment,therapy for the treatment of head and neck cancer according to the invention utilizes a combination of therapeutically effective amount of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib and one or more chemotherapy agents (e.g., paclitaxel [Taxol®], docetaxel [Taxotere®], gemcitabine [Gemzar®], doxorubicin [Doxil®]) which may be further combined with established chemotherapeutic agents (e.g., methotrexate [Trexall®, Methotrex®]). In another embodiment, therapy for the treatment of head and neck cancer according to the invention utilizes a combination of therapeutically effective amount of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib and Erbitux®.

Colorectal Cancer

[00264] COX-2 expression levels correlate with survival rates in colorectal cancer (see Figure 1.) Survival from colorectal cancer depends on the stage and grade of the tumor, for example precursor

adenomas to metastatic adenocarcinoma. Generally, colorectal cancer can be treated by surgically removing the tumor, but overall survival rates remain between 45 and 60 percent. Colonic excision morbidity rates are fairly low and are generally associated with the anastomosis and not the extent of the removal of the tumor and local tissue. In patients with a high risk of reoccurrence, however, chemotherapy has been incorporated into the treatment regimen in order to improve survival rates.

[00265] Tumor metastasis prior to surgery is generally believed to be the cause of surgical intervention failure and up to one year of chemotherapy is required to kill the non-excised tumor cells. As severe toxicity is associated with the chemotherapeutic agents, only patients at high risk of recurrence are placed on chemotherapy following surgery. Thus, the incorporation of an antiangiogenesis inhibitor into the management of colorectal cancer plays an important role in the treatment of colorectal cancer and lead to overall improved survival rates for patients diagnosed with colorectal cancer.

[00266] One embodiment of the invention provides a combination therapy for the treatment of colorectal cancer including surgery, followed by a regimen of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib. Further, another embodiment of the invention provides a combination therapy for the treatment of colorectal cancer including surgery, followed by a regimen of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib, and one or more antiangiogenic agents including an MMP inhibitor, or an integrin antagonist, cycled over a one year time period. A further embodiment of the invention provides a combination therapy for the treatment of colorectal cancer including a regimen of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib, followed by surgical removal of the tumor from the colon or rectum and then followed be a regimen of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib cycled over a one year time period. Another therapy for the treatment of colon cancer comprises administering a combination of therapeutically effective amounts of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib.

[00267] A further therapy for the treatment of colon cancer is a combination of a treatment with a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib in combination with the following antineoplastic agents: fluorouracil, Levamisole, camptothecin, oxaliplatin, bevacizumab, cetuximab, panitumumab, irinotecan, leucovorin, and capecitabine.

Breast Cancer

[00268] Today, among women in the United States, breast cancer remains the most frequent diagnosed cancer. One in 8 women in the United States is at risk of developing breast cancer in their lifetime. Age, family history, diet, and genetic factors have been identified as risk factors for breast cancer. Breast cancer is the second leading cause of death among women.

[00269] Different chemotherapeutic agents are known in art for treating breast cancer. Cytoxic agents used for treating breast cancer include doxorubicin, cyclophosphamide, methotrexate, 5-fluorouracil, mitomycin C, mitoxantrone, paclitaxel, taxane formulations such as by way of example only, Abraxane® (ABI-007), Paclitaxel-Cremophor EL, Paclitaxel poliglumex, and Paclitaxel injectable emulsion (PIE), gemcitabine, docetaxel, capecitabine, lapatanib, trastuzumab, anastrozole, letrozole, exemestane, and epirubicin. In the treatment of locally advanced noninflammatory breast cancer, a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib can be used to treat the disease. Additionally, in combination with surgery, radiation therapy or with chemotherapeutic or other antiangiogenic agents. Other combinations of chemotherapeutic agents, that can be used in combination with the present disclosure include, but are not limited to anastrozole, capecitabine, docetaxel, epirubicin, exemestane, fulvestrant, epothilone A, B or D, goserelin acetate, letrozole, bevacizumab, paclitaxel, pamidronate, tamoxifen, toremifene, and trastuzumab.

Hormone Positive

[00270] Many breast cancers require the hormone oestrogen to grow. In women who have had their menopause, the main source of oestrogen is through the conversion of androgens into oestrogens. This process is carried out by the aromatase enzyme. In the treatment of hormone positive breast cancer a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib can be used to treat the disease in combination with other agents, such as, aromatase inhibitors, for e.g., exemestane, letrozole, and anastrozole.

HER2/neu Positive Breast Cancer

[00271] In the treatment of HER2/neu positive breast cancer, compositions comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib can be used to treat the disease in combination with other antiangiogenic agents, or in combination with surgery, radiation therapy or with chemotherapeutic agents. Other chemotherapeutic agents include, for example, trastuzumab, lapatinib, and CL-387785.

Triple Negative Breast Cancer

In the treatment of triple negative breast cancer wherein the cancer is estrogen receptor-negative, progesterone receptor-negative and HER2-negative, compositions comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib can be used to treat the disease in combination with other therapeutic agents. Such agents include, by way of example only, cetuximab, paclitaxel, docetaxel, taxane formulations, for example, Abraxane® (ABI-007), Paclitaxel-Cremophor EL, Paclitaxel poliglumex, and Paclitaxel injectable emulsion (PIE).

Ovarian Cancer

[00272] Celomic epithelial carcinoma accounts for approximately 90% of ovarian cancer cases. One therapy for the treatment of ovary cancer is a combination of therapeutically effective amounts of a

composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib.

[00273] Other agents that can be used in combination with a composition comprising a combination 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib include, but are not limited to: alkylating agents, ifosfamide, cisplatin, carboplatin, paclitaxel, docetaxel, PEGylated liposomal doxorubicin, gemcitabine, doxorubicin, epothilone A, B, or D, topotecan, liposomal doxorubicin 5-fluorouracil, methotrexate, mitomycin, hexamethylmelamine, progestins, antiestrogens, prednimustine, dihydroxybusulfan, galactitol, interferon alpha, and interferon gama.

[00274] Other combinations for the treatment of celomic epithelial carcinoma is a combination of therapeutically effective amounts of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib and one of the following combinations of antineoplastic agents: 1) cisplatin, doxorubicin, cyclophosphamide; 2) hexamthylmelamine, cyclosphamide, doxorubicin, cisplatin; 3) cyclophosphamide, hexamehtylmelamine, 5-flurouracil, cisplatin; 4) melphalan, hexamethylmelamine, cyclophosphamide; 5) melphalan, doxorubicin, cyclophosphamide; 6) cyclophosphamide, cisplatin, carboplatin; 7) cyclophosphamide, doxorubicin, hexamethylmelamine, cisplatin; 8) cyclophosphamide, doxorubicin, hexamethylmelamine, carboplatin; 9) cyclophosphamide, cisplatin; 10) hexamethylmelamine, doxorubicin, carboplatin; 11) cyclophosphamide, hexamethimelamine, doxorubicin, cisplatin; 12) carboplatin, cyclophosphamide; 13) cisplatin, cyclophosphamide.

[00275] Cancer of the fallopian tube accounts for approximately 400 new cancer cases per year in the United States. One therapy according to the invention is for the treatment of fallopian tube cancer which includes administering a combination of therapeutically effective amount of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib. Other agents that can be used in combination with a composition comprising a combination 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib include, but are not limited to: alkylating agents, ifosfamide, cisplatin, carboplatin, paclitaxel, docetaxel, PEGylated liposomal doxorubicin, gemcitabine, doxorubicin, epothilone A, B, or D, topotecan, liposomal doxorubicin, 5-fluorouracil, methotrexate, mitomycin, hexamethylmelamine, progestins, antiestrogens, prednimustine, dihydroxybusulfan, galactitol, interferon α, and interferon γ.

[00276] Germ cell ovarian cancer accounts for approximately 5% of ovarian cancer cases. Germ cell ovarian carcinomas are classified into two main groups: dysgerminoma, and nondysgerminoma. Nondysgerminoma is further classified into teratoma, endodermal sinus tumor, embryonal carcinoma, chloricarcinoma, polyembryoma, and mixed cell tumors. One therapy for the treatment of germ cell carcinoma is a combination of therapeutically effective amount of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib.

[00277] One therapy according to the invention is for the treatment of germ cell carcinoma which comprises administering a combination of a therapeutically effective amount of a composition

comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib and the following combinations of antineoplastic agents: 1) vincristine, actinomycin D, cyclophosphamide; 2) bleomycin, etoposide, cisplatin; 3) vinblastine, bleomycin, cisplatin.

Pancreatic Cancer

[00278] Approximately 2% of new cancer cases diagnosed in the United States are pancreatic cancer. Pancreatic cancer is generally classified into two clinical types: 1) adenocarcinoma (metastatic and non-metastatic), and 2) cystic neoplasms (serous cystadenomas, mucinous cystic neoplasms, papillary cystic neoplasms, acinar cell systadenocarcinoma, cystic choriocarcinoma, cystic teratomas, angiomatous neoplasms). Erlotinib in combination with gemcitabine is indicated for treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

[00279] Combinations of therapy for the treatment of non-metastatic adenocarcinoma that may be used in the present disclosure include the use of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib along with preoperative bilary tract decompression (patients presenting with obstructive jaundice); surgical resection, including standard resection, extended or radial resection and distal pancreatectomy (tumors of body and tail); adjuvant radiation; antiangiogenic therapy; and chemotherapy.

[00280] For the treatment of metastatic adenocarcinoma, a combination therapy consists of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib of the present disclosure in combination with continuous treatment of 5-fluorouracil, followed by weekly cisplatin therapy.

[00281] Another combination therapy for the treatment of cystic neoplasms is the use of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib in combination with gemcitabine.

Pharmaceutical Compositions

[00282] Provided herein is a pharmaceutical composition for treating cancer comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor; and a pharmaceutically acceptable excipient or carrier.

[00283] In one embodiment, the invention provides a pharmaceutical composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof; and one or more pharmaceutically acceptable excipients or carriers.

[00284] In another embodiment, the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and a pharmaceutically acceptable excipient or carrier. In another embodiment, the EGFR inhibitor is erlotinib and a pharmaceutically acceptable excipient or carrier. In a further embodiment the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-

sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib and a pharmaceutically acceptable excipient or carrier.

[00285] In one embodiment, the invention provides a pharmaceutical composition for treating cancer comprising a combination of a 1,2-diphenylpyrrole derivative selected from the group consisting of: 4-methyl-2-(4-methylphenyl)-1-(4-sulfamoylphenyl)pyrrole; 2-(4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(4-chlorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 4-methyl-2-(4-methylthiophenyl)-1-(4-sulfamoylphenyl)pyrrole; 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(4-methoxy-3-methylphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(3-fluoro-4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 4-methyl-1-(4-methylthiophenyl)-2-(4-sulfamoylphenyl)pyrrole; 1-(4-acetylaminosulfonylphenyl)-4-methyl-2-(4-methoxyphenyl)pyrrole; and 1-(4-acetylaminosulfonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole. In another embodiment, the invention provides a method wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and an EGFR inhibitor; and a pharmaceutically acceptable excipient or carrier.

[00286] Provided herein are pharmaceutical compositions comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof; and one or more pharmaceutically acceptable excipients or carriers. Also provided herein are pharmaceutical compositions comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof; and one or more release controlling excipients as described herein. Provided herein are pharmaceutical compositions comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof; and one or more release controlling excipients as described herein. Suitable modified release dosage vehicles include, but are not limited to, hydrophilic or hydrophobic matrix devices, water-soluble separating layer coatings, enteric coatings, osmotic devices, multi-particulate devices, and combinations thereof. The pharmaceutical compositions may also comprise non-release controlling excipients.

[00287] Provided herein are pharmaceutical compositions in film-coated dosage forms, which comprise a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more tabletting excipients to form a tablet core using conventional tabletting processes and subsequently coating the core. The tablet cores can be produced using conventional granulation methods, for

example wet or dry granulation, with optional comminution of the granules and with subsequent compression and coating. Granulation methods are described, for example, in Voigt, pages 156-69 (Voigt, R. (1984): Lehrbuch der pharmazeutischen Technologie (Textbook of Pharmaceutical Technology); Verlag Chemie Weinheim—Beerfield Beach/Florida—Basle).

[00288] Suitable excipients for the production of granules are, for example pulverulent fillers optionally having flow-conditioning properties, for example talcum, silicon dioxide, for example synthetic amorphous anhydrous silicic acid of the Syloid® type (Grace), for example SYLOID 244 FP, microcrystalline cellulose, for example of the Avicel® type (FMC Corp.), for example of the types AVICEL PH101, 102, 105, RC581 or RC 591, Emcocel® type (Mendell Corp.) or Elcema® type (Degussa); carbohydrates, such as sugars, sugar alcohols, starches or starch derivatives, for example lactose, dextrose, saccharose, glucose, sorbitol, mannitol, xylitol, potato starch, maize starch, rice starch, wheat starch or amylopectin, tricalcium phosphate, calcium hydrogen phosphate or magnesium trisilicate; binders, such as gelatin, tragacanth, agar, alginic acid, cellulose ethers, for example methylcellulose, carboxymethylcellulose or hydroxypropylmethylcellulose, polyethylene glycols or ethylene oxide homopolymers, especially having a degree of polymerization of approximately from $2.0x10^3$ to $1.0x10^5$ and an approximate molecular weight of about from $1.0x10^5$ to $5.0x10^6$, for example excipients known by the name Polyox® (Union Carbide), polyvinylpyrrolidone or povidones, especially having a mean molecular weight of approximately 1000 and a degree of polymerization of approximately from about 500 to about 2500, and also agar or gelatin; surface-active substances, for example anionic surfactants of the alkyl sulfate type, for example sodium, potassium or magnesium n-dodecyl sulfate, n-tetradecyl sulfate, n-hexadecyl sulfate or n-octadecyl sulfate, of the alkyl ether sulfate type, for example sodium, potassium or magnesium n-dodecyloxyethyl sulfate, n-tetradecyloxyethyl sulfate, n-hexadecyloxyethyl sulfate or n-octadecyloxyethyl sulfate, or of the alkanesulfonate type, for example sodium, potassium or magnesium n-dodecanesulfonate, n-tetradecanesulfonate, n-hexadecanesulfonate or n-octadecanesulfonate, or non-ionic surfactants of the fatty acid polyhydroxy alcohol ester type, such as sorbitan monolaurate, monooleate, monostearate or monopalmitate, sorbitan tristearate or trioleate, polyoxyethylene adducts of fatty acid polyhydroxy alcohol esters, such as polyoxyethylene sorbitan monolaurate, monooleate, monostearate, monopalmitate, tristearate or trioleate, polyethylene glycol fatty acid esters, such as polyoxyethyl stearate, polyethylene glycol 400 stearate, polyethylene glycol 2000 stearate, especially ethylene oxide/propylene oxide block polymers of the Pluronics® (BWC) or Synperonic® (ICI) type

[00289] Further provided herein are pharmaceutical compositions in enteric coated dosage forms, which comprise a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more release controlling excipients for use in an enteric coated dosage form. Provided herein are pharmaceutical compositions in enteric coated dosage forms comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-

methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof; and one or more release controlling excipients for use in an enteric coated dosage form. The pharmaceutical compositions may also comprise non-release controlling excipients.

[00290] Further provided herein are pharmaceutical compositions in effervescent dosage forms, which comprise a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more release controlling excipients for use in effervescent dosage forms. Also provided herein are pharmaceutical compositions in effervescent dosage forms comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof; and one or more release controlling excipients for use in an effervescent dosage forms. The pharmaceutical compositions may also comprise non-release controlling excipients.

[00291] Additionally provided are pharmaceutical compositions in a dosage form that has an instant releasing component and at least one delayed releasing component, and is capable of giving a discontinuous release of the compound in the form of at least two consecutive pulses separated in time from 0.1 up to 24 hours. The pharmaceutical compositions comprise a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more release controlling and non-release controlling excipients, such as those excipients suitable for a disruptable semi-permeable membrane and as swellable substances. Additionally, the invention provides pharmaceutical compositions comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more release controlling and non-release controlling excipients, such as those excipients suitable for a disruptable semi-permeable membrane and as swellable substances.

[00292] Provided herein also are pharmaceutical compositions in a dosage form for oral administration to a subject, which comprises a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more pharmaceutically acceptable excipients or carriers, enclosed in an intermediate reactive layer comprising a gastric juice-resistant polymeric layered material partially neutralized with alkali and having cation exchange capacity and a gastric juice-resistant outer layer. Additionally, the invention provides pharmaceutical compositions in a dosage form for oral administration to a subject comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-

diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib enclosed in an intermediate reactive layer comprising a gastric juice-resistant polymeric layered material partially neutralized with alkali and having cation exchange capacity and a gastric juice-resistant outer layer.

[00293] Provided herein are pharmaceutical compositions that comprise about 0.1 to about 1200 mg, about 1 to about 500 mg, about 2 to about 100 mg, about 1 mg, about 2 mg, about 3 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600mg, about 800 mg, about 1200mg of a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in the form of enteric-coated granules, as delayed-release capsules for oral administration. Also, the invention provides for pharmaceutical compositions that comprise about 0.1 to about 1000 mg, about 1 to about 500 mg, about 2 to about 100 mg, about 1 mg, about 2 mg, about 3 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 500 mg of a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in the form of enteric-coated granules, as delayed-release capsules for oral administration.

[00294] Provided herein are pharmaceutical compositions that comprise about 0.1 to about 1200 mg, about 1 to about 500 mg, about 2 to about 100 mg, about 1 mg, about 2 mg, about 3 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 500 mg, about 600 mg, about 800 mg, about 1200 mg of a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof in the form of enteric-coated pellets, as delayed-release capsules for oral administration. Also, the invention provides for pharmaceutical compositions that comprise about 0.1 to about 1200 mg, about 1 to about 500 mg, about 2 to about 100 mg, about 1 mg, about 2 mg, about 3 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 500 mg, about 600 mg, about 800 mg, about 1200 mg of a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof in the form of enteric-coated pellets, as delayed-release capsules for oral administration. The pharmaceutical compositions further comprise glyceryl monostearate 40-50, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate.

[00295] Provided herein are pharmaceutical compositions that comprise about 0.1 to about 1200 mg, about 1 to about 500 mg, about 2 to about 100 mg, about 1 mg, about 2 mg, about 3 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 500 mg,

about 600 mg, about 800 mg, about 1200 mg of a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, as enteric-coated delayed-release tablets for oral administration. Also, the pharmaceutical compositions that comprise about 0.1 to about 1200 mg, about 1 to about 500 mg, about 2 to about 100 mg, about 1 mg, about 2 mg, about 3 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 500 mg, about 600 mg, about 800 mg, about 1200 mg of a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, as enteric-coated delayed-release tablets for oral administration. The pharmaceutical compositions further comprise carnauba wax, crospovidone, diacetylated monoglycerides, ethylcellulose, hydroxypropyl cellulose, hypromellose phthalate, magnesium stearate, mannitol, sodium hydroxide, sodium stearyl fumarate, talc, titanium dioxide, and yellow ferric oxide.

[00296] Provided herein are pharmaceutical compositions that comprise about 0.1 to about 1200 mg, about 1 to about 500 mg, about 2 to about 100 mg, about 1 mg, about 2 mg, about 3 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 500 mg, about 600 mg, about 800 mg, about 1200 mg of a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, as enteric-coated delayed-release tablets for oral administration. Also provided herein are pharmaceutical compositions that comprise about 0.1 to about 1200 mg, about 1 to about 500 mg, about 2 to about 100 mg, about 1 mg, about 2 mg, about 3 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 500 mg, about 600 mg, about 800 mg, about 1200 mg of a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib as an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, as enteric-coated delayed-release tablets for oral administration. The pharmaceutical compositions further comprise calcium stearate, crospovidone, hydroxypropyl methylcellulose, iron oxide, mannitol, methacrylic acid copolymer, polysorbate 80, povidone, propylene glycol, sodium carbonate, sodium lauryl sulfate, titanium dioxide, and triethyl citrate.

[00297] The pharmaceutical compositions provided herein may be provided in unit-dosage forms or multiple-dosage forms. Unit-dosage forms, as used herein, refer to physically discrete units suitable for administration to human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of unit-dosage forms include ampules, syringes, and individually packaged tablets and capsules. Unit-dosage forms may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be

administered in segregated unit-dosage form. Examples of multiple-dosage forms include vials, bottles of tablets or capsules, or bottles of pints or gallons.

[00298] The compositions provided herein may be administered alone, or in combination with one or more other compounds provided herein, one or more other active ingredients. The pharmaceutical compositions that comprise a compound provided herein may be formulated in various dosage forms for oral, parenteral, buccal, intranasal, epidural, sublingual, pulmonary, local, rectal, transdermal, or topical administration. The pharmaceutical compositions may also be formulated as a modified release dosage form, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Deliver Technology*, Rathbone et al., Eds., Drugs and the Pharmaceutical Science, Marcel Dekker, Inc.: New York, NY, 2002; Vol. 126).

[00299] The pharmaceutical compositions provided herein may be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

[00300] In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the combinations may be administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00301] In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the combinations may be given continuously or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday").

[00302] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00303] As described herein, the compositions and methods for using the composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor, may be formulated without carriers or excipients or may be combined with one or more pharmaceutically acceptable carriers for administration. For example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from

about 0.05 to about 5% of suspending agent, syrups containing, for example, from about 10 to about 50% of sugar, and elixirs containing, for example, from about 20 to about 50% ethanol, and the like. Such pharmaceutical preparations may contain, for example, from about 0.05 up to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and about 60% by weight. Also, the compositions and methods for using the composition comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib, may be formulated without carriers or excipients or may be combined with one or more pharmaceutically acceptable carriers for administration.

[00304] The effective dosage of each active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. The projected daily dosage of the EGFR inhibitor will depend on many factors. Numerous methods for evaluating and comparing 1,2-diphenylpyrrole derivative inhibitor potency are known to one of skill in the art. In one embodiment, an oral daily dosage of the 1,2-diphenylpyrrole derivative inhibitor is in the range of about 0.01 to about 30 mg/kg, and the projected daily dosage of the EGFR inhibitor is in the range of about 0.3 to about 8 mg/kg. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. The 1,2-diphenylpyrrole derivative inhibitor and the EGFR inhibitor may also be administered as a combined dosage unit, or as separate components. When administered as separate components, each component may be administered at the same time, or at different times during the treatment period.

[00305] It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors such as, for example, decreases in the liver and kidney function.

[00306] Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from in vitro studies initially can provide useful guidance on the proper doses for patient administration. Studies in animal models also generally may be used for guidance regarding effective dosages for treatment of cancers in accordance with the present disclosure. In terms of treatment protocols, it should be appreciated that the dosage to be administered will depend on several factors, including the particular agent that is administered, the route administered, the condition of the particular patient, etc. Determination of these parameters are well within the skill of the art. These considerations, as well as effective formulations and administration procedures are well known in the art and are described in standard textbooks.

Oral Formulations

[00307] Oral formulations containing the active combinations described herein may comprise any conventionally used oral forms, including: tablets, capsules, pills, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, granules, bulk powders, effervescent or non-effervescent powders or granules, solutions, emulsions, suspensions, solutions, wafers, sprinkles, elixirs, syrups, buccal forms,

and oral liquids. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. In some embodiments are surface modifying agents which include nonionic and anionic surface modifying agents. For example, surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). The oral formulation may also consist of administering the active ingredient in water or a fruit juice, containing appropriate solubilizers or emulsifiers as needed.

Oral Administration

[00308] As described herein, the combination regimen can be given simultaneously or can be given in a staggered regimen, with a 1,2-diphenylpyrrole derivative being given at a different time during the course of chemotherapy than an EGFR inhibitor. This time differential may range from several minutes, hours, days, weeks, or longer between administration of the two compounds. Therefore, the term combination does not necessarily mean administered at the same time or as a unitary dose, but that each of the components are administered during a desired treatment period. The agents may also be administered by different routes. As is typical for chemotherapeutic regimens, a course of chemotherapy may be repeated several weeks later, and may follow the same timeframe for administration of the two compounds, or may be modified based on patient response.

[00309] In other embodiments, the pharmaceutical compositions provided herein may be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also include buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, capsules, pills, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, granules, bulk powders, effervescent or non-effervescent powders or granules, solutions, emulsions, suspensions, solutions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions may contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting

agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, and flavoring agents.

[00310] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, Panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

[00311] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets.

[00312] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[00313] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL®

200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[00314] Suitable glidants include colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Coloring agents include any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Flavoring agents include natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Sweetening agents include sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suspending and dispersing agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrolidone. Preservatives include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Solvents include glycerin, sorbitol, ethyl alcohol, and syrup. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate.

[00315] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[00316] In further embodiments, the pharmaceutical compositions provided herein may be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenylsalicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[00317] The tablet dosage forms may be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[00318] The pharmaceutical compositions provided herein may be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[00319] In other embodiments, the pharmaceutical compositions provided herein may be provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquids or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde (the term "lower" means an alkyl having between 1 and 6 carbon atoms), e.g., acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be measured conveniently for administration.

[00320] Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s) provided herein, and a dialkylated mono- or poly-alkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These

formulations may further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

[00321] The pharmaceutical compositions provided herein for oral administration may be also provided in the forms of liposomes, micelles, microspheres, or nanosystems. Miccellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[00322] In other embodiments, the pharmaceutical compositions provided herein may be provided as non- effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[00323] Coloring and flavoring agents can be used in all of the above dosage forms.

[00324] The pharmaceutical compositions provided herein may be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00325] In further embodiments, the pharmaceutical compositions provided herein may be co-formulated with other active ingredients which do not impair the desired therapeutic action, or with substances that supplement the desired action, such as other cholinergic agents, other serotoninergic agents, alpha adrenergic agents, CCK_A antagonists, $5\text{-}HT_3$ antagonists, NMDA receptor antagonists, opioids, prokinetics, tachykinins, antalarmin, and Z-338.

Parenteral Administration

[00326] In some embodiments, the pharmaceutical compositions provided herein may be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, and subcutaneous administration.

[00327] In other embodiments, the pharmaceutical compositions provided herein may be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy*, supra).

[00328] The pharmaceutical compositions intended for parenteral administration may include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against

the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[00329] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, dimethylacetamide, and dimethylsulfoxide.

[00330] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzates, thimerosal, benzalkonium chloride, benzethonium chloride, methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents include those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

[00331] In some embodiments, the pharmaceutical compositions provided herein may be formulated for single or multiple dosage administration. The single dosage formulations are packaged in an ampule, a vial, or a syringe. The multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungistatic concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[00332] In one embodiment, the pharmaceutical compositions are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-

use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

[00333] The pharmaceutical compositions provided herein may be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00334] The pharmaceutical compositions may be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

[00335] Suitable inner matrixes include polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

Suitable outer polymeric membranes include polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

Modified Release

[00336] In other embodiments, the pharmaceutical compositions provided herein may be formulated as a modified release dosage form. As used herein, the term "modified release" refers to a dosage form in which the rate or place of release of the active ingredient(s) is different from that of an immediate dosage form when administered by the same route. Modified release dosage forms include delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. The pharmaceutical compositions in modified release dosage forms can be prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix controlled release devices, osmotic controlled release devices, multiparticulate controlled release devices, ion-exchange resins, enteric coatings, multilayered coatings, microspheres, liposomes, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes and polymorphorism of the active ingredient(s).

[00337] Examples of modified release include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500.

Matrix Controlled Release Devices

[00338] In some embodiments, the pharmaceutical compositions provided herein in a modified release dosage form may be fabricated using a matrix controlled release device known to those skilled in the art (*see*, Takada et al in "Encyclopedia of Controlled Drug Delivery," Vol. 2, Mathiowitz ed., Wiley, 1999).

[00339] In one embodiment, the pharmaceutical compositions provided herein in a modified release dosage form is formulated using an erodible matrix device, which is water-swellable, erodible, or soluble polymers, including synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

[00340] Materials useful in forming an erodible matrix include, but are not limited to, chitin, chitosan, dextran, and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum, and scleroglucan; starches, such as dextrin and maltodextrin; hydrophilic colloids, such as pectin; phosphatides, such as lecithin; alginates; propylene glycol alginate; gelatin; collagen; and cellulosics, such as ethyl cellulose (EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethylhydroxy ethylcellulose (EHEC); polyvinyl pyrrolidone; polyvinyl alcohol; polyvinyl acetate; glycerol fatty acid esters; polyacrylamide; polyacrylic acid; copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®, Rohm America, Inc., Piscataway, NJ); poly(2-hydroxyethyl-methacrylate); polylactides; copolymers of L-glutamic acid and ethyl-L-glutamate; degradable lactic acid-glycolic acid copolymers; poly-D-(-)-3-hydroxybutyric acid; and other acrylic acid derivatives, such as homopolymers and copolymers of butylmethacrylate, methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, and (trimethylaminoethyl)methacrylate chloride.

[00341] In further embodiments, the pharmaceutical compositions are formulated with a non-erodible matrix device. The active ingredient(s) is dissolved or dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once administered. Materials suitable for use as a non-erodible matrix device included, but are not limited to, insoluble plastics, such as polyethylene, polypropylene, polyisoprene, polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated polyethylene, polyvinylchloride, methyl acrylate-methyl methacrylate copolymers, ethylene-vinylacetate copolymers, ethylene/propylene copolymers,

ethylene/ethyl acrylate copolymers, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, polyvinyl chloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, and ; hydrophilic polymers, such as ethyl cellulose, cellulose acetate, crospovidone, and cross-linked partially hydrolyzed polyvinyl acetate,; and fatty compounds, such as carnauba wax, microcrystalline wax, and triglycerides.

[00342] In a matrix controlled release system, the desired release kinetics can be controlled, for example, via the polymer type employed, the polymer viscosity, the particle sizes of the polymer and/or the active ingredient(s), the ratio of the active ingredient(s) versus the polymer, and other excipients or carriers in the compositions.

[00343] In other embodiments, the pharmaceutical compositions provided herein in a modified release dosage form may be prepared by methods known to those skilled in the art, including direct compression, dry or wet granulation followed by compression, melt-granulation followed by compression.

2. Osmotic Controlled Release Devices

[00344] In some embodiments, the pharmaceutical compositions provided herein in a modified release dosage form may be fabricated using an osmotic controlled release device, including one-chamber system, two-chamber system, asymmetric membrane technology (AMT), and extruding core system (ECS). In general, such devices have at least two components: (a) the core which contains the active ingredient(s); and (b) a semipermeable membrane with at least one delivery port, which encapsulates the core. The semipermeable membrane controls the influx of water to the core from an aqueous environment of use so as to cause drug release by extrusion through the delivery port(s).

[00345] In addition to the active ingredient(s), the core of the osmotic device optionally includes an osmotic agent, which creates a driving force for transport of water from the environment of use into the core of the device. One class of osmotic agents water-swellable hydrophilic polymers, which are also referred to as "osmopolymers" and "hydrogels," including, but not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[00346] The other class of osmotic agents are osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-tolunesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[00347] Osmotic agents of different dissolution rates may be employed to influence how rapidly the active ingredient(s) is initially delivered from the dosage form. For example, amorphous sugars, such as Mannogeme EZ (SPI Pharma, Lewes, DE) can be used to provide faster delivery during the first couple of hours to promptly produce the desired therapeutic effect, and gradually and continually release of the remaining amount to maintain the desired level of therapeutic or prophylactic effect over an extended period of time. In this case, the active ingredient(s) is released at such a rate to replace the amount of the active ingredient metabolized and excreted.

[00348] The core may also include a wide variety of other excipients and carriers as described herein to enhance the performance of the dosage form or to promote stability or processing.

[00349] Materials useful in forming the semi-permeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of suitable polymers useful in forming the coating, include plasticized, unplasticized, and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxylated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly(acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00350] Semi-permeable membrane may also be a hydrophobic microporous membrane, wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Pat. No. 5,798,119. Such hydrophobic but water-vapor permeable membrane are typically composed of hydrophobic polymers such as polyalkenes, polyethylene,

polypropylene, polytetrafluoroethylene, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinylidene fluoride, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00351] The delivery port(s) on the semi-permeable membrane may be formed post-coating by mechanical or laser drilling. Delivery port(s) may also be formed in situ by erosion of a plug of water-soluble material or by rupture of a thinner portion of the membrane over an indentation in the core. In addition, delivery ports may be formed during coating process, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Pat. Nos. 5,612,059 and 5,698,220.

[00352] The total amount of the active ingredient(s) released and the release rate can substantially by modulated via the thickness and porosity of the semi-permeable membrane, the composition of the core, and the number, size, and position of the delivery ports.

[00353] The pharmaceutical compositions in an osmotic controlled-release dosage form may further comprise additional conventional excipients or carriers as described herein to promote performance or processing of the formulation.

[00354] The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; Santus and Baker, *J. Controlled Release* **1995**, *35*, 1-21; Verma et al., *Drug Development and Industrial Pharmacy* **2000**, *26*, 695-708; Verma et al., *J. Controlled Release* **2002**, *79*, 7-27).

[00355] In other embodiments, the pharmaceutical compositions provided herein are formulated as AMT controlled-release dosage form, which comprises an asymmetric osmotic membrane that coats a core comprising the active ingredient(s) and other pharmaceutically acceptable excipients or carriers. *See*, U.S. Pat. No. 5,612,059 and WO 2002/17918. The AMT controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art, including direct compression, dry granulation, wet granulation, and a dip-coating method.

[00356] In certain embodiments, the pharmaceutical compositions provided herein are formulated as ESC controlled-release dosage form, which comprises an osmotic membrane that coats a core comprising the active ingredient(s), a hydroxylethyl cellulose, and other pharmaceutically acceptable excipients or carriers.

3. Multiparticulate Controlled Release Devices

[00357] In some embodiments, the pharmaceutical compositions provided herein in a modified release dosage form may be fabricated a multiparticulate controlled release device, which comprises a multiplicity of particles, granules, or pellets, ranging from about 10 μm to about 3 mm, about 50 μm to about 2.5 mm, or from about 100 μm to about 1 mm in diameter. Such multiparticulates may be made by the processes know to those skilled in the art, including wet-and dry-granulation, extrusion/spheronization, roller-compaction, melt-congealing, and by spray-coating seed cores. *See,* for example, *Multiparticulate Oral Drug Delivery*; Marcel Dekker: 1994; and *Pharmaceutical Pelletization Technology*; Marcel Dekker: 1989.

[00358] Other excipients or carriers as described herein may be blended with the pharmaceutical compositions to aid in processing and forming the multiparticulates. The resulting particles may themselves constitute the multiparticulate device or may be coated by various film-forming materials, such as enteric polymers, water-swellable, and water-soluble polymers. The multiparticulates can be further processed as a capsule or a tablet.

4. Targeted Delivery

[00359] In some embodiments, the pharmaceutical compositions provided herein may also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated, including liposome-, resealed erythrocyte-, and antibody-based delivery systems. Examples include, but are not limited to, U.S. Pat. Nos. 6,316,652; 6,274,552; 6,271,359; 6,253,872; 6,139,865; 6,131,570; 6,120,751; 6,071,495; 6,060,082; 6,048,736; 6,039,975; 6,004,534; 5,985,307; 5,972,366; 5,900,252; 5,840,674; 5,759,542; and 5,709,874, all of which are incorporated herein by their entirety.

Immediate Release

[00360] In some embodiments, the pharmaceutical compositions provided herein in an immediate release dosage form are capable of releasing not less than 75 % of the therapeutically active ingredient or combination and/or meet the disintegration or dissolution requirements for immediate release tablets of the particular therapeutic agents or combination included in the tablet core, as set forth in USP XXII, 1990 (The United States Pharmacopeia.)

Topical Administration

[00361] In other embodiments, the pharmaceutical compositions provided herein may be administered topically to the skin, orifices, or mucosa. The topical administration, as used herein, include (intra)dermal, conjuctival, intracorneal, intraocular, ophthalmic, auricular, transdermal, nasal, vaginal, uretheral, respiratory, and rectal administration.

[00362] In further embodiments, the pharmaceutical compositions provided herein may be formulated in any dosage forms that are suitable for topical administration for local or systemic effect, including emulsions, solutions, suspensions, creams, gels, hydrogels, ointments, dusting powders, dressings, elixirs, lotions, suspensions, tinctures, pastes, foams, films, aerosols, irrigations, sprays, suppositories,

bandages, dermal patches. The topical formulation of the pharmaceutical compositions provided herein may also comprise liposomes, micelles, microspheres, nanosystems, and mixtures thereof.

[00363] Pharmaceutically acceptable carriers and excipients suitable for use in the topical formulations provided herein include, but are not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, penetration enhancers, cryopretectants, lyoprotectants, thickening agents, and inert gases.

[00364] In some embodiments, the pharmaceutical compositions may also be administered topically by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free injection, such as POWDERJECT™ (Chiron Corp., Emeryville, CA), and BIOJECT™ (Bioject Medical Technologies Inc., Tualatin, OR).

[00365] The pharmaceutical compositions provided herein may be provided in the forms of ointments, creams, and gels. Suitable ointment vehicles include oleaginous or hydrocarbon vehicles, including such as lard, benzoinated lard, olive oil, cottonseed oil, and other oils, white petrolatum; emulsifiable or absorption vehicles, such as hydrophilic petrolatum, hydroxystearin sulfate, and anhydrous lanolin; water-removable vehicles, such as hydrophilic ointment; water-soluble ointment vehicles, including polyethylene glycols of varying molecular weight; emulsion vehicles, either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, including cetyl alcohol, glyceryl monostearate, lanolin, and stearic acid (*see, Remington: The Science and Practice of Pharmacy*, supra). These vehicles are emollient but generally require addition of antioxidants and preservatives.

[00366] Suitable cream base can be oil-in-water or water-in-oil. Cream vehicles may be water-washable, and contain an oil phase, an emulsifier, and an aqueous phase. The oil phase is also called the "internal" phase, which is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation may be a nonionic, anionic, cationic, or amphoteric surfactant.

[00367] Gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the liquid carrier. Suitable gelling agents include crosslinked acrylic acid polymers, such as carbomers, carboxypolyalkylenes, Carbopol®; hydrophilic polymers, such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers, and polyvinylalcohol; cellulosic polymers, such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose; gums, such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, and/or stirring.

[00368] The pharmaceutical compositions provided herein may be administered rectally, urethrally, vaginally, or perivaginally in the forms of suppositories, pessaries, bougies, poultices or cataplasm, pastes, powders, dressings, creams, plasters, contraceptives, ointments, solutions, emulsions, suspensions, tampons, gels, foams, sprays, or enemas. These dosage forms can be manufactured using conventional processes as described in *Remington: The Science and Practice of Pharmacy*, supra.

[00369] Rectal, urethral, and vaginal suppositories are solid bodies for insertion into body orifices, which are solid at ordinary temperatures but melt or soften at body temperature to release the active ingredient(s) inside the orifices. Pharmaceutically acceptable carriers utilized in rectal and vaginal suppositories include bases or vehicles, such as stiffening agents, which produce a melting point in the proximity of body temperature, when formulated with the pharmaceutical compositions provided herein; and antioxidants as described herein, including bisulfite and sodium metabisulfite. Suitable vehicles include, but are not limited to, cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol), spermaceti, paraffin, white and yellow wax, and appropriate mixtures of mono-, di- and triglycerides of fatty acids, hydrogels, such as polyvinyl alcohol, hydroxyethyl methacrylate, polyacrylic acid; glycerinated gelatin. Combinations of the various vehicles may be used. Rectal and vaginal suppositories may be prepared by the compressed method or molding. The typical weight of a rectal and vaginal suppository is about 2 to about 3 g.

[00370] The pharmaceutical compositions provided herein may be administered ophthalmically in the forms of solutions, suspensions, ointments, emulsions, gel-forming solutions, powders for solutions, gels, ocular inserts, and implants.

[00371] The pharmaceutical compositions provided herein may be administered intranasally or by inhalation to the respiratory tract. The pharmaceutical compositions may be provided in the form of an aerosol or solution for delivery using a pressurized container, pump, spray, atomizer, such as an atomizer using electrohydrodynamics to produce a fine mist, or nebulizer, alone or in combination with a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. The pharmaceutical compositions may also be provided as a dry powder for insufflation, alone or in combination with an inert carrier such as lactose or phospholipids; and nasal drops. For intranasal use, the powder may comprise a bioadhesive agent, including chitosan or cyclodextrin.

[00372] Solutions or suspensions for use in a pressurized container, pump, spray, atomizer, or nebulizer may be formulated to contain ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active ingredient provided herein, a propellant as solvent; and/or an surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

[00373] In another embodiment, the pharmaceutical compositions provided herein may be micronized to a size suitable for delivery by inhalation, such as about 50 micrometers or less, or about 10 micrometers or less. Particles of such sizes may be prepared using a comminuting method known to

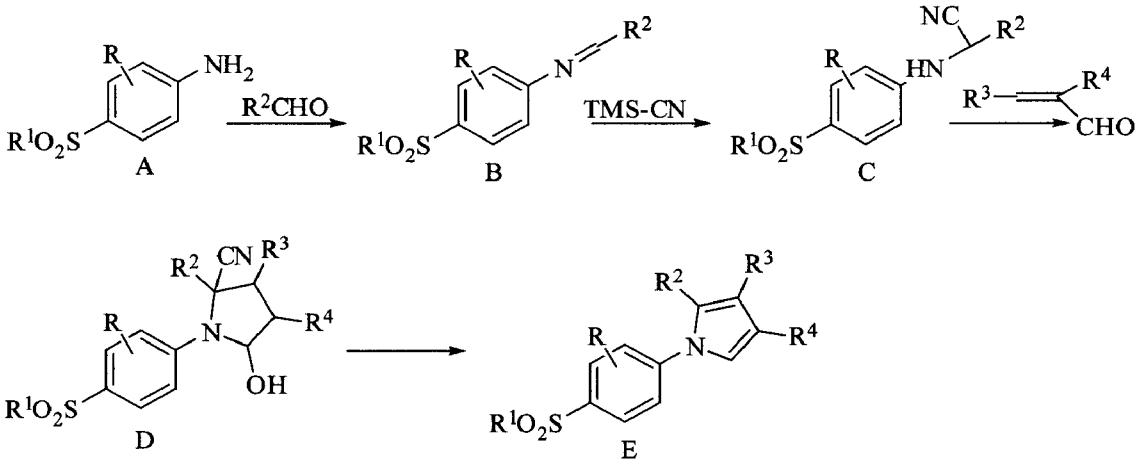
those skilled in the art, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

[00374] Capsules, blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the pharmaceutical compositions provided herein; a suitable powder base, such as lactose or starch; and a performance modifier, such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose. The pharmaceutical compositions provided herein for inhaled/intranasal administration may further comprise a suitable flavor, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium.

[00375] In one embodiment, the pharmaceutical compositions provided herein for topical administration may be formulated to be immediate release or modified release, including delayed-, sustained-, pulsed-, controlled-, targeted, and programmed release.

EXAMPLES

Example 1
Synthesis of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole

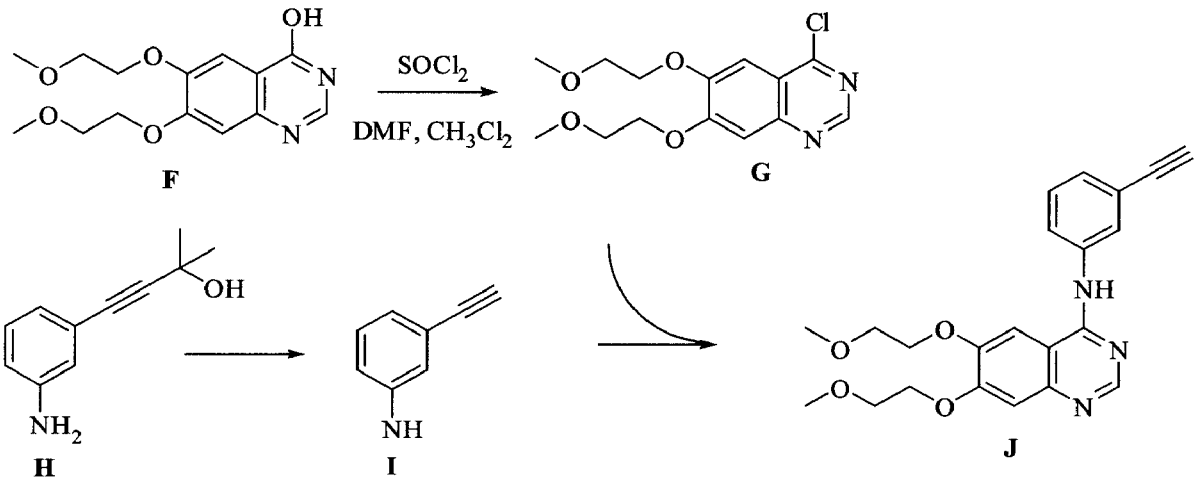


Scheme 1.

[00376] Substituted benzaldehyde undergoes dehydration condensation by reaction with aniline compound **A** in an inert solvent at a temperature of between 5 °C to 200 °C to give aldimine compound **B**. Trimethylsilyl cyanide is then reacted with aldimine compound **B** in the presence of a Lewis acid to afford anilinonitrile **C**. An α–β-unsaturated aldehyde is then reacted with anilinonitrile **C** to afford compound **D** which then undergoes dehydration and dehydrogencyanation under basic conditions in a modification of the method described in Ann. Chem. 589, 176 (**1954**).

Example 2

Synthesis of Erlotinib



Scheme 2.

[00377] Starting material compound **H** is heated in a suspension of metal alkali and solvent, then heated to give compound **I**. Starting material alcohol **F**, is placed in a solvent mixture of thionyl chloride, methylene chloride and dimethylformamide to give the chloride **G**. Chloride **G** is then coupled with compound **I** to give erlotinib **J**.

Example 3

Pharmacokinetics and Metabolism of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole

[00378] Orally administered 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole was rapidly absorbed in all species examined (mice, rats, dogs, and monkeys). Peak plasma concentrations were achieved between 1 and 3 hours after a dose of 5 mg/kg. The elimination half life ($t_{1/2}$) was 4-5 hours in rodents and dogs, and approximately 2 hours in monkeys. Oral availability was greatest in rodent, and was reduced in dogs and monkeys (59 and 34% respectively). Pharmacokinetics in human subjects demonstrated a linear dose exposure relationship from doses of 2 mg to 800 mg given orally. The half-life in human subjects is 15-18 hours.

Example 4

Toxicology of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole

[00379] Toxicological evaluation of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole in mice, rats, dogs and monkeys revealed expected findings related to inhibition of cyclooxygenase and consistent with animal safety observations with other COX-2 selective inhibitors. In single dose studies, the minimum lethal dose of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole was 600 mg/kg in rats and >2000 mg/kg in dogs. An endoscopy study conducted in human subjects demonstrated no increase in gastric or duodenal toxicity compared to placebo.

Example 5

Biological Evaluation

COX-2 Selective Inhibitors

HT-29 Model:

[00380] Mice are injected subcutaneously in the left paw ($1x10^6$ tumor cells suspended in 30% Matrigel) and tumor volume is evaluated using a phlethysmometer twice a week for 30-60 days. Implantation of human colon cancer cells (HT-29) into nude mice produces tumors that will reach 0.6-2 ml between 30-50 days. Blood is drawn twice during the experiment in a 24 h protocol to assess plasma concentration and total exposure by AUC analysis. The data is expressed as the mean+/-SEM. Student's and Mann-Whitney tests are used to assess differences between means using the InStat software package.

[00381] A. Mice injected with HT-29 cancer cells are treated with cytoxin i.p at doses of 50 mg/kg on days 5, 7 and 9 in the presence or absence of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole with erlotinib in the diet. The efficacy of both agents are determined by measuring tumor volume. The results from these studies may demonstrate that a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole with erlotinib administered in the diet to tumor bearing mice can delay the growth of tumors and metastasis when administered as sole therapy.

[00382] B. In a second assay, mice are injected with HT-29 cancer cells are then treated with 5-FU on days 12 through 15. Mice injected with HT-29 cancer cells are treated with 5-FU i.p at doses of 50 mg/kg on days 12, 13, 14, and 15 in the presence or absence of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole with erlotinib in the diet. The efficacy of both agents are determined by measuring tumor volume. Treatment using the composition may reduce tumor volume by up to 70%. In the same assay, 5-FU decreases tumor volume by 61%. Further, the composition and 5-FU may decrease tumor volume by 83%.

[00383] C. In a third assay, mice injected with HT-29 colon cancer cells are treated with 5-FU i.p 50 mg/kg on days 14 through 17 in the presence or absence of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole with erlotinib (1600 ppm) and valdecoxib (160 ppm) in the diet. The efficacy of both agents are determined by measuring tumor volume. Treatment with 5-FU may result in a 35% reduction in tumor volume. Treatment with the composition and valdecoxib may reduce tumor volume by 52% and 69%, respectively. In the same assay, the combination of 5-FU and the composition may decrease tumor volume by 72% while the combination of 5-FU and valdecoxib may decrease tumor volume by 74%.

Example 6

In Vitro Inhibition of EGFR Kinase Activity

[00384] The in vitro activity of the combinations described herein in inhibiting the receptor tyrosine kinase may be determined by the following procedure. The activity of the combinations of the present

disclosure, in vitro, can be determined by the amount of inhibition of the phosphorylation of an exogenous substrate (e.g., Lys_3 -- Gastrin or polyGluTyr (4:1) random copolymer (Posner et al., *J. Biol. Chem.*, **1992**, 267 (29), 20638-472)) on tyrosine by epidermal growth factor receptor kinase by a test compound relative to a control. Affinity purified, soluble human EGF receptor (96 ng) is obtained according to the procedure in G. N. Gill, W. Weber, *Methods in Enzymology*, **1987**, 146, 82-8 from A431 cells (American Type Culture Collection, Rockville, Md.) and preincubated in a microfuge tube with EGF (2 μg/ml) in phosphorylation buffer+vanadate (PBV: 50 mM HEPES, pH 7.4; 125 mM NaCl; 24 mM $MgCl_2$; 100 μM sodium orthovanadate), in a total volume of 10 μl, for 20-30 minutes at room temperature. The composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole with erlotinib, dissolved in dimethylsulfoxide (DMSO), is diluted in PBV, and 10 μl is mixed with the EGF receptor/EGF mix, and incubated for 10-30 minutes at 30 °C. The phosphorylation reaction is initiated by addition of 20 μl ^{33} P-ATP/substrate mix (120 μM Lys_3 - Gastrin (sequence in single letter code for amino acids, KKKGPWLEEEEEAYGWLDF), 50 mM Hepes pH 7.4, 40 μM ATP, 2 pCi .gamma.-[^{33} P]-ATP) to the EGFr/EGF mix and incubated for 20 minutes at room temperature. The reaction is stopped by addition of 10 μl stop solution (0.5 M EDTA, pH 8; 2 mM ATP) and 6 μl 2N HCl. The tubes are centrifuged at 14,000 RPM, 4 °C., for 10 minutes. 35 μl of supernatant from each tube is pipetted onto a 2.5 cm circle of Whatman P81 paper, bulk washed four times in 5% acetic acid, 1 liter per wash, and then air dried. This results in the binding of substrate to the paper with loss of free ATP on washing. The [^{33} P] incorporated is measured by liquid scintillation counting. Incorporation in the absence of substrate (e.g., lys_3-gastrin) is subtracted from all values as a background and percent inhibition is calculated relative to controls without the composition present. Such assays, carried out with a range of doses of test combinations, allow the determination of an approximate IC_{50} value for the in vitro inhibition of EGFR kinase activity. Other methods for determining the activity of the combinations presented herein are described in U.S. Pat. No. 5,747,498, the disclosure of which is incorporated herein.

Example 7

Pharmaceutical Compositions and Dosage Forms

[00385] Dosage formulations comprising pharmaceutical excipients and carriers and a pharmaceutical composition comprising a combination of erlotinib (**A**) and 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole (**B**) include:

Combination	Amount of **A** per tablet (mg)	Amount of **B** per tablet (mg)
A/B	25	1, 5, 10, 25, 50, 100, 200, 300, 400, 600, 800, 1000, 1200
A/B	100	1, 5, 10, 25, 50, 100, 200, 300, 400, 600, 800, 1000, 1200
A/B	150	1, 5, 10, 25, 50, 100, 200, 300, 400,

		600, 800, 1000, 1200
A/B	200	1, 5, 10, 25, 50, 100, 200, 300, 400, 600, 800, 1000, 1200
A/B	300	1, 5, 10, 25, 50, 100, 200, 300, 400, 600, 800, 1000, 1200
A/B	450	1, 5, 10, 25, 50, 100, 200, 300, 400, 600, 800, 1000, 1200

[00386] Dosage formulations described herein, including the formulations set forth in the above table, may be administered in a single fixed dose comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib or as a separate administration of a single dose of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and a single dose of erlotinib.

Example 8

Biological Evaluation

COX-2 Selective Inhibitors

A431 Squamous Vulvar Carcinoma Model

Mice are injected subcutaneously in the left paw ($1x10^6$ tumor cells suspended in 30% Matrigel) and tumor volume is evaluated using a phlethysmometer twice a week for 30-60 days. Implantation of squamous vulvar carcinoma (A431) into nude mice produces tumors that reach 0.6-2 ml between 30-50 days. Blood is drawn twice during the experiment in a 24 h protocol to assess plasma concentration and total exposure by AUC analysis. The data is expressed as the mean+/-SEM. Student's and Mann-Whitney tests are used to assess differences between means using the InStat software package.

Mice injected with A431 cancer cells are treated with a composition comprising one of the following: 1. erlotinib (75 or 100 mg/kg); 2. 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole (3, 10, 30, or 100 mg/kg); 3. celecoxib (10, 30, 100, or 300 mg/kg); 4. erlotinib (75 mg/kg) and 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole (3, 10, or 30 mg/kg); 4. erlotinib (75 mg/kg) and celecoxib (10, 30, or 100 mg/kg). The efficacy is determined by measuring tumor volume. The results from these studies, shown in Figure 3, demonstrate that a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole with erlotinib administered to tumor bearing mice delayed the growth of tumors by 55% compared to erlotinib alone. The combination of erlotinib and celecoxib demonstrated a tumor growth delay of only 36%.

Example 9

Study of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole in combination with erlotinib in metastatic or recurrent non-small cell lung cancer (NSCLC) patients

Methods: Subjects with recurrent or metastatic NSCLC were treated with erlotinib (150 mg/day PO) and escalating doses of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole (100 - 1200

mg/day PO). Pharmacokinetics for 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib were evaluated.

Results: Nineteen subjects were treated: 3 at 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole 100 mg; 4 at 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole 200 mg; 12 at 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole 400 mg. The optimal biologic dose selected was 400 mg. 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole pharmacokinetics reveal a median Tmax of 2 hours (range 1.5-4), mean (SD) T1/2 of 11.8 (5.3) hours, Cmax of 313.0 (99.6) ng/ml and AUC (0-t) of 2816 (1204) ng·h/ml.

The results show that 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib have been safely administered in this study.

Example 10

Study of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole in combination with erlotinib in metastatic or recurrent non-small cell lung cancer (NSCLC) patients

This study compares the anti-tumor efficacy of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib with placebo and erlotinib as measured by time to disease progression. The experimental arm consists of 400 mg/day 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole, in combination with 150 mg/day erlotinib. The placebo arm consists of 400 mg/day placebo tablets, in combination with 150 mg/day erlotinib.

Example 11

Study of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole in combination with erlotinib and gemcitabine in advanced pancreatic cancer patients

This study compares the anti-tumor efficacy of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and erlotinib/gemcitabine with placebo and erlotinib/gemcitabine as measured by time to disease progression. The experimental arm will consist of 400 mg/day 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole, in combination with 100 mg/day erlotinib, and gemcitabine administered as an intravenous infusion of a 1000 mg/m^2 dose over 30 minutes once a week for up to 7 weeks followed by one week of rest and then subsequent cycles of weekly infusions for 3 weeks of a 4 week cycle. The placebo arm consists of 400 mg/day placebo tablets, in combination with 100 mg/day erlotinib, and gemcitabine administered as an intravenous infusion of a 1000 mg/m^2 dose over 30 minutes once a week for up to 7 weeks followed by one week of rest and then subsequent cycles of weekly infusions for 3 weeks of a 4 week cycle.

Example 12

Treatment of Non-Small Cell Lung Cancer

[00387] A method for treating a subject having non-small cell lung cancer comprising administering to the subject a therapeutically effective amount of a combination comprising 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-pyrrole and erlotinib or their respective pharmaceutically acceptable

salt, solvate or prodrug is contemplated. The subject is treated using a single dosage form of a combination of 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-pyrrole in about 100, about 200, about 300, about 400, about 600, about 800, and about 1000 and about 1200 mg aliquots and erlotinib in about a 150 mg aliquot. The treatment of the subject using a separate administration of 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-pyrrole in about 200, about 400, and about 800 mg aliquots and erlotinib in about a 150 mg aliquot is also contemplated. The maximum tolerated dose of this combination will be an endpoint for this study.

Example 13

Treatment of Breast Cancer

[00388] A method for treating a subject having breast cancer comprising administering to the subject a therapeutically effective amount of a combination comprising 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-pyrrole and erlotinib or their respective pharmaceutically acceptable salt, solvate or prodrug is contemplated. Combined treatment with erlotinib and 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-pyrrole is expected to achieve increased tumor inhibition compared with erlotinib administered as a single agent.

Example 14

Treatment of Colorectal Cancer

[00389] A method for treating a subject having colorectal cancer comprising administering to the subject a therapeutically effective amount of a combination comprising 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-pyrrole and erlotinib or their respective pharmaceutically acceptable salt, solvate or prodrug is contemplated. Combined treatment with erlotinib and 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-pyrrole are expected to achieve significantly increased tumor inhibition compared with either 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-pyrrole or erlotinib administered as single agents.

Example 15

Treatment of Glioma

[00390] A method for treating a subject having glioma comprising administering to the subject a therapeutically effective amount of a combination comprising 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-pyrrole and erlotinib or their respective pharmaceutically acceptable salt, solvate or prodrug is contemplated. The subject is treated using a single dosage form of a combination of 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-pyrrole in about 1, about 5, about 10, about 25, about 50, about 100, about 200, about 300, about 400, about 600, about 800, about 1000, and about 1200 mg aliquots and erlotinib in about a 25 mg aliquot. The treatment of the subject using a separate administration of 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-pyrrole in about 1, about 5, about 10, about 25, about 50, about 100, about 200, about 300, about 400, about 600, about 800, about 1000, and about 1200 mg aliquots and erlotinib in about 100, 150, 200, 300, or 450 mg aliquot is also contemplated. The treatment will also be administered in subjects with 2nd temozolomide failures.

Example 16

Treatment of Head and Neck Cancer

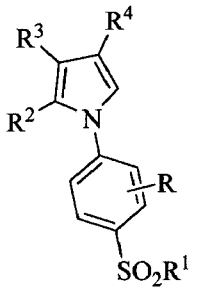
[00391] A method for treating a subject having head and neck cancer comprising administering to the subject a therapeutically effective amount of a combination comprising 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-pyrrole and erlotinib or their respective pharmaceutically acceptable salt, solvate or prodrug is contemplated. The subject is treated using a single dosage form of a combination of 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-pyrrole in about 1, about 5, about 10, about 25, about 50, about 100, about 200, about 300, about 400, about 600, about 800, about 1000, and about 1200 mg aliquots and erlotinib in about a 25 mg aliquot. The treatment of the subject using a separate administration of 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-pyrrole in about 1, about 5, about 10, about 25, about 50, about 100, about 200, about 300, about 400, about 600, about 800, about 1000, and about 1200 mg aliquots and erlotinib in about 100, 150, 200, 300, or 450 mg aliquot is also contemplated. The treatment will also be administered in conjunction with one or one or more chemotherapy agents (e.g., paclitaxel [Taxol®], docetaxel [Taxotere®], gemcitabine [Gemzar®], doxorubicin [Doxil®]) which may be further combined with established chemotherapeutic agents (e.g., methotrexate [Trexall®, Methotrex®]). In another embodiment, therapy for the treatment of head and neck cancer according to the invention utilizes a combination of therapeutically effective amount of a composition comprising a combination of 2-(4-ethoxyphenyl)-4-methyl 1-(4-sulfamoylphenyl)-pyrrole and erlotinib and Erbitux®.

CLAIMS

What is claimed is:

1. A method for treating a subject having cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor or their respective pharmaceutically acceptable salt, solvate, polymorph or prodrug.

2. The method of claim 1 wherein the 1,2-diphenylpyrrole derivative has the following formula:



wherein:

R is a hydrogen atom, a halogen atom or an alkyl group having from 1 to 6 carbon atoms;

R^1 is an alkyl group having from 1 to 6 carbon atoms or an amino group;

R^2 is a phenyl group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents α and substituents β;

R^3 is a hydrogen atom, a halogen atom or an alkyl group which has from 1 to 6 carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6 carbon atoms and an alkylthio group having from 1 to 6 carbon atoms;

R^4 is a hydrogen atom; an alkyl group which has from 1 to 6 carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6 carbon atoms and an alkylthio group having from 1 to 6 carbon atoms; a cycloalkyl group having from 3 to 8 carbon atoms, an aryl group; or an aralkyl group; said aryl group having from 6 to 14 ring carbon atoms in a carbocyclic ring and are unsubstituted or are substituted by at least one substituent selected from the group consisting of substituents α and substituents β;

said aralkyl group are an alkyl group having from 1 to 6 carbon atoms and which are substituted by at least one aryl group as defined above;

said substituents α are selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6 carbon atoms and an alkylthio group having from 1 to 6 carbon atoms;

said substituents β are selected from the group consisting of an alkyl group which has from 1 to 6 carbon atoms and which is unsubstituted or are substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6

carbon atoms and an alkylthio group having from 1 to 6 carbon atoms; an alkanoyloxy group having from 1 to 6 carbon atoms; a mercapto group; an alkanoylthio group having from 1 to 6 carbon atoms; an alkylsulfinyl group having from 1 to 6 carbon atoms; a cycloalkloxy group having from 3 to 8 carbon atoms; a haloalkoxy group having from 1 to 6 carbon atoms; and an alkylenedioxy group having from 1 to 6 carbon atoms; or a pharmaceutically acceptable salt, solvate, or prodrug.

3. The method of claim 2 wherein:

R is a hydrogen atom, a halogen atom or an alkyl group having from 1 to 4 carbon atoms;

R^1 is a methyl group or an amino group;

R^2 is an unsubstituted phenyl group or a phenyl group which is substituted by at least one substituent selected from the group consisting of a halogen atom; an alkoxy group having from 1 to 4 carbon atoms; an alkylthio group having from 1 to 4 carbon atoms; an unsubstituted alkyl group having from 1 to 4 carbon atoms; an alkyl group having from 1 to 4 carbon atoms and which is substituted by at least one substituent selected from the group consisting of a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to 4 carbon atoms; a haloalkoxy group having from 1 to 4 carbon atoms; and an alkylenedioxy group having from 1 to 4 carbon atoms;

R^3 is a hydrogen atom, a halogen atom, an unsubstituted alkyl group having from 1 to 4 carbon atoms or a substituted alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to 4 carbon atoms;

R^4 is a hydrogen atom; an unsubstituted alkyl group having from 1 to 4 carbon atoms; a substituted alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to carbon atoms; a cycloalkyl group having from 3 to 6 carbon atoms; an aryl group which has from 6 to 10 ring carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a halogen atom; an alkoxy group having from 1 to 4 carbon atoms; an alkylthio group having from 1 to 4 carbon atoms; an unsubstituted alkyl group having from 1 to 4 carbon atoms; an alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to 4 carbon atoms; and a cycloalkyloxy group having from 3 to 7 carbon atoms; an aralkyl group having from 1 to 4 carbon atoms in the alkyl part and containing at least one said aryl group; or a pharmaceutically acceptable salt, solvate, or prodrug.

4. The method of claim 3 wherein:

R is a hydrogen atom;

R^1 is an amino group;

R^2 is an unsubstituted phenyl group or a phenyl group which is substituted by at least one substituent selected from the group consisting of a halogen atom, an alkoxy group having from 1 to 4 carbon atoms, an alkylthio group having from 1 to 4 carbon atoms, an alkyl group having from 1 to 4 carbon atoms, a haloalkyl group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 4 carbon atoms and a alkylenedioxy group having from 1 to 4 carbon atoms;

R^3 is a hydrogen atom, a halogen atom, an alkyl group having from 1 to 4 carbon atoms or a haloalkyl group having from 1 to 4 carbon atoms;

R^4 is a hydrogen atom; an unsubstituted alkyl group having from 1 to 4 carbon atoms; a substituted alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a hydroxy group and an alkoxy group having from 1 to 4 carbon atoms; a cycloalkyl group having from 3 to 6 carbon atoms; an aryl group which has from 6 to 10 ring carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a hydroxy group; a halogen atom; an alkoxy group having from 1 to 4 carbon atoms; an unsubstituted alkyl group having from 1 to 4 carbon atoms; an alkyl group having from 1 to 4 carbon atoms and which is unsubstituted or substituted by at least one halogen atom; and a cycloalkyloxy group having from 3 to 7 carbon atoms; and an aralkyl group having from 1 to 4 carbon atoms in the alkyl part and containing at least one said aryl group; or a pharmaceutically acceptable salt, solvate, or prodrug.

5. The method of claim 4 wherein the 1,2-diphenylpyrrole derivative is selected from the group consisting of: 4-methyl-2-(4-methylphenyl)-1-(4-sulfamoylphenyl)pyrrole; 2-(4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(4-chlorophenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 4-methyl-2-(4-methylthiophenyl)-1-(4-sulfamoylphenyl)pyrrole; 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(4-methoxy-3-methylphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(3-fluoro-4-methoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 2-(3,4-dimethylphenyl)-4-methyl-1-(4-sulfamoylphenyl)pyrrole; 4-methyl-1-(4-methylthiophenyl)-2-(4-sulfamoylphenyl)pyrrole; 1-(4-acetylaminosulfonylphenyl)-4-methyl-2-(4-methoxyphenyl)pyrrole; and 1-(4-acetylaminosulfonylphenyl)-4-methyl-2-(3,4-dimethylphenyl)pyrrole.
6. The method of claim 5 wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole.
7. The method of claim 1 wherein the EGFR inhibitor is erlotinib.
8. The method of claim 1 wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.
9. The method of claim 1 wherein the 1,2-diphenylpyrrole derivative and the EGFR inhibitor are administered sequentially in either order or simultaneously.
10. The method of claim 1 wherein the 1,2-diphenylpyrrole derivative is administered first.
11. The method of claim 1 wherein the EGFR inhibitor is administered first.

12. The method of claim 1 wherein administering the combination enhances treatment of the subject.
13. The method of claim 1 wherein administering the combination reduces the side effects of the treatment of cancer compared to a treatment of the EGFR inhibitor alone or a treatment of the 1,2-diphenylpyrrole derivative alone.
14. The method of clam 1 wherein administering the combination is through oral, parenteral, buccal, intranasal, epidural, sublingual, pulmonary, local, rectal, or transdermal administration.
15. The method of claim 14 wherein administering the combination is through parenteral administration.
16. The method of claim 15 wherein parenteral administration is intravenous, subcutaneous, intrathecal, or intramuscular.
17. The method of claim 14 wherein oral administration is in a single dosage form.
18. The method of claim 17 wherein the single dosage form enhances patient compliance and/or reduces pill burden.
19. The method of claim 17 wherein the single dosage form is a single capsule or a single tablet.
20. The method of claim 19 wherein the composition is a single tablet.
21. The method of claim 20 wherein the single tablet comprises from about 1 mg to about 1200 mg of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and from about 25 mg to about 450 mg of erlotinib.
22. The method of claim 21 wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 25 mg of erlotinib.
23. The method of claim 21 wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 100 mg of erlotinib.
24. The method of claim 21 wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 150 mg of erlotinib.
25. The method of claim 21 wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 200 mg of erlotinib.
26. The method of claim 21 wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 300 mg of erlotinib.
27. The method of claim 21 wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 450 mg of erlotinib.
28. The method of claim 1 wherein the cancer is selected from the group consisting of: oral cancer, prostate cancer, rectal cancer, non-small cell lung cancer, lip and oral cavity cancer, liver cancer, lung cancer, anal cancer, kidney cancer, vulvar cancer, breast cancer, oropharyngeal cancer, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, urethra cancer, small intestine cancer, bile duct cancer, bladder cancer, ovarian cancer, laryngeal cancer, hypopharyngeal cancer, gallbladder cancer, colon cancer, colorectal cancer, head and neck cancer, parathyroid cancer,

penile cancer, vaginal cancer, thyroid cancer, pancreatic cancer, esophageal cancer, Hodgkin's lymphoma, leukemia-related disorders, mycosis fungoides, and myelodysplastic syndrome.

29. The method of claim 28 wherein the cancer is non-small cell lung cancer, pancreatic cancer, breast cancer, ovarian cancer, colorectal cancer, and head and neck cancer.

30. The method of claim 1 wherein the cancer is a carcinoma, a tumor, a neoplasm, a lymphoma, a melanoma, a glioma, a sarcoma, and a blastoma.

31. The method of claim 30 wherein the carcinoma is selected from the group consisting of: carcinoma, adenocarcinoma, adenoid cystic carcinoma, adenosquamous carcinoma, adrenocortical carcinoma, well differentiated carcinoma, squamous cell carcinoma, serous carcinoma, small cell carcinoma, invasive squamous cell carcinoma, large cell carcinoma, islet cell carcinoma, oat cell carcinoma, squamous carcinoma, undifferentiatied carcinoma, verrucous carcinoma, renal cell carcinoma, papillary serous adenocarcinoma, merkel cell carcinoma, hepatocellular carcinoma, soft tissue carcinomas, bronchial gland carcinomas, capillary carcinoma, bartholin gland carcinoma, basal cell carcinoma, carcinosarcoma, papilloma/carcinoma, clear cell carcinoma, endometrioid adenocarcinoma, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, cholangiocarcinoma, actinic keratoses, cystadenoma, and hepatic adenomatosis.

32. The method of claim 30 wherein the tumor is selected from the group consisting of: astrocytic tumors, malignant mesothelial tumors, ovarian germ cell tumor, supratentorial primitive neuroectodermal tumors, Wilm's tumor, pituitary tumors, extragonadal germ cell tumor, gastrinoma, germ cell tumors, gestational trophoblastic tumor, brain tumors, pineal and supratentorial primitive neuroectodermal tumors, pituitary tumor, somatostatin-secreting tumor, endodermal sinus tumor, carcinoids, central cerebral astrocytoma, glucagonoma, hepatic adenoma, insulinoma, medulloepithelioma, plasmacytoma, vipoma, and pheochromocytoma.

33. The method of claim 30 wherein the neoplasm is selected from the group consisting of: intaepithelial neoplasia, multiple myeloma/plasma cell neoplasm, plasma cell neoplasm, interepithelial squamous cell neoplasia, endometrial hyperplasia, focal nodular hyperplasia, hemangioendothelioma, and malignant thymoma.

34. The method of claim 30 wherein the lymphoma is selected from the group consisting of: nervous system lymphoma, AIDS-related lymphoma, cutaneous T-cell lymphoma, non-Hodgkin's lymphoma, lymphoma, and Waldenstrom's macroglobulinemia.

35. The method of claim 30 wherein the melanoma is selected from the group consisting of: acral lentiginous melanoma, superficial spreading melanoma, uveal melanoma, lentigo maligna melanomas, melanoma, intraocular melanoma, adenocarcinoma nodular melanoma, and hemangioma.

36. The method of claim 30 wherein the sarcoma is selected from the group consisting of: adenomas, adenosarcoma, chondosarcoma, endometrial stromal sarcoma, Ewing's sarcoma, Kaposi's sarcoma,

leiomyosarcoma, , rhabdomyosarcoma, sarcoma, uterine sarcoma, osteosarcoma, and pseudosarcoma.

37. The method of claim 30 wherein the glioma is selected from the group consisting of: glioma, brain stem glioma, and hypothalamic and visual pathway glioma.

38. The method of claim 30 wherein the blastoma is selected from the group consisting of: pulmonary blastoma, pleuropulmonary blastoma, retinoblastoma, neuroblastoma, medulloblastoma, glioblastoma, and hemangiblastomas.

39. The method of claim 1 wherein the EGFR inhibitor is a small molecule compound or an antibody.

40. The method of claim 39 wherein the small molecule compound is selected from the group consisting of: ZM-254530, BIBX-1382, reveromycin A, gefitinib, CGP-57148, CGP-59326, 4-(3-chloro)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine, tyrphostin, PKI-166, PD 153035, EKB-569, and 4-(phenylamino)quinazolines, or their pharmaceutically acceptable salts, solvates, or prodrugs.

41. The method of claim 39 wherein the antibody is selected from the group consisting of: EGF receptor antibody, MR1scFvPE38KDEL MDX-447, MDX-210, MD-72000, MDX-260, wayne anti-EGFR Mabs, anti-EGFr Mab, anti-EGFr MAb, Genen anti-EGFR Mab, MAb DC-101, trastuzumab, anti-VEGF monoclonal, anti-EGFR-DM1 Ab, MAb 4D5, BAB-447, EMD-55900, EMD-6200, -82633, anti-EGFR Mab, MAb 4D5, cetuximab, anti-EGFr MAb, anti-flk-1, CCX, CCZ, anti-flk-1, AG-514, AG-568, nti-EGFR-DM1 Ab, MDX-447, TgDCC-E1A, C225, matuzumab, panitumumab, DWP-408, and RC-3940II.

42. The method of claim 1 wherein the EGFR inhibitor is selected from the group consisting of: muellerian-inhibiting hormone, TNP-470, tecogalan sodium, EGF receptor antisense, PI-88, oligonucleotide, bromelain molecules, amphiregulin, EGF fusion toxin, EGF fusion protein, Amphiregulin hbEGF-toxin, hbEGF-toxin, and EGF fusion protein.

43. A method of inducing differentiation of tumor cells, the method comprising contacting the cells with an effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor whereby the combination induces differentiation of tumor cells.

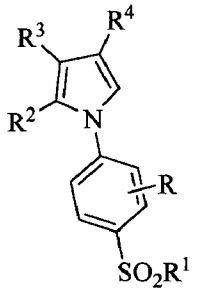
44. A method of inhibiting proliferation of cancer cells, the method comprising contacting a cancer cell with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor whereby the combination inhibits proliferation of cancer cells.

45. A method for reducing proliferation of cancer cells, the method comprising delivering to the cells a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor, whereby the reduction of cell proliferation is greater than a reduction caused by either a 1,2-diphenylpyrrole derivative alone or an EGFR inhibitor alone.

46. A method of modulating autophosphorylation with a molecule of ATP, the method comprising delivering to a cancer cell an effective amount of a combination comprising a 1,2-diphenylpyrrole

derivative and an EGFR inhibitor wherein the combination inhibits autophosphorylation with a molecule of ATP.

47. A method of inhibiting metastases of tumor cells, the method comprising administering an effective amount of a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor such that the combination inhibits metastatic activity of tumor cells.
48. A method for inducing apoptosis in cancer cells, the method comprising contacting the cancer cells with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR kinase sufficient to induce apoptosis.
49. A method for sensitizing EGFR inhibitor resistant cancer cells to an EGFR inhibitor, the method comprising administering a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination sensitizes the cancer cells to the EGFR inhibitor.
50. A method of treating EGFR resistance in a cancer cell, the method comprising, administering a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor.
51. A method of modulating prostaglandin synthesis in a cancer cell, the method comprising contacting the cell with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination inhibits prostaglandin synthesis in a cancer cell.
52. A method of modulating cyclooxygenase expression in a cancer cell, the method comprising delivering to the cell a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination inhibits cyclooxygenase expression in a cancer cell.
53. A method of modulating angiogenesis in a cancer cell, the method comprising contacting the cell with a combination comprising a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination inhibits angiogenesis in a cancer cell.
54. A method of reducing the dosage in conventional treatment for neoplasia and/or neoplasia related disorders in a subject, the method comprising administering to a subject a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor wherein the combination reduces the dosage in conventional treatment for neoplasia and/or neoplasia-related disorders.
55. A method of treating neoplasia and/or neoplasia related disorders, the method comprising administering a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor.
56. A composition for treating cancer comprising, a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor or their respective pharmaceutically acceptable salt, solvate or prodrug.
57. The composition of claim 56 wherein the 1,2-diphenylpyrrole derivative has the following formula:



wherein:

R is a hydrogen atom, a halogen atom or an alkyl group having from 1 to 6 carbon atoms;

R^1 is an alkyl group having from 1 to 6 carbon atoms or an amino group;

R^2 is a phenyl group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents α and substituents β;

R^3 is a hydrogen atom, a halogen atom or an alkyl group which has from 1 to 6 carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6 carbon atoms and an alkylthio group having from 1 to 6 carbon atoms;

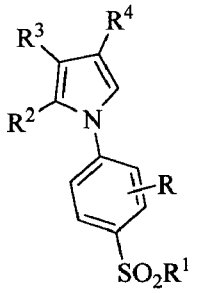
R^4 is a hydrogen atom; an alkyl group which has from 1 to 6 carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6 carbon atoms and an alkylthio group having from 1 to 6 carbon atoms; a cycloalkyl group having from 3 to 8 carbon atoms, an aryl group; or an aralkyl group; said aryl group having from 6 to 14 ring carbon atoms in a carbocyclic ring and are unsubstituted or are substituted by at least one substituent selected from the group consisting of substituents α and substituents β;

said aralkyl group are an alkyl group having from 1 to 6 carbon atoms and which are substituted by at least one aryl group as defined above;

said substituents α are selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6 carbon atoms and an alkylthio group having from 1 to 6 carbon atoms;

said substituents β are selected from the group consisting of an alkyl group which has from 1 to 6 carbon atoms and which is unsubstituted or are substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 6 carbon atoms and an alkylthio group having from 1 to 6 carbon atoms; an alkanoyloxy group having from 1 to 6 carbon atoms; a mercapto group; an alkanoylthio group having from 1 to 6 carbon atoms; an alkylsulfinyl group having from 1 to 6 carbon atoms; a cycloalkloxy group having from 3 to 8 carbon atoms; a haloalkoxy group having from 1 to 6 carbon atoms; and an alkylenedioxy group having from 1 to 6 carbon atoms; or a pharmaceutically acceptable salt, solvate, or prodrug.

58. The composition of claim 57 wherein the 1,2-diphenylpyrrole derivative has the following formula:



wherein:

R is a hydrogen atom, a halogen atom or an alkyl group having from 1 to 4 carbon atoms;

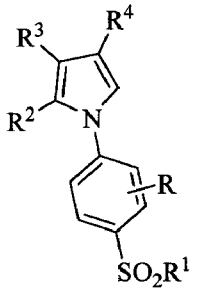
R^1 is a methyl group or an amino group;

R^2 is an unsubstituted phenyl group or a phenyl group which is substituted by at least one substituent selected from the group consisting of a halogen atom; an alkoxy group having from 1 to 4 carbon atoms; an alkylthio group having from 1 to 4 carbon atoms; an unsubstituted alkyl group having from 1 to 4 carbon atoms; an alkyl group having from 1 to 4 carbon atoms and which is substituted by at least one substituent selected from the group consisting of a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to 4 carbon atoms; a haloalkoxy group having from 1 to 4 carbon atoms; and an alkylenedioxy group having from 1 to 4 carbon atoms;

R^3 is a hydrogen atom, a halogen atom, an unsubstituted alkyl group having from 1 to 4 carbon atoms or a substituted alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to 4 carbon atoms;

R^4 is a hydrogen atom; an unsubstituted alkyl group having from 1 to 4 carbon atoms; a substituted alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to carbon atoms; a cycloalkyl group having from 3 to 6 carbon atoms; an aryl group which has from 6 to 10 ring carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a halogen atom; an alkoxy group having from 1 to 4 carbon atoms; an alkylthio group having from 1 to 4 carbon atoms; an unsubstituted alkyl group having from 1 to 4 carbon atoms; an alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a hydroxy group, a halogen atom, an alkoxy group having from 1 to 4 carbon atoms and an alkylthio group having from 1 to 4 carbon atoms; and a cycloalkyloxy group having from 3 to 7 carbon atoms; an aralkyl group having from 1 to 4 carbon atoms in the alkyl part and containing at least one said aryl group; or a pharmaceutically acceptable salt, solvate, or prodrug.

59. The composition of claim 57 wherein the 1,2-diphenylpyrrole derivative has the following formula:



wherein:

R is a hydrogen atom;

R^1 is an amino group;

R^2 is an unsubstituted phenyl group or a phenyl group which is substituted by at least one substituent selected from the group consisting of a halogen atom, an alkoxy group having from 1 to 4 carbon atoms, an alkylthio group having from 1 to 4 carbon atoms, an alkyl group having from 1 to 4 carbon atoms, a haloalkyl group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 4 carbon atoms and a alkylenedioxy group having from 1 to 4 carbon atoms;

R^3 is a hydrogen atom, a halogen atom, an alkyl group having from 1 to 4 carbon atoms or a haloalkyl group having from 1 to 4 carbon atoms;

R^4 is a hydrogen atom; an unsubstituted alkyl group having from 1 to 4 carbon atoms; a substituted alkyl group having from 1 to 4 carbon atoms and substituted by at least one substituent selected from the group consisting of a hydroxy group and an alkoxy group having from 1 to 4 carbon atoms; a cycloalkyl group having from 3 to 6 carbon atoms; an aryl group which has from 6 to 10 ring carbon atoms and which is unsubstituted or is substituted by at least one substituent selected from the group consisting of a hydroxy group; a halogen atom; an alkoxy group having from 1 to 4 carbon atoms; an unsubstituted alkyl group having from 1 to 4 carbon atoms; an alkyl group having from 1 to 4 carbon atoms and which is unsubstituted or substituted by at least one halogen atom; and a cycloalkyloxy group having from 3 to 7 carbon atoms; and an aralkyl group having from 1 to 4 carbon atoms in the alkyl part and containing at least one said aryl group; or a pharmaceutically acceptable salt, solvate, or prodrug.

60. The composition of claim 59 wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole.

61. The composition of claim 56 wherein the EGFR inhibitor is erlotinib.

62. The composition of claim 56 wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.

63. The composition of claim 56 wherein the composition is a single dosage form.

64. The composition of claim 63 wherein the single dosage form enhances patient compliance and/or reduces pill burden.

65. The composition of claim 62 wherein the combination is in an oral, parenteral, buccal, intranasal, epidural, sublingual, pulmonary, local, rectal, or transdermal form.

66. The composition of claim 65 wherein the combination is in the parenteral form.
67. The composition of claim 66 wherein the parenteral form is intravenous, subcutaneous, intrathecal, or intramuscular.
68. The composition of claim 63 wherein the single dosage form is a single capsule or a single tablet.
69. The composition of claim 68 wherein the composition is a single tablet.
70. The composition of claim 69 wherein the single tablet comprises from about 1 mg to about 1200 mg of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and from about 25 mg to about 450 mg of erlotinib.
71. The composition of claim 70 wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 25 mg of erlotinib.
72. The composition of claim 70 wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 100 mg of erlotinib.
73. The composition of claim 70 wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 150 mg of erlotinib.
74. The composition of claim 70 wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 200 mg of erlotinib.
75. The composition of claim 70 wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 300 mg of erlotinib.
76. The composition of claim 70 wherein the single tablet comprises from about 1 mg to about 1200 mg 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and about 450 mg of erlotinib.
77. The composition of claim 70 wherein the composition is suitable for once-daily administration.
78. The composition of claim 56 wherein the EGFR inhibitor is a small molecule compound or an antibody.
79. The composition of claim 78 wherein the small molecule compound is selected from the group consisting of: ZM-254530, BIBX-1382, reveromycin A, gefitinib, CGP-57148, CGP-59326, 4-(3-chloro)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine, tyrphostin, PKI-166, PD 153035, EKB-569, and 4-(phenylamino)quinazolines, or their pharmaceutically acceptable salts, solvates, or prodrugs.
80. The composition of claim 78 wherein the antibody is selected from the group consisting of: EGF receptor antibody, MR1scFvPE38KDEL MDX-447, MDX-210, MD-72000, MDX-260, wayne anti-EGFR Mabs, anti-EGFr Mab, anti-EGFr MAb, Genen anti-EGFR Mab, MAb DC-101, trastuzumab, anti-VEGF monoclonal, anti-EGFR-DM1 Ab, MAb 4D5, BAB-447, EMD-55900, EMD-6200, -82633, anti-EGFR Mab, MAb 4D5, cetuximab, anti-EGFr MAb, anti-flk-1, CCX, CCZ, anti-flk-1, AG-514, AG-568, nti-EGFR-DM1 Ab, MDX-447, TgDCC-E1A, C225, matuzumab, panitumumab, DWP-408, and RC-3940II.
81. The composition of claim 56 wherein the composition contains a lower dose of EGFR inhibitor than a conventional treatment for cancer.

82. The composition of claim 56 wherein the composition reduces the side effects of the treatment of cancer.
83. The composition of claim 56 wherein the composition enhances treatment of cancer.
84. A pharmaceutical composition for treating cancer comprising, a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor, and a pharmaceutically acceptable excipient or carrier.
85. The pharmaceutical composition of claim 84 wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole.
86. The pharmaceutical composition of claim 84 wherein the EGFR inhibitor is erlotinib.
87. The pharmaceutical composition of claim 84 wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.
88. A kit for treating cancer comprising a single dosage form comprising a combination of a 1,2-diphenylpyrrole derivative and an EGFR inhibitor and instructions on how to administer the dosage form.
89. The kit of claim 88 wherein the 1,2-diphenylpyrrole derivative is 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor is erlotinib.
90. The method of claim 6 further comprising administering to the subject one or more therapies in addition to the combination of 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole and the EGFR inhibitor.
91. The method of claim 90 wherein the one or more therapies comprise one or more of surgery, radiation therapy, chemotherapy, high dose chemotherapy with stem cell transplant; hormone therapy, and monoclonal antibody therapy.
92. The method of claim 91 wherein radiation therapy comprises internal and/or external radiation therapy.
93. The method of 91 wherein the chemotherapy comprisies administering to the subject gemcitabine.
94. A method for treating a subject having cancer, comprising administering to the subject, a therapeutically effective amount of a combination comprising 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole, erlotinib and gemcitabine, or their respective pharmaceutically acceptable salt, solvate, polymorph or prodrug.
95. The method of claim 94 wherein the 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole is administered at a dose of 100-1200 mg per day, the erlotinib is administered at a dose of 50-250 mg per day, and the gemcitabine is administered at a dose of 500-1500 mg per meter squared of body surface area per weekly intravenous administration.
96. The method of claim 95 wherein the 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole is administered at a dose of 400 mg per day, the erlotinib is administered at a dose of 100 mg per day, and the gemcitabine is administered at a dose of 1000 mg per meter squared of body surface area per weekly intravenous administration.

97. The method of claim 95 wherein the 2-(4-ethoxyphenyl)-4-methyl-1-(4-sulfamoylphenyl)-pyrrole is administered at a dose of 400 mg per day, the erlotinib is administered at a dose of 150 mg per day, and the gemcitabine is administered at a dose of 1000 mg per meter squared of body surface area per weekly intravenous administration.

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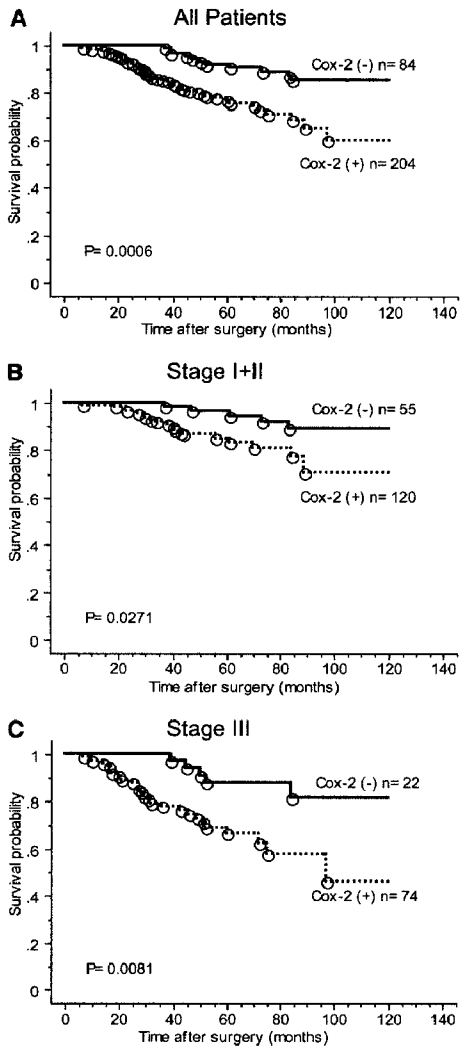

Fig. 1 Expression Levels Correlate with Survival in Colorectal Cancer. The overall 10-year survival curves of patients with Cox-2 negative and Cox-2 positive are shown for the entire cohort, $P = 0.0006$ (*A*), as well as for patients with stage I/II, $P = 0.0271$ (*B*), or stage III, $P = 0.0081$ (*C*) disease.

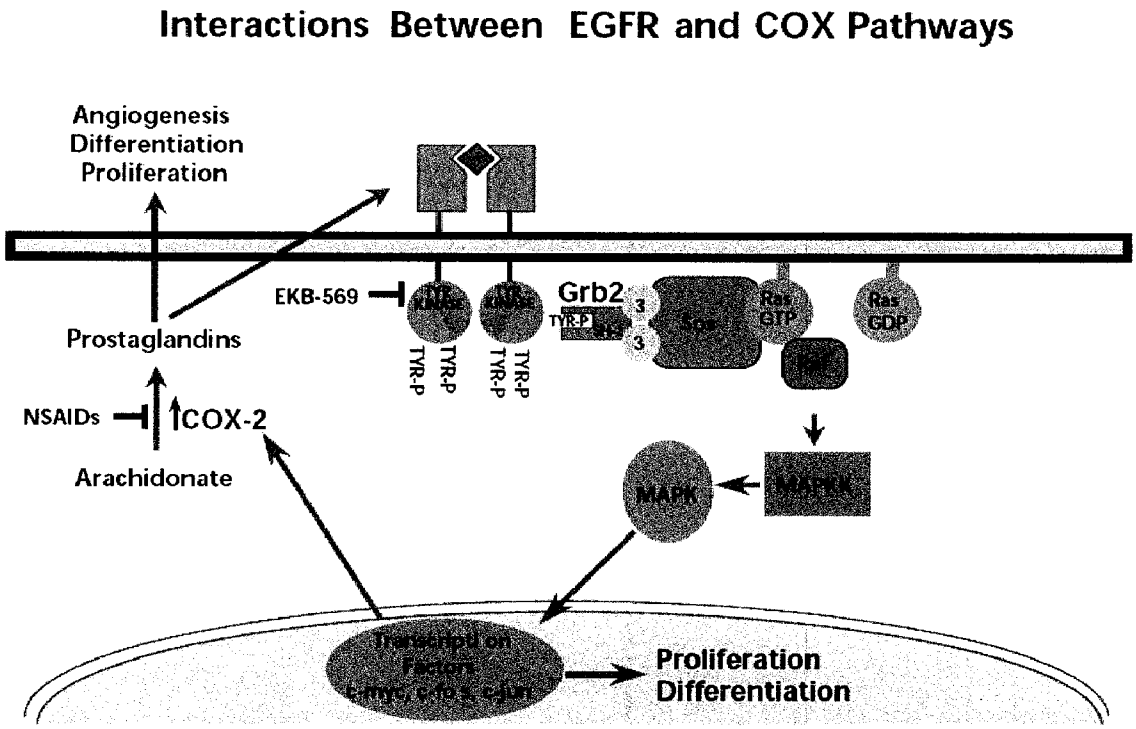

Fig. 2 Interactions between the EGFR and COX pathways.

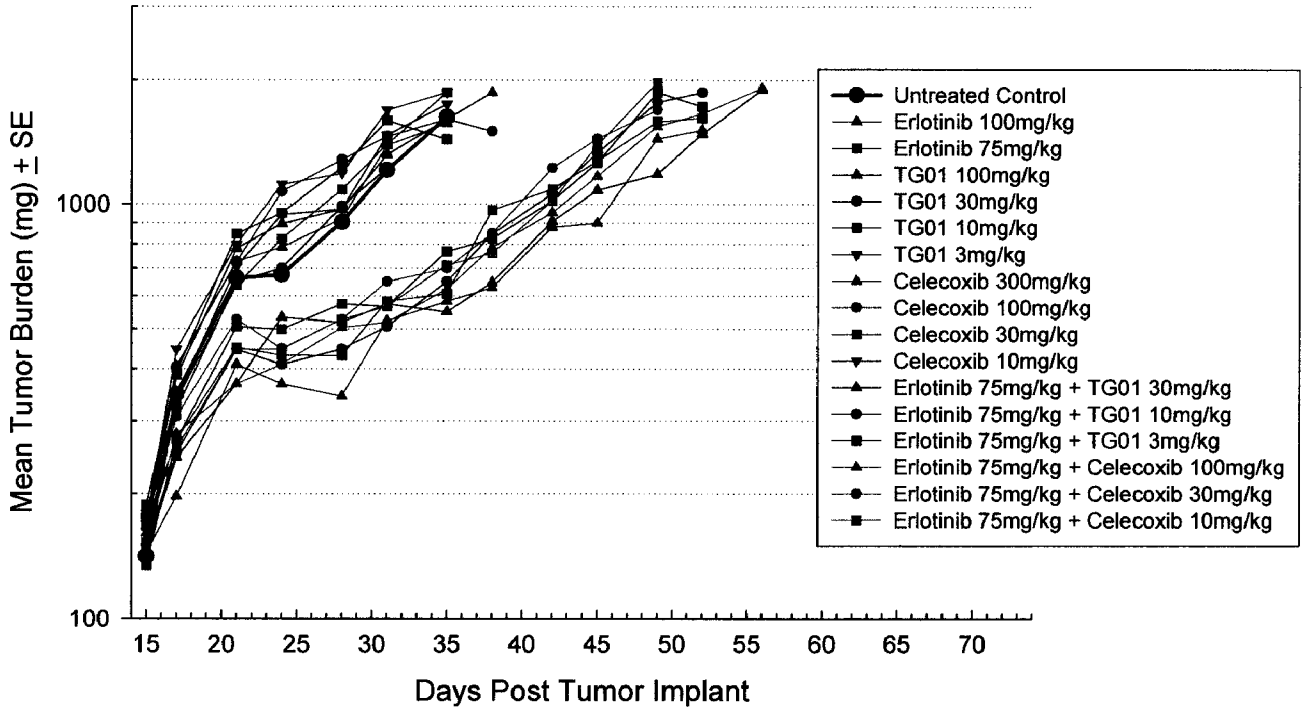

Fig. 3 A431squamous vulvar carcinoma xenograft study.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/69894

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/36; A61K 31/40 (2008.04)
USPC - 514/427; 435/334
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/427; 435/334

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/7.2, 7.23, 336; 514/176, 234.5, 265.1, 709; 424/9.2 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Databases Searched: USPTO WEST (PGPUB, EPAB, JPAB, USPT), Google Patent, Google Scholar. Search Terms Used: 1,2-diphenylpyrrole and EGFR inhibitor, cancer, tabl$ or pill, admin$, intrave$

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2004/0127470 A1 (Masferrer) 01 July 2004 (01.07.2008) abstract; table 3 and 10; para [0015], [0085], [0089], [0100], [0182], [0185], [1130], [0074], [1159]-[1160], [1178], [1199], [1209], [1212], [1264], [1320]-[1321], [1324]	1, 7, 9-20, 28-56, 61, 63, 68-69, 81-84, 86 and 88 --- 2-6, 8, 21-27, 57-60, 62, 64-67, 70-80, 85, 87 and 89-97
Y	US 5,908,858 A (Kimura et al.) 01 Jun 1999 (01.06.1999) col 2, ln 56 to col 4, ln 24	2-6, 8, 21-27, 57-60, 62, 64-67, 70-80, 85, 87 and 89-97

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 September 2008 (30.09.2008)	06 OCT 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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A61K 31/40(2006.01)

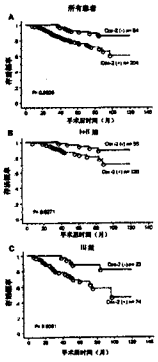
权利要求书 9 页 说明书 61 页 附图 2 页

(54)发明名称

治疗癌症、肿瘤和肿瘤相关性疾病的方法和组合物

(57)摘要

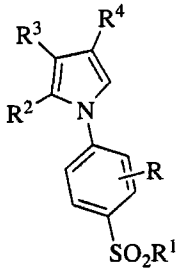
本文描述了组合物以及使用这些组合物在对象中治疗癌症、肿瘤和肿瘤相关性疾病的方法。



CN 101801188 A

1. 一种治疗患有癌症的对象的方法，其包括给予所述对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂或它们各自药学上可接受的盐、溶剂合物、多晶型物或前体药物的组合。

2. 根据权利要求 1 所述的方法，其中所述 1,2- 二苯基吡咯衍生物具有下式：



其中：

R 是氢原子、卤素原子或具有 1 至 6 个碳原子的烷基；

R^1 是具有 1 至 6 个碳原子的烷基或氨基；

R^2 是苯基，所述苯基是未取代的或被选自由取代基 α 和取代基 β 组成的群组的至少一个取代基取代；

R^3 是氢原子、卤素原子或烷基，所述烷基具有 1 至 6 个碳原子并且其是未取代的或被选自由羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基组成的群组的至少一个取代基取代；

R^4 是氢原子；烷基，所述烷基具有 1 至 6 个碳原子并且其是未取代的或被选自由羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基组成的群组的至少一个取代基取代；具有 3 至 8 个碳原子的环烷基、芳基；或芳烷基；所述芳基在碳环中具有 6 至 14 个环碳原子并且是未取代的或被选自由取代基 α 和取代基 β 组成的群组的至少一个取代基取代；

所述芳烷基是具有 1 至 6 个碳原子并且被上述限定的至少一个芳基取代的烷基；

所述取代基 α 选自由羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基组成的群组；

所述取代基 β 选自由如下组成的群组：烷基，其具有 1 至 6 个碳原子并且是未取代的或被选自由羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基组成的群组的至少一个取代基取代；具有 1 至 6 个碳原子的烷酰氧基；巯基；具有 1 至 6 个碳原子的烷酰硫基；具有 1 至 6 个碳原子的烷亚硫酰基；具有 3 至 8 个碳原子的环烷氧基；具有 1 至 6 个碳原子的卤烷氧基；以及具有 1 至 6 个碳原子的亚烷二氧基；或药学上可接受的盐、溶剂合物或前体药物。

3. 根据权利要求 2 所述的方法，其中：

R 是氢原子、卤素原子或具有 1 至 4 个碳原子的烷基；

R^1 是甲基或氨基；

R^2 是未取代的苯基或被选自由如下组成的群组的至少一个取代基取代的苯基：卤素原子；具有 1 至 4 个碳原子的烷氧基；具有 1 至 4 个碳原子的烷硫基；具有 1 至 4 个碳原子的未取代烷基；具有 1 至 4 个碳原子并且被选自由卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至 4 个碳原子的烷硫基组成的群组的至少一个取代基取代的烷基；具有 1 至 4 个碳

原子的卤烷氧基；和具有 1 至 4 个碳原子的亚烷二氧基；

R^3 是氢原子、卤素原子、具有 1 至 4 个碳原子的未取代烷基或取代烷基，所述取代烷基具有 1 至 4 个碳原子并且被选自由卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至 4 个碳原子的烷硫基组成的群组的至少一个取代基取代；

R^4 是氢原子；具有 1 至 4 个碳原子的未取代烷基；取代烷基，其具有 1 至 4 个碳原子并且被选自由羟基、卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至个碳原子的烷硫基组成的群组的至少一个取代基取代；具有 3 至 6 个碳原子的环烷基；芳基，其具有 6 至 10 个环碳原子并且是未取代的或被选自由如下组成的群组的至少一个取代基取代：卤素原子、具有 1 至 4 个碳原子的烷氧基、具有 1 至 4 个碳原子的烷硫基、具有 1 至 4 个碳原子的未取代烷基、具有 1 至 4 个碳原子并且被选自由羟基、卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至 4 个碳原子的烷硫基组成的群组的至少一个取代基取代的烷基、和具有 3 至 7 个碳原子的环烷氧基；芳烷基，其在烷基部分具有 1 至 4 个碳原子并且包含至少一个所述芳基；或药学上可接受的盐、溶剂合物或前体药物。

4. 根据权利要求 3 所述的方法，其中：

R 是氢原子；

R^1 是氨基；

R^2 是未取代的苯基或被选自由如下组成的群组的至少一个取代基取代的苯基：卤素原子、具有 1 至 4 个碳原子的烷氧基、具有 1 至 4 个碳原子的烷硫基、具有 1 至 4 个碳原子的烷基、具有 1 至 4 个碳原子的卤烷基、具有 1 至 4 个碳原子的卤烷氧基和具有 1 至 4 个碳原子的亚烷二氧基；

R^3 是氢原子、卤素原子、具有 1 至 4 个碳原子的烷基或具有 1 至 4 个碳原子的卤烷基；

R^4 是氢原子；具有 1 至 4 个碳原子的未取代烷基；取代烷基，其具有 1 至 4 个碳原子并且被选自由羟基和具有 1 至 4 个碳原子的烷氧基组成的群组的至少一个取代基取代；具有 3 至 6 个碳原子的环烷基；芳基，其具有 6 至 10 个环碳原子并且是未取代的或被选自由下列组成的群组的至少一个取代基取代：羟基、卤素原子、具有 1 至 4 个碳原子的烷氧基、具有 1 至 4 个碳原子的未取代烷基、具有 1 至 4 个碳原子并且是未取代的或被至少一个卤素原子取代的烷基、和具有 3 至 7 个碳原子的环烷氧基；以及芳烷基，其在烷基部分中具有 1 至 4 个碳原子并且包含至少一个所述芳基；或药学上可接受的盐、溶剂合物或前体药物。

5. 根据权利要求 4 所述的方法，其中所述 1,2- 二苯基吡咯衍生物选自由如下组成的群组：4- 甲基 -2-(4- 甲苯基)-1-(4- 氨磺酰苯基) 吡咯；2-(4- 甲氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；2-(4- 氯苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；4- 甲基 -2-(4- 甲基苯硫基)-1-(4- 氨磺酰苯基) 吡咯；2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；2-(4- 甲氧基 -3- 甲苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；2-(3- 氟 -4- 甲氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；2-(3,4- 二甲基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；4- 甲基 -1-(4- 甲基苯硫基)-2-(4- 氨磺酰苯基) 吡咯；1-(4- 乙酰氨基磺酰苯基)-4- 甲基 -2-(4- 甲氧基苯基) 吡咯；和 1-(4- 乙酰氨基磺酰苯基)-4- 甲基 -2-(3,4- 二甲基苯基) 吡咯。

6. 根据权利要求 5 所述的方法，其中所述 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯。

7. 根据权利要求 1 所述的方法，其中所述 EGFR 抑制剂是埃罗替尼。

8. 根据权利要求 1 所述的方法，其中所述 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及所述 EGFR 抑制剂是埃罗替尼。

9. 根据权利要求 1 所述的方法，其中所述 1,2- 二苯基吡咯衍生物和所述 EGFR 抑制剂以任一顺序或同时给药。

10. 根据权利要求 1 所述的方法，其中所述 1,2- 二苯基吡咯衍生物首先给药。

11. 根据权利要求 1 所述的方法，其中所述 EGFR 抑制剂首先给药。

12. 根据权利要求 1 所述的方法，其中给予所述组合提高对所述对象的治疗。

13. 根据权利要求 1 所述的方法，其中与单独所述 EGFR 抑制剂治疗或单独所述 1,2- 二苯基吡咯衍生物治疗相比，给予所述组合减少癌症治疗的副作用。

14. 根据权利要求 1 所述的方法，其中通过口服、肠胃外、口腔、鼻内、硬膜外、舌下、肺部、局部、直肠或经皮给药，给予所述组合。

15. 根据权利要求 14 所述的方法，其中通过肠胃外给药给予所述组合。

16. 根据权利要求 15 所述的方法，其中肠胃外给药是静脉内、皮下、鞘内或肌肉内。

17. 根据权利要求 14 所述的方法，其中口服给药是单一剂型。

18. 根据权利要求 17 所述的方法，其中所述单一剂型提高患者顺应性和 / 或减少药丸负担。

19. 根据权利要求 17 所述的方法，其中所述单一剂型是单一胶囊或单一片剂。

20. 根据权利要求 19 所述的方法，其中所述组合物是单一片剂。

21. 根据权利要求 20 所述的方法，其中所述单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 25mg 至约 450mg 埃罗替尼。

22. 根据权利要求 21 所述的方法，其中所述单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 25mg 埃罗替尼。

23. 根据权利要求 21 所述的方法，其中所述单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 100mg 埃罗替尼。

24. 根据权利要求 21 所述的方法，其中所述单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 150mg 埃罗替尼。

25. 根据权利要求 21 所述的方法，其中所述单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 200mg 埃罗替尼。26. 根据权利要求 21 所述的方法，其中所述单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 300mg 埃罗替尼。

27. 根据权利要求 21 所述的方法，其中所述单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 450mg 埃罗替尼。

28. 根据权利要求 1 所述的方法，其中所述癌症选自由如下组成的群组 ：口癌、前列腺癌、直肠癌、非小细胞肺癌、唇及口腔癌、肝癌、肺癌、肛门癌、肾癌、外阴癌、乳腺癌、口咽癌、鼻腔和鼻窦癌、鼻咽癌、尿道癌、小肠癌、胆管癌、膀胱癌、卵巢癌、喉癌、下咽癌、胆囊癌、结肠癌、结肠直肠癌、头颈癌、旁甲状腺癌、阴茎癌、阴道癌、甲状腺癌、胰腺癌、食道癌、霍奇金氏淋巴瘤、白血病相关性疾病、蕈样肉芽肿病和骨髓增生异常综合征。

29. 根据权利要求 28 所述的方法，其中所述癌症是非小细胞肺癌、胰腺癌、乳腺癌、卵

巢癌、结肠直肠癌和头颈癌。

30. 根据权利要求 1 所述的方法，其中所述癌症是癌、肿瘤、瘤、淋巴瘤、黑素瘤、神经胶质瘤、肉瘤和胚细胞瘤。

31. 根据权利要求 30 所述的方法，其中所述癌选自由如下组成的群组：癌、腺癌、腺样囊性癌、腺鳞癌、肾上腺皮质癌、高分化癌、鳞状细胞癌、浆液性癌、小细胞癌、侵袭性鳞状细胞癌、大细胞癌、胰岛细胞癌、燕麦细胞癌、鳞状癌、未分化的癌、疣状癌、肾细胞癌、乳头状浆液性腺癌、默克尔 (merkel) 细胞癌、肝细胞癌、软组织癌、支气管腺癌、毛细管癌、前庭大腺癌、基底细胞癌、癌肉瘤、乳头状瘤 / 癌、透明细胞癌、子宫内膜样腺癌、间皮癌、转移性癌、粘液表皮样癌、胆管癌、光化性角化病、囊腺瘤和肝腺瘤病。

32. 根据权利要求 30 所述的方法，其中所述肿瘤选自由如下组成的群组：星形细胞肿瘤、恶性间皮肿瘤、卵巢生殖细胞肿瘤、幕上原始神经外胚层肿瘤、威姆氏肿瘤、垂体肿瘤、性腺外生殖细胞肿瘤、胃泌素瘤、生殖细胞肿瘤、妊娠滋养细胞肿瘤、脑肿瘤、松果体和幕上原始神经外胚层肿瘤、垂体肿瘤、生长激素抑制素分泌肿瘤、内胚窦肿瘤、类癌瘤、中枢脑星形细胞瘤、胰高血糖素瘤、肝腺瘤、胰岛素瘤、髓质上皮瘤、浆细胞瘤、血管活性肠多肽瘤和嗜铬细胞瘤。

33. 根据权利要求 30 所述的方法，其中所述瘤选自由如下组成的群组：上皮内瘤、多发性骨髓瘤 / 浆细胞瘤、浆细胞瘤、上皮内鳞状细胞瘤、子宫内膜增生、灶性结节性增生、血管内皮瘤和恶性胸腺瘤。

34. 根据权利要求 30 所述的方法，其中所述淋巴瘤选自由如下组成的群组：神经系统淋巴瘤、AIDS- 相关性淋巴瘤、皮肤 T 淋巴细胞瘤、非霍奇金氏淋巴瘤、淋巴瘤和瓦尔登斯特伦巨球蛋白血症。

35. 根据权利要求 30 所述的方法，其中所述黑素瘤选自由如下组成的群组：肢端雀斑样痣黑素瘤、浅表扩散性黑素瘤、葡萄膜黑素瘤、恶性雀斑样痣黑素瘤、黑素瘤、眼内黑素瘤、腺癌结节性黑素瘤和血管瘤。

36. 根据权利要求 30 所述的方法，其中所述肉瘤选自由如下组成的群组：腺瘤、腺肉瘤、软骨肉瘤、子宫内膜间质肉瘤、尤因氏肉瘤、卡波西氏肉瘤、平滑肌肉瘤、横纹肌肉瘤、肉瘤、子宫肉瘤、骨肉瘤和假性肉瘤。

37. 根据权利要求 30 所述的方法，其中所述神经胶质瘤选自由如下组成的群组：神经胶质瘤、脑干神经胶质瘤以及下丘脑和视觉通路神经胶质瘤。

38. 根据权利要求 30 所述的方法，其中所述胚细胞瘤选自由如下组成的群组：肺母细胞瘤、胸膜肺母细胞瘤、视网膜母细胞瘤、神经母细胞瘤、髓母细胞瘤、胶质母细胞瘤和血管母细胞瘤。

39. 根据权利要求 1 所述的方法，其中所述 EGFR 抑制剂是小分子化合物或抗体。

40. 根据权利要求 39 所述的方法，其中所述小分子化合物选自由如下组成的群组：ZM-254530、BIBX-1382、雷弗霉素 A(reveromycin A)、吉非替尼、CGP-57148、CGP-59326、4-(3- 氯)-5,6- 二甲基 -7H- 吡咯并 [2,3-d] 嘧啶、酪氨酸磷酸化抑制剂、PKI-166、PD 153035、EKB-569 和 4-(苯基氨基) 喹唑啉或它们药学上可接受的盐、溶剂合物或前体药物。

41. 根据权利要求 39 所述的方法，其中所述抗体选自由如下组成的群组：EGF 受体抗体、MR1scFvPE38KDEL MDX-447、MDX-210、MD-72000、MDX-260、韦恩 (wayne) 抗 -EGFR 单克隆

抗体 (Mabs)、抗 -EGFr Mab、抗 -EGFr MAb、Genen 抗 -EGFR Mab、MAb DC-101、曲妥珠单抗、抗 -VEGF 单克隆抗体、抗 -EGFR-DM1Ab、MAb 4D5、BAB-447、EMD-55900、EMD-6200、-82633、抗 -EGFR Mab、MAb 4D5、西妥昔单抗、抗 -EGFr MAb、抗 -flk-1、CCX、CCZ、抗 -flk-1、AG-514、AG-568、抗 -EGFR-DM1Ab、MDX-447、TgDCC-E1A、C225、马妥珠单抗、帕尼单抗、DWP-408 和 RC-3940II。

42. 根据权利要求 1 所述的方法，其中所述 EGFR 抑制剂选自由如下组成的群组 ：缪勒管 - 抑制激素、TNP-470、替可加兰钠、EGF 受体反义、PI-88、寡核苷酸、菠萝蛋白酶分子、双调蛋白、EGF 融合毒素、EGF 融合蛋白、双调蛋白 hbEGF- 毒素、hbEGF- 毒素和 EGF 融合蛋白。

43. 一种诱导肿瘤细胞分化的方法，所述方法包括使所述细胞与有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触，从而所述组合诱导肿瘤细胞分化。

44. 一种抑制癌细胞增殖的方法，所述方法包括使癌细胞与包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触，从而所述组合抑制癌细胞的增殖。

45. 一种减少癌细胞增殖的方法，所述方法包括向所述细胞输送包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，从而所述细胞增殖的减少大于单独 1,2- 二苯基吡咯衍生物或单独 EGFR 抑制剂引起的减少。

46. 一种调节用 ATP 分子的自磷酸化的方法，所述方法包括向癌细胞输送有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中所述组合抑制用 ATP 分子的自磷酸化。

47. 一种抑制肿瘤细胞转移的方法，所述方法包括给予有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，以便所述组合抑制肿瘤细胞的转移活性。

48. 一种诱导癌细胞凋亡的方法，所述方法包括使所述癌细胞与足以诱导凋亡的包含 1,2- 二苯基吡咯衍生物和 EGFR 激酶的组合接触。

49. 一种使EGFR抑制剂抗性癌细胞对EGFR抑制剂敏化的方法，所述方法包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中所述组合使所述癌细胞对所述 EGFR 抑制剂敏化。

50. 一种治疗癌细胞中EGFR抵抗的方法，所述方法包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合。

51. 一种调节癌细胞中前列腺素合成的方法，所述方法包括使所述细胞与包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触，其中所述组合抑制癌细胞中前列腺素合成。

52. 一种调节癌细胞中环加氧酶表达的方法，所述方法包括向所述细胞输送包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中所述组合抑制癌细胞中环加氧酶表达。

53. 一种调节癌细胞中血管生成的方法，所述方法包括使所述细胞与包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触，其中所述组合抑制癌细胞中血管生成。

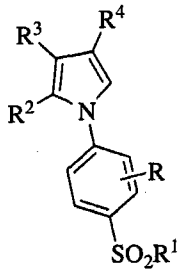
54. 一种减少对象瘤和 / 或瘤相关性疾病传统治疗中的剂量的方法，所述方法包括给予对象 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中所述组合减少瘤和 / 或瘤相关性疾病传统治疗中的剂量。

55. 一种治疗瘤和 / 或瘤相关性疾病的方法，所述方法包括给予 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合。

56. 一种治疗癌症的组合物，其包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂或它们各自

药学上可接受的盐、溶剂合物或前体药物的组合。

57. 根据权利要求 56 所述的组合物，其中所述 1,2- 二苯基吡咯衍生物具有下式：



其中：

R 是氢原子、卤素原子或具有 1 至 6 个碳原子的烷基；

R^1 是具有 1 至 6 个碳原子的烷基或氨基；

R^2 是苯基，所述苯基是未取代的或被选自由取代基 α 和取代基 β 组成的群组的至少一个取代基取代；

R^3 是氢原子、卤素原子或烷基，所述烷基具有 1 至 6 个碳原子并且其是未取代的或被选自由羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基组成的群组的至少一个取代基取代；

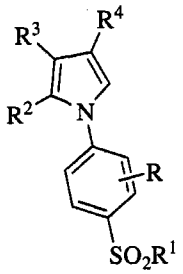
R^4 是氢原子；烷基，所述烷基具有 1 至 6 个碳原子并且其是未取代的或被选自由羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基组成的群组的至少一个取代基取代；具有 3 至 8 个碳原子的环烷基、芳基；或芳烷基；所述芳基在碳环中具有 6 至 14 个环碳原子并且是未取代的或被选自由取代基 α 和取代基 β 组成的群组的至少一个取代基取代；

所述芳烷基是具有 1 至 6 个碳原子并且被上述限定的至少一个芳基取代的烷基；

所述取代基 α 选自由羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基组成的群组；

所述取代基 β 选自由如下组成的群组：烷基，其具有 1 至 6 个碳原子并且是未取代的或被选自由羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基组成的群组的至少一个取代基取代；具有 1 至 6 个碳原子的烷酰氧基；巯基；具有 1 至 6 个碳原子的烷酰硫基；具有 1 至 6 个碳原子的烷亚硫酰基；具有 3 至 8 个碳原子的环烷氧基；具有 1 至 6 个碳原子的卤烷氧基；以及具有 1 至 6 个碳原子的亚烷二氧基；或药学上可接受的盐、溶剂合物或前体药物。

58. 根据权利要求 57 所述的组合物，其中所述 1,2- 二苯基吡咯衍生物具有下式：



其中：

R 是氢原子、卤素原子或具有 1 至 4 个碳原子的烷基；

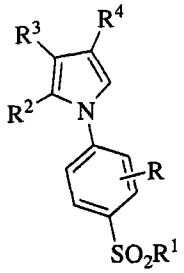
R^1 是甲基或氨基；

R^2 是未取代的苯基或被选自由如下组成的群组的至少一个取代基取代的苯基：卤素原子；具有 1 至 4 个碳原子的烷氧基；具有 1 至 4 个碳原子的烷硫基；具有 1 至 4 个碳原子的未取代烷基；具有 1 至 4 个碳原子并且被选自由卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至 4 个碳原子的烷硫基组成的群组的至少一个取代基取代的烷基；具有 1 至 4 个碳原子的卤烷氧基；以及具有 1 至 4 个碳原子的亚烷二氧基；

R^3 是氢原子、卤素原子、具有 1 至 4 个碳原子的未取代烷基或取代烷基，所述取代烷基具有 1 至 4 个碳原子并且被选自由卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至 4 个碳原子的烷硫基组成的群组的至少一个取代基取代；

R^4 是氢原子；具有 1 至 4 个碳原子的未取代烷基；取代烷基，其具有 1 至 4 个碳原子并且被选自由羟基、卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至个碳原子的烷硫基组成的群组的至少一个取代基取代；具有 3 至 6 个碳原子的环烷基；芳基，其具有 6 至 10 个环碳原子并且是未取代的或被选自由如下组成的群组的至少一个取代基取代：卤素原子、具有 1 至 4 个碳原子的烷氧基、具有 1 至 4 个碳原子的烷硫基、具有 1 至 4 个碳原子的未取代烷基、具有 1 至 4 个碳原子并且被选自由羟基、卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至 4 个碳原子的烷硫基组成的群组的至少一个取代基取代的烷基、和具有 3 至 7 个碳原子的环烷氧基；芳烷基，其在烷基部分具有 1 至 4 个碳原子并且包含至少一个所述芳基；或药学上可接受的盐、溶剂合物或前体药物。

59. 根据权利要求 57 所述的组合物，其中所述 1,2- 二苯基吡咯衍生物具有下式：



其中：

R 是氢原子；

R^1 是氨基；

R^2 是未取代的苯基或被选自由如下组成的群组的至少一个取代基取代的苯基：卤素原子、具有 1 至 4 个碳原子的烷氧基、具有 1 至 4 个碳原子的烷硫基、具有 1 至 4 个碳原子的烷基、具有 1 至 4 个碳原子的卤烷基、具有 1 至 4 个碳原子的卤烷氧基和具有 1 至 4 个碳原子的亚烷二氧基；

R^3 是氢原子、卤素原子、具有 1 至 4 个碳原子的烷基或具有 1 至 4 个碳原子的卤烷基；

R^4 是氢原子；具有 1 至 4 个碳原子的未取代烷基；取代烷基，其具有 1 至 4 个碳原子并且被选自由羟基和具有 1 至 4 个碳原子的烷氧基组成的群组的至少一个取代基取代；具有 3 至 6 个碳原子的环烷基；芳基，其具有 6 至 10 个环碳原子并且是未取代的或被选自由如下组成的群组的至少一个取代基取代：羟基、卤素原子、具有 1 至 4 个碳原子的烷氧基、具有 1 至 4 个碳原子的未取代烷基、具有 1 至 4 个碳原子并且是未取代的或被至少一个卤素原子取代的烷基、和具有 3 至 7 个碳原子的环烷氧基；以及芳烷基，其在烷基部分中具有 1 至 4

个碳原子并且包含至少一个所述芳基；或药学上可接受的盐、溶剂合物或前体药物。

60. 根据权利要求 59 所述的组合物，其中所述 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯。

61. 根据权利要求 56 所述的组合物，其中所述 EGFR 抑制剂是埃罗替尼。

62. 根据权利要求 56 所述的组合物，其中所述 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及所述 EGFR 抑制剂是埃罗替尼。

63. 根据权利要求 56 所述的组合物，其中所述组合物是单一剂型。

64. 根据权利要求 63 所述的组合物，其中所述单一剂型提高患者顺应性和 / 或减少药丸负担。

65. 根据权利要求 62 所述的组合物，其中所述组合是口服、肠胃外、口腔、鼻内、硬膜外、舌下、肺部、局部、直肠或经皮的形式。

66. 根据权利要求 65 所述的组合物，其中所述组合是肠胃外形式。

67. 根据权利要求 66 所述的组合物，其中所述肠胃外形式是静脉内、皮下、鞘内或肌肉内。

68. 根据权利要求 63 所述的组合物，其中所述单一剂型是单一胶囊或单一片剂。

69. 根据权利要求 68 所述的组合物，其中所述组合物是单一片剂。

70. 根据权利要求 69 所述的组合物，其中所述单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 25mg 至约 450mg 埃罗替尼。

71. 根据权利要求 70 所述的组合物，其中所述单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 25mg 埃罗替尼。

72. 根据权利要求 70 所述的组合物，其中所述单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 100mg 埃罗替尼。

73. 根据权利要求 70 所述的组合物，其中所述单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 150mg 埃罗替尼。

74. 根据权利要求 70 所述的组合物，其中所述单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 200mg 埃罗替尼。

75. 根据权利要求 70 所述的组合物，其中所述单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 300mg 埃罗替尼。

76. 根据权利要求 70 所述的组合物，其中所述单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 450mg 埃罗替尼。

77. 根据权利要求 70 所述的组合物，其中所述组合物适于每日一次给药。

78. 根据权利要求 56 所述的组合物，其中所述 EGFR 抑制剂是小分子化合物或抗体。

79. 根据权利要求 78 所述的组合物，其中所述小分子化合物选自由如下组成的群组：ZM-254530、BIBX-1382、雷弗霉素 A、吉非替尼、CGP-57148、CGP-59326、4-(3- 氯)-5,6- 二甲基 -7H- 吡咯并 [2,3-d] 嘧啶、酪氨酸磷酸化抑制剂、PKI-166、PD 153035、EKB-569 和 4-(苯基氨基) 喹唑啉或它们药学上可接受的盐、溶剂合物或前体药物。

80. 根据权利要求 78 所述的组合物，其中所述抗体选自由如下组成的群组：EGF 受体抗体、MR1scFvPE38KDEL MDX-447、MDX-210、MD-72000、MDX-260、韦恩抗 -EGFR Mabs、抗 -EGFr Mab、抗 -EGFr MAb、Genen 抗 -EGFR Mab、MAb DC-101、曲妥珠单抗、抗 -VEGF 单克隆抗体、

抗 -EGFR-DM1Ab、MAb 4D5、BAB-447、EMD-55900、EMD-6200、-82633、抗 -EGFR Mab、MAb 4D5、西妥昔单抗、抗 -EGFrMAb、抗 -flk-1、CCX、CCZ、抗 -flk-1、AG-514、AG-568、抗 -EGFR-DM1Ab、MDX-447、TgDCC-E1A、C225、马妥珠单抗、帕尼单抗、DWP-408 和 RC-3940II。

81. 根据权利要求 56 所述的组合物，其中所述组合物包含低于癌症传统治疗剂量的 EGFR 抑制剂。

82. 根据权利要求 56 所述的组合物，其中所述组合物减少癌症治疗的副作用。

83. 根据权利要求 56 所述的组合物，其中所述组合物提高对癌症的治疗。

84. 一种治疗癌症的药物组合物，其包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合以及药学上可接受的赋形剂或载体。

85. 根据权利要求 84 所述的药物组合物，其中所述 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯。

86. 根据权利要求 84 所述的药物组合物，其中所述 EGFR 抑制剂是埃罗替尼。

87. 根据权利要求 84 所述的药物组合物，其中所述 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及所述 EGFR 抑制剂是埃罗替尼。

88. 一种治疗癌症的试剂盒，其包括包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的单一剂型以及有关如何给予所述剂型的说明。

89. 根据权利要求 88 所述的试剂盒，其中所述 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及所述 EGFR 抑制剂是埃罗替尼。

90. 根据权利要求 6 所述的方法，除所述 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和 EGFR 抑制剂的组合外，进一步包括给予所述对象一种或更多种疗法。

91. 根据权利要求 90 所述的方法，其中所述一种或更多种疗法包括下列中的一种或更多种 ：手术、放射疗法、化学疗法、与干细胞移植一起的高剂量化学疗法 ；激素疗法和单克隆抗体疗法。

92. 根据权利要求 91 所述的方法，其中放射疗法包括内部和 / 或外部放射疗法。

93. 根据权利要求 91 所述的方法，其中所述化学疗法包括给予所述对象吉西他滨。

94. 一种治疗患有癌症的对象的方法，包括给予所述对象治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯、埃罗替尼和吉西他滨或它们各自药学上可接受的盐、溶剂合物、多晶型物或前体药物的组合。

95. 根据权利要求 94 所述的方法，其中所述 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以每天 100-1200mg 的剂量给予，所述埃罗替尼以每天 50-250mg 的剂量给予，以及所述吉西他滨这样给予 ：静脉内给药，每周一次，每平方米体表面积 500-1500mg 的剂量。

96. 根据权利要求 95 所述的方法，其中所述 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以每天 400mg 的剂量给予，所述埃罗替尼以每天 100mg 的剂量给予，以及所述吉西他滨这样给予 ：静脉内给药，每周一次，每平方米体表面积 1000mg 的剂量。

97. 根据权利要求 95 所述的方法，其中所述 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以每天 400mg 的剂量给予，所述埃罗替尼以每天 150mg 的剂量给予，以及所述吉西他滨这样给予 ：静脉内给药，每周一次，每平方米体表面积 1000mg 的剂量。

治疗癌症、肿瘤和肿瘤相关性疾病的方法和组合物

[0001] 交叉参考

[0002] 本申请要求 2007 年 7 月 12 日提交的美国临时申请号 60/949,483 ;2007 年 11 月 28 日提交的美国临时申请号 60/990,900 ;以及 2008 年 4 月 11 日提交的美国临时申请号 61/044,425 的权益,其内容通过引用全部并入本文。

技术领域

[0003] 本发明涉及联合组合物和这些组合物治疗癌症、肿瘤和肿瘤相关性疾病的应用。

背景技术

[0004] 癌症、肿瘤、肿瘤相关性疾病和瘤性疾病状态是严重的并且常常是威胁生命的病症。这些疾病 (disease/disorder)——其特征在于快速增殖的细胞生长——一直是研究努力的对象,所述努力针对在其治疗中有效的治疗剂的鉴定。这些药剂延长患者的存活,抑制与瘤相关的快速增殖的细胞生长或影响瘤的退化。

[0005] 一般而言,手术和放射治疗是被认为局限于局部的癌症治疗的首选方式并且提供最佳的预后。某些癌症的化学疗法治疗通常导致令人失望的存活率但仍旧提供存活益处。例如,在患有非小细胞肺癌的患者中,使用基于铂的化学治疗方案,如使用顺铂或碳铂之一加紫杉醇、多烯紫杉醇、吉西他滨、长春瑞滨、依立替康、依托泊苷、长春碱或贝伐单抗之一。如果患者无法忍受这种疗法,可以使用单一药剂,如 N-(3- 乙炔基苯基)-6,7- 双 (2- 甲氧基乙氧基) 喹唑啉 -4- 胺,常称为埃罗替尼(Tarceva®)。埃罗替尼靶向表皮生长因子受体酪氨酸激酶,其在各种癌症中高度表达并且偶尔突变。如果患者未能对埃罗替尼治疗响应,另外的传统治疗提供有限的益处。

[0006] 尽管埃罗替尼批准用于治疗 IIIB 和 IV 阶段非小细胞肺癌,但与大部分治疗剂一样,其应用带来副作用。例如,常见的副作用——发生在多于 30%的服用埃罗替尼的患者中——包括皮疹、腹泻、食欲差、疲劳、呼吸短促、咳嗽、恶心和呕吐。另外,较少见的副作用包括感染、口疡、瘙痒、皮肤干燥、眼刺激、肺纤维化和腹痛。更受关注的是,越来越多人持这样的观点 :尽管采用埃罗替尼治疗肿瘤最初可以使肿瘤大小缩小,但肿瘤大小最后变大,这表明耐药的形成等等。埃罗替尼可以代表用于癌症治疗的治疗剂类型,其应用对癌症有效,但由于不完全了解的其它因素,肿瘤形成抗性和进展。

[0007] 因此,所需求的是癌症治疗的组合物和 / 或方法,其利用治疗组合中发现的协同作用,所述治疗组合可以增加药剂的效力并且减少和 / 或消除通常与传统治疗相关的副作用。

发明内容

[0008] 本发明至少部分基于通过包含 COX-2 选择性抑制剂和 EGFR 抑制剂的组合在治疗病症 (condition) 如癌症中获得的协同效应。协同作用的一些可能有利的结果包括 1) 增加治疗效果的功效,2) 减少剂量但增加或保持相同的功效以避免毒性,3) 最小化或减慢抗

药性的形成，以及 4）对宿主（或毒性拮抗作用）提供针对目标（或功效协同作用）的选择性协同作用。

[0009] 尽管本发明的一些实施方式通过包含 COX-2 抑制剂和 EGFR 抑制剂的固定剂量组合进行了说明，但本发明的实施方式涵盖其中 COX-2 抑制剂和 EGFR 抑制剂以单独剂型提供的组合物和方法。

[0010] 本发明至少部分基于这样的发现：1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合在癌症、肿瘤和肿瘤相关性疾病治疗中提供许多优势。这些组合可以允许更少量的待被输送的每种具体药剂并且可以产生与更大量的每种具体药剂相同或更好的效果。例如，1,2- 二苯基吡咯衍生物和 EGFR 抑制剂（以一种固定剂量或以两种单独的剂型提供）的组合增加疗效、减少副作用、降低耐药性，以及当使用固定剂量时减少丸剂配料 (pill burden)、增强患者顺应性，从而支持更有利的治疗处理 (setting) 和结果 (outcome)。这些组合可以进一步增加每种具体药剂的益处，所述每种具体药剂否则仅仅轻微有效。同样地，这种协同或增强效应可以用于癌症、肿瘤和肿瘤相关性疾病的治疗并且可以克服肿瘤在传统剂量下对药物的抵抗。

[0011] 应用的方法

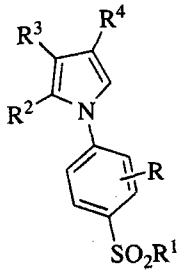
[0012] 本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法。例如，该方法包括以联合疗法给予对象一定量的 COX-2 选择性抑制剂和 EGFR 抑制剂，其中 COX-2 选择性抑制剂和 EGFR 抑制剂组合以给出适于治疗癌症、肿瘤和肿瘤相关性疾病的疗法。

[0013] 本发明进一步提供 COX-2 选择性抑制剂和 EGFR 抑制剂的组合，用于抗瘤 (antineoplastic)、抗肿瘤、抗癌联合疗法。在一个实施方式中，本发明提供包含 COX-2 选择性抑制剂和 EGFR 抑制剂组合的组合物。本发明还提供 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂和 / 或它们药学上可接受的盐、溶剂合物或前体药物的组合作为抗瘤、抗肿瘤或抗癌联合疗法的应用。

[0014] 在一个实施方式中，本发明提供治疗患有癌症的对象的方法，包含给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂或它们各自药学上可接受的盐、溶剂合物或前体药物的组合。

[0015] 在一个实施方式中，联合组合物中的 1,2- 二苯基吡咯衍生物具有下式：

[0016]



[0017] 其中：

[0018] R 是氢原子、卤素原子或具有 1 至 6 个碳原子的烷基；

[0019] R^1 是具有 1 至 6 个碳原子的烷基或氨基；

[0020] R^2 是未取代的的苯基或被至少一个选自取代基 α 和取代基 β 的取代基取代的苯基；

[0021] R^3 是氢原子、卤素原子或烷基，所述烷基具有 1 至 6 个碳原子以及是未取代的或被至少一个选自羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基的取代基取代；

[0022] R^4 是氢原子；烷基，其具有 1 至 6 个碳原子以及是未取代的或被至少一个选自羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基的取代基取代；具有 3 至 8 个碳原子的环烷基，芳基；或芳烷基；所述芳基在碳环中具有 6 至 14 个环碳原子并且是未取代的或被至少一个选自取代基 α 和取代基 β 的取代基取代；

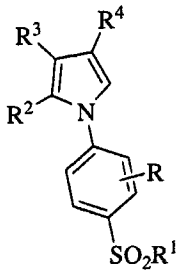
[0023] 所述芳烷基是具有 1 至 6 个碳原子并且其被至少一个上面所限定的芳基取代的烷基；

[0024] 所述取代基 α 选自羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基；

[0025] 所述取代基 β 选自烷基，其具有 1 至 6 个碳原子并且是未取代的或被至少一个选自羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基取代基取代；具有 1 至 6 个碳原子的烷酰氧基；巯基；具有 1 至 6 个碳原子的烷酰硫基；具有 1 至 6 个碳原子的烷亚硫酰基；具有 3 至 8 个碳原子的环烷氧基；具有 1 至 6 个碳原子的卤烷氧基；以及具有 1 至 6 个碳原子的亚烷二氧基；或药学上可接受的盐、溶剂合物或前体药物。

[0026] 在另一个实施方式中，联合组合物中的 1,2- 二苯基吡咯衍生物具有下式：

[0027]



[0028] R 是氢原子、卤素原子或具有 1 至 4 个碳原子的烷基；

[0029] R^1 是甲基或氨基；

[0030] R^2 是未取代的苯基或被至少一个选自下列的取代基取代的苯基：卤素原子；具有 1 至 4 个碳原子的烷氧基；具有 1 至 4 个碳原子的烷硫基；具有 1 至 4 个碳原子的未取代烷基；烷基，其具有 1 至 4 个碳原子并且其被至少一个选自卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至 4 个碳原子的烷硫基的取代基取代；具有 1 至 4 个碳原子的卤烷氧基；以及具有 1 至 4 个碳原子的亚烷二氧基；

[0031] R^3 是氢原子、卤素原子、具有 1 至 4 个碳原子未取代烷基或具有 1 至 4 个碳原子并且被至少一个选自卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至 4 个碳原子的烷硫基的取代基取代的取代烷基；

[0032] R^4 是氢原子；具有 1 至 4 个碳原子的未取代烷基；具有 1 至 4 个碳原子并且被至少一个选自羟基、卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至 4 个碳原子的烷硫基的取代基取代的取代烷基；具有 3 至 6 个碳原子的环烷基；芳基，其具有 6 至 10 个环碳原子并且其是未取代的或被至少一个选自如下的取代基取代：卤素原子；具有 1 至 4 个碳原子的烷氧基；具有 1 至 4 个碳原子的烷硫基；具有 1 至 4 个碳原子的未取代烷基；具有 1 至

4 个碳原子并且被至少一个选自羟基、卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至 4 个碳原子的烷硫基的取代基取代的烷基；以及具有 3 至 7 个碳原子的环烷氧基；在烷基部分中具有 1 至 4 个碳原子并且包含至少一个所述芳基的芳烷基；或药学上可接受的盐、溶剂合物或前体药物。

[0033] 在进一步的实施方式中，本发明提供 1,2- 二苯基吡咯衍生物的联合组合物，其中：

[0034] R 是氢原子；

[0035] R^1 是氨基；

[0036] R^2 是未取代的苯基或被至少一个选自下列的取代基取代的苯基：卤素原子、具有 1 至 4 个碳原子的烷氧基、具有 1 至 4 个碳原子的烷硫基、具有 1 至 4 个碳原子的烷基、具有 1 至 4 个碳原子的卤烷基、具有 1 至 4 个碳原子的卤烷氧基和具有 1 至 4 个碳原子的亚烷二氧基；

[0037] R^3 是氢原子、卤素原子、具有 1 至 4 个碳原子的烷基或具有 1 至 4 个碳原子的卤烷基；

[0038] R^4 是氢原子；具有 1 至 4 个碳原子的未取代烷基；取代烷基，其具有 1 至 4 个碳原子并且被至少一个选自羟基和具有 1 至 4 个碳原子的烷氧基的取代基取代；具有 3 至 6 个碳原子的环烷基；芳基，其具有 6 至 10 个环碳原子并且其是未取代的或被选自下列的至少一个取代基取代：羟基；卤素原子；具有 1 至 4 个碳原子的烷氧基；具有 1 至 4 个碳原子的未取代烷基；烷基，其具有 1 至 4 个碳原子并且其是未取代的或被至少一个卤素原子取代；以及具有 3 至 7 个碳原子的环烷氧基；以及在烷基部分中具有 1 至 4 个碳原子并且包含至少一个所述芳基的芳烷基；或药学上可接受的盐、溶剂合物或前体药物。

[0039] 在又一个实施方式中，1,2- 二苯基吡咯衍生物选自：4- 甲基 -2-(4- 甲苯基)-1-(4- 氨磺酰苯基) 吡咯；2-(4- 甲氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；2-(4- 氯苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；4- 甲基 -2-(4- 甲基苯硫基)-1-(4- 氨磺酰苯基) 吡咯；2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；2-(4- 甲氧基 -3- 甲苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；2-(3- 氟 -4- 甲氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；2-(3,4- 二甲基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；4- 甲基 -1-(4- 甲基苯硫基)-2-(4- 氨磺酰苯基) 吡咯；1-(4- 乙酰氨基磺酰苯基)-4- 甲基 -2-(4- 甲氧基苯基) 吡咯；和 1-(4- 乙酰氨基磺酰苯基)-4- 甲基 -2-(3,4- 二甲基苯基) 吡咯。

[0040] 在一个实施方式中，1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯。

[0041] 在另一个实施方式中，EGFR 抑制剂是埃罗替尼 (erlotinib)。

[0042] 在进一步的实施方式中，1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0043] 在又一个实施方式中，1,2- 二苯基吡咯衍生物和 EGFR 抑制剂以任一顺序相继给药或同时给药。

[0044] 在一个实施方式中，1,2- 二苯基吡咯衍生物被首先给药。

[0045] 在另一个实施方式中，EGFR 抑制剂被首先给药。

[0046] 在一个实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，包括通过包含下列的给药方式给予所述组合：口服、肠胃外、口腔、鼻内、硬膜外、舌下、肺部、局部、直肠或经皮给药。

[0047] 在一个实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中所述组合作为单一剂型口服给药。

[0048] 在另一个实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中单一剂型增强患者顺应性和 / 或减少丸剂配料。

[0049] 在进一步的实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中单一剂型是单一胶囊或单一片剂。

[0050] 在又一个实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中所述组合物作为单一片剂被提供。

[0051] 在进一步的实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，包含通过选自静脉内、皮下、鞘内和肌肉内给药的肠胃外给药方式给予所述组合。

[0052] 剂量

[0053] 在一个实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，包含以单一片剂给予所述组合，其中单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 25mg 至约 450mg 的埃罗替尼。

[0054] 在另一个实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 25mg 的埃罗替尼。

[0055] 在进一步的实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 100mg 的埃罗替尼。

[0056] 在又一个实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 150mg 的埃罗替尼。

[0057] 在另一个实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 200mg 的埃罗替尼。

[0058] 在又一实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 300mg 的埃罗替尼。

[0059] 在进一步的实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 450mg 的埃罗替尼。

[0060] 在一个实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中单一片剂包含约 1mg、约 5mg、约 10mg、约 25mg、约 50mg、约 100mg、约 200mg、约 300mg、约 400mg、约 600mg、约 800mg、约 1000mg 或约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 25mg 的埃罗替尼。

[0061] 在一个实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中单一片剂包含约 1mg、约 5mg、约 10mg、约 25mg、约 50mg、约 100mg、约 200mg、约 300mg、约 400mg、约 600mg、约 800mg、约 1000mg 或约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 100mg 的埃罗替尼。

[0062] 在另一个实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中单一片剂包含约 1mg、约 5mg、约 10mg、约 25mg、约 50mg、约 100mg、约 200mg、约 300mg、约 400mg、约 600mg、约 800mg、约 1000mg 或约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 150mg 的埃罗替尼。

[0063] 在一个实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中单一片剂包含约 1mg、约 5mg、约 10mg、约 25mg、约 50mg、约 100mg、约 200mg、约 300mg、约 400mg、约 600mg、约 800mg、约 1000mg 或约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 200mg 的埃罗替尼。

[0064] 在另一个实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中单一片剂包含约 1mg、约 5mg、约 10mg、约 25mg、约 50mg、约 100mg、约 200mg、约 300mg、约 400mg、约 600mg、约 800mg、约 1000mg 或约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡和约 300mg 的埃罗替尼。

[0065] 在进一步的实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其中单一片剂包含约 1mg、约 5mg、约 10mg、约 25mg、约 50mg、约 100mg、约 200mg、约 300mg、约 400mg、约 600mg、约 800mg、约 1000mg 或约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 450mg 的埃罗替尼。

[0066] 在一个实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，包含给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中所述组合物适于每日一次给药。

[0067] 在进一步的实施方式中，本发明提供这样的方法 :其中给予所述组合与单独给予所述组合的一种组分相比增强对象的治疗。

[0068] 癌症类型

[0069] 在又一个实施方式中，本发明提供这样的方法 :其中给予所述组合减少癌症、肿瘤和肿瘤相关性疾病治疗的副作用。

[0070] 在一个实施方式中，癌症选自 :口腔癌、前列腺癌、直肠癌、非小细胞肺癌、唇及口腔癌、肝癌、肺癌、肛门癌、肾癌、外阴癌、乳腺癌、口咽癌、鼻腔和鼻窦癌、鼻咽癌、尿道癌、小肠癌、胆管癌、膀胱癌、卵巢癌、喉癌、下咽癌、胆囊癌、结肠癌、结肠直肠癌、头颈癌、神经胶质瘤 ;副甲状腺癌、阴茎癌、阴道癌、甲状腺癌、胰腺癌、食道癌、霍奇金氏淋巴瘤、白血病相关性疾病、蕈样肉芽肿病和骨髓增生异常综合征。

[0071] 在另一个实施方式中，癌症是非小细胞肺癌、胰腺癌、乳腺癌、卵巢癌、结肠直肠癌或头颈癌。

[0072] 在又一实施方式中，癌症是癌 (carcinoma)、肿瘤、瘤、淋巴瘤、黑素瘤、神经胶质瘤、肉瘤或胚细胞瘤。

[0073] 在一个实施方式中，癌选自癌、腺癌、腺样囊性癌、腺鳞癌、肾上腺皮质癌、高分化癌、鳞状细胞癌、浆液性癌、小细胞癌、侵袭性鳞状细胞癌、大细胞癌、胰岛细胞癌、燕麦细胞

癌、磷状癌、未分化的癌、疣状癌、肾细胞癌、乳头状浆液性腺癌、merkel 细胞癌、肝细胞癌、软组织癌、支气管腺癌、毛细管癌、前庭大腺癌、基底细胞癌、癌肉瘤、乳头状瘤 / 癌、透明细胞癌、子宫内膜样腺癌、间皮癌、转移性癌、粘液表皮样癌、胆管癌、光化性角化病、囊腺瘤和肝腺瘤病。

[0074] 在另一个实施方式中，肿瘤选自：星形细胞肿瘤、恶性间皮肿瘤、卵巢生殖细胞肿瘤、幕上原始神经外胚层肿瘤、维尔姆斯肿瘤、垂体肿瘤、性腺外生殖细胞肿瘤、胃泌素瘤、生殖细胞肿瘤、妊娠性滋养层细胞肿瘤、脑肿瘤、松果体和幕上原始神经外胚层肿瘤、垂体肿瘤、生长激素抑制素分泌肿瘤、内胚窦肿瘤、类瘤、中枢大脑星形细胞瘤、胰高血糖素瘤、肝腺瘤、胰岛素瘤、髓质上皮瘤、浆细胞瘤、血管活性肠多肽瘤和嗜铬细胞瘤。

[0075] 在又一实施方式中，瘤选自：上皮内瘤、多发性骨髓瘤 / 浆细胞瘤、浆细胞瘤、上皮内磷状细胞瘤、子宫内膜增生、灶性结节性增生、血管内皮瘤和恶性胸腺瘤。

[0076] 在进一步的实施方式中，淋巴瘤选自：神经系统淋巴瘤、AIDS- 相关性淋巴瘤、皮肤 T 淋巴细胞瘤、非霍奇金氏淋巴瘤、淋巴瘤和瓦尔登斯特伦巨球蛋白血症。

[0077] 在另一个实施方式中，黑素瘤选自：肢端雀斑样痣黑素瘤、浅表扩散性黑素瘤、葡萄膜黑素瘤、恶性雀斑样痣黑素瘤、黑素瘤、眼内黑素瘤、腺癌结节性黑素瘤和血管瘤。

[0078] 在又一实施方式中，肉瘤选自腺瘤、腺肉瘤、软骨肉瘤、子宫内膜间质肉瘤、尤因氏肉瘤、卡波西氏肉瘤、平滑肌肉瘤、横纹肌肉瘤、肉瘤、子宫肉瘤、骨肉瘤和假性肉瘤。

[0079] 在一个实施方式中，神经胶质瘤选自：神经胶质瘤、脑干神经胶质瘤和下丘脑和视觉通路神经胶质瘤。

[0080] 在另一个实施方式中，胚细胞瘤选自：肺母细胞瘤、胸膜肺母细胞瘤、视网膜母细胞瘤、神经母细胞瘤、髓母细胞瘤、胶质母细胞瘤和血管母细胞瘤。

[0081] EGFR 抑制剂

[0082] 在进一步的实施方式中，本发明提供其中 EGFR 抑制剂是小分子化合物或抗体的方法。

[0083] 在一个实施方式中，本发明提供其中小分子化合物选自下列的方法：ZM-254530、BIBX-1382、雷弗霉素 (reveromycin)A、吉非替尼、CGP-57148、CGP-59326、4-(3- 氯)-5,6- 二甲基 -7H- 吡咯并 [2,3-d] 嘧啶、酪氨酸磷酸化抑制剂、PKI-166、PD 153035、EKB-569 和 4-(苯基氨基) 喹唑啉或它们的药学上可接受的盐、溶剂合物或前体药物。

[0084] 在另一个实施方式中，本发明提供其中抗体选自下列的方法：EGF 受体抗体、MR1scFvPE38KDEL MDX-447、MDX-210、MD-72000、MDX-260、韦恩抗 -EGFR Mab、抗 -EGFr Mab、抗 -EGFr MAb、Genen 抗 -EGFR Mab、MAb DC-101、曲妥珠单抗、抗 -VEGF 单克隆、抗 -EGFR-DM1Ab、MAb 4D5、BAB-447、EMD-55900、EMD-6200、-82633、 抗 -EGFR Mab、MAb 4D5、西妥昔单抗、抗 -EGFr MAb、抗 -flk-1、CCX、CCZ、抗 -flk-1、AG-514、AG-568、抗 -EGFR-DM1Ab、MDX-447、TgDCC-E1A 和 C225、马妥珠单抗、帕尼单抗、DWP-408 和 RC-3940II。

[0085] 在另一个实施方式中，EGFR 抑制剂选自：缪勒管 (muellerian)- 抑制激素、TNP-470、替可加兰钠、EGF 受体反义、PI-88、寡核苷酸、菠萝蛋白酶分子、双调蛋白、EGF 融合毒素、EGF 融合蛋白、双调蛋白 hbEGF- 毒素、hbEGF- 毒素和 EGF 融合蛋白。

[0086] 应用的进一步方法

[0087] 在一个实施方式中，本发明提供诱导肿瘤细胞分化的方法，该方法包括使细胞与有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触从而该组合诱导肿瘤细胞分化。

[0088] 在一个实施方式中，本发明提供抑制癌细胞增殖的方法，该方法包括使癌细胞与包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触从而该组合抑制癌细胞的增殖。

[0089] 在另一个实施方式中，本发明提供减少癌细胞增生的方法，该方法包括向细胞输送包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，从而细胞增殖的减少大于单独 1,2- 二苯基吡咯衍生物或单独 EGFR 抑制剂引起的减少。

[0090] 在一个实施方式中，本发明提供调节用 ATP 分子自磷酸化的方法，该方法包括给癌细胞输送有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中所述组合抑制通过 ATP 分子的自磷酸化。

[0091] 在进一步的实施方式中，本发明提供抑制肿瘤细胞转移的方法，该方法包括给予有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，以便所述组合抑制肿瘤细胞的转移活性。

[0092] 在一个实施方式中，本发明提供诱导癌细胞凋亡的方法，该方法包括使癌细胞与足以诱导凋亡的包含 1,2- 二苯基吡咯衍生物和 EGFR 激酶的组合接触。

[0093] 在另一个实施方式中，本发明提供使 EGFR- 抑制剂抵抗癌细胞对 EGFR 抑制剂敏化的方法，该方法包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中所述组合使癌细胞对 EGFR 抑制剂敏化。

[0094] 在一个实施方式中，本发明提供治疗癌细胞中 EGFR 抵抗的方法，该方法包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合。

[0095] 在进一步的实施方式，本发明提供调节癌细胞中前列腺素合成的方法，该方法包括使细胞与包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触，其中所述组合抑制癌细胞中的前列腺素合成。

[0096] 在一个实施方式中，本发明提供调节癌细胞中环加氧酶表达的方法，该方法包括向细胞输送包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中所述组合抑制癌细胞中的环加氧酶表达。

[0097] 在一个实施方式中，本发明提供调节癌细胞中血管生成的方法，该方法包括使细胞与包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触，其中所述组合抑制癌细胞中的血管生成。

[0098] 在另一个实施方式中，本发明提供减少对象瘤和 / 或瘤相关性疾病的传统治疗中剂量的方法，该方法包括给予对象 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中所述组合减少瘤和 / 或瘤相关性疾病的传统治疗中的剂量。

[0099] 在一个实施方式中，本发明提供治疗瘤和 / 或瘤相关性疾病的方法，该方法包括给予 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合。

[0100] 在一个实施方式中，本发明提供治疗癌症的组合物，其包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂或它们各自的药学上可接受的盐、溶剂合物或前体药物的组合。

[0101] 在一个实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲

基 -1-(4- 氨磺酰苯基)- 吡咯。

[0102] 在另一个实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生和 EGFR 抑制剂组合的组合物，其中 EGFR 抑制剂是埃罗替尼。

[0103] 在又一实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0104] 在一个实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中所述组合物为单一剂型。

[0105] 在进一步的实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中单一剂型增强患者顺应性和 / 或减少丸剂配料。

[0106] 在一个实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其包括通过包含口服、肠胃外、口腔、鼻内、硬膜外、舌下、肺部、局部、直肠或经皮给药的给药方式给予本发明所述的组合。

[0107] 在进一步的实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，其包括通过选自静脉内、皮下、鞘内和肌肉内给药的肠胃外给药给予本发明的组合。

[0108] 在一个实施方式中，本发明提供包括以单一剂型给予所述组合的方法。

[0109] 在又一个实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂单一片剂组合的组合物，其中单一剂型是单一胶囊或单一片剂。

[0110] 在一个实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中所述组合物为单一片剂的形式。

[0111] 在另一个实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 25mg 至约 450mg 的埃罗替尼。

[0112] 在又一实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 25mg 的埃罗替尼。

[0113] 在一个实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的单一片剂组合物，其中单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 100mg 的埃罗替尼。

[0114] 在另一个实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 150mg 的埃罗替尼。

[0115] 在另一个实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 200mg 的埃罗替尼。

[0116] 在另一个实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 300mg 的埃罗替尼。

[0117] 在另一个实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍

生物和 EGFR 抑制剂组合的组合物，其中单一片剂包含约 1mg 至约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 450mg 埃罗替尼。

[0118] 在进一步的实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的单一片剂组合物，其中单一片剂包含约 1mg、约 5mg、约 10mg、约 25mg、约 50mg、约 100mg、约 200mg、约 300mg、约 400mg、约 600mg、约 800mg、约 1000mg 或约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 25mg 埃罗替尼。

[0119] 在进一步的实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的单一片剂组合物，其中单一片剂包含约 1mg、约 5mg、约 10mg、约 25mg、约 50mg、约 100mg、约 200mg、约 300mg、约 400mg、约 600mg、约 800mg、约 1000mg 或约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 100mg 埃罗替尼。

[0120] 在进一步的实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的单一片剂组合物，其中单一片剂包含约 1mg、约 5mg、约 10mg、约 25mg、约 50mg、约 100mg、约 200mg、约 300mg、约 400mg、约 600mg、约 800mg、约 1000mg 或约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 150mg 埃罗替尼。

[0121] 在进一步的实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的单一片剂组合物，其中单一片剂包含约 1mg、约 5mg、约 10mg、约 25mg、约 50mg、约 100mg、约 200mg、约 300mg、约 400mg、约 600mg、约 800mg、约 1000mg 或约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 200mg 埃罗替尼。

[0122] 在进一步的实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的单一片剂组合物，其中单一片剂包含约 1mg、约 5mg、约 10mg、约 25mg、约 50mg、约 100mg、约 200mg、约 300mg、约 400mg、约 600mg、约 800mg、约 1000mg 或约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 300mg 埃罗替尼。

[0123] 在进一步的实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的单一片剂组合物，其中单一片剂包含约 1mg、约 5mg、约 10mg、约 25mg、约 50mg、约 100mg、约 200mg、约 300mg、约 400mg、约 600mg、约 800mg、约 1000mg 或约 1200mg 的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和约 450mg 埃罗替尼。

[0124] 在一个实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中所述组合物适于每天一次给药。

[0125] 在另一个实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 EGFR 抑制剂是小分子化合物火抗体。

[0126] 在进一步的实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和小分子组合的组合物，其中小分子化合物选自 :ZM-254530、BIBX-1382、雷弗霉素 A、吉非替尼、CGP-57148、CGP-59326、4-(3- 氯)-5,6- 二甲基 -7H- 吡咯并 [2,3-d] 嘧啶、酪氨酸磷酸化抑制剂、PKI-166、PD 153035、EKB-569 和 4-(苯基氨基) 喹唑啉或它们药学上可接受的盐、溶剂合物或前体药物。

[0127] 在另一个实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 EGFR 抑制剂是选自下列的抗体 :EGF 受体抗体、MR1scFvPE38KDEL MDX-447、MDX-210、MD-72000、MDX-260、韦恩抗 -EGFR Mabs、抗 -EGFr Mab、抗 -EGFr MAb、Genen 抗 -EGFR Mab、MAb DC-101、曲妥珠单抗、抗 -VEGF 单

克隆、抗 -EGFR-DM1Ab、MAb 4D5、BAB-447、EMD-55900、EMD-6200、-82633、抗 -EGFR Mab、MAb 4D5、西妥昔单抗、抗 -EGFr MAb、抗 -flk-1、CCX、CCZ、抗 -flk-1、AG-514、AG-568、抗 -EGFR-DM1Ab、MDX-447、TgDCC-E1A、C225、马妥珠单抗、帕尼单抗、DWP-408 和 RC-3940II。

[0128] 在又一实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中所述组合物包含低于癌症传统治疗剂量的 EGFR 抑制剂。

[0129] 在进一步的实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中所述组合物减少癌症治疗的副作用。

[0130] 在又一个实施方式中，本发明提供治疗方法，其包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中所述组合物增强癌症的治疗。

[0131] 药物组合物

[0132] 在一个实施方式中，本发明提供治疗癌症的药物组合物，其包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合以及药学上可接受的赋形剂或载体。

[0133] 在一个实施方式中，本发明提供治疗癌症的药物组合物，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯。

[0134] 在另一个实施方式中，本发明提供治疗癌症的药物组合物，其中 EGFR 抑制剂是埃罗替尼。

[0135] 在又一实施方式中，本发明提供治疗癌症的药物组合物，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0136] 制造的试剂盒 / 产品

[0137] 在一个实施方式中，本发明提供治疗癌症的试剂盒，其包含单一剂型和关于给药的说明书，所述单一剂型包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合。

[0138] 在一个实施方式中，本发明提供具有组合物的治疗癌症的试剂盒，所述组合物包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0139] 通过引用而并入

[0140] 在本说明书中描述的所有出版物、专利和专利申请通过引用并入本文，达到与每个单独的出版物、专利和专利申请特别地和个别地被表示通过引用而并入的相同的程度。

附图说明

[0141] 图 1 提供说明结肠直肠癌中 COX-2 表达水平的图。

[0142] 图 2 提供 EGFR 和 COX 途径之间相互作用的说明。

[0143] 图 3 提供说明 A431 外阴磷状细胞癌异体移植研究结果的图。

具体实施方式

[0144] 为了帮助对本文阐述的公开内容的理解，下面对许多术语进行了定义。

[0145] 定义

[0146] 如本文所用，“异常的细胞生长”指不依赖正常调节机制 (例如，接触抑制的丧失)

的细胞生长，包括正常细胞的异常生长和异常细胞的生长。其包括，但不限于，下列细胞的异常生长：(1) 良性和恶性肿瘤细胞（肿瘤），其表达激活的 Ras 致癌基因；(2) 良性和恶性肿瘤细胞，其中 Ras 蛋白由于另一个基因中致癌基因的突变而激活；(3) 良性和恶性的其它增殖性疾病的细胞，其中存在异常的 Ras 激活。这些良性增殖性疾病的实例是牛皮癣、良性前列腺肥大、人乳头状瘤病毒 (HPV) 和再狭窄。异常的细胞生长还指和包括细胞的异常生长——良性和恶性，其由酶：法尼基蛋白转移酶、蛋白激酶、蛋白磷酸酶、脂质激酶、脂质磷酸酶的活性或者转录因子或细胞内或细胞表面受体蛋白的活性引起。

[0147] 如本文所用，“瘤”是异常的、不受调控的和紊乱的细胞增殖，其由于自主生长和体细胞突变而区别于正常细胞。瘤性细胞的积聚也被称为瘤或肿瘤。随着瘤细胞生长和分化它们将其基因突变和增殖特征传递给子代细胞。在一些实施方式中，瘤可以是良性的或恶性的。

[0148] 如本文所用“转移”指肿瘤细胞经由淋巴管或血管的散播。转移还指肿瘤细胞通过直接蔓延而迁移穿过浆膜腔或蛛网膜下或其它空间。通过转移过程，迁移至身体其它区域的肿瘤细胞在远离初始出现的位置的区域中形成瘤。

[0149] 如本文所讨论，“血管生成”在肿瘤和转移中是显著的。已经发现，血管生成因子与几种实体肿瘤如横纹肌肉瘤、视网膜母细胞瘤、尤因肉瘤、神经母细胞瘤和骨肉瘤相关。肿瘤在没有血液供应以提供营养和去除细胞废物的情况下无法扩散。血管生成是重要的肿瘤包括实体肿瘤如肾细胞癌、肝细胞癌和良性肿瘤如听神经瘤和神经纤维瘤、沙眼和化脓性肉芽肿。血管生成已经与来自血液的肿瘤如白血病相关。相信血管生成在引起白血病的骨髓异常中起作用。防止血管生成可以阻止癌性肿瘤的生长和由于肿瘤的存在而对对象造成的损害。

[0150] 术语“对象”指动物，包括，但不限于，灵长类（例如人）、牛、绵羊、山羊、马、狗、猫、兔、大鼠或小鼠。术语“对象”和“患者”在本文中可以交换地用于指，例如，哺乳动物对象如人对象。

[0151] 术语“治疗 (treat/treating/treatment)”含义包括缓解或除去疾病 (disorder/disease) 或病症；或与疾病或病症相关的一种或更多种症状；或者缓解或根除疾病或病症本身的原因（一个或多个）。

[0152] 术语“治疗有效量”指这样的化合物量：其在给药时足以预防被治疗疾病或病症的一种或更多种症状的发展或在某种程度上缓解被治疗疾病或病症的一种或更多种症状。术语“治疗有效量”还指这样的化合物量：其足以引起研究者、兽医、医学博士或临床医生所探究的细胞、组织、系统、动物或人的生物或医学应答。

[0153] 术语“药学上可接受的载体”、“药学上可接受的赋形剂”、“生理上可接受的载体”或“生理上可接受的赋形剂”指药学上可接受的物质、组合物或运载体，如液体或固体填料、稀释剂、赋形剂、溶剂或胶囊化物质。从与药物配制物的其它成分相容的意义上来看每种组分必须是“药学上可接受的”。其也必须适合用于与人和动物的组织或器官接触而没有过多的毒性、刺激、变态反应、免疫原性或其它问题或并发症，符合合理的益处 / 风险比。参见 Remington：The Science and Practice of Pharmacy，第 21 版；LippincottWilliams & Wilkins；Philadelphia，PA，2005；Handbook of Pharmaceutical Excipients，第 5 版；Rowe 等，Eds.，The Pharmaceutical Press and the American Pharmaceutical

Association:2005；以及 Handbook of Pharmaceutical Additives，第 3 版;Ash and Ash Eds.，GowerPublishing Company:2007;Pharmaceutical Preformulation and Formulation,Gibson Ed.,CRC Press LLC:Boca Raton,FL,2004)。

[0154] 术语“药物组合物”指本文公开的化合物与其它化学组分如稀释剂或载体的混合物。药物组合物促进化合物向有机体的给药。在现有技术中存在的给予化合物的多种技术，包括，但不限于口服、注射、气雾剂、肠胃外和局部给药。药物组合物还可以通过使化合物与无机或有机酸反应而获得，所述无机或有机酸如盐酸、氢溴酸、硫酸、硝酸、磷酸、甲磺酸、乙磺酸、对甲苯磺酸、水杨酸等等。

[0155] 环加氧酶

[0156] 环加氧酶 (COX) 负责称为前列腺素类的重要生物调节剂的形成的酶，前列腺素类包括前列腺素、环前列腺素和血栓烷。COX 将花生四烯酸，ω-6 必需脂肪酸，转化成前列腺素 H_2(PGH_2)，系列 -2 前列腺素类的前体。该酶包含两个活性位点：具有过氧化物酶活性的血红素，其负责将 PGG_2 还原为 PGH_2，以及环加氧酶位点，其中花生四烯酸被转化成过氧羟基内过氧化物前列腺素 G_2(hydroperoxy endoperoxide prostaglandinG_2)(PGG_2)。该反应通过过氧化物酶活性位点产生的酪氨酸根从花生四烯酸夺取氢原子来进行，然后两个氧分子与花生四烯酸根反应，得到 PGG_2。

[0157] COX-1 是组成酶，其负责胃粘膜和肾脏等位点中前列腺素的生物合成。COX-2 是可诱导基因产生的酶，其负责炎性细胞中前列腺素的生物合成。炎症引起 COX-2 的减少，导致前列腺素类（前列腺素 E2）的释放，这敏化外周伤害性感受器末端并且产生局部的疼痛超敏性、炎症和水肿。

[0158] 在以前，医师已经用 NSAID 的方案如，例如，阿司匹林和异丁苯丙酸治疗炎症相关性疾病。不期望的是，然而，一些 NSAID 已知引起经受持续长期的 NSAID 治疗方案的患者胃肠道 (GI) 出血或溃疡。Henry 等，Lancet,1991,337,730。通过这样的发现来减少常用的 NSAID 的不期望的副作用是可能的：与前列腺素合成途径中作为第一个步骤的花生四烯酸的转化有关的两种环加氧酶是环加氧酶 -1(COX-1) 和环加氧酶 -2(COX-2)。

[0159] 许多常用的 NSAID 现在已知是 COX-1 和 COX-2 的抑制剂。因此，当以足够高的水平给药时，这些 NSAID 不仅缓解 COX-2 活性的炎性后果而且抑制 COX-1 的有益的胃部维持活性。对花生四烯酸代谢区域的研究已经导致这样的化合物的发现，所述化合物选择性抑制 COX-2 酶的程度比抑制 COX-1 的程度大。相信这些 COX-2 选择性抑制剂提供这些优势：其包括预防或减少炎症的能力而避免与 COX-1 抑制相关的有害副作用。因此，COX-2 选择性抑制剂已经显示很大的希望，以用于治疗，特别是要求维持给药的治疗中，如对于疼痛和炎症控制。

[0160] 如本文所用，术语“环加氧酶 -2 抑制剂”和“Cox-2 抑制剂”——其在本文中可以交换使用——指抑制环加氧酶 -2 酶 (COX-2) 而与环加氧酶 -1 酶 (COX-1) 抑制程度无关的化合物，以及包括这些化合物的药学上可接受的外消旋物、对映异构体、互变异构体、盐、酯和前体药物。因此，为了本公开，化合物被认为是 COX-2 抑制剂——尽管该混合物抑制 COX-2 的程度等于、大于或小于其抑制 COX-1 的程度。因此，本文中 COX-2 抑制剂包含许多传统的非选择性 NSAID。

[0161] COX-2 选择性抑制剂

[0162] 本公开的实施方式有用的COX-2抑制剂是选择性或优先抑制COX-2的程度大于抑制COX-1的程度的药剂或化合物。在本文中这些药剂和化合物的术语为“COX-2选择性抑制剂”。

[0163] 实践中，在对COX-2选择性抑制剂的选择性的试验中，观察到的选择性随进行试验的条件和被测试化合物的不同而不同。例如，COX-2抑制剂的选择性可以测量为COX-1抑制的体外或体内IC_{50}值除以COX-2抑制的相应的IC_{50}值的比值（$COX\text{-}1IC_{50}/COX\text{-}2IC_{50}$）。本文中COX-2选择性抑制剂因此是$COX\text{-}1IC_{50}/COX\text{-}2IC_{50}$大于1的任意抑制剂。在各种实施方式中，该比值大于约2、大于约5、大于约10、大于约50或大于约100。

[0164] 在一个实施方式中，本发明提供包含1,2-二苯基吡咯衍生物和EGFR抑制剂组合的组合物，其中COX-2与COX-1抑制选择性的比值大于约1。在另一个实施方式中，本发明提供包含1,2-二苯基吡咯衍生物和EGFR抑制剂组合的组合物，其中COX-2与COX-1抑制选择性的比值大于约2。在进一步的实施方式中，本发明提供包含1,2-二苯基吡咯衍生物和EGFR抑制剂组合的组合物，其中COX-2与COX-1抑制选择性的比值大于约5。在另一个实施方式中，本发明提供包含1,2-二苯基吡咯衍生物和EGFR抑制剂组合的组合物，其中COX-2与COX-1抑制选择性的比值大于约7.8。在又一个实施方式中，本发明提供包含1,2-二苯基吡咯衍生物和EGFR抑制剂组合的组合物，其中COX-2与COX-1抑制选择性的比值大于约10。在另一个实施方式中，本发明提供包含1,2-二苯基吡咯衍生物和EGFR抑制剂组合的组合物，其中COX-2与COX-1抑制选择性的比值大于约20。在进一步的实施方式中，本发明提供包含1,2-二苯基吡咯衍生物和EGFR抑制剂组合的组合物，其中COX-2与COX-1抑制选择性的比值大于约50。在又一个实施方式中，本发明提供包含1,2-二苯基吡咯衍生物和EGFR抑制剂组合的组合物，其中COX-2与COX-1抑制选择性的比值大于约100。在一个实施方式中，本发明提供包含1,2-二苯基吡咯衍生物和EGFR抑制剂组合的组合物，其中1-2-二苯基吡咯衍生物是2-(4-乙氧基苯基)-4-甲基-1-(4-氨磺酰苯基)-吡咯。在另一个实施方式中，本发明提供包含1,2-二苯基吡咯衍生物和EGFR抑制剂组合的组合物，其中EGFR抑制剂是埃罗替尼。在进一步的实施方式中，本发明提供包含1,2-二苯基吡咯衍生物和EGFR抑制剂组合的组合物，其中1-2-二苯基吡咯衍生物是2-(4-乙氧基苯基)-4-甲基-1-(4-氨磺酰苯基)-吡咯以及EGFR抑制剂是埃罗替尼并且其中COX-2与COX-1抑制选择性的比值大于约1、约2、约5、约7.8、约10、约20、约50和约100。

[0165] 在一个实施方式中，本发明提供治疗肿瘤和/或肿瘤相关性疾病的方法，其包括给予1,2-二苯基吡咯衍生物和EGFR抑制剂的组合其中COX-2与COX-1抑制选择性的比值大于约1。在一个实施方式中，本发明提供治疗肿瘤和/或肿瘤相关性疾病的方法，其包括给予1,2-二苯基吡咯衍生物和EGFR抑制剂的组合，其中COX-2对于COX-1抑制的选择性的比值大于约2。在进一步的实施方式中，本发明提供治疗肿瘤和/或肿瘤相关性疾病的方法，其包括给予1,2-二苯基吡咯衍生物和EGFR抑制剂的组合，其中COX-2与COX-1抑制选择性的比值大于约5。在又一个实施方式中，本发明提供治疗肿瘤和/或肿瘤相关性疾病的方法，其包括给予1,2-二苯基吡咯衍生物和EGFR抑制剂的组合，其中COX-2与COX-1抑制选择性的比值大于约10。在一些实施方式中，本发明提供治疗肿瘤和/或肿瘤相关性疾病的方法，其包括给予1,2-二苯基吡咯衍生物和EGFR抑制剂的组合，其中COX-2与COX-1抑制选择性的比值大于约20、约50和约100。在其它实施方式中，本发明提供治疗肿瘤和

/ 或肿瘤相关性疾病的方法，其包括给予 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中 1-2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼，其中 COX-2 与 COX-1 抑制选择性的比值大于约 1、约 2、约 5、约 7.8、约 10、约 20、约 50 和约 100。

[0166] 如本文所用，对于 COX-1 或 COX-2 抑制剂，术语“IC_{50}”指需要产生 COX-1 或 COX-2 活性 50％抑制的化合物浓度。在一个实施方式中，用于本公开的 1,2- 二苯基吡咯衍生物具有低于约 3μM 的 COX-2IC_{50}。在另一个实施方式中，1,2- 二苯基吡咯衍生物具有低于约 2.8μM 的 COX-2IC_{50}。在又一实施方式中，1,2- 二苯基吡咯衍生物具有低于约 2μM 的 COX-2IC_{50}。在一些实施方式中，用于本公开的 1,2- 二苯基吡咯衍生物具有低于约 1μM、低于约 0.5μM 或低于约 0.2μM 的 COX-2IC_{50}。用于本公开的 1,2- 二苯基吡咯衍生物可以具有大于约 1μM 的 COX-1IC_{50}，例如大于约 20μM。在一个实施方式中，本发明提供包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 IC_{50} 低于约 1μM。在另一个实施方式中，本发明提供包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 IC_{50} 低于约 0.5μM。在进一步的实施方式中，本发明提供包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 IC_{50} 低于约 0.2μM。在一个实施方式中，1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯。在另一个实施方式中，EGFR 抑制剂是埃罗替尼。在进一步的实施方式中，1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼，其中 IC_{50} 低于约 3μM、约 2.8μM、约 2μM、约 1μM、约 0.5μM 和约 0.2μM。

[0167] 相比 COX-1 抑制对 COX-2 显示出高度选择性的 COX-2 抑制剂可以表示出减少常用 NSAID- 诱发的副作用发生率的能力。在一个实施方式中，本发明提供包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 NSAID- 诱发的副作用基本上被减弱。例如，NSAID- 诱发的副作用包括，但不限于，恶心、呕吐、腹泻、便秘、食欲降低、皮疹、眩晕、头痛、嗜睡、液体滞留、水肿、肾衰竭、肝衰竭、溃疡和术后出血延长。在另一个实施方式中，本发明提供包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼并且其中 NSAID- 诱发的副作用基本上被减弱了。

[0168] COX-2 选择性抑制剂可以以其前体药物的形式使用。如本文所用，“COX-2 前体药物”为通过对象体内代谢或简单的化学过程可以转化成活性 COX-2 选择性抑制剂的化合物。COX-2 选择性抑制剂的前体药物的一个实例是例如盐形式的帕瑞昔布，如帕瑞昔布钠，其是三环 COX-2 选择性抑制剂伐地考昔的治疗上有效的前体药物。

[0169] COX-2 的过量表达和癌症

[0170] COX-2 的过量表达及前列腺素合成途径的上游和下游酶已经在多种癌症类型和一些瘤前病变中被证明。前列腺素通过自分泌或旁分泌途径与它们的受体直接相互作用以提高细胞存活率或刺激血管生成，这已经作为 COX 酶前致癌功能的分子机制被提出。就此而言，临床前研究表明，COX-2 可能与一些种类的肺癌的分子发病机理有关。大部分研究表明，其与非小细胞肺癌有关。患有表达高水平 COX-2 的非小细胞肺癌的患者存活率明显降低。用选择性 COX-2 抑制剂赛来昔布治疗人增加患有非小细胞肺癌的患者中化学疗法的抗癌作用。

[0171] 研究表明，环加氧酶合成的前列腺素在癌症的发生和发展中起关键作用。异常的COX-2表达被报道在结肠直肠癌和腺瘤中，并且已经在各种人癌症，包括乳腺癌中检测到。而且，COX-2在结肠、乳腺、肺、前列腺、食道、胰腺、肠、子宫颈、卵巢、膀胱和头颈部的瘤性病变中过量表达（参见下述表1）。

[0172]

肿瘤类型	%表达COX-2的组织
结肠直肠癌	70-95
非小细胞肺癌	70-90
胃部癌	45-75
胰腺癌	40-80
多形性胶质母细胞瘤	40-70
膀胱癌	50-60
食道癌	50-60
乳腺癌	40-50
卵巢癌	40-60
前列腺癌	40-60

[0173] 表1. 肿瘤中的COX-2表达

[0174] 在鼠乳腺中COX-2过量表达足以引起肿瘤。在几种体外动物模型中，COX-2抑制剂抑制肿瘤生长和转移。

[0175] 除了癌症本身，COX-2也在增生性和瘤性病变内和附近的血管生成的维管结构中表达，表明COX-2在血管生成中起作用。在小鼠和大鼠中，COX-2抑制剂明显抑制bFGF-诱导新血管形成。采用COX-2抑制剂作为化学预防剂、抗血管生成剂和化疗剂被描述在文献中。Koki等，Exp.Opin.，Invest.Drugs，1999，8(10)1623-38。

[0176] 已经显示，COX-2调控与肿瘤相关的血管生成的一些实施方式。血管生成是吸引人的治疗目标，这是因为其是以特定顺序出现的多级过程，因此提供药物作用的几种可能的靶标。血管生成在肿瘤转移的两个阶段中是重要的。第一个阶段——其中血管生成刺激是重要的——是在肿瘤的血管形成中，其允许肿瘤细胞进入血流并且在整个体内循环。在肿瘤细胞离开原发部位并且停留在第二转移部位后，在新的肿瘤可以生长和扩散之前，血管生成必须发生。因此，防止血管生成可以导致防止肿瘤转移并且可能包含在原发部位的瘤生长。干预其中几个步骤的药剂的实例包括制管张素、内皮抑制素、干扰素α和COX-2选择性抑制剂，其防止形成新血管的细胞生长；以及基于蛋白质的化合物，其同时干预其中几个靶标。

[0177] 另外，几个研究表明，COX-2 表达与侵袭性乳腺癌的参数相关，包括大肿瘤大小、阳性腋窝淋巴结转移和 HER2- 阳性肿瘤位置。小鼠和大鼠的乳腺肿瘤研究已经表明，中度至高度 COX-2 表达与乳腺肿瘤的发生有关，所述乳腺肿瘤对用非特异性和特异性 COX-2 抑制剂治疗敏感。进一步的研究已经显示，前列腺素和 COX-2 量增加普遍存在于许多癌变前的组织和恶性肿瘤中，包括宫颈发育异常和宫颈癌。升高的前列腺素和 COX-2 水平基本上是由于抑制细胞凋亡和刺激血管生成的致癌作用。Tsujii and DuBois，Cell，1995，83，493-501。

[0178] 进一步，COX-2 也高度表达于前列腺癌，特别是高级前列腺上皮内瘤和癌的上皮细胞中。用选择性 COX-2 抑制剂处理人前列腺癌细胞系显示诱导体外和体内细胞凋亡。体内结果也表明，COX-2 抑制剂降低肿瘤微血管密度和血管生成。COX-2 抑制剂可以防止强效的血管生成因子、血管内皮生长因子的 hypnoxic 上调。

[0179] COX-2 的过量表达已经被证实存在于几种癌变前和恶性组织中。Subbaramaiah 等，Trends Pharmacol.Sci.，2003，24，96-102。不希望受任何具体理论的限制，表达的增加被认为是 PKC 信号传导的刺激产物，其刺激 MAPK 的活性，通过核因子提高 COX-2 的转录。另外，由于 RNA- 结合蛋白 HuR 的结合增强导致癌细胞中 COX-2mRNA 转录物的稳定性增加，以及细胞外信号相关激酶 1 和 2(ERK 1 和 2) 及 p38 的活化，被被认为是导致 COX-2 表达增加。

[0180] 这些结果表明，COX-2 抑制剂可以充当前列腺癌中有效的化学预防剂和化学治疗剂。

[0181] COX-2 选择性抑制剂

[0182] 最近发现，非甾体抗炎药 (NSAID) 的应用与几种癌症类型的预防和治疗相关。Thun 等，J.National Cancer Inst.，2002，94(4)，252-66。COX-2 抑制剂已经用于治疗癌症和治疗肿瘤。例如，塞来昔布，COX-2 选择性抑制剂，对大鼠中成纤维细胞生长因子诱导的角膜血管生成有强有力的抑制。Masferrer 等，Proc.Am.Assoc.Cancer Research，1999，40，396。其它 COX-2 抑制剂已经被描述用于治疗癌症、肿瘤和瘤。FR 27 71 005 描述了用于治疗癌症和其它疾病的含有 COX-2 抑制剂和 N- 甲基 -d- 天冬氨酸 (NMDA) 拮抗剂的组合物。进一步，WO 99/18960 描述了包含 COX-2 抑制剂的组合，其可以用于治疗结肠直肠癌和乳腺癌。另外，WO 97/36497 描述了用于治疗癌症的包含 COX-2 抑制剂和 5- 脂肪加氧酶抑制剂的组合。

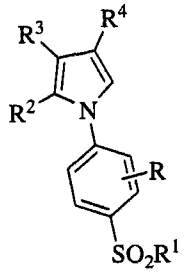
[0183] 1，2- 二苯基吡咯衍生物

[0184] 1，2- 二苯基吡咯衍生物和药学上可接受的盐、溶剂合物或前体药物已知具有止痛和抗炎性质。进一步，它们已经显示担当 COX-2 选择性抑制剂并且从而对于 COX-2 和 / 或炎性细胞因子介导的疾病的治疗和预防是有效的。另外，1，2- 二苯基吡咯衍生物已经显示治疗与骨再吸收有关或由骨再吸收引起的疾病，如骨质疏松症、风湿性关节炎和骨关节炎。

[0185] 这些种类的止痛剂、抗炎剂和 / 或解热剂不仅对炎性疾病，如疼痛、发热和水肿有效，而且对慢性炎性疾病，如慢性风湿性关节炎和骨关节炎、过敏性炎性疾病、哮喘、脓血症、牛皮癣、各种自身免疫性疾病、系统性红斑狼疮、青少年型糖尿病、自身免疫性肠道疾病 (如溃疡性结肠炎、克罗恩氏病)、病毒感染和肾小球肾炎也有效。

[0186] 本文描述的 1，2- 二苯基吡咯衍生物具有通式 ：

[0187]



[0188] 其中：

[0189] R 是氢原子、卤素原子或具有 1 至 6 个碳原子的烷基；

[0190] R^1 是具有 1 至 6 个碳原子的烷基或氨基；

[0191] R^2 是苯基，其是未取代的或被选自取代基 α 和取代基 β 的至少一个取代基取代；

[0192] R^3 是氢原子、卤素原子或烷基，所述烷基具有 1 至 6 个碳原子并且其是未取代的或被选自羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基的至少一个取代基取代；

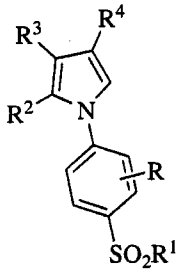
[0193] R^4 是氢原子；烷基，其具有 1 至 6 个碳原子并且其是未取代的或被选自羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基的至少一个取代基取代；具有 3 至 8 个碳原子的环烷基，芳基；或芳烷基；所述芳基在碳环中具有 6 至 14 个环碳原子并且是未取代的或被选自取代基 α 和取代基 β 的至少一个取代基取代；所述芳烷基是具有 1 至 6 个碳原子并且被上述定义的至少一个芳基取代的烷基；

[0194] 所述取代基 α 选自羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基；

[0195] 所述取代基 β 选自烷基，其具有 1 至 6 个碳原子并且其是未取代的或被选自羟基、卤素原子、具有 1 至 6 个碳原子的烷氧基和具有 1 至 6 个碳原子的烷硫基的至少一个取代基取代；具有 1 至 6 个碳原子的烷酰氧基；巯基；具有 1 至 6 个碳原子的烷酰硫基；具有 1 至 6 个碳原子的烷亚硫酰基；具有 3 至 8 个碳原子的环烷氧基；具有 1 至 6 个碳原子的卤烷氧基；以及具有 1 至 6 个碳原子的亚烷二氧基；或药学上可接受的盐、溶剂合物或前体药物。

[0196] 在一个实施方式中，本发明提供具有下式的 1,2- 二苯基吡咯衍生物：

[0197]



[0198] 其中：

[0199] R 是氢原子、卤素原子或具有 1 至 4 个碳原子的烷基；

[0200] R^1 是甲基或氨基；

[0201] R^2 是未取代的苯基或被选自卤素原子的至少一个取代基取代的苯基；具有 1 至 4 个碳原子的烷氧基；具有 1 至 4 个碳原子的烷硫基；具有 1 至 4 个碳原子的未取代烷基；具

有 1 至 4 个碳原子的并且被选自卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至 4 个碳原子的烷硫基的至少一个取代基取代的烷基；具有 1 至 4 个碳原子的卤烷氧基；以及具有 1 至 4 个碳原子的亚烷二氧基；

[0202] R^3 是氢原子、卤素原子、具有 1 至 4 个碳原子的未取代烷基或具有 1 至 4 个碳原子的并且被选自卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至 4 个碳原子的烷硫基的至少一个取代基取代的取代烷基；

[0203] R^4 是氢原子；具有 1 至 4 个碳原子的未取代烷基；具有 1 至 4 个碳原子的并且被选自羟基、卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至 4 个碳原子的烷硫基的至少一个取代基取代的取代烷基；具有 3 至 6 个碳原子的环烷基；具有 6 至 10 个环碳原子的并且是未取代的或被选自卤素原子的至少一个取代基取代的芳基；具有 1 至 4 个碳原子的烷氧基；具有 1 至 4 个碳原子的烷硫基；具有 1 至 4 个碳原子的未取代烷基；具有 1 至 4 个碳原子的并且被选自羟基、卤素原子、具有 1 至 4 个碳原子的烷氧基和具有 1 至 4 个碳原子的烷硫基的至少一个取代基取代的烷基；以及具有 3 至 7 个碳原子环烷氧基；在烷基部分中具有 1 至 4 个碳原子的并且含有至少一个所述芳基的芳烷基；或药学上可接受的盐、溶剂合物或前体药物。

[0204] 在一个实施方式中，本发明提供 1,2- 二苯基吡咯衍生物，其中：

[0205] R 是氢原子；

[0206] R^1 是氨基；

[0207] R^2 是未取代苯基或被选自如下的至少一个取代基取代的苯基：卤素原子、具有 1 至 4 个碳原子的烷氧基、具有 1 至 4 个碳原子的烷硫基、具有 1 至 4 个碳原子的烷基、具有 1 至 4 个碳原子的卤烷基、具有 1 至 4 个碳原子的卤烷氧基和具有 1 至 4 个碳原子的亚烷二氧基；

[0208] R^3 是氢原子、卤素原子、具有 1 至 4 个碳原子的烷基或具有 1 至 4 个碳原子的卤烷基；

[0209] R^4 是氢原子；具有 1 至 4 个碳原子的未取代烷基；具有 1 至 4 个碳原子的并且被选自羟基和具有 1 至 4 个碳原子的烷氧基的至少一个取代基取代的取代烷基；具有 3 至 6 个碳原子的环烷基；芳基，其具有 6 至 10 个环碳原子并且其是未取代的或被选自如下的至少一个取代基取代；羟基；卤素原子；具有 1 至 4 个碳原子的烷氧基；具有 1 至 4 个碳原子的未取代烷基；具有 1 至 4 个碳原子的并且是未取代的或被至少一个卤素原子取代的烷基；和具有 3 至 7 个碳原子的环烷氧基；以及在烷基部分中具有 1 至 4 个碳原子并且包含至少一个所述芳基的芳烷基；或药学上可接受的盐、溶剂合物或前体药物。

[0210] 在一个实施方式中，R 是氢原子。在另一个实施方式中，R 是氟原子。在进一步的实施方式中，R 是氯原子。在又一个实施方式中，R 是甲基。

[0211] 在一个实施方式中，R^1 是甲基。在另一个实施方式中，R^1 是氨基。

[0212] 在一个实施方式中，R^2 是苯基。

[0213] 在一个实施方式中，R^3 是氢原子。在另一个实施方式中，R^3 是卤素原子。

[0214] 在一个实施方式中，R^4 是氢原子。

[0215] 术语“芳基”指在一个或更多个芳香环中具有 6 至 14 个碳原子的碳环芳香烃基团或稠合到具有 3 至 10 个碳原子的环烷基的基团，以及该基团是未取代的或其被选自如下

的至少一个取代基取代：羟基、卤素原子、低级烷氧基、低级烷硫基、低级烷基、烷酰氧基、巯基、烷酰硫基、低级烷亚硫酰基、具有选自环烷氧基、低级卤烷氧基和低级亚烷二氧基的至少一个取代基的低级烷基。

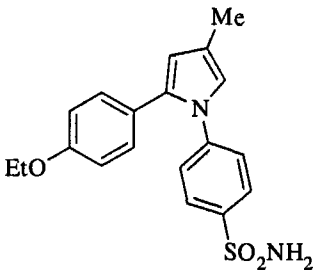
[0216] 在一些实施方式中，1,2- 二苯基吡咯衍生物选自表 2 的化合物 2-1-2-213，如在美国 6,887,893 中所公开，通过引用以其全部并入本文。

[0217] 在一个实施方式中，1,2- 二苯基吡咯衍生物选自：4- 甲基 -2-(4- 甲苯基)-1-(4- 氨磺酰苯基) 吡咯；2-(4- 甲氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；2-(4- 氯苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；4- 甲基 -2-(4- 甲基苯硫基)-1-(4- 氨磺酰苯基) 吡咯；2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；2-(4- 甲氧基 -3- 甲苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；2-(3- 氟 -4- 甲氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；2-(3,4- 二甲基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯；4- 甲基 -1-(4- 甲基苯硫基)-2-(4- 氨磺酰苯基) 吡咯；1-(4- 乙酰氨基磺酰苯基)-4- 甲基 -2-(4- 甲氧基苯基) 吡咯；以及 1-(4- 乙酰氨基磺酰苯基)-4- 甲基 -2-(3,4- 二甲基苯基) 吡咯。在另一个实施方式中，本发明提供方法，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯。

[0218] 在另一个实施方式中，1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯。

[0219] 合成本文说明的 1,2- 二苯基吡咯衍生物的方法描述在实施例部分中和美国 RE39,420 中，其通过引用以其全部并入本文。

[0220]



[0221] 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯

[0222] 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯具有可选择的化学名称，包括 4-[2-(4- 乙氧基苯基)-4- 甲基 -1H- 吡咯 -1- 基] 苯磺酰胺、TG01、CS-706 和 apricoxib。其分子式为 $C_{19}H_{20}N_2O_3S$，分子量为 356.4 以及 CAS 注册号为 197904-84-0。

[0223] 受体酪氨酸激酶

[0224] 蛋白酪氨酸激酶是一类催化磷酸基从 ATP 或 GTP 向位于蛋白底物上的酪氨酸残基转移的酶。蛋白酪氨酸激酶显然在正常细胞生长中起作用。许多生长因子受体蛋白作为酪氨酸激酶发挥功能并且其正是通过该过程来影响信号传导。生长因子与这些受体的相互作用是细胞生长的正常调控中必需事件。在某些条件下，然而，由于突变或过量表达，这些受体可以变得失调；其结果是不受控制的细胞增殖，这可以导致肿瘤生长并且最终导致称作癌症的疾病。Wilks, Adv. Cancer Res., 1993,60,43。生长因子受体激酶和它们的原癌基因——其已经被鉴定并且其是本文提供的组合的靶标——中有表皮生长因子受体激酶

(EGFR 激酶，erbB 致癌基因的蛋白产物)，以及 erbB-2(也成为 neu 或 HER2) 致癌基因产生的产物。因为磷酸化事件是细胞分裂发生必需的信号以及因为过量表达的或突变的激酶与癌症相关，所以该事件的抑制剂，蛋白酪氨酸抑制剂，对于特征在于不受控制或异常的细胞生长的癌症和其它疾病的治疗具有治疗价值。例如，erbB-2 致癌基因受体激酶产物的过量表达与人乳腺癌和卵巢癌相关。Slamon 等，Science，1989，244，707。EGFR 激酶的失调与表皮样肿瘤和涉及其它主要器官的肿瘤相关。由于失调的受体激酶在癌症发病机理中所起的作用的重要性，因此许多最新的研究已经涉及开发特异性 PTK 抑制剂作为潜在的抗 - 癌治疗剂。

[0225] 受体酪氨酸激酶横跨细胞膜并且具有生长因子如表皮生长因子 (EGF) 的细胞外结合结构域、跨膜结构域和细胞内部分，作为激酶其功能是使蛋白中特异性酪氨酸激酶残基磷酸化以及因此影响细胞增殖。EGF 受体酪氨酸激酶家族有四个成员 :EGFR(HER1、erbB1) ;HER2(c-erbB2、erbB2、neu) ;HER3(erbB3) ;以及 HER4(erbB4)。ErbB 受体一般通过两种途径转导信号。已知这些激酶经常和异常地表达在常见的人癌症中，如乳腺癌、结肠、直肠或胃的胃肠癌、白血病以及卵巢癌、支气管癌或胰腺癌中。如先前所讨论，表皮生长因子受体 (EGFR) 突变和 / 或过量表达在许多人癌症中，如脑肿瘤、肺肿瘤、鳞状细胞肿瘤、膀胱肿瘤、胃部肿瘤、乳腺肿瘤、头颈部肿瘤、食管肿瘤、妇产科肿瘤和甲状腺肿瘤。

[0226] 表皮生长因子受体

[0227] 细胞生长的控制受可溶性生长因子和细胞膜受体的相互作用调节。表皮细胞的有丝分裂刺激中第一个步骤是表皮生长因子 (EGF) 特异性结合到已知为表皮生长因子受体 (EGFR) 的膜糖蛋白。EGFR 由 1,186 个氨基酸组成，它们被分成 621 个残基的细胞外部分和 542 个残基的细胞质部分，两者通过 23 个残基的单疏水性跨膜片段连接。Ullrich 等，Nature，1986，vol.309，418-25。EGFR 的外面部分可以再分成四个结构域。最近，已经证实，结构域 III，残基 333 至 460——其两侧是两个半胱氨酸结构域——有可能包含受体的 EGFR 结合位点。Lax 等，Mol.And Cell Biol.，1988，vol.8，1831-34。EGF 与结构域 III 的结合导致多效应答的开启，这导致 DNA 合成和细胞增殖。

[0228] EGFR 也已经被发现在各种类型的肿瘤细胞中并且这些细胞过量表达 EGFR。例如，膀胱肿瘤的癌性细胞已经显示具有相对大量的 EGF 受体。Neal 等，Lancet，1985，vol.1，366-67。乳腺癌细胞显示 EGFR 密度和肿瘤大小之间的正相关和与分化程度的负相关。Sainsbury 等，Lancet，1985，vol.1，364-66。一系列外阴上皮性癌 (A431) 克隆变体的致瘤性发现与 EGF 受体表达水平直接相关，所述变体被植入具有不同水平的 EGFR 的无胸腺小鼠中。Santon 等，Cancer Res.，1986，vol.46，4700-01。因此，已经提出，EGFR 的过量表达在癌细胞的起源或肿瘤生成中起作用。

[0229] EGFR 和 COX 途径

[0230] EGFR 和 COX 途径之间的关系目前还没有完全阐明。然而，已经提出，诱导 COX-2 导致产生前列腺素的水平增加，然后前列腺素以自分泌和 / 或旁分泌方式刺激血管生成、细胞增殖和细胞分化。如上所述，NSAID 抑制该过程。前列腺素促进血管生成，以及细胞分化和增殖。它们也通过 EGFR 刺激信号传导。EGFR 刺激通过受体的酪氨酸激酶结构域导致酪氨酸残基上的磷酸化，开启包括分子 Grb-2、SOS、小 G 蛋白 Raf 在内的信号传导途径。Raf 激活促分裂原激活的蛋白激酶的激酶 (MAPKK) 和核转录因子组 (c-myc、c-fos、c-jun) ;(参见图

2)。这些因子启动与细胞增殖和分化的调节有关的基因的转录。此外,这些因子诱导 COX-2 转录。这些作用可以明显放大最初 EGFR 介导的信号并导致促瘤效应 (pro-neoplastic effects)。抑制两种信号传导途径可以导致明显的抗瘤效果。

[0231] 研究已经提供了这样的支持 :EGFR 诱导肠上皮细胞中的 COX-2 以及抗 -HER2 抗体可以抑制结肠直肠癌细胞中 COX-2 表达。另外,结肠癌细胞中 COX-1 或 COX-2 的过量表达已经显示增加 EGFR 表达。因此,COX 和 EGFR 水平似乎在结肠癌发展期间以正反馈循环而联系起来。尽管失调的 EGF 信号传导促进结肠致癌作用的精确机制没有清楚地了解,但已经提出,各种细胞类型中 EGFR 活化导致激活细胞增殖和细胞游动性和 / 或对细胞外基质粘附的改变。研究已经表明,COX 可以通过促进肿瘤相关的血管生成正向地影响肿瘤生长。

[0232] 最近也已经提出,腺瘤性息肉中 COX-2 的过量表达和激活是由于 EGFR 的激活。在极化的结肠上皮细胞中,通过其配体和双调蛋白 (AR) 中之一的 EGFR 刺激诱导 COX-2 的核靶向、前列腺素的释放和随后的有丝分裂发生。COX-2 抑制剂已经显示防止这一系列事件。

[0233] EGFR 抑制剂

[0234] 因此,已经认识到,受体酪氨酸激酶抑制剂可以用作哺乳动物癌细胞生长的选择性抑制剂。例如,厄尔他丁 (erbstatin),一种酪氨酸激酶抑制剂,选择性减弱表达 EGFR 的移植人乳腺癌的无胸腺裸鼠中的生长,但对不表达 EGFR 的另一种癌的生长没有影响。

[0235] 各种其它化合物,如苯乙烯衍生物,也显示具有酪氨酸激酶抑制剂性质。其他人已经公开了某些喹唑啉衍生物具有抗 - 癌性质,其由它们的酪氨酸抑制剂性质产生。

[0236] 如本文所用,“EGFR 抑制剂”是抑制表皮生长因子受体激酶结构域的分子。本领域的技术人员可以使用方法如,例如,标准药理学测试方法容易地鉴定 EGFR 抑制剂的化合物,所述标准药理学测试方法测量 EGFR 催化的肽底物酪氨酸残基磷酸化的抑制。简要地,肽底物 (RR-SRC) 具有序列 arg-arg-leu-ile-glu-asp-ala-glu-tyr-ala-ala-arg-gly。酶作为 A431 细胞 (American Type Culture Collection, Rockville, Md.) 的膜提取物而获得。将 A431 细胞生长在 T175 烧瓶中至 80％汇合。用不含 Ca^{2+} 的磷酸缓冲盐水 (PBS) 将细胞洗涤两次。室温下在具有 1.0mM 乙二胺四乙酸 (EDTA) 的 20ml PBS 中将烧瓶旋转 1.5 小时并且在 600g 下离心 10 分钟。在冰上于具有 10 个振幅的杜恩斯匀浆器中将细胞以每 5×10^6 细胞 1ml 溶于冷裂解缓冲液 {10mM 4-(2- 羟乙基)-1- 哌嗪乙磺酸 (HEPES),pH7.6、10mM NaCl、2mM EDTA、1mM 苯甲基磺酰基氟化物 (PMSF)、10mg/ml 抑酶肽、10mg/ml 亮抑酶肽、0.1mM 正钒酸钠 }。将裂解物首先在 600g 下离心 10 分钟以分离细胞碎片和上清液,进一步以 4℃在 100,000g 下离心 30 分钟。将膜沉淀悬浮在 1.5mlHNG 缓冲液 (50mM HEPES, pH 7.6、125mM NaCl、10％甘油) 中。将膜提取物分成等份,立即在液氮中冷冻并且储存在 -70℃下。

[0237] 将待被评价的组合物在 100％二甲亚砜 (DMSO) 中制成 10mg/ml 原液。将原液用缓冲液 (30mM Hepes pH 7.4) 稀释至 500mM,然后连续稀释至期望的浓度。将等份的 A431 膜提取物 (10mg/ml) 在 30mM HEPES(pH 7.4) 中稀释以得到 50μg/ml 的蛋白浓度。向 4μl 酶制剂中添加 EGF(1μl,12μg/ml) 并且在冰上温育 10 分钟,接着添加 4μl 测试化合物或缓冲液 ;将该混合物在冰上温育 30 分钟。向其中添加在测定缓冲液中稀释成 1 ： 10 的 ^{33}P-ATP(10mCi/ml) 以及在 0.5mM 浓度下的底物肽 (对照反应不含测试化合物) 并且使反应在 30℃下进行 30 分钟。用 10％ TCA 停止反应并且在冰上放置至少 10 分钟,其后将试管

以全速微量离心 15 分钟。然后将上清液部分点滴在 P81 磷酸纤维素盘上并且在 1％乙酸中洗涤两次然后在水中洗涤 5 分钟，接着通过闪烁计数方法对每个进行计数。获得的结果可以表示成 IC_{50}。IC_{50} 是使磷酸化底物的总量降低 50％所需的测试化合物的浓度。对至少三种不同浓度测定测试化合物的％抑制并且从剂量响应曲线来评价 IC_{50} 值。用下式来评价％抑制：

[0238] ％抑制＝ 100-[CPM（药物）/CPM（对照）]×100

[0239] 其中 CPM（药物）是每分钟计数的单位并且是表示在液体闪烁计数所测定的测试化合物存在的情况下在 30℃下 30 分钟后放射标记的 ATP（$g-^{33}P$）的量的数，所述放射标记的 ATP 通过酶结合到 RR-SRC 肽底物上。CPM（对照）是每分钟计数的单位并且是表示在液体闪烁计数所测定的测试化合物不存在的情况下在 30℃下 30 分钟后放射标记的 ATP（$g-^{33}P$）的量的数，所述放射标记的 ATP 通过酶结合到 RR-SRC 肽底物中。相对于在不存在酶促反应的情况下 ATP 产生的背景计数，对 CPM 值进行校正。具有约 200nM 或更低的 IC_{50} 的化合物被认为是明显有活性的 EGFR 抑制剂。

[0240] 将 EGFR 鉴定为致癌基因已经导致针对 EGFR 的抗癌治疗剂的开发，包括用于结肠癌的吉非替尼和西妥昔单抗。西妥昔单抗是单克隆抗体抑制剂的实例，而吉非替尼是小分子抑制剂的实例。

[0241] 单克隆抗体

[0242] 单克隆抗体阻滞细胞外配体结合结构域。由于结合位点被阻滞，信号分子不能再连接到该位点并激活酪氨酸激酶。

[0243] 西妥昔单抗是鼠抗 -EGFR 单克隆抗体 M225 的可变区和人 IgG1 恒定区融合而产生的嵌合单克隆抗体。所形成的抗体保留对 EGFR 的高亲和性和特异性并且降低免疫原性。临床前研究已经证实，西妥昔单抗在体外有效抑制多种表达 EGFR 的癌细胞的增殖以及其抑制异种移植模型中肿瘤生长。在原位胰腺癌模型中，西妥昔单抗明显抑制原位植入的胰腺肿瘤的生长，以及该效果通过添加吉西他滨而增强。肿瘤样品的组织学分析揭示，西妥昔单抗诱导细胞凋亡并且抑制肿瘤细胞增殖。感兴趣的是，西妥昔单抗还诱导内皮细胞凋亡，内皮细胞不被认为是 EGFR 抑制的直接靶标。而且，观察到抗血管生成效应，其特征是与肿瘤相关性 VEGF 和白介素 -8 表达减少相关的微血管密度降低。这些数据表明，除直接的抗增殖活性外，抗血管生成活性明显造就了 EGFR 抑制剂的抗肿瘤效应。

[0244] 帕尼单抗 (ABX-EGF) 是对 EGFR 特异的完全人单克隆抗体并且通过对转基因小鼠的免疫产生，所述转基因小鼠能够产生人免疫球蛋白轻链和重链。在免疫后，选择产生针对 EGFR 的抗体的 B 细胞特异性克隆并且使其永生化以产生抗体。

[0245] 有效的抗 -EGFR 单克隆抗体与内源性配体，主要是 EGF 和转化生长因子竞争受体配体 - 结合位点。结合至 EGFR 阻滞关键的信号传导途径并且干预表达 EGFR 的肿瘤生长。当前正在研究的抗 -EGFR 单克隆抗体包括 EMD 55900 和 ICR 62。

[0246] 小分子

[0247] 另一种方法是使用小分子抑制在受体的细胞质侧的 EGFR 酪氨酸激酶。如果没有激酶活性，EGFR 就不能激活自身，这对于下游衔接蛋白的结合是先决条件。通过终止依赖该途径生长的细胞中信号传导级联反应，肿瘤增殖和迁移明显减少。

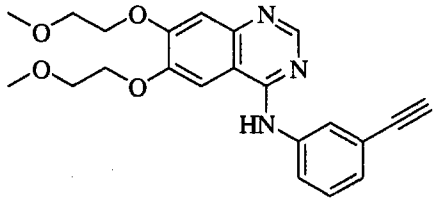
[0248] 吉非替尼目前仅仅指示用于治疗先前已经接受化学疗法的患者的局部晚期或转

移性非小细胞肺癌 (NSCLC)。然而，吉非替尼已经证明在其它癌症中是有效的，对于其在其它癌症治疗中的应用具有潜力，所述其它癌症与 EGFR 过量表达有关。

[0249] 埃罗替尼

[0250] N-(3- 乙炔基苯基)-6,7- 双 (2- 甲氧基乙氧基) 喹唑啉 -4- 胺，也称为埃罗替尼 (Tarceva®)，当前被用于帮助治疗晚期非小细胞肺癌以及联合吉西他滨用于治疗晚期转移性胰腺癌。美国专利 5,747,498 描述了埃罗替尼的制备和其它化学上相关的化合物。另外，美国专利 6,900,221 描述了埃罗替尼稳定的多晶型物作为 erbB 家族致癌性和原致癌性蛋白激酶如 EGFR 的抑制剂的应用。还有，该专利阐明了治疗人乳头状瘤病毒 (HPV) 引起或促发的非小细胞肺癌、幼儿肿瘤、子宫颈和其它肿瘤、黑素瘤、巴瑞特氏食道症 (癌变前综合征)、肾上腺和皮肤癌及自身免疫、瘤性皮肤疾病和动脉硬化症的方法。

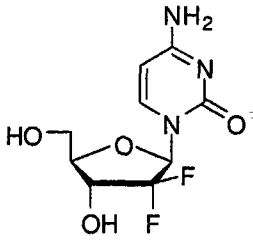
[0251]



[0252] N-(3- 乙炔基苯基)-6,7- 双 (2- 甲氧基乙氧基) 喹唑啉 -4- 胺

[0253] 吉西他滨

[0254]



吉西他滨

[0255] 吉西他滨是显示抗肿瘤活性的核苷类似物。吉西他滨的化学名称为 β-2'- 脱氧 -2',2'- 二氟胞嘧啶并且作为盐酸盐给药。吉西他滨的细胞毒性效应是由于两种作用。首先，吉西他滨二磷酸盐抑制核糖核苷酸还原酶，所述核糖核苷酸还原酶引起可用于 DNA 合成的脱氧核苷酸的减少。其次，吉西他滨三磷酸盐与 dCTP 竞争参入 DNA。这两种作用联合起来导致高水平的吉西他滨核苷酸参入生长的 DNA 链。这导致进一步 DNA 合成的抑制和链终止。

[0256] 吉西他滨指明用于治疗卵巢癌、乳腺癌、NSCL 和胰腺癌。吉西他滨盐酸盐的给药为 :1000mg/m^2 剂量静脉输注，一周一次，每次 30 分钟，共 7 周。其后停止一周，然后每周输注一次，进行 3 周，4 周一循环。全部详细内容提供在吉西他滨的处方说明书中，其通过引用全部被包括。

[0257] 在一个实施方式中，本发明提供包含本文公开的 COX-2 选择性抑制剂和 EGFR 抑制剂组合的组合物，其用于治疗和预防癌症、肿瘤和肿瘤相关性疾病，以及瘤性疾病状态。在一个实施方式中，EGFR 抑制剂是小分子化合物或抗体。

[0258] 在一个实施方式中，EGFR 抑制剂选自吉非替尼、西妥昔单抗和埃罗替尼。在另一个实施方式中，EGFR 抑制剂是埃罗替尼。

[0259] 在另一个实施方式中，小分子化合物选自 :ZM-254530、BIBX-1382、雷弗霉素 A、吉非替尼、CGP-57148、CGP-59326、4-(m- 氯)-5,6- 二甲基 -7H- 吡咯并 [2,3-d] 嘧啶、酪氨酸

磷酸化抑制剂、PKI-166、PD 153035、EKB-569 和 4-(苯基氨基)喹唑啉，或它们的药学上可接受的盐、溶剂合物或前体药物。在另一个实施方式中，小分子选自 PCT/US04/027574 中公开的化合物，其通过引用全部并入本文。

[0260] 在另一个实施方式中，抗体选自：EGF 受体抗体、MR1scFvPE38KDEL MDX-447、MDX-210、MD-72000、MDX-260、韦恩抗 -EGFR Mabs、抗 -EGFr Mab、抗 -EGFr MAb、Genen 抗 -EGFR Mab、MAb DC-101、曲妥珠单抗、抗 -VEGF 单克隆、抗 -EGFR-DM1Ab、MAb 4D5、BAB-447、EMD-55900、EMD-6200、-82633、抗 -EGFR Mab、MAb 4D5、西妥昔单抗、抗 -EGFr MAb、抗 -flk-1、CCX、CCZ、抗 -flk-1、AG-514、AG-568、抗 -EGFR-DM1Ab、MDX-447、TgDCC-E1A，选自：缪勒管 - 抑制激素、TNP-470、替可加兰钠、C C225、马妥珠单抗、帕尼单抗、DWP-408 和 RC-3940II。在另一个实施方式中，提供组合物，其中 EGFR 抑制剂选自 PCT/US04/027574 中公开的抑制剂，其通过引用全部并入本文。

[0261] 在进一步的实施方式中，EGFR 抑制剂选自 EGF 受体反义物、PI-88、寡核苷酸、菠萝蛋白酶分子、双调蛋白、EGF 融合毒素、EGF 融合蛋白、双调蛋白 hbEGF- 毒素、hbEGF- 毒素和 EGF 融合蛋白。

[0262] 如本文所用，“选择性 EGFR 抑制效应”含义是包含 1,2- 二苯基吡咯衍生物与埃罗替尼组合的组合物相对于其它激酶显示针对 EGFR 的选择性抑制。在一些实施方式中，本文公开的组合相对于其它酪氨酸激酶如其它 erbBR 如 erbB2 显示针对 EGFR 激酶的选择性抑制。例如，在一个实施方式中，本发明提供包含 1,2- 二苯基吡咯衍生物与埃罗替尼组合的组合物，其针对 EGFR 的选择性是针对 erbB2 的至少 5 倍或至少 10 倍，如从适合的测定（例如，对于如上所述给出的组合物，比较 KB 细胞测定的 IC_{50} 值与克隆 24 磷酸 -erbB2 细胞测定的 IC_{50} 值）中相对 IC_{50} 值所测得。在另一个实施方式中，本发明提供包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼，其中所述组合针对 EGFR 的选择性是针对 erbB2 的至少 5 倍或至少 10 倍。

[0263] 本文提供的组合物可以是对映体纯的，如单一对映体或单一非对映体，或是立体异构体的混合物，如对映体混合物、外消旋混合物或非对映体混合物，或活性药剂的多晶型物，例如埃罗替尼多晶型物，包括但不限于多晶型物 A、B 和 E，以及 US20060154941 中公开的无定形形式或固体无定形分散体。同样地，本领域技术人员知晓，对于体内经受差向异构的化合物，给予 (R) 形式的化合物等价于给予 (S) 形式的化合物。单个对映体制备 / 分离的传统技术包括从适合的光学纯母体的手性合成或外消旋物的拆分，其使用例如，手性层析、重结晶、拆分、非对映体盐形成或衍生成非对映体加合物然后分离。

[0264] 当本文描述的组合物包含酸性或碱性部分时，其可以以药学上可接受的盐提供（参见 Berge 等，J.Pharm.Sci.1977,66,1-19；和“Handbook of Pharmaceutical Salts, Properties, and Use,”Stah and Wermuth, Ed.;Wiley-VCH and VHCA, Zurich, 2002）。

[0265] 在药学上可接受的盐的制备中使用的适合的酸包括，但不限于乙酸、2,2- 二氯乙酸、酰化的氨基酸、己二酸、藻酸、抗坏血酸、L- 天冬氨酸、苯磺酸、苯甲酸、4- 乙酰氨基苯甲酸、硼酸、(+)- 樟脑酸、樟脑磺酸、(+)-(1S)- 樟脑 -10- 磺酸、癸酸、己酸、辛酸、肉桂酸、柠檬酸、环拉酸、环己烷氨基磺酸、十二烷基硫酸、乙烷 -1,2- 二磺酸、乙磺酸、2- 羟基 - 乙磺酸、甲酸、富马酸、半乳糖二酸、龙胆酸、葡庚糖酸、D- 葡萄糖酸、D- 葡萄糖醛酸、L- 谷氨酸、

α-氧代-戊二酸、乙醇酸、马尿酸、氢溴酸、盐酸、氢碘酸、(+)-L-乳酸、(±)-DL-乳酸、乳碳酸、月桂酸、马来酸、(-)-L-苹果酸、丙二酸、(±)-DL-扁桃酸、甲磺酸、萘-2-磺酸、萘-1,5-二磺酸、1-羟基-2-萘甲酸、烟酸、硝酸、油酸、乳清酸、草酸、棕榈酸、扑酸、高氯酸、磷酸、L-焦谷氨酸、糖二酸、水杨酸、4-氨基-水杨酸、癸二酸、硬脂酸、琥珀酸、硫酸、单宁酸、(+)-L-酒石酸、硫氰酸、对甲苯磺酸、十一碳烯酸和戊酸。

[0266] 在药学上可接受的盐的制备中使用的适合的碱包括,但不限于无机碱,如氢氧化镁、氢氧化钙、氢氧化钾、氢氧化锌或氢氧化钠;以及有机碱,如伯、仲、叔和季脂肪或芳香胺,包括L-精氨酸、苯乙苄胺、苄星、胆碱、二甲基乙醇胺、二乙醇胺、二乙胺、二甲胺、二丙胺、二异丙胺、2-(二乙基氨基)-乙醇、乙醇胺、乙胺、乙二胺、异丙胺、N-甲基-葡糖胺、哈胺(hydrabamine)、1H-咪唑、L-赖氨酸、吗啉、4-(2-羟乙基)-吗啉、甲胺、哌啶、哌嗪、丙胺、吡咯烷、1-(2-羟乙基)-吡咯烷、吡啶、喹核碱、喹啉、异喹啉、仲胺、三乙醇胺、三甲胺、三乙胺、N-甲基-D-葡糖胺、2-氨基-2-(羟甲基)-1,3-丙二醇和缓血酸胺(tromethamine)。

[0267] 本文提供的组合物可以作为前体药物提供,前体药物是1,2-二苯基吡咯衍生物和/或EGFR抑制剂的功能衍生物并且可以容易地在体内转化成母体化合物。经常使用前体药物,是因为在一些情况下它们可以比母体化合物更容易给药。例如,它们可以通过口服给药而可被生物利用而母体化合物则不能。前体药物也可以相对于母体化合物在药物组合物中具有提高的溶剂性。前体药物可以通过各种机制转化成母体药物,包括酶过程和代谢水解。参见Harper,Progress in Drug Research 1962,4,221-294;Morozowich等.in“Design of Biopharmaceutical Properties through Prodrugs and Analogs,”Roche编辑,APHA Acad.Pharm.Sci.1977;“Bioreversible Carriers in Drug in Drug Design,Theory andApplication,”Roche编辑,APHA Acad.Pharm.Sci.1987;“Design of prodrugs,”Bundgaard,Elsevier,1985;Wang等,Curr.Pharm.Design 1999,5,265-287;Pauletti等,Adv.Drug.Delivery Rev.1997,27,235-256;Mizen等,Pharm.Biotech.1998,11,345-365;Gaignault等,Pract.Med.Chem.1996,671-696;Asgharnejadin“Transport Processes inPharmaceutical Systems,”Amidon等,编辑,Marcell Dekker,185-218,2000;Balant等,Eur.J.Drug Metab.Pharmacokinet.1990,15,143-53;Balimane和Sinko,Adv.Drug DeliveryRev.1999,39,183-209;Browne,Clin.Neuropharmacol.1997,20,1-12;Bundgaard,Arch.Pharm.Chem.1979,86,1-39;Bundgaard,Controlled Drug Delivery 1987,17,179-96;Bundgaard,Adv.Drug Delivery Rev.1992,8,1-38;Fleisher等,Adv.Drug Delivery Rev.1996,19,115-130;Fleisher等,Methods Enzymol.1985,112,360-381;Farquhar等,J.Pharm.Sci.1983,72,324-325;Freeman等,J.Chem.Soc.,Chem.Commun.1991,875-877;Friis andBundgaard,Eur.J.Pharm.Sci.1996,4,49-59;Gangwar等,Des.Biopharm.Prop.ProdrugsAnalogs,1977,409-421;Nathwani and Wood,Drugs 1993,45,866-94;Sinhababu和Thakker,Adv.Drug Delivery Rev.1996,19,241-273;Stella等,Drugs 1985,29,455-73;Tan等,Adv.Drug Delivery Rev.1999,39,117-151;Taylor,Adv.Drug Delivery Rev.1996,19,131-148;Valentino and Borchardt,Drug Discovery Today 1997,2,148-155;Wiebe andKnaus,Adv.Drug Delivery Rev.1999,39,63-80;Waller等,Br.J.Clin.Pharmac.1989,28,497-507。

[0268] 应用的方法

[0269] 本发明提供治疗患有肿瘤、肿瘤相关性疾病和/或癌症的对象的方法，包括给予对象治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼的组合。

[0270] 在一个实施方式中，本发明提供治疗患有肿瘤、肿瘤相关性疾病和/或癌症的对象的方法，括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯。

[0271] 在另一个实施方式中，本发明提供治疗患有肿瘤、肿瘤相关性疾病和/或癌症的对象的方法，包括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中 EGFR 抑制剂是埃罗替尼。

[0272] 在又一实施方式中，本发明提供治疗患有肿瘤、肿瘤相关性疾病和/或癌症的对象的方法，包括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂或它们各自药学上可接受的盐、溶剂合物或前体药物的组合。

[0273] 在一个实施方式中，本发明提供治疗患有肿瘤、肿瘤相关性疾病和/或癌症的对象的方法，包括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中 1,2- 二苯基吡咯衍生物选自 :4- 甲基 -2-(4- 甲苯基)-1-(4- 氨磺酰苯基) 吡咯 ;2-(4- 甲氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯 ;2-(4- 氯苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯 ;4- 甲基 -2-(4- 甲基苯硫基)-1-(4- 氨磺酰苯基) 吡咯 ;2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯 ;2-(4- 甲氧基 -3- 甲苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯 ;2-(3- 氟 -4- 甲氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯 ;2-(3,4- 二甲基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯 ;4- 甲基 -1-(4- 甲基苯硫基)-2-(4- 氨磺酰苯基) 吡咯 ;1-(4- 乙酰氨基磺酰苯基)-4- 甲基 -2-(4- 甲氧基苯基) 吡咯 ;以及 1-(4- 乙酰氨基磺酰苯基)-4- 甲基 -2-(3,4- 二甲基苯基) 吡咯。

[0274] 在又一实施方式中，本发明提供治疗患有肿瘤、肿瘤相关性疾病和/或癌症的对象的方法，包括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂以任一顺序依次给药或同时给药。在进一步的实施方式中，本发明提供治疗患有肿瘤、肿瘤相关性疾病和/或癌症对象的方法，包括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中 1,2- 二苯基吡咯衍生物被首先给予。在一个实施方式中，本发明提供治疗患有肿瘤、肿瘤相关性疾病和/或癌症对象的方法，包括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中 EGFR 抑制剂被首先给予。在另一个实施方式中，本发明提供治疗患有肿瘤、肿瘤相关性疾病和/或癌症对象的方法，包括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中给予所述组合与单独 1,2- 二苯基吡咯衍生物或 EGFR 抑制剂的治疗相比提高对象的治疗。在又一实施方式中，本发明提供治疗患有肿瘤、肿瘤相关性疾病和/或癌症对象的方法，包括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中给予所述组合减少肿瘤、肿瘤相关性疾病和/或癌症治疗的副作用。

[0275] 在一个实施方式中，本发明提供治疗患有肿瘤、肿瘤相关性疾病和/或癌症的对象的方法，包括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，

其中癌症选自：口腔癌、前列腺癌、直肠癌、非小细胞肺癌、唇及口腔癌、肝癌、肺癌、肛门癌、肾癌、外阴癌、乳腺癌、口咽癌、鼻腔和鼻窦癌、鼻咽癌、尿道癌、小肠癌、胆管癌、膀胱癌、卵巢癌、喉癌、下咽癌、胆囊癌、结肠癌、结肠直肠癌、头颈癌、旁甲状腺癌、阴茎癌、阴道癌、甲状腺癌、胰腺癌、食道癌、霍奇金氏淋巴瘤、白血病相关性疾病、蕈样肉芽肿病和骨髓增生异常综合征。

[0276] 在另一个实施方式中，本发明提供治疗患有肿瘤、肿瘤相关性疾病和/或癌症的对象的方法，包括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中癌症是非小细胞肺癌、胰腺癌、乳腺癌、卵巢癌、结肠直肠癌和头颈癌。

[0277] 在一个实施方式中，本发明提供治疗患有肿瘤、肿瘤相关性疾病和/或癌症的对象的方法，包括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中癌症是癌、肿瘤、瘤、淋巴瘤、黑素瘤、神经胶质瘤、肉瘤和胚细胞瘤。在另一个实施方式中，本发明提供治疗患有癌的对象的方法，包括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中癌选自：癌、腺癌、腺样囊性癌、腺鳞癌、肾上腺皮质癌、高分化癌、鳞状细胞癌、浆液性癌、小细胞癌、侵袭性鳞状细胞癌、大细胞癌、胰岛细胞癌、燕麦细胞瘤、磷状癌、未分化的癌、疣状癌、肾细胞癌、乳头状浆液性腺癌、merkel 细胞癌、肝细胞癌、软组织癌、支气管腺癌、毛细管癌、前庭大腺癌、基底细胞癌、癌肉瘤、乳头状瘤/癌、透明细胞癌、子宫内膜样腺癌、间皮癌、转移性癌、粘液表皮样癌、胆管癌、光化性角化病、囊腺瘤和肝腺瘤病。在进一步的实施方式中，肿瘤选自：星形细胞瘤、恶性间皮瘤、卵巢生殖细胞肿瘤、幕上原始神经外胚层瘤、威姆氏瘤、垂体瘤、性腺外生殖细胞瘤、胃泌素瘤、生殖细胞肿瘤、妊娠滋养细胞肿瘤、脑肿瘤、松果体和幕上原始神经外胚层瘤、垂体肿瘤、生长激素抑制素分泌瘤、内胚窦瘤、类瘤、中枢脑星形细胞肿瘤、胰高血糖素瘤、肝腺瘤、胰岛素瘤、髓质上皮瘤、浆细胞瘤、血管活性肠多肽瘤和嗜铬细胞瘤。在又一实施方式中，本发明提供患有瘤的患者的方法，包括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中瘤选自：上皮内瘤、多发性骨髓瘤/浆细胞瘤、浆细胞瘤、上皮内磷状细胞瘤、子宫内膜增生、灶性结节性增生、血管内皮瘤和恶性胸腺瘤。在一个实施方式中，淋巴瘤选自：神经系统淋巴瘤、AIDS- 相关性淋巴瘤、皮肤 T 淋巴细胞瘤、非霍奇金氏淋巴瘤、淋巴瘤和瓦尔登斯特伦巨球蛋白血症。在另一个实施方式中，黑素瘤选自：肢端雀斑样痣黑素瘤、浅表扩散性黑素瘤、葡萄膜黑素瘤、恶性雀斑样痣黑素瘤、黑素瘤、眼内黑素瘤、腺癌结节性黑素瘤和血管瘤。

[0278] 在进一步的实施方式中，本发明提供治疗患有肉瘤的对象的方法，包括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中肉瘤选自：腺瘤、腺肉瘤、软骨肉瘤、子宫内膜间质肉瘤、尤因氏肉瘤、卡波西氏肉瘤、平滑肌肉瘤、横纹肌肉瘤、肉瘤、子宫肉瘤、骨肉瘤和假性肉瘤。在一个实施方式中，神经胶质瘤选自：神经胶质瘤、脑干胶质瘤以及下丘脑和视觉通路神经胶质瘤。在另一个实施方式中，本发明提供治疗患有胚细胞瘤的对象的方法，包括给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中胚细胞瘤选自：肺母细胞瘤、胸膜肺母细胞瘤、视网膜母细胞瘤、神经母细胞瘤、髓母细胞瘤、胶质母细胞瘤和血管母细胞瘤。

[0279] 在一个实施方式中，EGFR 抑制剂是小分子化合物或抗体。在另一个实施方式中，EGFR 抑制剂是小分子化合物，其选自：ZM-254530、BIBX-1382、雷弗霉素 A、吉非替尼、

CGP-57148、CGP-59326、4-(m- 氯)-5,6- 二甲基 -7H- 吡咯并 [2,3-d] 嘧啶、酪氨酸磷酸化抑制剂、PKI-166、PD 153035、EKB-569 和 4-(苯基氨基) 喹唑啉或它们的药学上可接受的盐、溶剂合物或前体药物。在进一步的实施方式中，EGFR 抑制剂是抗体，其选自 :EGF 受体抗体、MR1scFvPE38KDEL MDX-447、MDX-210、MD-72000、MDX-260、韦恩抗 -EGFR Mab、抗 -EGFr Mab、抗 -EGFr MAb、Genen 抗 -EGFR Mab、MAb DC-101、曲妥珠单抗、抗 -VEGF 单抗、抗 -EGFR-DM1Ab、MAb 4D5、BAB-447、EMD-55900、EMD-6200、-82633、抗 -EGFR Mab、MAb 4D5、西妥昔单抗、抗 -EGFr MAb、抗 -flk-1、CCX、CCZ、抗 -flk-1、AG-514、AG-568、抗 -EGFR-DM1Ab、MDX-447、TgDCC-E1A、C225、马妥珠单抗、帕尼单抗、DWP-408 和 RC-3940II。在又一个实施方式中，EGFR 抑制剂选自 :缪勒管 - 抑制激素、TNP-470、替可加兰钠、EGF 受体反义物、PI-88、寡核苷酸、菠萝蛋白酶分子、双调蛋白、EGF 融合毒素、EGF 融合蛋白、双调蛋白 hbEGF- 毒素、hbEGF- 毒素和 EGF 融合蛋白。

[0280] 在一个实施方式中，本发明提供诱导肿瘤细胞分化的方法，该方法包括使细胞与有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触，从而所述组合诱导肿瘤细胞分化。在一个实施方式中，本发明提供诱导肿瘤细胞分化的方法，该方法包括使细胞与有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0281] 在一个实施方式中，本发明提供抑制癌细胞增殖的方法，该方法包括使癌细胞与包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触，从而所述组合抑制癌细胞的增殖。在一个实施方式中，本发明提供抑制癌细胞增殖的方法，该方法包括使癌细胞与包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0282] 在另一个实施方式中，本发明提供减少癌细胞增殖的方法，该方法包括向细胞输送包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，从而细胞增殖的减少大于单独 1,2- 二苯基吡咯衍生物或单独 EGFR 抑制剂引起的减少。在一个实施方式中，本发明提供减少癌细胞增殖的方法，该方法包括向细胞输送包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0283] 在一个实施方式中，本发明提供调节用 ATP 分子的自磷酸化的方法，该方法包括向癌细胞输送有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中所述组合抑制通过 ATP 分子的自磷酸化。在一个实施方式中，本发明提供调节用 ATP 分子的自磷酸化的方法，该方法包括向癌细胞输送有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0284] 在进一步的实施方式中，本发明提供抑制肿瘤细胞转移的方法，该方法包括给予有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，以便所述组合抑制肿瘤细胞的转移活性。在一个实施方式中，本发明提供抑制肿瘤细胞转移的方法，该方法包括给予有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0285] 在一个实施方式中，本发明提供诱导癌细胞凋亡的方法，该方法包括使癌细胞与足以诱导凋亡的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触。在一个实施方式中，本发明提供诱导癌细胞凋亡的方法，该方法包括使癌细胞与包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0286] 在另一个实施方式中，本发明提供使 EGFR 抑制剂抗性癌细胞对 EGFR 抑制剂敏化的方法，该方法包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中所述组合使癌细胞对 EGFR 抑制剂敏化。在一个实施方式中，本发明提供使 EGFR 抑制剂抗性癌细胞对 EGFR 抑制剂敏化的方法，该方法包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0287] 在进一步的实施方式中，本发明提供调节癌细胞中前列腺素合成的方法，该方法包括使细胞与包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触，其中所述组合抑制癌细胞中的前列腺素合成。在一个实施方式中，本发明提供调节癌细胞中前列腺素合成的方法，该方法包括使细胞与包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0288] 在一个实施方式中，本发明提供调节癌细胞中环加氧酶表达的方法，该方法包括向细胞输送包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中所述组合抑制癌细胞中环加氧酶表达。在一个实施方式中，本发明提供调节癌细胞中环加氧酶表达的方法，该方法包括向细胞输送包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0289] 在一个实施方式中，本发明提供调节癌细胞中血管生成的方法，该方法包括使细胞与包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触，其中所述组合抑制癌细胞中的血管生成。在一个实施方式中，本发明提供调节癌细胞中血管生成的方法，该方法包括使细胞与包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合接触，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。在另一个实施方式中，本发明提供减少对象瘤和 / 或瘤相关性疾病传统治疗中的剂量的方法，该方法包括给予对象 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中所述组合减少瘤和 / 或瘤相关性疾病传统治疗中的剂量。在一个实施方式中，本发明提供减少对象瘤和 / 或瘤相关性疾病传统治疗中剂量的方法，该方法包括给予对象 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0290] 在一个实施方式中，本发明提供治疗瘤和 / 或瘤相关性疾病的方法，该方法包括给予 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合。在一个实施方式中，本发明提供治疗瘤和 / 或瘤相关性疾病的方法，该方法包括给予 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0291] 本文现在描述的组合也可以用于治疗另外的疾病，在所述另外的疾病中，涉及与各种蛋白酪氨酸激酶有关的异常表达配体 / 受体相互作用或激活或信号传导事件。这些疾病可以包括：神经元、神经胶质、星形胶质细胞、下丘脑、腺体、巨噬细胞、上皮、基质或囊胚腔性质的疾病，它们与 erbB 酪氨酸激酶的异常功能、表达、激活或信号传导有关。另外，本文提供的组合可以在炎性、血管生成或免疫性疾病中具有治疗效用，所述疾病与本文提供的组合所抑制的鉴定的和至今未鉴定的酪氨酸激酶有关。

[0292] 联合疗法

[0293] 在一些实施方式中，本文描述的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物具有单独 1,2- 二苯基吡咯衍生物效应和单独 EGFR 抑制剂效应的加合效应。在另一个实施方式中，本发明提供包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼，其中所述组合具有单独 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯效应和单独埃罗替尼效应的加合效应。

[0294] 在一些其它实施方式中，本文描述的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物具有大于单独 1,2- 二苯基吡咯衍生物效应和单独 EGFR 抑制剂效应的加合效应的效应。在另一个实施方式中，本发明提供包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼，其中所述组合具有大于单独 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯效应和单独埃罗替尼效应的加合效应的效应。

[0295] 在一些实施方式中，本文描述的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物具有大于单独 1,2- 二苯基吡咯衍生物 (例如，单独环加氧酶 -2 抑制) 效应的效应。在另一个实施方式中，本发明提供包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼，其中所述组合具有大于单独 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯效应的效应。

[0296] 在其它实施方式中，包含本文描述的 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物具有大于单独 EGFR 抑制剂 (单独表皮生长因子受体激酶抑制) 效应的效应。在另一个实施方式中，本发明提供包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼，其中所述组合具有大于单独埃罗替尼效应的效应。

[0297] 在其它实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，包括给予包含本文描述的 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中所述组合具有单独 1,2- 二苯基吡咯衍生物效应和单独 EGFR 抑制剂效应的加合效应。在进一步的实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼，其中所述组合具有单独 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯效应和单独埃罗替尼效应的加合效应。

[0298] 在一些其它实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，包

括给予包含本文描述的 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中所述组合具有大于单独 1,2- 二苯基吡咯衍生物效应和单独 EGFR 抑制剂效应的加合效应的效应。在其它实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼，其中所述组合具有大于单独 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯效应和单独埃罗替尼效应的加合效应的效应。

[0299] 在一些实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，包括给予包含本文描述的 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中所述组合具有大于单独 1,2- 二苯基吡咯衍生物（例如，单独环加氧酶 -2 抑制）效应的效应。在其它实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼，其中所述组合具有大于单独 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯效应的效应。

[0300] 在进一步的实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，包括给予包含本文描述的 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中所述组合具有大于单独 EGFR 抑制剂（单独表皮生长因子受体激酶抑制）效应的效应。在其它实施方式中，本发明提供治疗癌症、肿瘤和肿瘤相关性疾病的方法，包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼，其中所述组合具有大于单独埃罗替尼效应的效应。

[0301] 包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物的协同作用可以用于在副作用最小的剂量下获得期望的效应。例如可以治疗患者的疾病或病症——其受益于 EGFR 抑制，如肿瘤、肿瘤相关性疾病、癌症、瘤，同时通过 1,2- 二苯基吡咯衍生物抑制剂的益处治疗 EGFR 抑制的副作用，如炎症。在一个实施方式中，本发明提供 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼的组合，其可以用于在副作用最小的剂量下获得期望的效应。

[0302] 包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物可以作为唯一的治疗施用或可以包括一种或更多种其它物质和治疗剂，如但不限于下列的组合 :MMP（基质金属蛋白酶）抑制剂、其它的酪氨酸激酶，包括 VEGFR（血管内皮生长因子受体）、法尼基转移酶 $CTLA_4$（细胞毒素 T- 淋巴细胞抗原 4）和 erbB2，以及 VEGFr 的 MAb 和其它癌相关性抗体，包括 rhuMAb-VEGF、erbB2MAb 或 avb3。

[0303] 因此，包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物可以与一种或更多种其它抗 - 肿瘤物质一起施用，所述其它抗 - 肿瘤物质例如选自下列的那些，:有丝分裂抑制剂，例如长春碱 ;烷化剂，例如顺铂、碳铂和环磷酰胺 ;抗 - 代谢物，例如 5- 氟尿嘧啶、阿糖胞苷和羟基脲，或者例如，抗 - 代谢物如 N-(5-[N-(3,4- 二氢 -2- 甲基 -4- 氧代喹唑啉 -6- 基甲基)-N- 甲基氨基]-2- 噻吩甲酰)-L- 谷氨酸 ;生长因子抑制剂 ;细胞周期抑制剂 ;插入抗生素，例如阿霉素和博来霉素 ;酶，例如干扰素 ;以及抗 - 激素，例如抗 - 雌激素如**Nolvadex®**（它莫西芬）或，例如抗 - 雄激素如**Casodex®**（4’- 氰基 -3-(4- 氟苯基磺酰

基)-2- 羟基 -2- 甲基 -3'-(三氟甲基)N- 丙酰苯胺)。在一个实施方式中,本发明提供 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合,其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼,所述组合可以与一种或更多种其它抗 - 肿瘤物质一起施用,例如选自下列的那些 :有丝分裂抑制剂,例如长春碱 ;烷化剂,例如顺铂、碳铂和环磷酰胺 ;抗 - 代谢物,例如 5- 氟尿嘧啶、阿糖胞苷或羟基脲,或例如,抗 - 代谢物如 N-(5-[N-(3,4- 二氢 -2- 甲基 -4- 氧代喹唑啉 -6- 基甲基)-N- 甲基氨基]-2- 噻吩甲酰)-L- 谷氨酸 ;生长因子抑制剂 ;细胞周期抑制剂 ;插入抗生素,例如阿霉素和博来霉素 ;酶,例如干扰素 ;以及抗 - 激素,例如抗 - 雌激素如**Nolvadex®**(它莫西芬) 或,例如抗 - 雄激素如**Casodex®** (4' - 氰基 -3-(4- 氟苯基磺酰基)-2- 羟基 -2- 甲基 -3' -(三氟甲基)N- 丙酰苯胺)。

[0304] 对于联合疗法——包括具有本文描述的药物组合物的联合疗法,用于抑制异常的细胞生长的本文现在描述的化合物的有效量 (例如,其它抗增殖剂、抗 - 血管生成、信号转导抑制剂或免疫系统增强剂) 可以由本领域的普通技术人员基于本文描述的化合物的有效量和已知的或对化学治疗剂或其它药剂描述的有效量来确定。这些疗法和组合物的制剂和给药途径可以基于本文描述的组合物和疗法——其包含本文提供的组合作为唯一活性药剂——的信息和所提供的与其联合的化学治疗剂或其它药剂的信息。

[0305] 在一个实施方式中,本发明提供抑制对象异常细胞生长的方法,包括联合在抑制对象异常细胞生长中有效的放射疗法,给予对象有效量的包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂或它们药学上可接受的盐、溶剂合物或前体药物组合的组合物。给予放射疗法的技术对本领域的技术人员而言是已知的并且这些技术可以用于本文描述的联合疗法。

[0306] 另外的治疗

[0307] 可利用的另外的癌症治疗——其可以有利地与本文公开的疗法和组合物联合使用——无限制地包括手术、放射疗法、化学疗法、与干细胞移植一起的高剂量化学疗法 ;激素疗法以及单克隆抗体疗法。

[0308] 手术程序经常用于治疗癌症。

[0309] 放射疗法是使用高能量 x- 射线或其它种类的放射线杀死癌细胞或阻止它们生长的癌症治疗。

[0310] 化学疗法是使用药物阻止癌细胞生长的癌症治疗,其或者通过杀死细胞或者通过阻止它们分裂来进行。当通过口或注射入血管或肌肉来进行化学疗法时,药物进入血流并且可以到达整个身体中的癌细胞 (系统性化学疗法)。当化学疗法被直接放进脊柱、器官或体腔如腹部时,药物主要影响这些区域中的癌细胞 (区域性化学疗法)。给出化学疗法的方式取决于被治疗癌症的类型和状态。

[0311] 在本领域中已知不同的化学治疗剂用于治疗癌症。用于治疗癌症的细胞毒性剂包括阿霉素、环磷酰胺、氨甲蝶呤、5- 氟尿嘧啶、丝裂霉素 C、米托蒽醌、紫杉醇、紫杉烷制剂,仅列举以下实例 :**Abraxane®** (ABI-007)、紫杉醇 - 聚氧乙烯蓖麻油、聚谷氨酸紫杉醇和紫杉醇可注射乳液 (PIE)、吉西他滨、多烯紫杉醇、卡培他滨和表阿霉素。

[0312] 针对癌症的其它化学疗法包括用下列一种或更多种药剂的治疗 :苯达莫司汀、碳铂 (例如,**Paraplatin®**)、卡莫司汀 (例如,**BCNU®**)、苯丁酸氮芥 (例如,**Leukeran®**)、顺铂 (例如,**Platinol®**)、环磷酰胺注射剂 (例如,**Cytoxan®**)、口服的环磷酰胺 (例如,**Cytoxan®**

)、达卡巴嗪（例如，DTIC®）、异环磷酰胺（例如，ifex®）、洛莫司汀（例如，CCNU®）、双氯乙基甲胺（例如，氮芥，Mustargen®）、美法仑（例如，Alkeran®）、丙卡巴肼（例如，Matulane®）、博来霉素（例如，Blenoxane®）、阿霉素（例如，Adriamycin®，Rubex®）、表阿霉素、Idarubicin（例如，Idamycin®）、米托蒽醌（例如，Novantrone®）、吉西他滨（例如，Gemzar®）、口服的巯嘌呤（例如，Purinethol®）、氨甲蝶呤、喷司他丁 IV（例如，Nipent®）、口服的硫鸟嘌呤（例如，Lanvis®）、口服的依托泊苷（例如，VP-16、VePesid®、Etopophos）、依托泊苷 IV（例如，VP-16、VePesid®、Etopophos）、长春碱（例如，Velban®）、长春新碱（例如，Oncovin®）、长春瑞滨（例如，Navelbine®）、地塞米松（例如，Decadron®）、甲基强的松龙（例如，Medrol®）和强的松（例如，Deltasone®）。埃罗替尼联合吉西他滨适用于晚期胰腺癌的治疗。

[0313] 单克隆抗体疗法是使用从单一类型的免疫系统细胞于实验室中制备的抗体的癌症治疗。这些抗体可以识别癌细胞上的物质或可以帮助癌细胞生长的正常物质。抗体连接到所述物质并且杀死癌细胞、阻滞它们生长或阻止它们扩散。单克隆抗体通过注入给药。它们可以单独使用或可以用于直接将药物、毒素或放射性物质携带至癌细胞。单克隆抗体也作为辅助疗法与化学疗法联合使用。

[0314] 曲妥珠单抗(Herceptin®)是阻止将生长信号传输至乳腺癌细胞的生长因子蛋白 HER2 效应的单克隆抗体。

[0315] 曲妥珠单抗作为单一药剂产生临床疗效并且当添加至晚期 HER2- 阳性乳腺癌的化学疗法时提高存活率。然而，一些患者对曲妥珠单抗没有响应并且大部分最终形成临床耐药性。对先天性和后天性曲妥珠单抗耐药的机制了解的不够。已报道了一项研究，其利用基于细胞系的方法来描述与耐药相关的遗传性和蛋白改变。(D. Tripathy 等，Journal of Clinical Oncology，2005Vol 23，No 16S，3121)。这些研究者研究了两种 HER2- 阳性乳腺癌细胞系 (BT474 和 SKBR3)，其在曲妥珠单抗存在的情况下被连续传代直至证实体外耐药性。12 个月后出现耐药性的细胞系并且在曲妥珠单抗存在的情况下显示 3 倍多的快速生长速度。在曲妥珠单抗暴露后，与耐药的细胞相比敏感的细胞观察到 G_0/G_1 抑制 (84 对 68％)，以及在 S- 期较少的细胞 (3 对 14％)。与敏感细胞相比，耐药细胞系显示，使用曲妥珠单抗时基因表达改变较少以及趋化因子受体 CXCR4 和有丝分裂限制点调节子上调，和 PTEN 下调。

[0316] 可以有利地与本文公开的组合物和疗法联合的另外的说明性治疗无限制地包括给予下列药剂，包括，但不限于，卡培他滨、多烯紫杉醇、表阿霉素、埃博霉素 A、B 或 D、醋酸戈舍瑞林、紫杉醇、帕米膦酸盐、贝伐单抗和曲妥珠单抗。

[0317] EGFR 抗性

[0318] 研究已经显示，在约 8-12 个月的 EGFR- 定向治疗后，癌细胞变得对治疗具有抗性，其常常通过 1) 募集突变的 IGF-1 受体，以充当同型二聚体中 EGFR 配偶体之一，从而形成异质二聚体（这使在 EGFR 抑制剂存在的情况下，其也允许信号传递）；2) 多余酪氨酸激酶受体的存在；3) 增加的血管生成；4) 下游媒介的组成型激活；以及 5) 特异性 EGFR 突变的存在。理解耐药性和敏感性的分子机制可以导致靶向 EGFR 的疗法的改善。

[0319] IGF-1R 激活许多与 EGFR 相同的下游途径并且可以导致肿瘤发生、增殖增加、血管生成和转移。PI-3K/Akt 信号传导是 EGFR 下游调节的关键组分并且也在 IGF-1R 信号传导中起功能性作用。不希望受任何具体理论的限制，该冗余 (redundancy) 可以解释受体如何

可以模仿彼此的功能。Chakravarti 等鉴定了两种成胶质细胞瘤细胞系，每一种过量表达 EGFR 但对 EGFR 抑制剂显示非常不同的响应。耐药细胞系明显地过量表达 IGF-1R 并且对于通过 AG1478、EGFR TKI 的 EGFR 抑制显示 IGF-1R 表达进一步增加。对于 AG1478 治疗，PI-3K/Akt 信号传导持续存在于这些耐药细胞系中，以及这些细胞也保持其侵袭性和抗凋亡特性。这些研究支持经由 IGF-1R 的多余信号传导的概念，其在 EGFR 抑制存在的情况下维持对生存关键途径的激活。抑制 IGF-1R 和 EGFR 可以明显减少对 EGFR 抑制剂耐药的细胞的生长和侵袭性。IGF-1R 激活可以避开其它酪氨酸激酶受体抑制的进一步的证据来自于 Lu 等，其显示了 IGF-1R 过量表达的程度与乳腺癌细胞对曲妥珠单抗——直接针对 ErbB2 的抗体——的响应呈相反关系。SKBR3 人乳腺癌细胞——其通常过量表达 HER2/neu 并且最低程度地表达 IGF-1R——对于曲妥珠单抗显示增殖减少 42％。

[0320] 不像亲代细胞系一样，被改造成过量表达 IGF-1R 的 SKBR3 细胞对曲妥珠单抗不显示响应。当在改造的细胞系中 IGF-1R 被 IGF- 结合蛋白 -3 抑制时，对曲妥珠单抗的响应恢复至正常。这些研究清楚地说明，肿瘤细胞中选择性酪氨酸激酶受体的激活可以压制 EGFR 家族抑制剂的效应。这些实例表明，联合可以能够克服对单一受体抑制剂的耐药性，从而更有效地抑制导致癌症生长和存活的途径。最近，在乳腺癌细胞系中显示了与任一单独抗体相比提高的响应，其用重组的对 EGFR 和 IGF-1R 双特异性的抗体或单一受体抗体的组合处理。受体下游的信号传导途径也更有效地被组合疗法抑制。通过联合攻击多种细胞表面和细胞内信号传导途径的疗法，多余的受体信号传导可以被阻滞并且实现更大的临床效益。因此，鉴定生长因子受体信号会聚的关键下游信号传导分子在治疗剂的开发中可能是重要的，所述治疗剂阻滞多种激活的生长因子受体的信号。类似地，Jung 等公开了，mAb 与 EGFR 以及 mAb 与 VEGFR-2 的联合用于治疗生长在裸鼠中的胃癌。两种 mAb 适度有效地抑制肿瘤生长，但联合明显达到了更大的肿瘤生长抑制，其也与肿瘤血管分布减少和肿瘤细胞凋亡增加相关。

[0321] 在一个实施方式中，本发明提供治疗具有 EGFR 抑制剂抗性癌细胞对象的方法，包括联合 EGFR 抑制剂给予对象治疗有效量的包含 1,2- 二苯基吡咯衍生物的组合物。在一个实施方式中，1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯。在另一个实施方式中，1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼。

[0322] 在一个实施方式中，本发明提供使 EGFR 抑制剂抗性癌细胞对 EGFR 抑制剂敏化的方法，该方法包括给予包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，其中所述组合使癌细胞对 EGFR 抑制剂敏感。在一个实施方式中，本发明提供使 EGFR 抑制剂抗性癌细胞对埃罗替尼敏感的方法，该方法包括给予包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼的组合，其中所述组合使癌细胞对埃罗替尼敏感。

[0323] 肺癌

[0324] 在许多国家包括日本、欧洲和美国，患有肺癌的患者数是相当大的并且每年在继续增加以及是男性和女性中癌症死亡最常见的原因。尽管存在许多肺癌的潜在原因，但烟草使用，具体而言吸烟，是最重要的。另外，病因因素如暴露于石棉，特别是吸烟者中，或氡是促成因素。还有职业危害如暴露于铀已经确定为重要的因素。最后，遗传因素也已经确定为增加癌症风险的另一个因素。

[0325] 组织学上可以将肺癌分为非小细胞肺癌（例如磷状细胞癌（表皮）、腺癌、大细胞癌（大细胞间变性）等）和小细胞肺癌（燕麦细胞）。非小细胞肺癌 (NSCLC) 具有不同于小细胞肺癌 (SCLC) 的生物特性并且对化学治疗剂响应。因此，在这两种类型的肺癌之间化学治疗方式和放射治疗是不同的。

[0326] 非小细胞肺癌

[0327] 在非小细胞肺癌肿瘤位置可以容易切除的情况下 (I 和 II 期疾病)，手术是首选的疗法并且提供相对好的治愈机会。然而，在更晚期的疾病中 (IIIa 期或更晚)，在肿瘤已经扩展到支气管肺淋巴结外的组织的情况下，手术不可能导致完全切除肿瘤。在这些情况下，患者通过单独手术治愈的机会极大地减小。在手术无法提供完全去除 NSCLC 肿瘤的情况下，必须采用其它类型的疗法。现今，化学放射疗法是标准的治疗，以控制不可切除或不宜手术的 NSCLC。当放射疗法与化学疗法联合时已经看到改善的结果，但收益适度并且对组合方式的改善方法的研究继续进行。

[0328] 放射疗法基于这样的原理：输送到靶区域的高剂量放射引起肿瘤组织和正常组织中生殖细胞死亡。放射剂量方案一般根据放射吸收剂量 (rad)、时间和分部分离 (fractionation) 限定，并且必须由肿瘤学家谨慎限定。患者接受的放射量取决于各种考虑但两个重要的考虑是肿瘤相对于身体其它关键结构或器官的位置以及肿瘤扩散的程度。经受 NSCLC 放射疗法的患者的一个疗程将是：5 至 6 周的治疗时间表，总剂量为 50 至 60Gy，以每日一次分剂量 1.8 至 2.0Gy，一周 5 天给予患者。Gy 是 Gray 的缩写并且指 100rad 剂量。

[0329] 因为 NSCLC 是系统性疾病，而放射疗法是局部形式，所以作为单一治疗模式的放射疗法不可能治愈 NSCLC，至少在治疗区域外向远处转移的那些肿瘤的治愈。因此，放射疗法与其它形式方案一起使用对于 NSCLC 治疗具有重要的有益效果。

[0330] 一般地，放射疗法与化学疗法暂时联合以提高治疗结果。存在几个术语来描述组合 COX-2 抑制剂和化学疗法给予放射疗法的暂时关系，以及下列实例是治疗方案并且被提供仅仅用于说明而不是意图限制其它联合的应用。“序贯”疗法指及时分别给予包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物和 / 或放射疗法，以便允许分别给予组合物和 / 或放射疗法。“同时”疗法指在同一天给予组合物和 / 或放射疗法。

[0331] 最后，“交替”疗法指在不给于组合物的那天给予放射疗法——如果其单独给出。据报道，晚期非小细胞肺癌不有利地对单一药剂的化学疗法响应以及对晚期不宜手术的癌症有用的治疗已经被限制。(Journal of Clinical Oncology, vol. 10, pp. 829-838(1992))。

[0332] 日本专利 Kokai 5-163293 提到一些特定的 16 元环大环内酯类抗生素作为药物输送载体，所述载体能够将蒽环类抗生素 - 型抗癌药物运输到肺中以治疗肺癌。因此，本文考虑使用包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物以及作为药物输送载体的大环内酯类用于非小细胞肺癌的治疗。

[0333] 几种化学治疗剂已经显示对 NSCLC 有效。可以用于本公开的针对 NSCLC 的化学治疗剂包括顺铂、碳铂、紫杉醇、多烯紫杉醇、紫杉烷制剂如仅以实例举出的**Abraxane®** (ABI-007)、紫杉醇 - 聚氧乙烯蓖麻油、聚谷氨酸紫杉醇和紫杉醇可注射乳液 (PIE)、吉西他滨、异长春花碱、pemetrexate、依托泊苷、氨甲蝶呤、5- 氟尿嘧啶、表阿霉素、阿霉素、长春碱、环磷酰胺、异环磷酰胺、丝裂霉素 C、表阿霉素、长春地辛、喜树碱、福莫司汀和依达曲沙。

[0334] 在一个实施方式中，本发明提供治疗 NSCLC 的方法，其采用治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物。进一步，治疗 NSCLC 的疗法采用治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯与埃罗替尼组合的组合物和下列抗瘤药剂之一 ：贝伐单抗、多烯紫杉醇、吉非替尼、吉西他滨、顺铂、碳铂、依托泊苷、紫杉醇、pemetrexate、长春瑞滨或放射疗法。

[0335] 小细胞肺癌

[0336] 全世界报道的所有肺癌病例的约百分之 15 至 20 是小细胞肺癌 (SCLC)。Ihde DC ：Cancer 54 ：2722，1984。目前，SCLC 的治疗参入了多种形式的治疗，包括化学疗法和放射疗法。局部性或弥散性 SCLC 对系统性化学疗法保持高的响应比率，然而原发肿瘤的持续存在和相关的淋巴结中肿瘤的持续存在导致几种治疗形式并入 SCLC 治疗中。

[0337] 本发明的一个实施方式所述的肺癌治疗的疗法采用治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物的组合。在另一个实施方式中，本发明所述的肺癌治疗的疗法采用治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物以及下列抗瘤剂之一的组合物 ：长春新碱、多烯紫杉醇、喜树碱、托泊替康、顺铂、碳铂、环磷酰胺、表阿霉素 (高剂量)、依托泊苷 (VP-16) I.V.、口服的依托泊苷 (VP-16)、异环磷酰胺、替尼泊苷 (VM-26)、阿霉素和氨柔比星。可以用于本公开的其它优选的单一药剂化学治疗剂包括 BCNU(卡莫司汀)、长春地辛、六甲三聚氰胺 (六甲蜜胺)、氨甲蝶呤、氮芥和 CCNU(洛莫司汀)。已经显示对 SCLC 有活性的在研究中的其它化学治疗剂包括螺铂、吉西他滨、氯尼达明和紫杉醇。

[0338] 神经胶质瘤

[0339] 神经胶质瘤是一种来自于神经胶质细胞的原发性中枢神经系统 (CNS) 肿瘤。与神经胶质瘤有关的最常见的部位是脑，但它们也可以影响脊髓或 CNS 的任意其它部分，如视神经。脑神经胶质瘤的治疗取决于位置和等级。通常，治疗是使用手术、放射疗法和化学疗法的组合方法。放射疗法的形式为体外光束放射或使用放射手术的立体定向方法。脊髓肿瘤可以通过手术和放射治疗。替莫唑胺是能够有效穿过血脑屏障的化学治疗药物并且正在用于疗法中。

[0340] 在成胶质细胞瘤中 EGFR 经常被扩增、过量表达或突变，但一般仅仅 10 至 20％的患者对 EGFR 抑制剂响应，已经显示，过量表达 EGFRvIII 致癌基因并且是 PTEN 肿瘤抑制剂野生型的成胶质细胞瘤对埃罗替尼治疗敏感。

[0341] 本发明一个实施方式所述的神经胶质瘤治疗的疗法采用治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物的组合。在另一个实施方式中，本发明所述的神经胶质瘤治疗的疗法采用治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物和替莫唑胺的组合。

[0342] 头颈癌

[0343] 头颈癌包括口癌、鼻癌、窦癌、唾液腺癌、咽喉癌和颈部淋巴结癌。大部分开始在潮湿的组织中，沿口、鼻和咽喉排列。症状包括无法治愈的肿块或疼痛、无法消失的喉咙痛、吞咽问题以及声音改变或嘶哑。使用烟草或酒精增加癌症风险。头颈癌的治疗可以包括手术、放射疗法、化学疗法或组合。治疗可能影响吃饭、说话或甚至呼吸，因此患者可能需要恢复。

[0344] 由于许多不同的部位和分期系统，头颈癌常常是复杂的。然而，目前的治疗提供几种选择，包括手术、放射和化学疗法，或单独或联合。

[0345] 联合方式疗法正在成为治疗具有局部晚期头颈癌的患者的主要方法。同时，研究者正在积极地研究新的治疗如基因疗法。更新的化学治疗剂（例如，紫杉醇[Taxol®]、多烯紫杉醇[Taxotere®]、吉西他滨[Gemzar®]、阿霉素[Doxil®]）可以与确立的化学治疗剂（例如，氨甲蝶呤[Trexall®、Methotrex®]）联合，以提高效果。在 2006 年 3 月，食品与药品管理局 (FDA) 批准了西妥昔单抗(Erbitux®)联合放射以用于不能手术治疗的患有头颈部磷状细胞癌的患者。西妥昔单抗也可以在标准化学疗法后单独（称为单一疗法）用于已经扩散（转移）的患有头颈癌的患者中。

[0346] 本发明一个实施方式所述的治疗头颈癌的疗法采用治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物的组合。在另一个实施方式中，本发明所述的治疗头颈癌的疗法采用治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物以及一种或更多种化学治疗剂（例如，紫杉醇[Taxol®]、多烯紫杉醇[Taxotere®]、吉西他滨[Gemzar®]、阿霉素[Doxil®]）的组合，其可以进一步与确立的化学治疗剂（例如，氨甲蝶呤[Trexall®、Methotrex®]）联合。在另一个实施方式中，本发明所述的治疗头颈癌的疗法采用治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物以及Erbitux®的组合。

[0347] 结肠直肠癌

[0348] COX-2 表达水平与结肠直肠癌的存活率相关（参见图 1）。结肠直肠癌的存活取决于肿瘤的分期和分级，例如早期腺瘤与转移性腺癌。一般地，结肠直肠癌可以通过手术去除肿瘤来治疗，但总存活率保持在百分之 45 和 60 之间。结肠切除发病率相当低并且通常与吻合相关，而与肿瘤和局部组织去除的程度无关。然而，在具有高复发风险的患者中，化学疗法已经并入治疗方案中，以便提高存活率。

[0349] 手术前的肿瘤转移一般被认为是手术干预失败的原因以及需要多达一年的化学疗法来杀死未切除的肿瘤细胞。因为严重毒性与化学治疗剂有关，所以只有高复发风险的患者在手术后安排化学疗法。因此，将抗血管生成抑制剂并入结肠直肠癌的处理中在结肠直肠癌的治疗中起重要作用并且导致诊断有结肠直肠癌的患者总存活率提高。

[0350] 本发明的一个实施方式提供治疗结肠直肠癌的联合疗法，包括手术，接着是包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物的方案。进一步，本发明的另一个实施方式提供治疗结肠直肠癌的联合疗法，包括手术，接着是这样的方案 :包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物，以及一种或更多种抗血管生成剂，包括 MMP 抑制剂，或整联蛋白拮抗剂，进行为期一年的循环。本发明的进一步的实施方式提供治疗结肠直肠癌的联合疗法，包括这样的方案 :包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物，接着手术去除结肠或直肠的肿瘤以及然后是包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物方案，进行为期一年的循环。治疗结肠癌的另一个疗法包括给予治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物的组合。

[0351] 治疗结肠癌的进一步的疗法是联合下列抗肿瘤剂用包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物治疗的组合 :氟尿嘧啶、左旋咪唑、喜树碱、奥沙利铂、贝伐单抗、西妥昔单抗、帕尼单抗、伊立替康、甲酰四氢叶酸和卡培他滨。

[0352] 乳腺癌

[0353] 现今,在美国妇女中,乳腺癌一直是最经常诊断到的癌症。八分之一的美国妇女一生中都处在形成乳腺癌的风险下。年龄、家族史、饮食和遗传因素已经被确定是乳腺癌的风险因素。乳腺癌是妇女死亡的第二大原因。

[0354] 在本领域中已知不同的化学治疗剂用于治疗乳腺癌。用于治疗乳腺癌的细胞毒性剂包括阿霉素、环磷酰胺、氨甲蝶呤、5- 氟尿嘧啶、丝裂霉素 C、米托蒽醌、紫杉醇、紫杉烷制剂,仅举出以下实例 :**Abraxane®** (ABI-007)、紫杉醇 - 聚氧乙烯蓖麻油、聚谷氨酸紫杉醇和紫杉醇可注射乳液 (PIE)、吉西他滨、多烯紫杉醇、卡培他滨、拉帕替尼、曲妥珠单抗、阿那曲唑、来曲唑、依西美坦和表阿霉素。在局部晚期非炎性乳腺癌的治疗中,包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物可以用于治疗该疾病。另外,联合手术、放射疗法或化学治疗剂或其它抗血管生成剂。可以与本公开联合使用的化学治疗剂的其它组合包括,但不限于阿那曲唑、卡培他滨、多烯紫杉醇、表阿霉素、依西美坦、氟维斯群、埃博霉素 A、B 或 D、醋酸戈舍瑞林、来曲唑、贝伐单抗、紫杉醇、帕米膦酸盐、它莫西芬、托瑞米芬和曲妥珠单抗。

[0355] 激素阳性

[0356] 许多乳腺癌需要雌激素来生长。在绝经期的妇女中,雌激素的主要来源是通过将雄激素转化成雌激素。该过程通过芳化酶来进行。在激素阳性乳腺癌的治疗中,包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物可以联合其它药剂,如芳化酶抑制剂,例如依西美坦、来曲唑和阿那曲唑用于治疗该疾病。

[0357] HER2/neu 阳性乳腺癌

[0358] 在 HER2/neu 阳性乳腺癌的治疗中,包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物可以联合其它抗血管生成剂或联合手术、放射疗法或化学治疗剂用于治疗该疾病。其它化学治疗剂包括,例如曲妥珠单抗、拉帕替尼和 CL-387785。

[0359] 三阴乳腺癌

[0360] 在三阴乳腺癌——其中所述癌症为雌激素受体阴性、孕酮受体阴性和 HER2 阴性——的治疗中,包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物可以联合其它治疗剂用于治疗该疾病。这些药剂包括,仅举出以下示例 :西妥昔单抗、紫杉醇、多烯紫杉醇、紫杉烷制剂,例如**Abraxane®** (ABI-007)、紫杉醇 - 聚氧乙烯蓖麻油、聚谷氨酸紫杉醇和紫杉醇可注射乳液 (PIE)。

[0361] 卵巢癌

[0362] 体腔上皮癌占卵巢癌病例的大约 90%。治疗卵巢癌的一种疗法是治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物的组合。

[0363] 可以联合包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替

尼组合的组合物使用的其它药剂包括，但不限于：烷化剂、异环磷酰胺、顺铂、碳铂、紫杉醇、多烯紫杉醇、聚乙二醇化脂质体阿霉素、吉西他滨、阿霉素、埃博霉素 A、B 或 D、托泊替康、脂质体阿霉素、5- 氟尿嘧啶、氨甲蝶呤、丝裂霉素、六甲三聚氰胺、孕酮、抗雌激素、松龙苯芥、二羟马利兰、半乳糖醇、干扰素 α 和干扰素 γ。

[0364] 治疗体腔上皮癌的其它组合是治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物以及下列抗肿瘤剂的组合之一的组合：1) 顺铂、阿霉素、环磷酰胺；2) 六甲三聚氰胺、环磷酰胺、阿霉素、顺铂；3) 环磷酰胺、六甲三聚氰胺、5- 氟尿嘧啶、顺铂；4) 美法仑、六甲三聚氰胺、环磷酰胺；5) 美法仑、阿霉素、环磷酰胺；6) 环磷酰胺、顺铂、碳铂；7) 环磷酰胺、阿霉素、六甲三聚氰胺、顺铂；8) 环磷酰胺、阿霉素、六甲三聚氰胺、碳铂；9) 环磷酰胺、顺铂；10) 六甲三聚氰胺、阿霉素、碳铂；11) 环磷酰胺、六甲三聚氰胺、阿霉素、顺铂；12) 碳铂、环磷酰胺；13) 顺铂、环磷酰胺。

[0365] 在美国，输卵管癌每年占大约 400 个新癌症病例。本发明所述的一种疗法针对输卵管癌的治疗，其包括给予治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物的组合。可以与包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物联合使用的其它药剂包括，但不限于：烷化剂、异环磷酰胺、顺铂、碳铂、紫杉醇、多烯紫杉醇、聚乙二醇化脂质体阿霉素、吉西他滨、阿霉素、埃博霉素 A、B 或 D、托泊替康、脂质体阿霉素、5- 氟尿嘧啶、氨甲蝶呤、丝裂霉素、六甲三聚氰胺、孕酮、抗雌激素、松龙苯芥、二羟马利兰、半乳糖醇、干扰素 α 和干扰素 γ。

[0366] 生殖细胞卵巢癌占卵巢癌病例的大约 5％。生殖细胞卵巢癌分为两个主要组：无性细胞瘤和非无性细胞瘤。非无性细胞瘤进一步分为畸胎瘤、内胚窦瘤、胚胎癌、绒癌 (chloricarcinoma)、多胚瘤和混合细胞肿瘤。治疗生殖细胞癌的一种疗法是治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物的组合。

[0367] 本发明所述的一种疗法是针对生殖细胞癌的治疗，其包括给予治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物以及抗瘤剂的下列组合的组合：1) 长春新碱、放射菌素 D、环磷酰胺；2) 博来霉素、依托泊苷、顺铂；3) 长春碱、博来霉素、顺铂。

[0368] 胰腺癌

[0369] 在美国诊断的新癌病例中大约 2％是胰腺癌。胰腺癌一般分为两个临床类型 1) 腺癌 (转移性和非转移性)，以及 2) 囊性肿瘤 (浆液性囊腺瘤、粘液性囊性肿瘤、乳头状囊性肿瘤、腺细胞囊腺癌、囊性绒毛膜癌、囊性畸胎瘤、血管瘤肿瘤)。埃罗替尼组合吉西他滨适用于治疗患有局部晚期、不可切除的或转移性胰腺癌的患者。

[0370] 可以用于本公开的治疗非转移性腺癌的联合疗法包括使用包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物与术前胆道减压 (患有阻塞性黄疸的患者)；手术切除，包括标准切除术、扩大切除术或放射状切除术以及胰脏末端切除术 (体部和尾部肿瘤)；辅助性放射；抗血管生成治疗；或化学疗法。

[0371] 对于转移性腺癌的治疗，联合疗法由包含本公开的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物结合 5- 氟尿嘧啶治疗，然后每周一

次顺铂疗法组成。

[0372] 治疗囊性肿瘤的另一种联合疗法是联合吉西他滨使用包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合的组合物。

[0373] 药物组合物

[0374] 本文提供治疗癌症的药物组合物，其包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合 ；以及药学上可接受的赋形剂或载体。

[0375] 在一个实施方式中，本发明提供药物组合物，其包含 ：作为活性成分的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼组合，或其药学上可接受的盐、溶剂合物或前体药物，于药学上可接受的运载体、载体、稀释剂或赋形剂或其混合物中 ；以及一种或更多种药学上可接受的赋形剂或载体。

[0376] 在另一个实施方式中，1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及药学上可接受的赋形剂或载体。在另一个实施方式中，EGFR 抑制剂是埃罗替尼以及药学上可接受的赋形剂或载体。在进一步的实施方式中，1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼和药学上可接受的赋形剂或载体。

[0377] 在一个实施方式中，本发明提供治疗癌症的药物组合物，其包含选自下列的 1,2- 二苯基吡咯衍生物的组合 ：4- 甲基 -2-(4- 甲苯基)-1-(4- 氨磺酰苯基) 吡咯 ；2-(4- 甲氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯 ；2-(4- 氯苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯 ；4- 甲基 -2-(4- 甲基苯硫基)-1-(4- 氨磺酰苯基) 吡咯 ；2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯 ；2-(4- 甲氧基 -3- 甲苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯 ；2-(3- 氟 -4- 甲氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯 ；2-(3,4- 二甲基苯基)-4- 甲基 -1-(4- 氨磺酰苯基) 吡咯 ；4- 甲基 -1-(4- 甲基苯硫基)-2-(4- 氨磺酰苯基) 吡咯 ；1-(4- 乙酰氨基磺酰苯基)-4- 甲基 -2-(4- 甲氧基苯基) 吡咯 ；以及 1-(4- 乙酰氨基磺酰苯基)-4- 甲基 -2-(3,4- 二甲基苯基) 吡咯。在另一个实施方式中，本发明提供方法，其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和 EGFR 抑制剂 ；药学上可接受的赋形剂或载体。

[0378] 本文提供药物组合物，其包含作为活性成分的 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，或其药学上可接受的盐、溶剂合物或前体药物，于药学上可接受的运载体、载体、稀释剂或赋形剂或其混合物中 ；以及一种或更多种药学上可接受的赋形剂或载体。本文还提供药物组合物，其包含作为活性成分的 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，或其药学上可接受的盐、溶剂合物或前体药物，于药学上可接受的运载体、载体、稀释剂或赋形剂或其混合物中 ；以及本文所描述的一种或更多种控释赋形剂。本文提供药物组合物，其包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合——其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼作为活性成分，或其药学上可接受的盐、溶剂合物或前体药物，于药学上可接受的运载体、载体、稀释剂或赋形剂或其混合物中 ；以及本文所描述的一种或更多种控释赋形剂。适合的调节释放剂量运载体包括，但不限于，亲水性或疏水性基体装置、水溶性分离层包衣、肠溶性包衣、渗透装置、多颗粒装置，及其组合。药物组合物也可以包含非控释赋形剂。

[0379] 本文提供包膜剂形的药物组合物，其包含作为活性成分的 1,2- 二苯基吡咯

衍生物和 EGFR 抑制剂组合，或其药学上可接受的盐、溶剂合物或前体药物；以及一种或更多种压片赋形剂以形成片心，其使用使用传统的压片过程以及随后包覆该心。片心可以使用传统的制粒方法生产，例如湿法或干法制粒，以及任选颗粒粉碎和随后的压缩和包覆。制粒方法描述在，例如 Voigt，第 156-69 页 (Voigt，R.(1984)：Lehrbuch derpharmazeutischen Technologie(Textbook of Pharmaceutical Technology)；Verlag ChemieWeinheim-Beerfield Beach/Florida-Basle) 中。

[0380] 生产颗粒的适合的赋形剂是，例如任选具有流量调节性质的粉状填料，例如滑石、二氧化硅，例如**Syloid®**型号合成的无定形硅酸 (Grace)，例如 SYLOID 244FP，微晶纤维素，例如**Avicel®**型 (FMC Corp.) 的微晶纤维素，例如型号 AVICEL PH101、102、105、RC581 或 RC 591 的微晶纤维素，**Emcocel®**型 (Mendell Corp.) 的或**Elcema®**型 (Degussa)；碳水化合物，如糖、糖醇、淀粉或淀粉衍生物，例如乳糖、右旋糖、蔗糖、葡萄糖、山梨醇、甘露醇、木糖醇、马铃薯淀粉、玉米淀粉、大米淀粉、小麦淀粉或支链淀粉、磷酸三钙、磷酸氢钙或三硅酸镁；粘结剂，如凝胶、黄芪胶、琼脂、藻酸、纤维素醚，例如甲基纤维素、羧甲基纤维素或羟丙基甲基纤维素、聚乙二醇或环氧乙烷均聚物，特别是具有约 2.0×10^3 至 1.0×10^5 的聚合度和约 1.0×10^5 至 5.0×10^6 的大约分子量的聚乙二醇或环氧乙烷均聚物，例如赋形剂，其已知的名称为**Polyox®** (Union Carbide)，聚乙烯吡咯烷酮或聚烯吡酮，特别是具有约 1000 平均分子量和大致从约 500 至约 2500 的聚合度的聚乙烯吡咯烷酮或聚烯吡酮，以及还有琼脂或凝胶；表面活性物质，例如烷基硫酸盐型阴离子表面活性剂，例如正十二烷基硫酸、正十四烷基硫酸、正十六烷基硫酸或正十八烷基硫酸钠、钾或镁，烷基醚硫酸盐型阴离子表面活性剂，例如正十二烷氧基乙基硫酸、正十四烷氧基乙基硫酸、正十六烷氧基乙基硫酸或正十八烷氧基乙基硫酸钠、钾或镁，或烷磺酸盐型阴离子表面活性剂，例如正十二烷磺酸、正十四烷磺酸、正十六烷磺酸或正十八烷磺酸钠、钾或镁，或脂肪酸多元醇酯型非离子表面活性剂，如山梨糖醇酐单月桂酸酯、山梨糖醇酐单油酸酯、山梨糖醇酐单硬脂酸酯或山梨糖醇酐单棕榈酸酯、山梨糖醇酐三硬脂酸酯或山梨糖醇酐三油酸酯，脂肪酸多元醇酯的聚氧乙烯加合物，如聚氧乙烯山梨糖醇酐单月桂酸酯、聚氧乙烯山梨糖醇酐单油酸酯、聚氧乙烯山梨糖醇酐单硬脂酸酯、聚氧乙烯山梨糖醇酐单棕榈酸酯、聚氧乙烯山梨糖醇酐三硬脂酸酯或聚氧乙烯山梨糖醇酐三油酸酯，聚乙二醇脂肪酸酯，如聚氧乙基硬脂酸酯、聚乙二醇 400 硬脂酸酯、聚乙二醇 2000 硬脂酸酯，特别是**Pluronics®** (BWC) 或**Synperonic®** (ICI) 型的环氧乙烷 / 环氧丙烷嵌段共聚物。

[0381] 本文进一步提供肠溶衣剂型的药物组合物，其包含作为活性成分的 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合，或其药学上可接受的盐、溶剂合物或前体药物；以及用于肠溶衣剂型的一种或更多种控释赋形剂。本文提供肠溶衣剂型的药物组合物，其包含作为活性成分的 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合——其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼，或其药学上可接受的盐、溶剂合物或前体药物，于药学上可接受的运载体、载体、稀释剂或赋形剂或其混合物中；以及用于肠溶衣剂型的一种或更多种控释赋形剂。药物组合物也可以包含非控释赋形剂。

[0382] 本文进一步提供泡腾剂型的药物组合物，其包含作为活性成分的 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，或其药学上可接受的盐、溶剂合物或前体药物；以及用于

泡腾剂型的一种或更多种控释赋形剂。本文还提供泡腾剂型的药物组合物，其包含作为活性成分的 1，2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合——其中 1，2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼，或其药学上可接受的盐、溶剂合物或前体药物，于药学上可接受的运载体、载体、稀释剂或赋形剂或其混合物中；以及用于泡腾剂的一种或更多种控释赋形剂。药物组合物也可以包含非控释赋形剂。

[0383] 另外以这样的剂型提供药物组合物，所述剂型具有立即释放组分和至少一种延迟释放组分，并且能够以在从 0.1 小时直至 24 小时的时间内分隔的至少两个连续脉冲的形式给予化合物的间断释放。所述药物组合物包含作为活性成分的 1，2- 二苯基吡咯衍生物和 EGFR 抑制剂组合，或其药学上可接受的盐、溶剂合物或前体药物；以及一种或更多种控释和非控释赋形剂，如适于可崩解半透膜的那些赋形剂和可膨胀物质。另外，本发明提供药物组合物，其包含作为活性成分的 1，2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合——其中 1，2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼，或其药学上可接受的盐、溶剂合物或前体药物；以及一种或更多种控释和非控释赋形剂，如适于可崩解半透膜的那些赋形剂和可膨胀物质。

[0384] 本文还提供用于向对象口服给药的剂型的药物组合物，其包含作为活性成分的 1，2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合，或其药学上可接受的盐、溶剂合物或前体药物；以及一种或更多种药学上可接受的赋形剂或载体，其被装入中间反应层中，所述中间反应层包含抵抗胃液的聚合物层状材料，其被碱部分中和并且具有离子交换能力，以及抵抗胃液的外层。另外，本发明提供用于向对象口服给药的剂型的药物组合物，其包含 1，2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合——其中 1，2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼，其被装入中间反应层中，所述中间反应层包含抵抗胃液的聚合物层状材料，其被碱部分中和并且具有离子交换能力，以及抵抗胃液的外层。

[0385] 本文提供药物组合物，其包含约 0.1 至约 1200mg、约 1 至约 500mg、约 2 至约 100mg、约 1mg、约 2mg、约 3mg、约 5mg、约 10mg、约 20mg、约 30mg、约 40mg、约 50mg、约 100mg、约 200mg、约 300mg、约 400mg、约 500mg、约 600mg、约 800mg、约 1200mg 的 1，2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合作为活性成分，或其药学上可接受的盐、溶剂合物或前体药物，其为肠溶衣颗粒的形式，如用于口服给药的缓释胶囊。还有，本发明提供药物组合物，其包含约 0.1 至约 1000mg、约 1 至约 500mg、约 2 至约 100mg、约 1mg、约 2mg、约 3mg、约 5mg、约 10mg、约 20mg、约 30mg、约 40mg、约 50mg、约 100mg、约 500mg 的 1，2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合——其中 1，2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼作为活性成分，或其药学上可接受的盐、溶剂合物或前体药物，其为肠溶衣颗粒的形式，如用于口服给药的缓释胶囊。

[0386] 本文提供药物组合物，其包含约 0.1 至约 1200mg、约 1 至约 500mg、约 2 至约 100mg、约 1mg、约 2mg、约 3mg、约 5mg、约 10mg、约 20mg、约 30mg、约 40mg、约 50mg、约 100mg、约 500mg、约 600mg、约 800mg、约 1200mg 的 1，2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合作为活性成分，或其药学上可接受的盐、溶剂合物或前体药物，其为肠溶衣丸剂的形式，如用于口服给药的缓释胶囊。还有，本发明提供药物组合物，其包含约 0.1 至约 1200mg、约 1 至约

500mg、约 2 至约 100mg、约 1mg、约 2mg、约 3mg、约 5mg、约 10mg、约 20mg、约 30mg、约 40mg、约 50mg、约 100

[0387] mg、约 500mg、约 600mg、约 800mg、约 1200mg 的 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合——其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼作为活性成分,或其药学上可接受的盐、溶剂合物或前体药物,其为肠溶衣丸剂的形式,如用于口服给药的缓释胶囊。药物组合物进一步包含甘油单硬脂酸酯 40-50、羟丙基纤维素、羟丙甲纤维素、硬脂酸镁、甲基丙烯酸共聚物型 C、聚山梨醇酯 80、糖丸、滑石和柠檬酸三乙酯。

[0388] 本文提供药物组合物,其包含约 0.1 至约 1200mg、约 1 至约 500mg、约 2 至约 100mg、约 1mg、约 2mg、约 3mg、约 5mg、约 10mg、约 20mg、约 30mg、约 40mg、约 50mg、约 100mg、约 500mg、约 600mg、约 800mg、约 1200mg 的 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合作为活性成分,或其药学上可接受的盐、溶剂合物或前体药物,其为用于口服给药的肠溶衣型缓释片剂。还有,药物组合物,其包含约 0.1 至约 1200mg、约 1 至约 500mg、约 2 至约 100mg、约 1mg、约 2mg、约 3mg、约 5mg、约 10mg、约 20mg、约 30mg、约 40mg、约 50mg、约 100mg、约 500mg、约 600mg、约 800mg、约 1200mg 的 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合作为活性成分——其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼,或其药学上可接受的盐、溶剂合物或前体药物,其为用于口服给药的肠溶衣型缓释片剂。药物组合物进一步包含巴西棕榈蜡、交聚维酮、二乙酰甘油一酸酯、乙基纤维素、羟丙基纤维素、羟丙甲纤维素邻苯二甲酸酯、硬脂酸镁、甘露醇、氢氧化钠、硬脂酰富马酸钠、滑石、二氧化钛和黄色三氧化二铁。

[0389] 本文提供药物组合物,其包含约 0.1 至约 1200mg、约 1 至约 500mg、约 2 至约 100mg、约 1mg、约 2mg、约 3mg、约 5mg、约 10mg、约 20mg、约 30mg、约 40mg、约 50mg、约 100mg、约 500mg、约 600mg、约 800mg、约 1200mg 的 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合作为活性成分,或其药学上可接受的盐、溶剂合物或前体药物,其为用于口服给药的肠溶衣型缓释片剂。本文还提供药物组合物,其包含约 0.1 至约 1200mg、约 1 至约 500mg、约 2 至约 100mg、约 1mg、约 2mg、约 3mg、约 5mg、约 10mg、约 20mg、约 30mg、约 40mg、约 50mg、约 100mg、约 500mg、约 600mg、约 800mg、约 1200mg 的 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂的组合作为活性成分——其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼,或其药学上可接受的盐、溶剂合物或前体药物,其为用于口服给药的肠溶衣型缓释片剂。药物组合物进一步包含硬脂酸钙、交聚维酮、羟丙基甲基纤维素、氧化铁、甘露醇、甲基丙烯酸共聚物、聚山梨醇酯 80、聚烯吡酮、丙二醇、碳酸钠、月桂基硫酸钠、二氧化钛和柠檬酸三乙酯。

[0390] 本文提供的药物组合物可以以单元剂型或多元剂型提供。如本文所用,单元剂型指物理上不连续的单元,其适合给予人和动物对象并且被单独包装,如本领域中所已知的那样。每个单元剂量包含预先确定量的活性成分 (一种或多种),其足以产生期望的治疗效果,结合需要的药物载体或赋形剂。单元剂型的实例包括安瓿、注射器和单独包装的片剂和胶囊。单元剂型可以分次或多次给药。多元剂型是许多相同的单元剂型,其包装在一个容器中以便以分隔的单元剂型给药。多元剂型的实例包括管形瓶、片剂或胶囊瓶、或品脱或加仑瓶。

[0391] 本文提供的组合物可以单独给药或联合本文提供的一种或更多种其它化合物，一种或更多种其它活性成分给药。包含本文提供的化合物的药物组合物可以以各种剂型配制，以用于口服、肠胃外、口腔、鼻内、硬膜外、舌下、肺部、局部、直肠、经皮或局部给药。药物组合物也可以配制成调节释放型剂型，包括延迟释放、缓慢释放、延长释放、持续释放、脉冲释放、控制释放、加速释放和快速释放、靶向释放、程序释放和胃滞留剂型。这些制剂可以根据本领域技术人员已知的传统方法和技术来制备（参见，Remington :The Science and Practice of Pharmacy, supra ;Modified-Release Drug DeliverTechnology, Rathbone 等, Eds., Drugs and the Pharmaceutical Science, Marcel Dekker, Inc. :New York, NY, 2002 ;Vol. 126）。

[0392] 本文提供的药物组合物可以一次给药或以时间间隔多次给药。可以理解为，治疗的精确剂量和持续时间可以随被治疗患者的年龄、体重和状况不同而不同，以及可以使用已知的测试方案或通过从体内或体外测试或诊断数据推断来经验性地确定。进一步理解为，对于任意具体个体，特异性剂量方案应该根据个体需要和管理或监督制剂给予的人员的职业判断随时间而调整。

[0393] 在患者的状况没有改善的情况下，在医生判断后组合的给药可以长期给予，即一段延长的时间，包括整个患者生命持续时间，以便缓解或另外控制或限制患者疾病或病症的症状。

[0394] 在患者状况改善的情况下，在医生判断后组合的给药可以继续进行或暂停某一段时间（即，“药物假期”）。

[0395] 一旦患者状况出现改善，给予维持剂量——如果需要。随后，给药剂量或频率或两者可以根据症状减少至保持改善的疾病或病症的水平。然而，患者可以长期基于症状的任意复发而要求间歇治疗。

[0396] 如本文所用，包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物和使用该组合物的方法可以不需载体或赋形剂而配制，或可以联合一种或更多种用于给药的药学上可接受的载体配制。例如，溶剂、稀释剂等，以及可以以这样的形式口服给药 :片剂、胶囊、可分散粉末、颗粒或悬浮液，其包含，例如约 0.05 至约 5％悬浮剂、浆液，其包含，例如约 10 至约 50％糖，以及酏剂，其包含，例如约 20 至约 50％乙醇，等等。这些药物制备物可以包含，例如约 0.05％多至约 90％活性成分，以及载体，其更通常在按重量计约 5％和约 60％之间。还有，本文提供包含 1,2- 二苯基吡咯衍生物和 EGFR 抑制剂组合的组合物以及使用所述组合物的方法——其中 1,2- 二苯基吡咯衍生物是 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯以及 EGFR 抑制剂是埃罗替尼——其可以无载体或赋形剂而配制或可以联合一种或更多种用于给药的药学上可接受的载体。

[0397] 使用的每种活性成分的有效剂量可以根据使用的具体化合物、给药方式和被治疗病症的严重性而不同。EGFR 抑制剂的设计的日剂量取决于许多因素。评价和比较 1,2- 二苯基吡咯衍生物抑制剂效力的许多方法对本领域技术人员而言是已知的。在一个实施方式中，1,2- 二苯基吡咯衍生物抑制剂的口服日剂量在约 0.01 至约 30mg/kg 范围内，以及 EGFR 抑制剂的设计日剂量在约 0.3 至约 8mg/kg 范围内。该剂量方案可以调整以提供最佳治疗响应。例如，每日可以给予几种分剂量或剂量可以按比例减少，如治疗情况的紧急性所指示。1,2- 二苯基吡咯衍生物抑制剂和 EGFR 抑制剂也可以作为组合剂量单元给药或作为单独的

组分给药。当作为单独组分给药时，每种组分在治疗期间可以同时或在不同时间给药。

[0398] 然而，可以理解为，任意特定患者的具体剂量水平取决于多种因素，如，例如肝脏和肾脏功能降低。

[0399] 治疗剂量一般可以被滴定来优化安全性和功效。通常，来自体外研究的剂量－效应关系最初可以对患者给药的适当剂量提供有用的指导。动物模型中的研究一般也可以用于有关治疗本公开所述癌症的有效剂量的指导。鉴于治疗方案，应该意识到，待给药的剂量取决于几种因素，包括给予的具体药剂、给药途径、具体患者的状况等。这些参数的确定完全在本领域的技术内。这些考虑以及有效配制物和给药方法在本领域中是公知的并且描述在标准教科书中。

[0400] 口服制剂

[0401] 包含本文描述的活性组合的口服制剂可以包含任意传统使用的口服剂型，包括：片剂、胶囊、丸剂、锭剂、糖锭、软锭剂、扁囊剂、微球、含药的口香糖、颗粒剂、散剂、泡腾或非泡腾粉末或颗粒、溶液、乳状液、悬浮液、溶液、干胶片、喷洒剂、酏剂、糖浆、口腔形式剂和口服液。胶囊可以包含活性化合物（一种或多种）与惰性填料和/或稀释剂的混合物，惰性填料和/或稀释剂如药学上可接受的淀粉（例如玉米、马铃薯或木薯淀粉）、糖、人工甜味剂、粉末状纤维素，如结晶纤维素和微晶纤维素、面粉、凝胶、树胶等。有用的片剂制剂可以通过传统压缩、湿法制粒或干法制粒的方法来制作并且使用药学上可接受的稀释剂、粘结剂、润滑剂、崩解剂、表面改性剂（包括表面活性剂）、悬浮或稳定剂，包括，但不限于，硬脂酸镁、硬脂酸、滑石、月桂基硫酸钠、微晶纤维素、羧甲基纤维素钙、聚乙烯吡咯烷酮、凝胶、藻酸、阿拉伯树胶、黄原胶、柠檬酸钠、复杂硅酸盐、碳酸钙、糖胶、糊精、蔗糖、山梨醇、磷酸二钙、硫酸钙、乳糖、高岭土、甘露醇、氯化钠、滑石、干淀粉和糖粉。在一些实施方式中是表面改性剂，其包括非离子和阴离子表面改性剂。例如，表面改性剂包括，但不限于，泊洛沙姆188、苯扎氯铵、硬脂酸钙、十六十八醇、聚西托醇乳化蜡、山梨糖醇酯、胶态二氧化硅、膦酸酯、十二烷基磺酸钠、硅酸镁铝和三乙醇胺。本文的口服制剂可以采用缓释制剂或延时释放制剂以改变活性化合物（一种或多种）的吸收。口服制剂也可以由在包含所需适合的增溶剂或乳化剂的水或果汁中给予活性成分组成。

[0402] 口服给药

[0403] 如本文所描述，联合方案可以同时给予或可以以交替的方案给予，以及1,2-二苯基吡咯衍生物在化学疗法期间于不同于EGFR抑制剂的时间给予。该时间差的范围可以在两种化合物的给药之间几分钟、几小时、几天、几周或更长。因此，术语联合的含义不一定是同时或作为单一剂量给药，而是每一种组分在期望的治疗期间给药。药剂也可以通过不同途径给药。如典型的化学疗法方案，化学疗法过程可以重复几周后，以及可以按相同的时间表给予两种化合物，或可以基于患者响应进行修改。

[0404] 在其它实施方式中，本文提供的药物组合物可以以用于口服给药的固体、半固体或液体制剂提供。如本文所用，口服给药也包括口腔、舌和舌下给药。适合的口服剂型包括，但不限于，片剂、胶囊、丸剂、锭剂、糖锭、软锭剂、扁囊剂、微球、含药的口香糖、颗粒剂、散剂、泡腾或非泡腾粉末或颗粒、溶液、乳状液、悬浮液、溶液、干胶片、喷洒剂、酏剂、糖浆。除活性成分（一种或多种）外，药物组合物可以包含一种或更多种药学上可接受的载体或赋形剂，包括，但不限于，粘结剂、填料、稀释剂、崩解剂、湿润剂、润滑剂、助流剂、着色剂、染

料泳移抑制剂、甜味剂和调味剂。

[0405] 粘结剂或制粒剂 (granulator) 赋予片剂粘结性以确保压缩后片剂保持完整。适合的粘结剂或制粒剂包括，但不限于，淀粉，如玉米淀粉、马铃薯淀粉和预胶化淀粉 (例如，STARCH 1500) ；凝胶 ；糖，如蔗糖、葡萄糖、右旋糖、糖浆和乳糖 ；天然和合成树胶，如阿拉伯树胶、藻酸、藻酸盐、爱尔兰藓提取物、Panwar 树胶、印度树胶、车前子壳的粘液 (mucilage of isabgol husks)、羧甲基纤维素、甲基纤维素、聚乙烯吡咯烷酮 (PVP)、硅酸镁铝、落叶松阿拉伯半乳聚糖、粉状黄芪胶和瓜尔树胶 ；纤维素，如乙基纤维素、醋酸纤维素、羧甲基纤维素钙、羧甲基纤维素钠、甲基纤维素、羟乙基纤维素 (HEC)、羟丙基纤维素 (HPC)、羟丙基甲基纤维素 (HPMC) ；微晶纤维素，如 AVICEL-PH-101、AVICEL-PH-103、AVICEL RC-581、AVICEL-PH-105(FMC Corp.，Marcus Hook，PA) ；以及其混合物。适合的填料包括，但不限于，滑石、碳酸钙、微晶纤维素、粉状纤维素、葡萄糖结合剂、高岭土、甘露醇、硅酸、山梨醇、淀粉、预胶化淀粉及其混合物。粘结剂或填料可以以按重量计约 50 至约 99％存在于本文提供的药物组合物中。

[0406] 适合的稀释剂包括，但不限于，磷酸二钙、硫酸钙、乳糖、山梨醇、蔗糖、肌醇、纤维素、高岭土、甘露醇、氯化钠、干淀粉和糖粉。某些稀释剂，如甘露醇、乳糖、山梨醇、蔗糖和肌醇当以足够的量存在时可以赋予一些压制片剂这样的性质 ：其允许通过咀嚼在嘴中崩解。这些压制片剂可以用作咀嚼片剂。

[0407] 适合的崩解剂包括，但不限于，琼脂 ；膨润土 ；纤维素，如甲基纤维素和羧甲基纤维素 ；木材 ；天然海绵 ；阳离子交换树脂 ；褐藻酸 ；树胶，如瓜尔树胶和硅酸镁铝 HV ；柑桔渣 ；交联纤维素，如交联羧甲基纤维素 ；交联聚合物，如交聚维酮 ；交联淀粉 ；碳酸钙 ；微晶纤维素，如羧甲基淀粉纳 ；波拉克林钾 ；淀粉，如玉米淀粉、马铃薯淀粉、木薯淀粉和预胶化淀粉 ；粘土 ；aligns ；以及其混合物。本文提供的药物组合物中崩解剂的量根据制剂的类型而变化，以及本领域普通技术人员可以容易地判断。本文提供的药物组合物可以包含按重量计约 0.5 至约 15％或约 1 至约 5％的崩解剂。

[0408] 适合的润滑剂包括，但不限于，硬脂酸钙 ；硬脂酸镁 ；矿物油 ；轻矿物油 ；甘油 ；山梨醇 ；甘露醇 ；乙二醇，如甘油山嵛酸酯和聚乙二醇 (PEG) ；硬脂酸 ；十二烷基磺酸钠 ；滑石 ；氢化植物油，包括花生油、棉籽油、向日葵油、芝麻油、橄榄油、玉米油和大豆油 ；硬脂酸锌 ；油酸乙酯 ；月桂酸乙酯 ；琼脂 ；淀粉 ；石松粉 ；硅石或硅胶，如**AEROSIL®** 200(W.R.Grace Co.，Baltimore，MD) 和 CAB-O-**SIL®** (Cabot Co.of Boston，MA) ；以及其混合物。本文提供的药物组合物可以包含按重量计约 0.1 至约 5％的润滑剂。

[0409] 适合的助流剂包括胶态二氧化硅、CAB-O-**SIL®** (Cabot Co.of Boston，MA) 和不含石棉的滑石。着色剂包括任意批准的、认证的水溶性 FD&C 染料和悬浮在氢氧化铝上的水不溶性 FD&C 染料，以及色淀及其混合物。色淀是这样的结合 ：通过将水溶性染料吸附至重金属的含水氧化物，形成不溶性染料。调味剂包括从植物如水果中提取的天然香料和产生舒适味觉的化合物的合成掺合物，如薄荷油和水杨酸甲酯。甜味剂包括蔗糖、乳糖、甘露醇、糖浆、甘油和人造甜味剂，如糖精和天冬甜素。适合的乳化剂包括凝胶、阿拉伯树胶、黄芪胶、膨润土和表面活性剂，如聚氧乙烯山梨醇酐单月桂酸酯 (**TWEEN®** 20)、聚氧乙烯山梨醇酐单月桂酸酯 80(**TWEEN®** 80) 和油酸三乙醇胺酯。悬浮剂和分散剂包括羧甲基纤维素钠、果胶、黄芪胶、硅酸镁铝、阿拉伯树胶、羧甲基纤维素钠、羟丙基甲基纤维素和聚乙烯吡咯烷

酮。防腐剂包括甘油、对羟基苯甲酸甲酯和丙酯、苯甲酸、苯甲酸钠和醇。湿润剂包括丙二醇单硬脂酸酯、山梨醇酐单油酸酯、二甘醇月桂酸酯和月桂醇聚氧乙烯醚。溶剂包括甘油、山梨醇、乙醇和糖浆。乳状液中使用的非水性液体的实例包括矿物油和棉籽油。有机酸包括柠檬酸和酒石酸。二氧化碳的来源包括碳酸氢钠和碳酸钠。

[0410] 应该理解为，许多载体和赋形剂可以充当几种功能——即使在相同的制剂内。

[0411] 在进一步的实施方式中，本文提供的药物组合物可以提供为压制片、模印片、咀嚼锭、快速溶解片、多层压制片或肠溶衣片、糖衣片或薄膜包衣片。肠溶衣片是包有这样的物质的压制片，所述物质抵抗胃酸的作用但在肠中溶解或崩解，从而保护活性成分免受胃的酸性环境。肠溶包衣包括，但不限于，脂肪酸、脂肪、水杨酸苯酯、蜡、紫胶、含氨紫胶和邻苯二甲酸乙酸纤维素。糖衣片是被糖衣包裹的压制片，其可以有益于掩盖讨厌的味觉或气味以及保护片剂免受氧化。薄膜包衣片是用水溶性物质的薄层或薄膜覆盖的压制片。薄膜包衣包括，但不限于，羟乙基纤维素、羧甲基纤维素钠、聚乙二醇 4000 和邻苯二甲酸乙酸纤维素。薄膜包衣赋予与糖包衣相同的一般特性。多层压制片是通过一个以上压缩循环而制成的压制片，包括层片、压制包衣片或干压包衣片。

[0412] 可以单独或组合本文描述的一种或多种载体或赋形剂以粉末、结晶或颗粒的形式由活性成分来制备片剂剂型，所述载体或赋形剂包括粘结剂、崩解剂、控释聚合物、润滑剂、稀释剂和 / 或着色剂。调味剂和甜味剂特别用于形成咀嚼片剂和糖锭。

[0413] 本文提供的药物组合物可以提供为软胶囊或硬胶囊，其可以由凝胶、甲基纤维素、淀粉或藻酸钙制成。硬凝胶胶囊也称为干填充胶囊 (DFC)，由两部分组成，一部分套在另一部分上，从而完全包入活性成分。软弹性胶囊 (SEC) 是软的、球状壳，如凝胶壳，其通过加入甘油、山梨醇或类似的多元醇而增塑。软凝胶壳可以包含防腐剂以防止微生物的生长。适合的防腐剂是本文所描述的那些，包括对羟基苯甲酸甲酯和丙酯和山梨酸。本文提供的液体、半固体和固体制剂可以装在胶囊中。适合的液体和半固体制剂包括在碳酸丙烯、植物油或甘油三酯中的溶液和悬浮液。包含这些溶液的胶囊可以如美国专利号 4,328,245；4,409,239；以及 4,410,545 中所述而制备。胶囊也可以如本领域技术人员所已知的那样进行包衣，以便改变或维持活性成分的溶解。

[0414] 在其它实施方式中，本文提供的药物组合物可以以液体和半固体剂型提供，包括乳状液、溶液、悬浮液、酏剂和糖浆。乳状液是两相系统，其中一种液体以小球的形式分散在整个另一种液体中，其可以是水包油或油包水。乳状液可以包括药学上可接受的非水性液体或溶剂、乳化剂和防腐剂。悬浮液可以包括药学上可接受的悬浮剂和防腐剂。水醇溶液可以包括药学上可接受的缩醛，如低级烷基醛（术语“低级”含义是具有 1 至 6 个碳原子的烷基）的二（低级烷基）缩醛，例如，乙醛二乙缩醛；以及水溶性溶剂，其具有一个或更多个羟基，如丙二醇和乙醇。酏剂是透明的、甜的和水醇性溶液。糖浆是糖例如，蔗糖的浓缩水溶液以及也可以包含防腐剂。对于液体剂型，例如，聚乙二醇溶液可以用足够量的药学上可接受的液体载体例如，水稀释，以便对给药进行方便地测量。

[0415] 其它有用的液体和半固体剂型包括，但不限于那些，其包含本文提供的活性成分（一种或多种）以及二烷基化的单或聚亚烷基醇，包括 1,2- 二甲氧基甲烷、二甘醇二甲醚、三甘醇二甲醚、四甘醇二甲醚、聚乙二醇 -350- 二甲醚、聚乙二醇 -550- 二甲醚，聚乙二醇 -750- 二甲醚，其中 350、550 和 750 指聚乙二醇的大约平均分子量。这些制剂可以进一

步包含一种或更多种抗氧化剂，如丁基化羟基甲苯 (BHT)、丁基化羟基茴香醚 (BHA)、没食子酸丙酯、维生素 E、对苯二酚、羟基香豆素、乙醇胺、卵磷脂、脑磷脂、抗坏血酸、苹果酸、山梨醇、磷酸、亚硫酸盐、焦亚硫酸钠、硫二丙酸及其酯，以及二硫代氨基甲酸盐。

[0416] 本文提供的用于口服给药的药物组合物也可以以脂质体、胶束、微球或纳米体系的形式提供。胶束剂型可以如美国专利号 6,350,458 中所述而制备。

[0417] 在其它实施方式中，本文提供的药物组合物可以提供为非泡腾或泡腾的颗粒和粉末，以重构成液体剂型。用于非泡腾颗粒和粉末的药学上可接受的载体和赋形剂可以包括稀释剂、甜味剂和湿润剂。用于泡腾颗粒和粉末的药学上可接受的载体和赋形剂可以包括有机酸和二氧化碳源。

[0418] 着色剂和调味剂可以用于所有上述剂型中。

[0419] 本文提供的药物组合物可以配制成速释或调节释放剂型，包括延迟释放、持续释放、脉冲释放、控制释放、靶向释放和程序释放的形式。

[0420] 在进一步的实施方式中，本文提供的药物组合物可以与下列物质一起共同配制：不赋予期望治疗作用的其它活性成分；或补充期望作用的物质，如其它胆碱能剂、其它血清素能剂、α 肾上腺素能剂、CCK_A 拮抗剂、$5\text{-}HT_3$ 拮抗剂、NMDA 受体拮抗剂、阿片类、胃肠促动药、速激肽、antalarmin 和 Z-338。

[0421] 肠胃外给药

[0422] 在一些实施方式中，本文提供的药物组合物可以通过注射、输注或灌输来肠胃外给予，以用于局部或系统性给药。如本文所用，肠胃外给药包括静脉内、动脉内、腹腔内、鞘内、心室内、尿道内、胸骨内、头颅内、肌肉内、滑膜内和皮下给药。

[0423] 在其它实施方式中，本文提供的药物组合物可以配制在适合于肠胃外给药的任意剂型中，包括溶液、悬浮液、乳状液、胶束、脂质体、微球、纳米体系和固体形式，其在注射前适于溶解或悬浮于液体中。这些剂型可以根据药物科学领域技术人员已知的传统方法来制备（参见，Remington：The Science and Practice of Pharmacy，supra）。

[0424] 意图肠胃外给药的药物组合物可以包括一种或更多种药学上可接受的载体和赋形剂，包括，但不限于，水性运载体、水溶性运载体、非水性运载体、针对微生物有机体生长的抗菌剂或防腐剂、稳定剂、增溶剂、等渗剂、缓冲剂、抗氧化剂、局部麻醉剂、悬浮和分散剂、湿润或乳化剂、络合剂、掩蔽或螯合剂、冷冻保护剂、冻干保护剂、增稠剂、pH 调节剂和惰性气体。

[0425] 适合的水性运载体包括，但不限于，水、盐水、生理盐水或磷酸盐缓冲盐水 (PBS)、氯化钠注射液、林格注射液、等渗右旋糖注射液、无菌水注射液、右旋糖和乳酸盐化的林格注射液。非水性运载体包括，但不限于，植物来源的固定油、蓖麻油、玉米油、棉籽油、橄榄油、花生油、薄荷油、红花油、芝麻油、大豆油、氢化植物油、氢化大豆油以及棕榈籽油的中链甘油三酯和椰子油。水可混溶性运载体包括，但不限于，乙醇、1,3- 丁二醇、液体聚乙二醇（例如，聚乙二醇 300 和聚乙二醇 400）、丙二醇、甘油、N- 甲基 -2- 吡咯烷酮、二甲基乙酰胺和二甲亚砜。

[0426] 适合的抗菌剂或防腐剂包括，但不限于，苯酚、甲酚、汞制剂、苄醇、氯丁醇、对羟基苯甲酸甲酯和丙酯、乙基汞硫代水杨酸钠、苯扎氯铵、苄索氯铵、对羟基苯甲酸甲酯和丙酯和山梨酸。适合的等渗剂包括，但不限于，氯化钠、甘油和右旋糖。适合的缓冲剂包括，但不

限于，磷酸盐和柠檬酸盐。适合的抗氧化剂是本文所描述的那些，包括亚硫酸盐和焦亚硫酸钠。适合的局部麻醉剂包括，但不限于，盐酸普鲁卡因。适合的悬浮剂和分散剂是本文所描述的那些，包括羧甲基纤维素钠、羟丙基甲基纤维素和聚乙烯吡咯烷酮。适合的乳化剂包括本文所描述的那些，包括聚氧乙烯山梨糖醇酐单月桂酸酯、聚氧乙烯山梨醇酐单月桂酸酯 80 和油酸三乙醇胺酯。适合的掩蔽或螯合剂包括，但不限于 EDTA。适合的 pH 调节剂包括，但不限于，氢氧化钠、盐酸、柠檬酸和乳酸。适合的络合剂包括，但不限于，环糊精，包括 α－环糊精、β－环糊精、羟丙基－β－环糊精、磺丁基醚－β－环糊精和磺丁基醚 7-β－环糊精（**CAPTISOL®**, CyDex, Lenexa, KS）。

[0427] 在一些实施方式中，本文提供的药物组合物可以配制成单或多剂量给药。单剂量配制物包装在安瓿、管形瓶或注射器中。多剂量肠胃外配制物必须包含在细菌抑制或真菌抑制浓度下的抗菌剂。所有肠胃外配制物必须是无菌的，如本领域中已知和实践的那样。

[0428] 在一个实施方式中，药物组合物提供为即用型无菌溶液。在另一个实施方式中，药物组合物提供为无菌干可溶性产品，包括冻干粉和皮下注射用片剂，以便在使用前用运载体重构。在又一实施方式中，药物组合物提供为即用型无菌悬浮液。在又一实施方式中，药物组合物提供为无菌干不溶性产品，以在使用前用运载体重构。在另外一个实施方式中，药物组合物提供为即用型无菌乳状液。

[0429] 本文提供的药物组合物可以配制成速释或调节释放剂型，包括延迟释放、持续释放、脉冲释放、控制释放、靶向释放和程序释放的形式。

[0430] 药物组合物可以配制成悬浮液、固体、半固体或触变性液体，以作为植入的储液库给药。在一个实施方式中，本文提供的药物组合物被分散在固体惰性基质中，其被外部聚合膜包裹，所述聚合膜不溶于体液中但允许药物组合物中的活性成分扩散。

[0431] 适合的惰性基质包括聚甲基丙烯酸甲酯、聚丁基丙烯酸甲酯、增塑或未增塑的聚氯乙烯、增塑的尼龙、增塑的聚对苯二甲酸乙二酯、天然橡胶、聚异戊二烯、聚异丁烯、聚丁二烯、聚乙烯、乙烯－醋酸乙烯共聚物、硅橡胶、聚二甲硅氧烷、碳酸硅共聚物、亲水性聚合物，如丙烯酸和甲基丙烯酸酯的水凝胶、胶原、交联聚乙烯醇和交联的部分水解的聚乙酸乙烯酯。

[0432] 适合的外部聚合膜包括聚乙烯、聚丙烯、乙烯／丙烯共聚物、乙烯／丙烯酸乙酯共聚物、乙烯／乙酸乙烯酯共聚物、硅橡胶、聚二甲基硅氧烷、氯丁橡胶、氯化聚乙烯、聚氯乙烯、具有乙酸乙烯酯、偏氯乙烯、乙烯和丙烯的氯乙烯共聚物、离聚物聚对苯二甲酸乙二酯、丁基橡胶表氯醇橡胶、乙烯／乙烯醇共聚物、乙烯／乙酸乙烯酯／乙烯醇三元共聚物，以及乙烯／乙烯氧乙醇聚合物。

[0433] 调节释放

[0434] 在其它实施方式中，本文提供的药物组合物可以配制成调节释放剂型。如本文所用，术语“调节释放”指这样的剂型：当通过相同的途径给药时其中活性成分（一种或多种）的释放速度或位置不同于速释剂型。调节释放剂型包括延迟释放、缓慢释放、延长释放、持续释放、脉冲释放、控制释放、加速释放和快速释放、靶向释放、程序释放和胃滞留剂型。调节释放剂型中的药物组合物可以使用本领域技术人员已知的各种调节释放装置和方法来制备，所述装置和方法包括，但不限于，基质控释装置、渗透性控释装置、多颗粒控释装置、离子交换树脂、肠溶衣、多层衣、微球、脂质体及其组合。活性成分（一种或多种）的释放速

度也可以通过改变活性成分（一种或多种）的颗粒大小和多晶型来调节。

[0435] 调节释放的实例包括，但不限于，下列美国专利中描述的那些：美国专利号3,845,770；3,916,899；3,536,809；3,598,123；4,008,719；5,674,533；5,059,595；5,591,767；5,120,548；5,073,543；5,639,476；5,354,556；5,639,480；5,733,566；5,739,108；5,891,474；5,922,356；5,972,891；5,980,945；5,993,855；6,045,830；6,087,324；6,113,943；6,197,350；6,248,363；6,264,970；6,267,981；6,376,461；6,419,961；6,589,548；6,613,358；以及6,699,500。

[0436] 基质控释装置

[0437] 在一些实施方式中，调节释放剂型中本文提供的药物组合物可以使用本领域技术人员已知的基质控释装置来制备（参见，Takada等，于“Encyclopedia of Controlled DrugDelivery，”Vol.2，Mathiowitz ed.，Wiley，1999）。

[0438] 在一个实施方式中，调节释放剂型中本文提供的药物组合物使用溶蚀性基质装置配制，其为水可膨胀的、溶蚀性或可溶性聚合物，包括合成的聚合物和天然出现的聚合物及衍生物，如多糖和蛋白质。

[0439] 用于形成溶蚀性基质的物质包括，但不限于，几丁质、壳聚糖、葡聚糖和支链淀粉；树胶琼脂、阿拉伯树胶、梧桐胶、槐豆胶、黄芪胶、交叉胶、茄替胶、瓜尔树胶、黄原胶和硬葡聚糖；淀粉，如糊精和麦芽糊精；亲水胶体，如果胶；磷脂，如卵磷脂；藻酸盐；藻酸丙二醇酯；凝胶；胶原；和纤维素，如乙基纤维素（EC）、甲基乙基纤维素（MEC）、羧甲基纤维素（CMC）、CMEC、羟乙基纤维素（HEC）、羟丙基纤维素（HPC）、乙酸纤维素酯（CA）、丙酸纤维素酯（CP）、丁酸纤维素酯（CB）、乙酸丁酸纤维素酯（CAB）、CAP、CAT、羟丙基甲基纤维素（HPMC）、HPMCP、HPMCAS、乙酸苯六甲酸羟丙基甲基纤维素酯（HPMCAT）以及乙基羟基乙基纤维素（EHEC）；聚乙烯吡咯烷酮；聚乙烯醇；聚醋酸乙烯酯；脂肪酸甘油酯；聚丙烯酰胺；聚丙烯酸；乙基丙烯酸或甲基丙烯酸的共聚物（**EUDRAGIT®**，Rohm America，Inc.，Piscataway，NJ）；聚（2-羟乙基-甲基丙烯酸酯）；聚交酯；L-谷氨酸和乙基-L-谷氨酸酯的共聚物；可降解的乳酸-羟基乙酸共聚物；聚-D-(-)-3-羟基丁酸；以及其它丙烯酸衍生物，如甲基丙烯酸丁酯、甲基丙烯酸甲酯、甲基丙烯酸乙酯、丙烯酸乙酯、（2-二甲基氨基乙基）甲基丙烯酸酯和氯化（三甲基氨基乙基）甲基丙烯酸酯的均聚物和共聚物。

[0440] 在进一步的实施方式中，药物组合物用非溶蚀性基质装置配制。活性成分（一种或多种）溶于或分散于惰性基质中以及一旦给药其主要通过扩散通过惰性基质而释放。适于用作非溶蚀性基质装置的物质包括，但不限于，不溶性塑料，如聚乙烯、聚丙烯、聚异戊二烯、聚异丁烯、聚丁二烯、聚甲基丙烯酸甲酯、聚甲基丙烯酸丁酯、氯化聚乙烯、聚氯乙烯、丙烯酸甲酯-甲基丙烯酸甲酯共聚物、乙烯-醋酸乙烯共聚物、乙烯/丙烯共聚物、乙烯/丙烯酸乙酯共聚物、具有乙酸乙烯酯、偏二氯乙烯、乙烯和丙烯的氯乙烯共聚物、聚对苯二甲酸乙二酯离聚物、丁基橡胶表氯醇橡胶、乙烯/乙烯醇共聚物、乙烯/乙酸乙烯酯/乙烯醇三元共聚物以及乙烯/乙烯氧基乙醇共聚物、聚氯乙烯、增塑的尼龙、增塑的聚对苯二甲酸乙二酯、天然橡胶、硅橡胶、聚二甲硅氧烷、碳酸硅共聚物以及；亲水聚合物，如乙基纤维素、醋酸纤维素、交聚维酮和交联的部分水解的聚醋酸乙烯酯；以及脂肪族化合物，如巴西棕榈蜡、微晶蜡和甘油三酯。

[0441] 在基质控释系统中，期望的释放动力学可以控制，例如，通过使用的聚合物类型、

聚合物粘性、聚合物和 / 或活性成分（一种或多种）的颗粒大小、活性成分（一种或多种）与聚合物的比率，以及组合物中其它赋形剂或载体。

[0442] 在其它实施方式中，调节释放剂型中本文提供的药物组合物通过本领域技术人员已知的方法来制备，包括直接压缩、干法或湿法制粒然后压缩、熔融法制粒然后压缩。

[0443] 2. 渗透性控释装置

[0444] 在一些实施方式中，调节释放剂型中本文提供的药物组合物可以使用渗透性控释装置制备，其包括一室系统、二室系统、不对称膜技术 (AMT) 以及挤压片芯系统 (ECS)。一般而言，这些装置具有至少两个组件 :(a) 包含活性成分（一种或多种）的芯 ;以及 (b) 具有至少一个释药孔的的半透膜，其包裹芯。半透膜控制水从应用的水环境至芯的流量，以便经挤压通过释药孔（一个或多个）引起药物释放。

[0445] 除活性成分（一种或多种）外，渗透性装置的芯任选包括渗透剂，其产生驱动力，用于将水从应用的水环境运输到装置的芯中。一种渗透剂水可膨胀亲水聚合物，其也被称为“渗透聚合物”和“水凝胶”，包括，但不限于，亲水乙烯基和丙烯酸聚合物、多糖，如藻酸钙、聚环氧乙烷 (PEO)、聚乙二醇 (PEG)、聚丙二醇 (PPG)、聚 (2- 羟乙基甲基丙烯酸酯）、聚（丙烯）酸、聚（甲基丙烯）酸、聚乙烯吡咯烷酮 (PVP)、交联 PVP、聚乙烯醇 (PVA)、PVA/PVP 共聚物、PVA/PVP 共聚物，其具有疏水单体如甲基丙烯酸甲酯和乙酸乙烯酯、含有大 PEO 嵌段的亲水聚氨酯、交联羧甲基纤维素钠、角叉胶、羟乙基纤维素 (HEC)、羟丙基纤维素 (HPC)、羟丙基甲基纤维素 (HPMC)、羧甲基纤维素 (CMC) 和羧乙基纤维素 (CEC)、藻酸钠、聚卡波非、凝胶、黄原胶和羧基乙酸淀粉钠。

[0446] 其它种类的渗透剂是酶原，其能够吸收水以影响透过周围包衣屏障的渗透压梯度。适合的酶原包括，但不限于，无机盐，如硫酸镁、氯化镁、氯化钙、氯化钠、氯化锂、硫酸钾、磷酸钾、碳酸钠、亚硫酸钠、硫酸锂、氯化钾和硫酸钠 ;糖，如右旋糖、果糖、葡萄糖、肌醇、乳糖、麦芽糖、甘露醇、棉子糖、山梨醇、蔗糖、海藻糖和木糖醇 ;有机酸，如抗坏血酸、苯甲酸、富马酸、柠檬酸、马来酸、癸二酸、山梨酸、己二酸、乙二胺四乙酸、谷氨酸、对甲苯磺酸、琥珀酸和酒石酸 ;尿素 ;以及其混合物。

[0447] 可以使用不同溶解速度的渗透剂，以影响活性成分（一种或多种）最初多快地从剂型输送。例如，无定形糖，如 Mannogeme EZ(SPI Pharma,Lewes,DE) 可以用于在前两个小时期间提供更快的输送，以迅速产生期望的治疗效果，并且逐渐地和不断地释放保持量，以在一段延长的时间内维持期望水平的治疗或预防效果。这种情况下，活性成分（一种或多种）以替代代谢或排泄的活性成分量的速度释放。

[0448] 芯也可以包括本文所描述的许多其它赋形剂和载体，以提高剂型的性能或促进稳定性或加工。

[0449] 用于形成半透膜的物质包括各种等级的丙烯酸树脂、乙烯基树脂、醚、聚酰胺、聚酯和纤维素衍生物，其在生理上相应的 pH 下是水可渗透的和水不溶解的，或通过化学变化如交联容易变为水不溶性的。用于形成包衣的适合的聚合物的实例包括增塑的、未增塑的以及强化的乙酸纤维素 (CA)、二乙酸纤维素、三乙酸纤维素、丙烯酸 CA、硝酸纤维素、丁酸乙酸酯纤维素 (CAB)、氨基甲酸乙酯 CA、CAP、氨基甲酸甲酯 CA、琥珀酸 CA、偏苯三酸乙酸酯纤维素 (CAT)、乙酸二甲基氨基酯 CA、碳酸乙酯 CA、氯代乙酸 CA、草酸乙酯 CA、磺酸甲酯 CA、磺酸丁酯 CA、磺酸对甲苯酯 CA、乙酸盐琼脂、三乙酸直链淀粉、乙酸 β 葡聚糖、三乙酸 β 葡

聚糖、二甲基乙酸乙醛酯、槐豆胶的三乙酸酯、羟基化乙烯 - 乙酸乙烯酯、EC、PEG、PPG、PEG/PPG 共聚物、PVP、HEC、HPC、CMC、CMEC、HPMC、HPMCP、HPMCAS、HPMCAT、聚（丙烯）酸和酯以及聚 -（甲基丙烯）酸和酯以及其共聚物、淀粉、葡聚糖、糊精、壳聚糖、胶原、凝胶、聚烯烃、聚醚、聚砜、聚砜醚、聚苯乙烯、聚乙烯卤化物、聚乙烯酯和醚、天然蜡和合成蜡。

[0450] 半透膜也可以是疏水微孔膜，其中孔基本上被气体填充并且不被水介质湿润但对水汽是可渗透的，如美国专利号 5,798,119 中所公开。这些疏水但水汽可渗透膜通常由疏水聚合物组成，如聚烯烃、聚乙烯、聚丙烯、聚四氟乙烯、聚丙烯酸衍生物、聚醚、聚砜、聚醚砜、聚苯乙烯、聚乙烯卤化物、聚偏氟乙稀、聚乙烯酯和醚、天然蜡和合成蜡。

[0451] 半透膜上的释药孔（一个或多个）可以通过机械或激光钻孔在包衣后形成。释药孔（一个或多个）也可以通过水溶性物质塞的溶蚀或通过比芯中压痕薄的膜部分的破裂而在原位置形成。另外，释药孔可以在包衣过程中形成，如在美国专利号 5,612,059 和 5,698,220 中公开类型的不对称膜包衣的情况下。

[0452] 释放的活性成分（一种或多种）总量和释放速度可以通过半透膜的厚度和孔率、芯的组成以及释药孔的数量、大小和位置来大致调节。

[0453] 渗透性控释剂型中药物组合物可以进一步包含本文所描述的另外的传统赋形剂或载体，以促进制剂的性能或加工。

[0454] 渗透性控释剂型可以根据本领域技术人员已知的传统方法和技术制备（参见，Remington :The Science and Practice of Pharmacy, supra ;Santus and Baker, J.ControlledRelease 1995,35,1-21 ;Verma 等，Drug Development and Industrial Pharmacy 2000,26,695-708 ;Verma 等，J.Controlled Release 2002,79,7-27）。

[0455] 在其它实施方式中，本文提供的药物组合物被配制为 AMT 控释剂型，其包括包裹芯的不对称渗透膜，所述芯包含活性成分（一种或多种）和其它药学上可接受的赋形剂或载体。参见，美国专利号 5,612,059 和 WO 2002/17918。AMT 控释剂型可以根据本领域技术人员已知的传统方法和技术制备，包括直接压缩、干法制粒、湿法制粒和浸涂方法。

[0456] 在某些实施方式中，本文提供的药物组合物配制成 ESC 控释剂型，其包括包裹芯的渗透膜，所述芯包含活性成分（一种或多种）、羟基乙基纤维素和其它药学上可接受的赋形剂或载体。

[0457] 3. 多颗粒控释装置

[0458] 在一些实施方式中，调节释放剂型中本文提供的药物组合物可以使用多颗粒控释装置制备，所述多颗粒控释装置包括多种颗粒、微粒或微球，直径范围为约 10μm 至约 3mm、约 50μm 至约 2.5mm 或约 100μm 至约 1mm。这些多颗粒可以通过本领域技术人员已知的方法制备，包括湿法和干法制粒、挤压 / 滚圆法、碾压法、熔融 - 凝结法和喷涂种芯法。参见例如，Multiparticulate Oral Drug Delivery ;Marcel Dekker :1994 ;以及 Pharmaceutical Pelletization Technology ;Marcel Dekker :1989。

[0459] 本文所描述的其它赋形剂或载体可以与药物组合物掺合，以有助于加工和形成多颗粒。形成的颗粒本身可以构成多颗粒装置或可以被多种膜形成物质涂敷，如肠溶性聚合物、水可膨胀和水溶性聚合物。多颗粒可以进一步加工成胶囊或片剂。

[0460] 4. 靶向输送

[0461] 在一些实施方式中，本文提供的药物组合物也可以配制成靶向被治疗对象身体的

具体组织、受体或其它区域，其包括基于脂质体、重新包封的红细胞和抗体的输送系统。实例包括，但不限于，美国专利号 6,316,652 ;6,274,552 ;6,271,359 ;6,253,872 ;6,139,865 ;6,131,570 ;6,120,751 ;6,071,495 ;6,060,082 ;6,048,736 ;6,039,975 ;6,004,534 ;5,985,307 ;5,972,366 ;5,900,252 ;5,840,674 ;5,759,542 ；以及 5,709,874，所有这些专利全部并入本文。

[0462] 速释

[0463] 在一些实施方式中，速释剂型中本文提供的药物组合物能够释放不低于 75％的治疗活性成分或组合和 / 或符合对包含在片芯中的具体治疗剂或组合的速释片剂的崩解或溶解要求，如 USP XXII，1990（美国药典）中所述。

[0464] 局部给药

[0465] 在其它实施方式中，本文提供的药物组合物可以局部给药于皮肤、孔或粘膜。如本文所用，局部给药包括皮肤（内）、结膜、角膜内、眼内、眼部、耳部、经皮、鼻部、阴道、尿道、呼吸和直肠给药。

[0466] 在进一步的实施方式中，本文提供的药物组合物可以配制成适于局部给药的任意剂型，以获得局部或系统效应，其包括乳状液、溶液、悬浮液、乳膏、凝胶、水凝胶、软膏、隔离剂、调味品、酏剂、洗剂、悬浮液、酊剂、膏、泡沫、薄膜、气雾剂、冲洗剂、喷雾剂、栓剂、绑带、皮肤贴。本文提供的药物组合物的局部制剂也可以包括脂质体、胶束、微球、纳米体系及其混合物。

[0467] 适用于本文提供的局部制剂的药学上可接受的载体和赋形剂包括，但不限于，水性运载体、水溶性运载、非水性运载体、针对微生物生长的抗菌剂或防腐剂、稳定剂、增溶剂、等渗剂、缓冲剂、抗氧化剂、局部麻醉剂、悬浮和分散剂、湿润或乳化剂、络合剂、掩蔽或螯合剂、渗透增强剂、防冻剂、冻干保护剂、增稠剂以及惰性气体。

[0468] 在一些实施方式中，药物组合物也可以通过电穿孔、离子电渗疗法、超声透入疗法、sonophoresis 和微针注射或无针注射，如 POWDERJECT™(Chiron Corp.，Emeryville，CA) 和 BIOJECT™(Bioject Medical Technologies Inc.，Tualatin，OR) 局部给药。

[0469] 本文提供的药物组合物可以以软膏、乳膏和凝胶的形式提供。适合的软膏运载体包括油质或烃运载体，包括如猪脂、苯甲酸化的猪脂、橄榄油、棉籽油及其它油、白凡士林；可乳化或吸收运载体，如亲水凡士林、硫酸羟基硬脂和无水羊毛脂；水可去除运载体，如亲水软膏；水溶性软膏运载体，包括不同分子量的聚乙二醇；乳状液运载体，油包水 (W/O) 乳状液或水包油 (O/W) 乳状液，包括十六烷醇、单硬脂酸甘油酯、羊毛脂和硬脂酸（参见，Remington：The Science and Practice of Pharmacy，supra）。这些运载体是软化剂但一般需要加入抗氧化剂和防腐剂。

[0470] 适合的乳膏基体可以是水包油或油包水。乳膏运载体可以是水可洗涤的，并且包含油相、乳化剂和水相。油相也成为“内部”相，其一般由凡士林和脂肪醇如十六烷基醇或十八烷基醇组成。水相通常——尽管不是必需的——体积超过油相，并且一般包含保湿剂。乳膏制剂中的乳化剂可以是非离子、阴离子、阳离子或两性表面活性剂。

[0471] 凝胶是半固体悬浮液型体系。单相凝胶包含基本上均匀分布在整个液体载体中的有机大分子。适合的胶凝剂包括交联丙烯酸聚合物，如 carbomers、羧基聚亚烷基、**Carbopol®**；亲水聚合物，如聚乙烯氧化物、聚氧乙烯 - 聚氧丙烯共聚物和聚乙烯醇；纤维素

聚合物，如羟丙基纤维素、羟乙基纤维素、羟丙基甲基纤维素、邻苯二甲酸羟丙基甲基纤维素和甲基纤维素；树胶，如黄芪胶和黄原胶；藻酸钠；以及明胶。为了制备均匀的凝胶，可以加入分散剂如醇或甘油，或可以通过研磨、机械混合和/或搅拌来分散胶凝剂。

[0472] 本文提供的药物组合物可以以下列形式经直肠、尿道、阴道或阴道周围给药：塞剂、阴道栓剂、栓剂、敷剂或糊剂、糊状物、粉末、敷料、乳膏、膏药、避孕品、软膏、溶液、乳状液、悬浮液、棉塞、凝胶、泡沫、喷雾灌肠剂。这些剂型可以使用上述Remington：The Science and Practice of Pharmacy中描述的传统方法制造。

[0473] 直肠、尿道和阴道栓剂是固体，以用于插入体孔中，其在平常的温度下时固体但在体温下融化或软化，以便将活性成分（一种或多种）释放到孔中。用于直肠和阴道栓剂的药学上可接受的载体包括基体或运载体，如硬化剂，其产生在体温附近的熔点——当与本文提供的药物组合物配制时；以及本文所述的抗氧化剂，包括亚硫酸盐和焦亚硫酸钠。适合的运载体包括，但不限于，可可油(cocoa butter/theobroma oil)、甘油-明胶、聚乙二醇(carbowax/polyoxyethylene glycol)、鲸蜡、石蜡、白蜡和黄蜡以及脂肪酸甘油单酯、甘油二酯和甘油三酯的适合的混合物、水凝胶，如聚乙烯醇、甲基丙烯酸羟乙酯、聚丙烯酸；甘油化明胶。可以使用各种运载体的组合。直肠和阴道栓剂可以通过压缩法或模塑法制备。直肠和阴道栓剂的典型重量是约2至约3g。

[0474] 本文提供的药物组合物可以以下列形式经眼部给药：溶液、悬浮液、药膏、乳状液、凝胶形成溶液、形成溶液的粉末、凝胶、眼睛插入物以及植入物。

[0475] 本文提供的药物组合物可以鼻内给药或通过吸入到呼吸道给药。药物组合物可以以气雾剂或输送溶液的形式提供，其使用加压容器、泵、喷雾、喷雾器如使用电水动力学以产生细薄雾的喷雾器或雾化器，单独或与适合的推进剂组合，如1,1,1,2-四氟乙烷或1,1,1,2,3,3,3-七氟丙烷。药物组合物也可以作为用于吹入的干粉末提供，单独或结合惰性载体，如乳糖或磷脂；以及滴鼻剂。对于鼻内应用，粉末可以包含生物粘合剂，如壳聚糖或环糊精。

[0476] 用于加压容器、泵、喷雾、喷雾器或雾化器的溶液或悬浮液可以配制成包含乙醇、水乙醇或适合的可选择药剂，以分散、稳定或延迟释放本文提供的活性成分、作为溶剂的推进剂；和/或表面活性剂，如失水山梨糖醇三油酸、油酸或低聚乳酸。

[0477] 在另一个实施方式中，本文提供的药物组合物可以微粉化成适于吸入输送的大小，如约50微米或更小或约10微米或更小。这些大小的颗粒可以使用本领域技术人员已知的粉碎方法制备，如螺旋喷射研磨、流化床喷射研磨、用以形成纳米颗粒的超临界流体处理、高压均化或喷雾干燥。

[0478] 用于吸入器或吹入器的胶囊、泡和药筒可以配制成包含本文提供的药物组合物的粉末混合物；适合的粉末基体，如乳糖或淀粉；以及性能调节剂，如1-亮氨酸、甘露醇或硬脂酸镁。乳糖可以是无水的或一水合物的形式。其它适合的赋形剂包括右旋糖、葡萄糖、麦芽糖、山梨醇、木糖醇、果糖、蔗糖和海藻糖。用于吸入/鼻内给药的本文提供的药物组合物可以进一步包含适合的香料，如薄荷醇或左旋薄荷醇，或甜味剂，如糖精或糖精钠。

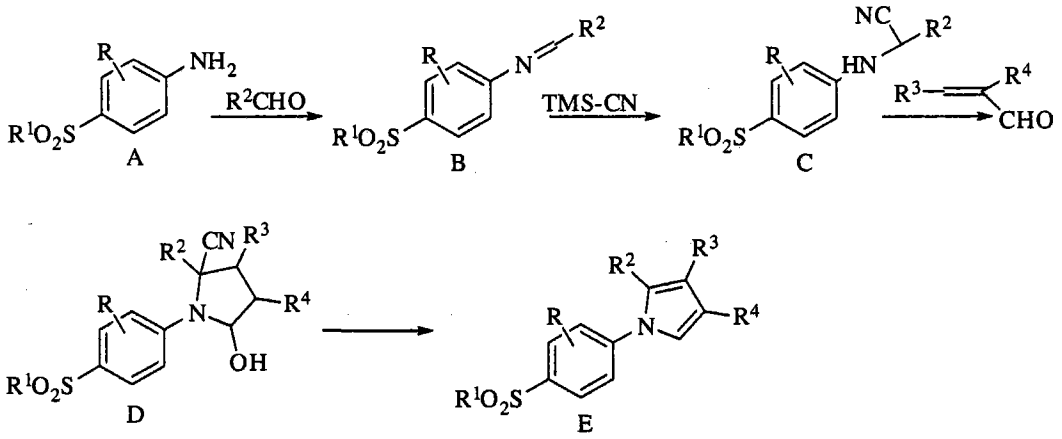
[0479] 在一个实施方式中，用于局部给药的本文提供的药物组合物可以配制成速释或调节释放，包括延迟释放、持续释放、脉冲释放、控制释放、靶向释放和程序释放。

[0480] 实施例

[0481] 实施例 1

[0482] 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯的合成

[0483]



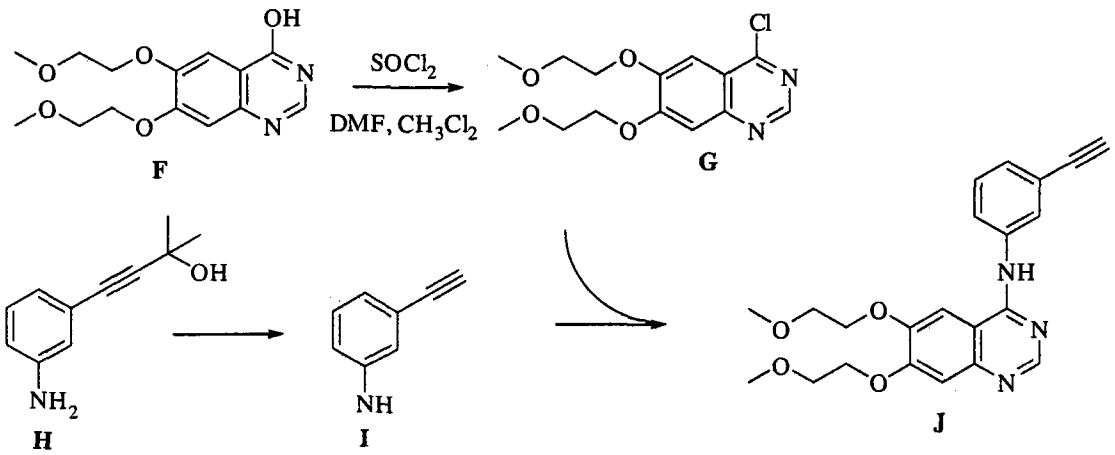
[0484] 方案 1.

[0485] 取代苯甲醛通过与苯胺化合物 A 在 5℃至 200℃之间的温度下于惰性溶剂中反应进行脱水缩合,以得到醛亚胺化合物 B。然后将氰化三甲基甲硅烷与醛亚胺化合物 B 在路易斯酸存在的情况下反应,以提供苯胺腈 C。然后将 α-β- 未取代醛与苯胺腈 C 反应,以提供化合物 D,其然后在 Ann 描述的方法的改良方法中在碱性条件下进行脱水和脱氢氰化。Chem. 589,176(1954)。

[0486] 实施例 2

[0487] 埃罗替尼的合成

[0488]



[0489] 方案 2.

[0490] 在碱金属和溶剂的悬浮液中加热原料化合物 H,然后加热以得到化合物 I。将原料醇 F 放置在亚硫酰氯、二氯甲烷和二甲基甲酰胺的溶剂混合物中,以得到氯化物 G。氯化物 G 然后与化合物 I 偶联,得到埃罗替尼 J。

[0491] 实施例 3

[0492] 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯的药物动力学和代谢

[0493] 在所有考查的物种中 (小鼠、大鼠、狗和猴) 中,口服给药的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯被快速吸收。在 5mg/kg 的剂量后 1 至 3 小时,达到血浆浓度峰值。消除半衰期 ($t_{1/2}$) 在啮齿动物和狗中是 4-5 小时,在猴中是约 2 小时。口服

利用度在在啮齿动物中最大，在狗和猴中降低（分别是 59 和 34％）。在人对象中的药物动力学证实，口服给予 2mg 至 800mg 剂量的线性剂量暴露关系。在人对象中的半衰期是 15-18 小时。

[0494] 实施例 4

[0495] 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯的毒理学

[0496] 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯在小鼠、大鼠、狗和猴中的毒理学评价揭示了这样期望的发现：与环加氧酶的抑制相关并且与对其它 COX-2 选择性抑制剂的动物安全性观察一致。在单剂量研究中，2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯的最小致死量在大鼠中为 600mg/kg，在狗中＞ 2000mg/kg。在人对象中进行的内窥镜研究证实，与安慰剂相比胃和十二指肠毒性没有增加。

[0497] 实施例 5

[0498] 生物学评价

[0499] COX-2 选择性抑制剂

[0500] HT-29 模型：

[0501] 在左爪中对小鼠进行皮下注射（悬浮在 30％ Matrigel 中的 1×10^6 肿瘤细胞）并且使用器官充满度测量器 (phlethysmometer) 评价肿瘤体积，30-60 天，一周两次。将人结肠癌细胞 (HT-29) 植入裸鼠，产生在 30-50 天达到 0.6-2ml 的肿瘤。在 24h 方案中在实验期间抽取血液两次，以通过 AUC 分析评定血浆浓度和总暴露。将数据表示成平均数 +/-SEM。使用 Student′ s 和 Mann-Whitney 测试方法，通过 InStat 软件包评定平均数之间的差异。

[0502] A. 在饮食中包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯与埃罗替尼组合的组合物存在或不存在的情况下，于第 5、7 和 9 天用 50mg/kg 剂量的细胞毒素 (cytoxin) 经腹膜内处理注射有 HT-29 癌细胞的小鼠。通过测量肿瘤体积来确定两种药剂的功效。这些研究结果可以证实，在饮食中给予患有肿瘤小鼠的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯与埃罗替尼组合的组合物，可以延迟肿瘤的生长和转移——当作为单一疗法给药时。

[0503] B. 在第二个测试中，用小鼠 HT-29 癌细胞注射小鼠，然后在第 12 至 15 天用 5-FU 处理。在饮食中包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯与埃罗替尼组合的组合物存在或不存在的情况下，于第 12、13、14 和 15 天用 50mg/kg 剂量的 5-FU 经腹膜内处理注射有 HT-29 癌细胞的小鼠。通过测量肿瘤体积来确定两种药剂的功效。使用组合物的处理可以将肿瘤体积减少多达 70％。在相同的测试中，5-FU 将肿瘤体积减少 61％。进一步，组合物和 5-FU 可以将肿瘤体积减少 83％。

[0504] C. 在第三个测试中，在饮食中包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯与埃罗替尼组合的组合物 (1600ppm) 和伐地考昔 (160ppm) 存在或不存在的情况下，于第 14 至 17 天以 50mg/kg 剂量用 5-FU 经腹膜内处理注射有 HT-29 结肠癌细胞的小鼠。通过测量肿瘤体积来确定两种药剂的功效。用 5-FU 处理可以导致肿瘤体积减小 35％。用组合物和伐地考昔处理可以分别将肿瘤体积减小 52％和 69％。在相同的测试中，5-FU 和组合物组合可以将肿瘤体积减小 72％，而 5-FU 和伐地考昔组合可以将肿瘤体积减小 74％。

[0505] 实施例 6

[0506] EGFR 激酶活性的体外抑制

[0507] 本文描述的组合抑制受体酪氨酸激酶的体外活性可以通过下列方法测定。本公开的组合的体外活性可以通过测试化合物相对于对照对外源性底物（例如，Lys_3-Gastrin 或 polyGluTyr(4 ： 1) 任意共聚物 (Posner 等，J.Biol.Chem.，1992，267(29)，20638-472)) 磷酸化抑制的量来测定——就表皮生长因子受体激酶对酪氨酸磷酸化而言。亲合力纯化的、可溶性 EGF 受体 (96ng) 根据 G.N.Gill，W.Weber，Methods in Enzymology，1987，146，82-8 中的方法从 A431 细胞 (American Type Culture Collection，Rockville，Md.) 获得并且将其在具有 EGF(2μg/ml) 的离心管中在室温下预温育 20-30 分钟，EGF 于磷酸化缓冲液 + 钒酸盐 (PBV：50mM HEPES，pH 7.4；125mM NaCl；24mM $MgCl_2$；100μM 正钒酸钠）中，总体积为 10μl。将包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯与埃罗替尼组合的组合物，溶于二甲亚砜 (DMSO) 中，在 PBV 中稀释，以及将 10μl 与 EGF 受体 /EGF 混合液进行混合，并且在 30℃下温育 10-30 分钟。通过加入 20μl ^{33}P-ATP/ 底物混合液 (120μM Lys_3-Gastrin（以编码氨基酸的单字母序列，KKKGPWLEEEEEAYGWLDF)、50mM Hepes pH 7.4、40μM ATP、2pCi. γ.-[^{33}P]-ATP) 至 EGFr/EGF 混合液来启动磷酸化反应，并且在室温下温育 20 分钟。通过加入 10μl 停止溶液 (0.5M EDTA，pH 8；2mM ATP) 和 6μl 2N HCl 来停止反应。将试管在 14,000RPM、4℃下离心 10 分钟。从每个试管吸取 35μl 上清液至 Whatman P81 纸的 2.5cm 圆圈，在 5％乙酸中大量洗涤四次，每次洗涤 1 升，然后空气干燥。这导致洗涤时底物结合至所述纸，丧失游离 ATP。掺入的 [^{33}P] 通过液体闪烁计数测量。从所有值中减去作为背景的缺乏底物（例如，lys_3- 胃泌素）的掺入，并且相对于没有组合物存在的对照计算抑制百分比。这些测验——用一系列剂量的测试组合施行——可以测定 EGFR 激酶活性体外抑制的大约 IC_{50} 值。测定本文提供的组合活性的其它方法描述在美国专利号 5,747,498 中，其公开内容并入本文。

[0508] 实施例 7

[0509] 药物组合物和剂型

[0510] 包含药物赋形剂和载体以及包含埃罗替尼 (A) 和 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯 (B) 组合的药物组合物的剂量配制物包括：

[0511]

组合	每片中 A 的量 (mg)	每片中 B 的量 (mg)
A/B	25	1、5、10、25、50、100、200、300、400、600、800、1000、1200
A/B	100	1、5、10、25、50、100、200、300、400、600、800、1000、1200
A/B	150	1、5、10、25、50、100、200、300、400、600、800、1000、1200
A/B	200	1、5、10、25、50、100、200、300、400、600、800、1000、1200

组合	每片中 A 的量 (mg)	每片中 B 的量 (mg)
A/B	300	1、5、10、25、50、100、200、300、400、600、800、1000、1200
A/B	450	1、5、10、25、50、100、200、300、400、600、800、1000、1200

[0512]

[0513] 本文描述的剂量配制物，包括上述表中所述的配制物，可以这样给药：以单一固定剂量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼的组合给药，或分别给予单一剂量的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和单一剂量的埃罗替尼。

[0514] 实施例 8

[0515] 生物学评价

[0516] COX-2 选择性抑制剂

[0517] A431 外阴磷状细胞癌模型

[0518] 在左爪中对小鼠进行皮下注射（悬浮在 30％ Matrigel 的 1×10^6 肿瘤细胞）并且使用器官充满度测量器 (phlethysmometer) 评价肿瘤体积，30-60 天，一周两次。将外阴磷状细胞癌 (A431) 植入裸鼠，产生在 30-50 天达到 0.6-2ml 的肿瘤。在 24h 方案中在实验期间抽取血液两次，以通过 AUC 分析评定血浆浓度和总暴露。将数据表示成平均数 +/-SEM。使用 Student′ s 和 Mann-Whitney 测试方法，通过 InStat 软件包评定平均数之间的差异。

[0519] 用包含下列之一的组合物处理注射有 A431 癌细胞的小鼠：1. 埃罗替尼 (75 或 100mg/kg)；2. 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯 (3、10、30 或 100mg/kg)；3. 塞来昔布 (10、30、100 或 300mg/kg)；4. 埃罗替尼 (75mg/kg) 和 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯 (3、10 或 30mg/kg)；4. 埃罗替尼 (75mg/kg) 和塞来昔布 (10、30 或 100mg/kg)。通过测量肿瘤体积来确定功效。这些研究的结果，显示在图 3 中，证实了：给予患有肿瘤的小鼠包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯与埃罗替尼组合的组合物与单独埃罗替尼相比将肿瘤生长延迟 55％。埃罗替尼和塞来昔布的组合证实，肿瘤生长的延迟仅为 36％。

[0520] 实施例 9

[0521] 在转移性或复发性非小细胞肺癌 (NSCLC) 患者中 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯联合埃罗替尼的研究

[0522] 方法：患有复发性或转移性 NSCLC 的对象用埃罗替尼 (150mg/ 天 PO) 和剂量递增的 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯 (100-1200mg/ 天 PO) 处理。评价 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼的药物动力学。

[0523] 结果：处理了 19 个对象：3 个在 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯 100mg 下；4 个在 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯 200mg 下；12 个在 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯 400mg 下。选择的最

佳生物剂量是 400mg。2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯药物动力学揭示了，中位数 $T_{最大值}$ 为 2 小时 (范围 1.5-4)，平均数 (SD)T1/2 值为 11.8(5.3) 小时，$C_{最大值}$ 为 313.0(99.6)ng/ml 以及 AUC(0-t) 为 2816(1204)ngh/ml。

[0524] 结果显示，2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼在该研究中被安全地给予。

[0525] 实施例 10

[0526] 在转移性或复发性非小细胞肺癌 (NSCLC) 患者中 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯联合埃罗替尼的研究

[0527] 该研究比较 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼与安慰剂和埃罗替尼的抗 - 肿瘤功效，如通过时间与疾病进展所测得的。实验组由 400mg/ 天 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯联合 150mg/ 天埃罗替尼组成。安慰剂组由 400mg/ 天安慰剂片联合 150mg/ 天埃罗替尼组成。

[0528] 实施例 11

[0529] 在晚期胰腺癌患者中 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯联合埃罗替尼和吉西他滨的研究

[0530] 该研究比较 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼 / 吉西他滨与安慰剂和埃罗替尼 / 吉西他滨的抗肿瘤功效，如通过时间与疾病进展所测得的。实验组组成为 :400mg/ 天 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯联合 100mg/ 天埃罗替尼，以及以 1000mg/m^2 剂量静脉内输注给予吉西他滨，共达 7 周，每周一次，每次 30 分钟，接着休息一周，然后每周输注一次，进行三周，4 周一个循环。安慰剂组组成为 :400mg/ 天安慰剂片联合 100mg/ 天埃罗替尼，以及以 1000mg/m^2 剂量静脉内输注给予吉西他滨，共达 7 周，每周一次，每次 30 分钟，接着休息一周，然后每周输注一次，进行三周，4 周一个循环。

[0531] 实施例 12

[0532] 非小细胞肺癌的治疗

[0533] 考虑治疗患有非小细胞肺癌对象的方法，其包括给予对象治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼或它们各自药学上可接受的盐、溶剂合物或前体药物的组合。使用约 100、约 200、约 300、约 400、约 600、约 800 和约 1000 以及约 1200mg 等分的 2-(4- 乙氧基苯基)-4- 甲基 1-(4- 氨磺酰苯基)- 吡咯和约 150mg 等分的埃罗替尼的组合的单一剂型治疗对象。也考虑，通过分别给予约 200、约 400 和约 800mg 等分的 2-(4- 乙氧基苯基)-4- 甲基 1-(4- 氨磺酰苯基)- 吡咯和约 150mg 等分的埃罗替尼治疗对象。该组合的最大耐受剂量将是该研究的终点。

[0534] 实施例 13

[0535] 乳腺癌的治疗

[0536] 考虑治疗患有乳腺癌对象的方法，其包含给予对象治疗有效量的包含 2-(4- 乙氧基苯基)-4- 甲基 -1-(4- 氨磺酰苯基)- 吡咯和埃罗替尼或它们各自药学上可接受的盐、溶剂合物或前体药物的组合。期望用埃罗替尼和 2-(4- 乙氧基苯基)-4- 甲基 1-(4- 氨磺酰苯基)- 吡咯组合治疗，以达到与作为单一药剂给予的埃罗替尼相比增加的肿瘤抑制。

[0537] 实施例 14

[0538] 结肠直肠癌的治疗

[0539] 考虑治疗患有结肠直肠癌对象的方法，其包括给予对象治疗有效量的包含2-(4-乙氧基苯基)-4-甲基-1-(4-氨磺酰苯基)-吡咯和埃罗替尼或它们各自药学上可接受的盐、溶剂合物或前体药物的组合。期望用埃罗替尼和2-(4-乙氧基苯基)-4-甲基1-(4-氨磺酰苯基)-吡咯组合治疗，以达到与作为单一药剂给予的2-(4-乙氧基苯基)-4-甲基-1-(4-氨磺酰苯基)-吡咯或埃罗替尼相比明显增加的肿瘤抑制。

[0540] 实施例15

[0541] 神经胶质瘤的治疗

[0542] 考虑治疗患有神经胶质瘤对象的方法，其包括给予对象治疗有效量的包含2-(4-乙氧基苯基)-4-甲基-1-(4-氨磺酰苯基)-吡咯和埃罗替尼或它们各自药学上可接受的盐、溶剂合物或前体药物的组合。使用约1、约5、约10、约25、约50、约100、约200、约300、约400、约600、约800、约1000、和约1200mg等分的2-(4-乙氧基苯基)-4-甲基1-(4-氨磺酰苯基)-吡咯和约25mg等分的埃罗替尼组合的单一剂型治疗对象。也考虑，通过分别给予约1、约5、约10、约25、约50、约100、约200、约300、约400、约600、约800、约1000和约1200mg等分的2-(4-乙氧基苯基)-4-甲基-1-(4-氨磺酰苯基)-吡咯和约100、150、200、300或450mg等分的埃罗替尼来治疗对象。治疗也在2^{nd}替莫唑胺失败的对象中给予。

[0543] 实施例16

[0544] 头颈癌的治疗

[0545] 考虑治疗患有头颈癌对象的方法，其包括给予对象治疗有效量的包含2-(4-乙氧基苯基)-4-甲基1-(4-氨磺酰苯基)-吡咯和埃罗替尼或它们各自药学上可接受的盐、溶剂合物或前体药物的组合。使用约1、约5、约10、约25、约50、约100、约200、约300、约400、约600、约800、约1000和约1200mg等分的2-(4-乙氧基苯基)-4-甲基1-(4-氨磺酰苯基)-吡咯和约25mg等分的埃罗替尼组合的单一剂型来治疗对象。也考虑，通过分别给予约1、约5、约10、约25、约50、约100、约200、约300、约400、约600、约800、约1000和约1200mg等分的2-(4-乙氧基苯基)-4-甲基1-(4-氨磺酰苯基)-吡咯和约100、150、200、300或450mg等分的埃罗替尼来治疗对象。治疗也将结合一种或一种或更多种化学治疗剂(例如，紫杉醇[Taxol®]、多烯紫杉醇[Taxotere®]、吉西他滨[Gemzar®]、阿霉素[Doxil®])给予，其可以进一步与已确立的化学治疗剂(例如，氨甲蝶呤[Trexall®、Methotrex®])联合。在另一个实施方式中，治疗本发明所述头颈癌的疗法采用治疗有效量的包含2-(4-乙氧基苯基)-4-甲基-1-(4-氨磺酰苯基)-吡咯和埃罗替尼组合的组合物以及Erbitux®的组合。

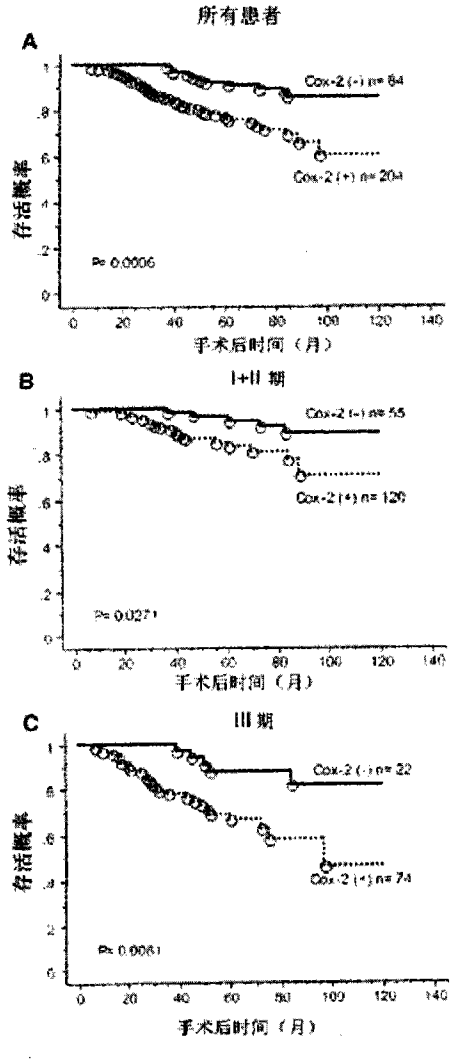


图 1. 与结肠直肠癌中存活相关的表达水平。显示了具有 Cox-2 阴性和 Cox-2 阳性患者的 10 年总存活曲线，对于整个组，P = 0.0006(A)，以及对于患有 I/II 期疾病的患者，P = 0.0271(B)，或对于患有 III 期疾病的患者，P = 0.0081(C).

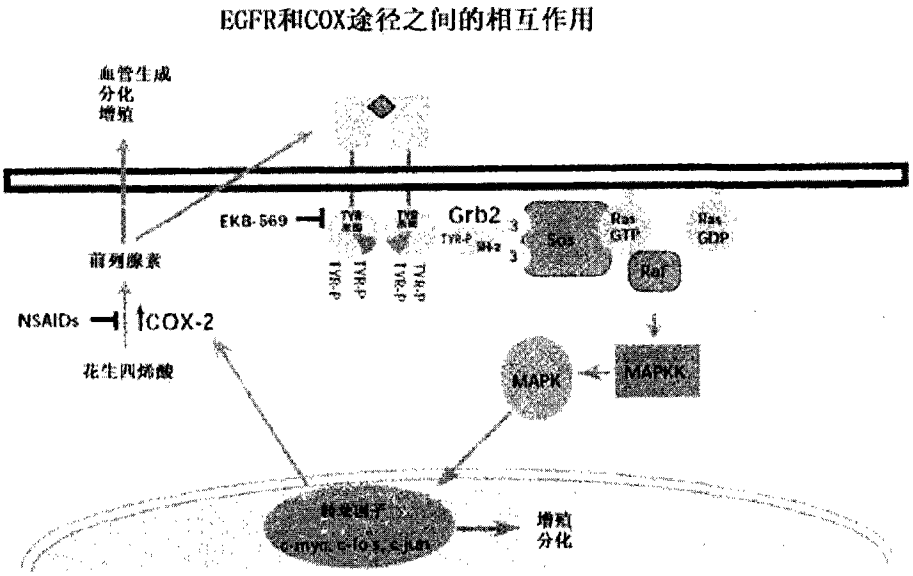


图 2. EGFR 和 COX 途径之间的相互作用

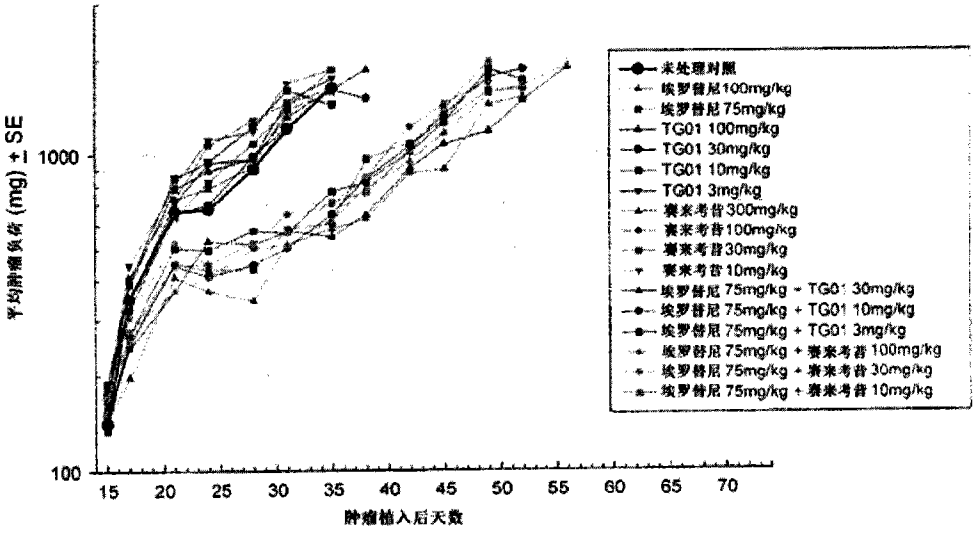


图 3. A431 外阴磷状细胞癌异体移植研究

METHODS AND COMPOSITIONS FOR THE TREATMENT OF CANCER, TUMORS, AND TUMOR-RELATED DISORDERS

Abstract

Described herein are compositions and methods for using these compositions in the treatment of cancer, tumors, and tumor-related disorders in a subject.

治疗癌症、肿瘤和肿瘤相关性疾病的方法和组合物

摘要

本文描述了组合物以及使用这些组合物在对象中治疗癌症、肿瘤和肿瘤相关性疾病的方法。