CANCER TREATMENT METHOD

BACKGROUND OF THE INVENTION

The present invention relates to a method of treating cancer in a mammal by administration of 4-quinazolinamines in combination with other anti-neoplastic compounds. In particular, the method relates to methods of treating cancers by administration of a combination of N-{3-chloro-4-[(3-fluorobenzyl) oxy]phenyl}-6-[5-({[2-(methanesulphonyl) ethyl]amino} methyl)-2-furyl]-4-quinazolinamine and salts and solvates thereof along with additional anti-neoplastic compounds.

Effective chemotherapy for cancer treatment is a continuing goal in the oncology field. Generally, cancer results from the deregulation of the normal processes that control cell division, differentiation and apoptotic cell death. Apoptosis (programmed cell death) plays essential roles in embryonic development and pathogenesis of various diseases, such as degenerative neuronal diseases, cardiovascular diseases and cancer. One of the most commonly studied pathways, which involves kinase regulation of apoptosis, is cellular signaling from growth factor receptors at the cell surface to the nucleus (Crews and Erikson, Cell, 74:215-17, 1993). In particular, cellular signalling from the growth factor receptors of the erbB family.

There is significant interaction among the erbB family that regulates the cellular effects mediated by these receptors. Six different ligands that bind to EGFR include EGF, transforming growth factor, amphiregulin, heparin binding EGF, betacellulin and epiregulin (Alroy & Yarden, FEBS Letters, 410:83-86, 1997; Burden & Yarden, Neuron, 18: 847-855, 1997; Klapper et al., ProcNatlAcadSci, 4994-5000, 1999). Herugulins, another class of ligands, bind directly to HER3 and/or HER4 (Holmes et al., Science, 256:1205, 1992; Klapper et al., 1997, Oncogene, 14:2099-2109; Peles et al., Cell, 69:205, 1992). Binding of specific ligands induces homo- or heterodimerization of the receptors within members of the erbB family (Carraway & Cantley, Cell, 78:5-8, 1994; Lemmon & Schlessinger, TrendsBiochemSci, 19:459-463, 1994). In contrast with the other erbB receptor members, a soluble ligand has not yet been identified for HER2, which seems to be transactivated following heterodimerization. The heterodimerization of the erbB-2 receptor with the EGFR,

HER3, and HER4 is preferred to homodimerization (Klapper et al., 1999; Klapper et al., 1997). Receptor dimerization results in binding of ATP to the receptor's catalytic site, activation of the receptor's tyrosine kinase, and autophosphorylation on C-terminal tyrosine residues. The phosphorylated tyrosine residues then serve as docking sites for proteins such as Grb2, Shc, and phospholipase C, that, in turn, activate downstream signaling pathways, including the Ras/MEK/Erk and the PI3K/Akt pathways, which regulate transcription factors and other proteins involved in biological responses such as proliferation, cell motility, angiogenesis, cell survival, and differentiation (Alroy & Yarden, 1997; Burgering & Coffer, Nature, 376:599-602, 1995; Chan et al., AnnRevBiochem, 68:965-1014,1999; Lewis et al., AdvCanRes, 74:49-139,1998; Liu et al., Genes and Dev, 13:786-791, 1999; Muthuswamy et al., Mol&CellBio, 19,10:6845-6857,1999; Riese & Stern, Bioessays, 20:41-48, 1998).

Several strategies including monoclonal antibodies (Mab), immunoconjugates, anti-EGF vaccine, and tyrosine kinase inhibitors have been developed to target the erbB family receptors and block their activation in cancer cells (reviewed in (Sridhar et al., Lancet, 4,7:397-406,2003)). Because ErbB2-containing heterodimers are the most stable and preferred initiating event for signaling, interrupting both erbB2 and EGFR simultaneously is an appealing therapeutic strategy. A series of 6-thiazolylquinazoline dual erbB-2/EGFR TK inhibitors that possess efficacy in pre-clinical models for cancer have been synthesized (Cockerill et al., BiorgMedChemLett, 11:1401-1405,2001 ; Rusnak et al., CanRes, 61:7196-7203, 2001a; Rusnak et al., MolCanTher, 1:85-94,2001b). GW572016 is a 6-furanylquinazoline, orally active, reversible dual kinase inhibitor of both EGFR and erbB2 kinases (Rusnak et al., 2001b). In human xenograft studies, GW572016 has shown dose-dependent kinase inhibition, and selectively inhibits tumor cells overexpressing EGFR or erbB2 (Rusnak et al., 2001b; Xia et al., Oncogene, 21:6255-6263, 2002).

Combination therapy is rapidly becoming the norm in cancer treatment, rather than the exception. Oncologists are continually looking for anti-neoplastic compounds which when utilized in combination provides a more effective and/or enhanced treatment to the individual suffering the effects of cancer. Typically, successful combination therapy provides improved and even synergistic effect over monotherapy.

The present inventors have now identified novel cancer treatment methods which include administration of N-{3-chloro-4-[(3-fluorobenzyl) oxy]phenyl}-6-[5-({[2- (methanesulphonyl) ethyl]amino}methyl)-2-furyl]-4-quinazolinamine (GW572016) as well as salts and/or solvates thereof in combination with additional anti-neoplastic compounds.

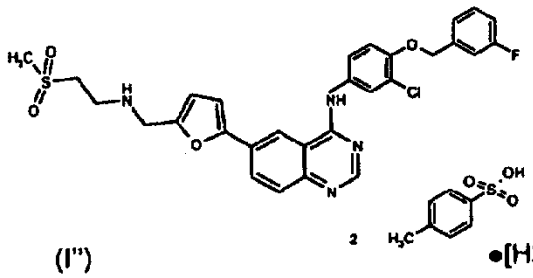
The discussion of the background to the invention herein is included to explain the context of the invention. This is not to be taken as an admission that any of the material referred to was published, known or part of the common general knowledge as at the priority date of any of the claims.

Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification (including the claims) they are to be interpreted as specifying the presence of the stated features, integers, steps or components, but not precluding the presence of one or more other features, integers, steps or components, or group thereof.

SUMMARY OF THE INVENTION

In a first aspect of the present invention, there is provided a method of treating breast cancer in a mammal, comprising: administering to said mammal therapeutically effective amounts of

(i) a compound of formula (I")

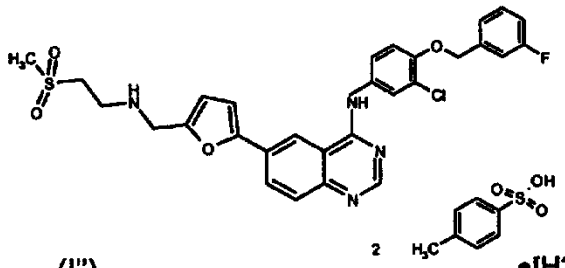


(I") •[H2O] and

(ii) trastuzumab.

In a second aspect of the present invention, there is provided a method of treating breast cancer in a mammal, comprising: administering to said mammal therapeutically effective amounts of

(i) compound of formula (I")

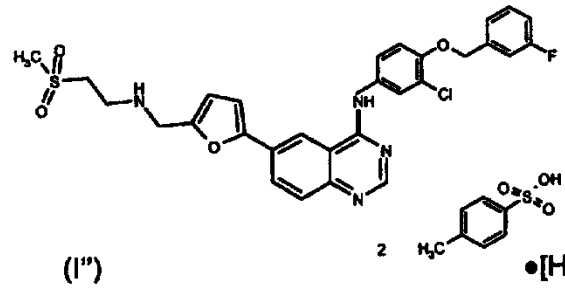


(I") 2 •[H2O] and

(ii) letrozole.

In a third aspect of the present invention, there is provided a method of treating breast cancer in a mammal, comprising: administering to said mammal therapeutically effective amounts of

(i) a compound of formula (I")

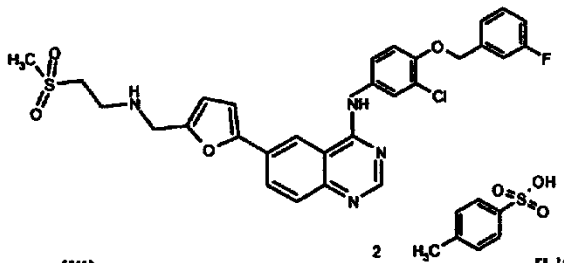


(I") 2 •[H2O] and

(ii) capecitabine.

In a fourth aspect of the present invention, there is provided a method of treating breast cancer in a mammal, comprising: administering to said mammal therapeutically effective amounts of

(i) a compound of formula (I")

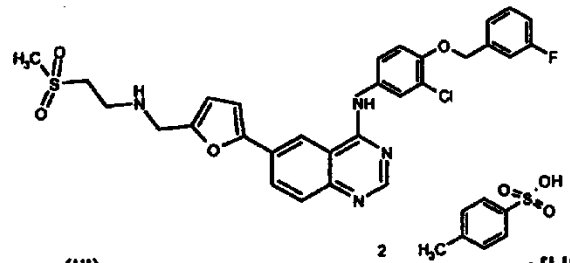


(I") 2 •[H2O] and

(ii) topotecan.

In a fifth aspect of the present invention, there is provided a method of treating lung cancer in a mammal, comprising: administering to said mammal therapeutically effective amounts of

(i) a compound of formula (I")

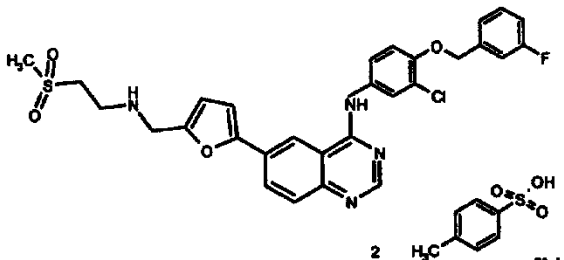


(I") 2 •[H2O] and

(ii) docetaxel.

In a sixth aspect of the present invention, there is provided a method of treating lung cancer in a mammal, comprising: administering to said mammal therapeutically effective amounts of

(i) a compound of formula (I")

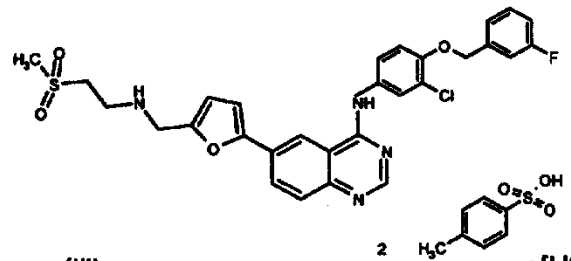


(I") 2 •[H2O] and

(ii) topotecan.

In a seventh aspect of the present invention, there is provided a method of treating colorectal cancer in a mammal, comprising: administering to said mammal therapeutically effective amounts of

(i) a compound of formula (I")

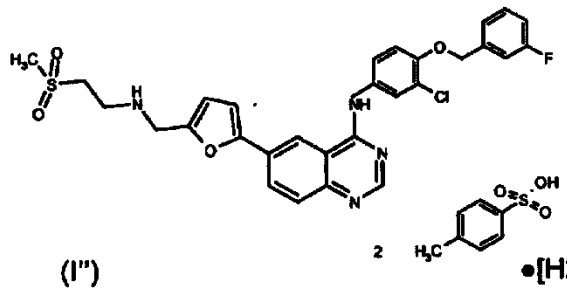


(I") 2 •[H2O] and

(ii) topotecan.

In an eighth aspect of the present invention, there is provided a method of treating breast cancer in a mammal, comprising: administering to said mammal therapeutically effective amounts of

(i) a compound of formula (I")



(I") •[H2O] and

(ii) an anti-estrogen compound.

DETAILED DESCRIPTION OF THE INVENTION

As used herein the term "neoplasm" refers to an abnormal growth of cells or tissue and is understood to include benign, i.e., non-cancerous growths, and malignant, i.e., cancerous growths. The term "neoplastic" means of or related to a neoplasm.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any

amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

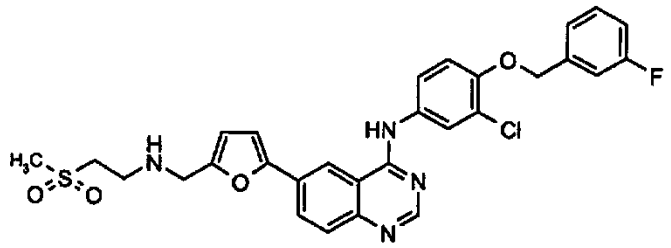
As is well known in the art, cancers or tumors are frequently metastatic, in that a first (primary) locus of cancerous tumor growth spreads to one or more anatomically separate sites. As used herein, reference to "a tumor" in a subject includes not only the primary tumor, but metastatic tumor growth as well. In a like manner reference to cancer or cancer treatment includes primary and metatatic cancer and treatment of the primary cancer as well as metastatic cancerous sites.

"EGFR", also known as "erbB-1", and "erbB-2" are protein tyrosine kinase transmembrane growth factor receptors of the erbB family. Protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth and differentiation (A.F. Wilks, Progress in Growth Factor Research, 1990, 2, 97-111; S.A. Courtneidge, Dev. Supp.l, 1993, 57-64; J.A. Cooper, Semin. Cell Biol., 1994, 5(6), 377-387; R.F. Paulson, Semin. Immunol., 1995, 7(4), 267-277; A.C. Chan, Curr. Opin. Immunol., 1996, 8(3), 394-401). The ErbB family of type I receptor tyrosine kinases includes ErbB1 (also known as the epidermal growth factor receptor (EGFR or HER1)), erbB2 (also known as Her2), erbB3, and erbB4. These receptor tyrosine kinases are widely expressed in epithelial, mesenchymal, and neuronal tissues where they play a role in regulating cell proliferation, survival, and differentiation (Sibilia and Wagner, *Science*, 269: 234 (1995); Threadgill et al., *Science*, 269: 230 (1995)). Increased expression of wild-type erbB2 or EGFR, or expression of constitutively activated receptor mutants, transforms cells *in vitro* (Di Fiore *et al.*, 1987; DiMarco et al, *Oncogene*, 4: 831 (1989); Hudziak et al., *Proc. Natl. Acad. Sci. USA.*, 84:7159 (1987); Qian et al., *Oncogene*, 10:211 (1995)). Increased expression of erbB2 or EGFR has been correlated with a poorer clinical outcome in some breast cancers and a variety of other malignancies (Slamon et al., *Science*, 235: 177 (1987); Slamon et al., *Science*, 244:707 (1989); Bacus et al, *Am. J. Clin. Path*, 102:S13 (1994)).

thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

As recited above the present invention is directed to cancer treatment methods which includes administration of N-{3-chloro-4-[(3-fluorobenzyl) oxy]phenyl}-6-[5-({[2-(methanesulphonyl) ethyl]amino}methyl)-2-furyl]-4-quinazolinamine (GW572016) as well as salts and/or solvates thereof in combination with other anti-neoplastic compounds.

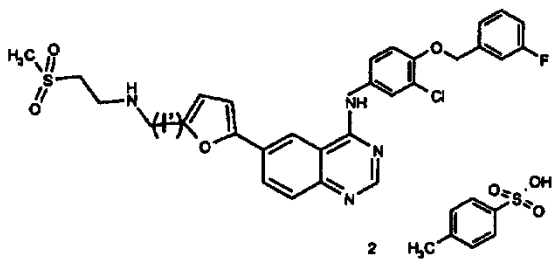
The methods of cancer treatment disclosed herein includes administering a compound of formula (I):



(I)

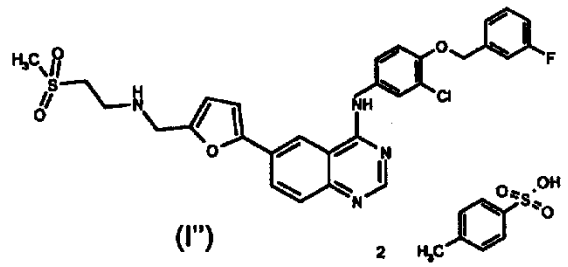
or salts or solvates thereof.

In another embodiment, the compound is a compound of formula (I') which is the ditosylate salt of the compound of formula (I) or anhydrate or hydrate forms thereof. The ditosylate salt of the compound of formula (I) has the chemical name N-{3-chloro-4-[(3-fluorobenzyl) oxy]phenyl}-6-[5-({[2-(methanesulphonyl) ethyl]amino}methyl)-2-furyl]-4-quinazolinamine (GW572016) ditosylate and is also known as lapatinib.



(I')

In one embodiment, the compound is the anhydrous ditosylate salt of the compound of formula (I'). In another embodiment, the compound is a compound of formula (I") which is the monohydrate ditosylate salt of the compound of formula (I').

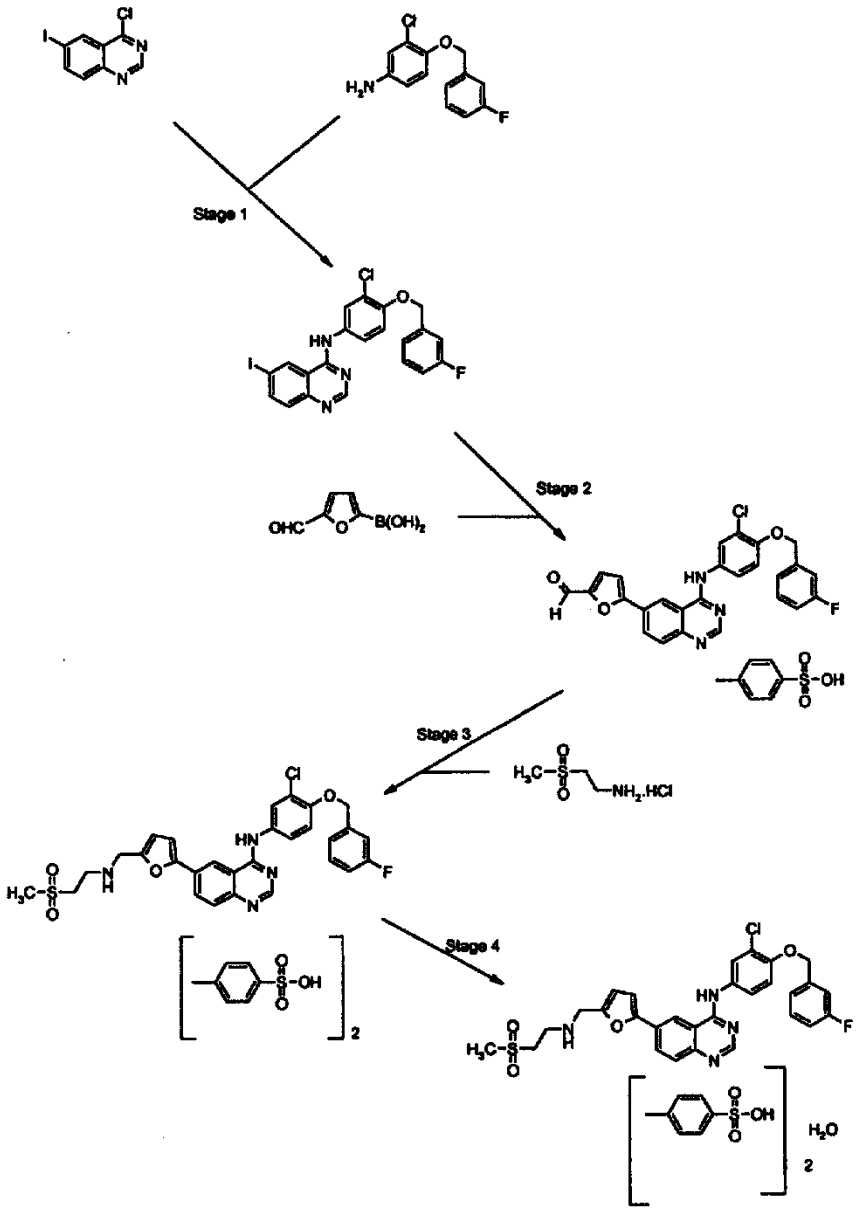


(I")

•H_2O

The free base, HCl salts, and ditosylate salts of the compound of Formula (I) may be prepared according to the procedures of International Patent Application No. PCT/EP99/00048, filed January 8, 1999, and published as WO 99/35146 on July 15, 1999, referred to above and International Patent Application No. PCT/US01/20706, filed June 28, 2001 and published as WO 02/02552 on January 10, 2002 and according to the appropriate Examples recited below. One such procedure for preparing the ditosylate salt of the compound of formula (I) is presented following in Scheme 1.

Scheme 1



In scheme 1, the preparation of the ditosylate salt of the compound of formula (III) proceeds in four stages: Stage 1: Reaction of the indicated bicyclic compound and amine to give the indicated iodoquinazoline derivative; Stage 2: preparation of the corresponding aldehyde salt; Stage 3: preparation of the quinazoline ditosylate salt; and Stage 4: monohydrate ditosylate salt preparation.

Typically, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen on a substituent in a compound of the present invention. Representative salts include the following salts: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, trimethylammonium and valerate. Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of this invention and these form a further aspect of the invention.

In one embodiment, the cancer treatment method is a method of treating breast cancer wherein the compound of formula (I") is administered with trastuzumab.

Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that selectively binds to the extracellular domain of HER2 (erbB2); which is commercially available as a lyophilized powder for I.V. injection as HERCEPTIN®. Trastuzumab is indicated as a single agent for treatment of patients with metastatic breast cancer which overexpresses erbB2 who have previously received one or two chemotherapy regimens.

In one embodiment, the cancer treatment method is a method of treating breast cancer wherein the compound of formula (I") is administered with at least one anti-estrogen compound. The anti-estrogen compound may be an estrogen receptor antagonist or an inhibitor of estrogen synthesis. Exemplary estrogen receptor antagonists include, but are not limited to, fulvestrant, tamoxifen and its metabolite 4-

OH-tamoxifen, and toremifene. Exemplary inhibitors of estrogen synthesis include the aromatase inhibitors letrozole, anastrozole, and exemestane.

Fulvestrant, 7-alpha-[9-(4,4,5,5-pentafluorosulfinyl)nonyl]estra-1,3,5-(10)-triene-3,17-beta-diol; is commercially available as an injectable solution as FASLODEX®. Fulvestrant is indicated for the treatment of hormone positive metastatic breast cancer in postmenopausal women following anti-estrogen therapy. Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner and down regulates the ER protein in human breast cancer cells.

Tamoxifen, (Z)2-[4-(1,2-diphenyl-1-butenyl) phenoxy]-N,N-dimethylethanamine 2 hydroxy-1,2,3-propanetricarboxylate(1:1); is commercially available as 10 or 20 mg tablets as NOLVADEX®. Tamoxifen is indicated for the treatment of metastatic breast cancer in men and women and as an adjuvant treatment in breast cancer. Tamoxifen is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner.

Toremifene, 2-{p[(Z)-4chloro-1,2-diphenyl-1-butenyl]phenoxy}-N,N-dimethylethylamine citrate (1:1); is commercially available as 60 mg tablets as FARESTON®. Toremifene is indicated for the treatment of estrogen receptor positive or unknown tumors in metastatic breast cancer in postmenopausal women. Toremifene is a selective estrogen receptor modulator that binds to the estrogen receptor and may exert estrogenic or anti-estrogenic activity depending on treatment duration, species, gender, target organ, or endpoint selected.

In another embodiment, the cancer treatment method is a method of treating breast cancer wherein the compound of formula (I") is administered with letrozole.

Letrozole is 4-4'-(1H-1,2,4-triazol-1-yl methylene) dibenzonitrile; which is commercially available as 2.5 mg tablets as FEMARA®. Letrozole is an orally administered non-steroidal aromatase inhibitor. Specifically, it is an inhibitor of estrogen synthesis in that it inhibits the conversion of androgens to estrogens.

Letrozole is indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

Anastrozole is 1,3-benzenediacetonitrile α, α, α', α'-tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl); which is commercially available as 1 mg tablets as ARIMIDEX®. Anastrozole is an orally administered non-steroidal aromatase inhibitor. Specifically, it is an inhibitor of estrogen synthesis in that it inhibits the conversion of androgens to estrogens. Anastrozole is indicated for the adjuvant treatment of early breast cancer in postmenopausal women.

Exemestane is 6-methylenandrosta-1,4-diene-3,17-dione; which is commercially available as 25 mg tablets as AROMASIN®. Exemestane is an orally administered steroidal aromatase inhibitor. Specifically it is an inhibitor of estrogen synthesis in that it inhibits the conversion of androgens to estrogens. Exemestane is indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.

In one embodiment, the cancer treatment method is a method of treating breast cancer wherein the compound of formula (I") is administered with capecitabine.

Capecitabine, 5'-deoxy-5-fluoro-N-[(pentyloxy)carbonyl]-cytidine; is commercially available as 150 or 500 mg tablets as XELODA®. Capecitabine is an orally administered pro-drug of 5'-deoxy-5-fluoruridine (5'-DFUR) which is converted into 5-fluorouracil in vivo. Capecitabine is indicated for treatment of metastatic breast cancer resistant to both paclitaxel and an anthracycline containing treatment regimen.

In one embodiment, the cancer treatment method is a method of treating breast cancer wherein the compound of formula (I") is administered with topotecan.

Topotecan HCl, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride, is commercially available as the injectable solution HYCAMTIN®. Topotecan is a

derivative of camptothecin which binds to the topoisomerase I – DNA complex and prevents religation of single strand breaks caused by Topoisomerase I in response to torsional strain of the DNA molecule. Topotecan is indicated for second line treatment of metastatic carcinoma of the ovary and small cell lung cancer. The dose limiting side effect of topotecan HCl is myelosuppression, primarily neutropenia.

In one embodiment, the cancer treatment method is a method of treating lung cancer wherein the compound of formula (I") is administered with docetaxel. In one embodiment, the lung cancer is non-small cell lung cancer.

Docetaxel, (2R,3S)- N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate; is commercially available as an injectable solution as TAXOTERE®. Docetaxel is indicated for the treatment of breast cancer. Docetaxel is a semisynthetic derivative of paclitaxel *q.v.*, prepared using a natural precursor, 10-deacetyl-baccatin III, extracted from the needle of the European Yew tree. The dose limiting toxicity of docetaxel is neutropenia.

In one embodiment, the cancer treatment method is a method of treating lung cancer wherein the compound of formula (I") is administered with topotecan. In one embodiment, the lung cancer is non small cell lung cancer.

Topotecan is as described above.

In one embodiment, the cancer treatment method is a method of treating colorectal cancer wherein the compound of formula (I") is administered with topotecan.

Topotecan is as described above.

In one embodiment, the cancer treatment method is a method of treating breast cancer wherein the compound of formula (I") is administered with at least one bcl-2 inhibitor.

Apoptosis or programmed cell death is a mechanism by which excess, unwanted, or damaged cells within the body are eliminated. Most malignancies suffer from aberrant apoptotic pathways in that apoptosis is blocked or inhibited leading to enhanced cell survival and possibly resistance to treatment. Bcl-2 is one of a family of apoptosis regulators. Bcl-2 is a suppressor of the apoptosis pathway and when overexpressed in cancer cells may have a role in promoting cancer development and growth. As such, it is thought that a bcl-2 inhibitor could be effective in cancer treatment. (Sara et al., Current Med Chem, 11:1031-1040, 2004; Lie et al, CurrMed Chem – AntiCancer Agents, 3:217-223, 2003.) One bcl-2 inhibitor known is HA14-1 which is ethyl [2-amino-6-bromo-4-(1-cyano-2-ethoxy-2oxoethyl)]-4H-chromene-3-carboxylate and which is available from Calbiochem of San Diego, California.

Combination therapies according to the present invention thus include the administration of the compound of formula (I") as well as use of at least one other anti-neoplastic agent. Such combination of agents may be administered together or separately and, when administered separately this may occur simultaneously or sequentially in any order, both close and remote in time. The amounts of the compound of formula (I") and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

Also contemplated in the present invention are pharmaceutical combinations including compounds of the Formula (I") and at least one anti-neoplastic agent. Such compounds of formulae (I") and the at least one anti-neoplastic agent are as described above and may be utilized in any of the combinations described above in the method of treating cancer of the present invention.

While it is possible that, for use in the cancer treatment methods of the present invention therapeutically effective amounts of a compound of formula (I") as well as salts or solvates thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the invention further provides pharmaceutical compositions, which may be administered in the cancer treatment methods of the present invention. The pharmaceutical compositions include therapeutically effective amounts of a compound of formula (I") and salts or solvates thereof, and one or more

pharmaceutically acceptable carriers, diluents, or excipients. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. .

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 0.5mg to 1g, preferably 1mg to 700mg, more preferably 5mg to 100mg of a compound of formula (I), depending on the condition being treated, the route of administration and the age, weight and condition of the patient, or pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

The compound of formula (I") may be administered by any appropriate route. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal, and parenteral (including subcutaneous, intramuscular, intraveneous, intradermal, intrathecal, and epidural). It will be appreciated that the preferred route may vary with, for example, the condition of the recipient of the combination.

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The agents for use according to the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Agents for use according to the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active

ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists that may be generated by means of various types of metered dose pressurised aerosols, nebulizers or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

As indicated, therapeutically effective amounts of a specific compound of formula (I) is administered to a mammal. Typically, the therapeutically effective amount of one of the administered agents of the present invention will depend upon a number of factors including, for example, the age and weight of the mammal, the precise condition requiring treatment, the severity of the condition, the nature of the formulation, and the route of administration. Ultimately, the therapeutically effective amount will be at the discretion of the attendant physician or veterinarian.

Typically, the compound of formula (I) will be given in the range of 0.1 to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 1 to 10 mg/kg body weight per day.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way.

EXAMPLES

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

g (grams);	mg (milligrams);
L (liters);	mL (milliliters);
µL (microliters);	psi (pounds per square inch);
M (molar);	mM (millimolar);
N (Normal)	Kg (kilogram)
i. v. (intravenous);	Hz (Hertz);
MHz (megahertz);	mol (moles);
mmol (millimoles);	RT (room temperature);
min (minutes);	h (hours);
mp (melting point);	TLC (thin layer chromatography);
T_r (retention time);	RP (reverse phase);
DCM (dichloromethane);	DCE (dichloroethane);
DMF (*N*,*N*-dimethylformamide);	HOAc (acetic acid);
TMSE (2-(trimethylsilyl)ethyl);	TMS (trimethylsilyl);
TIPS (triisopropylsilyl);	TBS (*t*-butyldimethylsilyl);
HPLC (high pressure liquid chromatography);	
THF (tetrahydrofuran);	DMSO (dimethylsulfoxide);
EtOAc (ethyl acetate);	DME (1,2-dimethoxyethane);
EDTA	ethylenediaminetetraacetic acid
FBS	fetal bovine serum
IMDM	Iscove's Modified Dulbecco's medium
IMS	Industrial Methylated Spirits
PBS	phosphate buffered saline

RPMI	Roswell Park Memorial Institute
RIPA buffer	*
RT	room temperature

*150 mM NaCl, 50 mM Tris-HCl, pH 7.5, 0.25% (w/v) -deoxycholate, 1% NP-40, 5 mM sodium orthovanadate, 2 mM sodium fluoride, and a protease inhibitor cocktail.

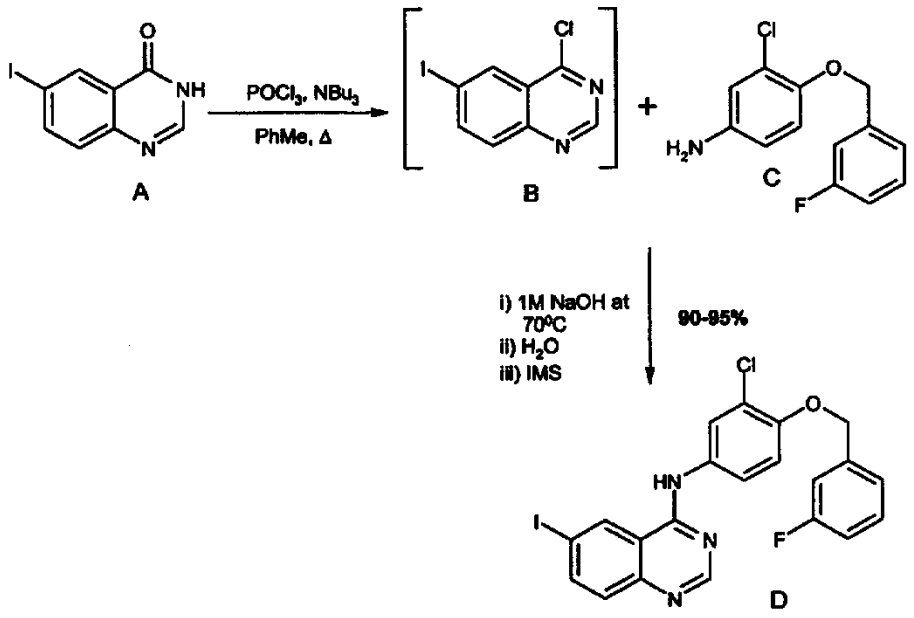
Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions conducted under an inert atmosphere at room temperature unless otherwise noted.

GW572016F is **lapatanib** whose chemical name is N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methane sulphonyl) ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monhydrate.

Example 1

Preparation of GW572016F

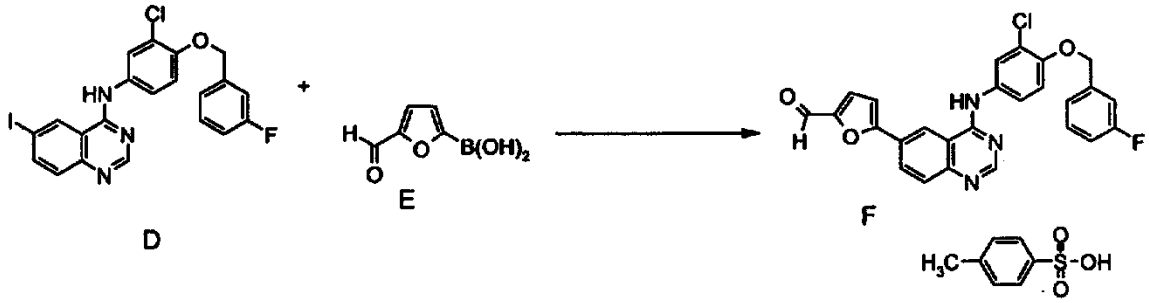
STAGE 1



A stirred suspension of 3*H*-6-iodoquinazolin-4-one (compound A) in toluene (5 vols) was treated with tri-*n*-butylamine (1.2 eq.) at 20 to 25°C, then heated to 90°C. Phosphorous oxychloride (1.1eq) was added, the reaction mixture was then

heated to reflux. The reaction mixture was cooled to 50°C and toluene (5vols) added. Compound C (1.03 eq.) was added as a solid, the slurry was warmed back to 90°C and stirred for 1 hour. The slurry was transferred to a second vessel; the first vessel was rinsed with toluene (2vol) and combined with the reaction mixture. The reaction mixture was cooled to 70°C and 1.0 M aqueous sodium hydroxide solution (16 vols) added dropwise over 1 hour to the stirred slurry maintaining the contents temperature between 68-72°C. The mixture was stirred at 65-70°C for 1 hour and then cooled to 20°C over 1 hour. The suspension was stirred at 20°C for 2 hours, the product collected by filtration, and washed successively with water (3 x 5 vols) and ethanol (IMS, 2 x 5 vols), then dried in vacuo at 50-60°C.
Volumes are quoted with respect of the quantity of Compound A used.
Percent yield range observed: 90 to 95% as white or yellow crystals.

STAGE 2

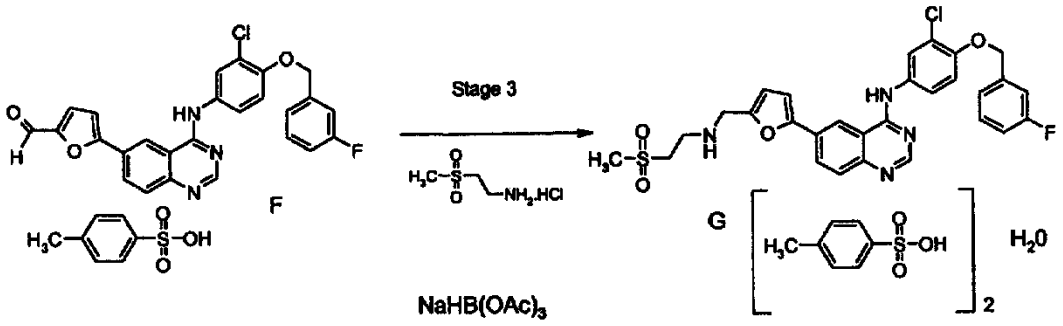


A mixture of N-[3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-iodo-4-quinazolinamine – compound D (1wt), boronic acid – compound E (0.37wt , 1.35equiv), and 10% palladium on charcoal (0.028wt ,50% water wet) was slurried in IMS (15vol). The resultant suspension was stirred for 5 minutes, treated with di-isopropylethylamine (0.39vol, 1.15equiv) and then heated to *ca* 70°C for *ca* 3 hours when the reaction was complete (determined by HPLC analysis). The mixture was diluted with tetrahydrofuran (THF, 15vol) and then hot-filtered to remove the catalyst. The vessel was rinsed with IMS (2vol).

A solution of p-toluenesulfonic acid monohydrate (1.5wt, 4 equiv) in water (1.5vol) was added over 5-10 minutes to the filtered solution maintained at 65°C. After crystallisation the suspension was stirred at 60°-65°C for 1 hour, cooled to *ca* 25°C over 1 hour and stirred at this temperature for a further 2 hours. The solid was collected by filtration, washed with IMS (3vol) then dried *in vacuo* at *ca* 50°C to give

the compound F as a yellow-orange crystalline solid (isolated as the ethanol solvate containing approximately 5%w/w EtOH).

STAGE 3



Compound F (1 wt) and 2-(methylsulfonyl)ethylamine hydrochloride (0.4 wt, *1.62* equiv.) were suspended in THF (10 vols). Sequentially, acetic acid (*0.354* vol., 4 equiv.) and di-isopropylethylamine (DIPEA, 1.08 vol., *4.01* equiv.) were added. The resulting solution was stirred at 30°-35°C for *ca* 1 hour then cooled to *ca* 22°C. Sodium tri-acetoxyborohydride (0.66 wt, *2.01* equiv.) was then added as a continual charge over approximately 15 minutes (some effervescence is seen at this point). The resulting mixture was stirred at ca 22°C for *ca* 2 hours then sampled for HPLC analysis. The reaction was quenched by addition of aqueous sodium hydroxide (25% w/w, 3 vols.) followed by water (2 vols.) and stirred for *ca* 30 minutes (some effervescence was seen at the start of the caustic addition).

The aqueous phase was then separated, extracted with THF (2 vols) and the combined THF extracts were then washed twice with 25% w/v aqueous ammonium chloride solution (2 x 5 vols)[2]. A solution of *p*-toluenesulfonic acid monohydrate (p-TSA, 0.74 wt, *2.5* equiv.) in water (1 vol)[1] was prepared, warmed to *ca* 60°C, and GW572016F (Compound G) (0.002 wt) seeds were added.

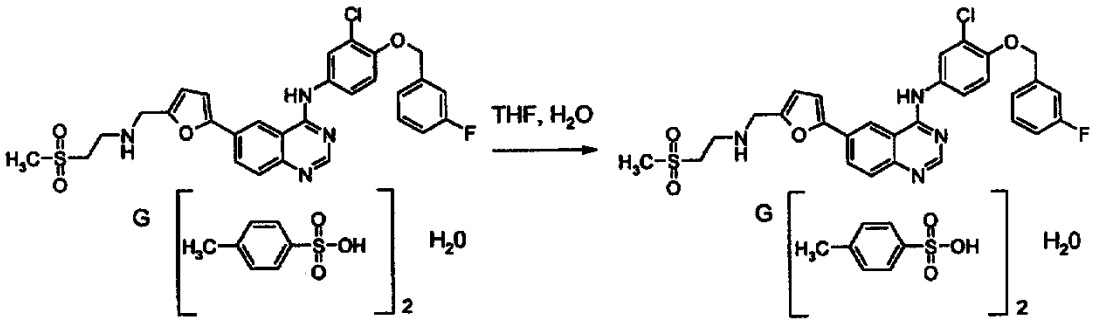
The THF solution of the free base of GW572016 was added to the p-TSA solution over at least 30 minutes, while maintaining the batch temperature at 60±3°C. The resulting suspension was stirred at *ca* 60°C for 1-2 hours, cooled to 20-25°C over an hour and aged at this temperature for *ca* 1hr. The solid was collected by filtration, washed with 95:5 THF:Water (3 x 2 vols) and dried *in vacuo* at *ca* 35°C to give GW572016F – compound G as a bright yellow crystalline solid. Expected yield 80% theory, 117% w/w.

[1] Minimum reaction volume *ca* 1 vol.

[2] Maximum reaction volume *ca* 17 vol.

Corrected for assay.

STAGE 4



A suspension of the ditosylate monohydrate salt of N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methane sulphonyl) ethyl]amino}methyl)-2-furyl]-4-quinazolinamine – compound G (1 wt), in tetrahydrofuran (THF, 14 vol) and water (6 vol) was heated to *ca* 55°-60°C for 30 minutes to give a solution which was clarified by filtration and the lines washed into the crystallisation vessel with THF/Water (7:3 ratio, 2 vol). The resultant solution was heated to reflux and tetrahydrofuran (9 vol, 95% w/w azeotrope with water) was distilled off at atmospheric pressure.

The solution was seeded with N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methane sulphonyl) ethyl]amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate (0.002 wt). Once the crystallisation was established water (6 vol) was added while maintaining the reaction temperature above 55°C. The mixture was cooled to 5°-15°C over *ca* 2 hours. The solid was collected by filtration, washed with tetrahydrofuran/water (3:7 ratio, 2 vol) then tetrahydrofuran/water (19:1 ratio, 2 vol) and dried *in vacuo* at 45°C to give N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methane sulphonyl) ethyl] amino}methyl)-2-furyl]-4-quinazolinamine ditosylate monohydrate – compound G as a bright yellow crystalline solid.

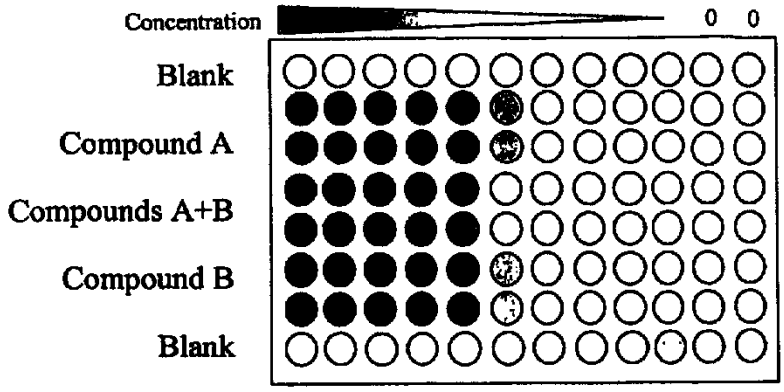
Example 2

Dosing with lapatinib and docetaxel or topotecan

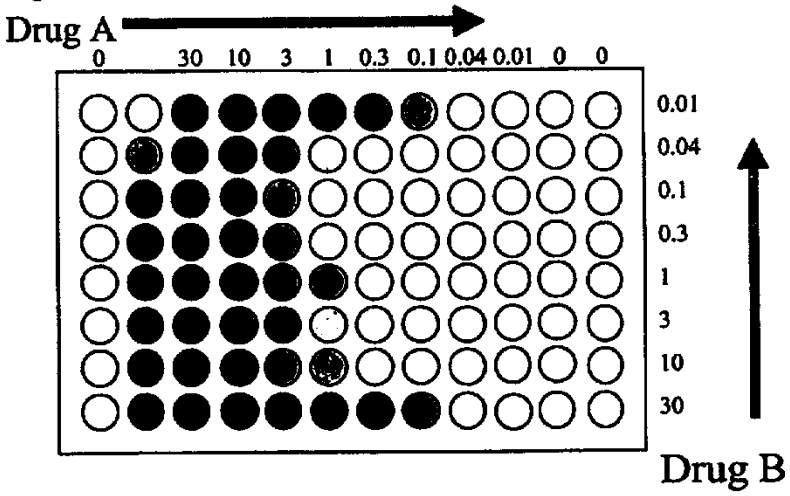
Cell lines were obtained from the American Type Culture Collection. The cells were maintained in tissue culture flasks in RPMI 1640 (Invitrogen # 22400-089) with 10 % fetal bovine serum (FBS, HyClone # SH30071.03) and were incubated at 37°Celsius in an atmosphere of 5% CO_2, until plating for IC_{50} determination. For IC_{50} determination, cells were plated in the appropriate medium at 5,000 cells per well in a 96-well tissue culture dish and returned to the incubator overnight. Approximately twenty-four hours after initial seeding, cells were exposed to the ditosylate salt form of GW 572016, GW 572016F alone, topotecan or docetaxel alone, or GW 572016F and topotecan or docetaxel in combination. Cells were dosed in 50% RPMI and 50% low glucose DMEM medium containing, 5% FBS, 50 micrograms/ml gentamicin and 0.3% DMSO. All dosing was performed concomitantly, and the dose ratio of each agent to GW 572016F was adjusted to approximately reflect the relative potency of each agent on each cell line. In most cases, the agents were dosed at a single fixed ratio. In some instances, the data also includes CI values generated by dosing in a matrix format. CI values from matrix dosing were included when the dose ratio in both dosing formats was 1:1. See dosing format following.

After three days of compound exposure, the growth medium was removed by aspiration. Cell biomass was estimated by staining cells in 0.1 ml per well of methylene blue (Sigma #M9140, 0.5% in 50:50, ethanol:water), followed by incubation at room temperature for at least 30 minutes. Stain was aspirated and the plates rinsed by immersion in deionized water, followed by air drying. Stain was released from cells by the addition of 0.1 ml of solubilization solution (1.0% N-lauryl sarcosine, Sodium salt, Sigma #L5121 in PBS). Plates were incubated at room temperature for 40 minutes. Absorbance was read at 620 nM in a Tecan Spectra micro-plate reader. Percent inhibition of cell growth was calculated relative to untreated control wells. IC_{50} values were interpolated using the method of Levenberg and Marquardt (Mager, 1972) and the equation: $y = V_{max} * [1 - (x^n/(K^n + x^n))]$, where "K" is equal to IC_{50}.

Single ratio dosing



Matrix dosing



IC50 values were generated for each agent individually and in combination. IC50 values were inserted into the combination index (CI) equation from Chou and Talalay:

$D_{a,comb}/D_a + D_{b,comb}/D_b$, where Da and Db are the IC50s of each agent alone. $D_{a,comb}$ is the amount of agent a in the combination where the effect is 50% inhibition. $D_{b,comb}$ is the amount of agent b in the combination where the effect is 50% inhibition. If the agents are dosed at a 1:1 ratio of each other, $D_{a,comb} = D_{b,comb}$. Values greater than 1 suggest antagonism. Values less than 1 suggest synergism. The extent of

antagonism or synergism can be assumed to be reflected by the difference of the value from 1.0, ie 0.5 is more synergistic than 0.8 and 2.0 is more antagonistic than 1.5. It is important to note that the value 1.0 is predicted additivity. It is possible for a combination to give a greater inhibitory effect than either agent alone, but still be considered antagonistic. This happens when the magnitude of combined effect is not as much as the mathematical model would predict. Another analysis template is being developed to compare the combination to the best single agent. The Chou and Talalay model also assumes that the individual agents are acting independently or on independent pathways and are mutually exclusive. Using a model that assumes the agents are working by the same mechanism as GW 572016F (mutually non-exclusive) increases some of the CI values, but does not change the ranking of the agents in this data set. The table below includes the combination index values for both mutually exclusive and mutually non-exclusive CI determination.

Table 1

Combination	Cell Line	CI Mutually Exclusive	CI Mutually Non-exclusive
Lapatinib/docetaxel	A549	1.22	1.29
Lapatinib/docetaxel	Colo205	1.50	1.80
Lapatinib/docetaxel	H1299	0.58	0.61
Lapatinib/docetaxel	MDA-MB-468	1.16	1.47
Lapatinib/topotecan	A549	0.46	0.48
Lapatinib/topotecan	Colo205	0.59	0.68
Lapatinib/topotecan	H1299	0.84	0.88
Lapatinib/topotecan	MDA-MB-468	0.90	1.04

Example 3

BT474 vs. lapatinib and docetaxel combination

Mice with BT474 tumors were administered lapatinib alone (200 and 100 mg/kg; SID X 21 Days, or 2 days and 1 day before docetaxel) and in combination with docetaxel (25 and 50 mg/kg IP, once weekly X 3 weeks).

In both experiments, docetaxel at 50 mg/kg alone, and in combination with lapatinib was highly effective. However, in both experiments, Taxotere at 25 and 50 mg/kg caused weight loss after 3 weekly doses. In the first experiment there were no deaths, and in the second experiment there was one death in a group of eight mice receiving docetaxel (25 mg/kg) and lapatinib (200 mg/kg X 21 days). All surviving mice rapidly regained body weight when dosing was completed. The treatment groups and results follow.

Treatment Group	% Inhibition
1. HPMCT80 Vehicle (qdX21days)	ND
2. Tax-25 (Days 3,10, 17)	77
3. Tax-50 (Days 3, 10, 17)	98
4. GW016-200 (sid X 21 Days)	102
5. GW016-100 (sid X 21 days)	79
6. GW016-200 (twice weekly on consecutive days X 3 weeks)	58
7. GW016-200 (twice weekly on consecutive days X 3 weeks) + Taxotere-50 (once weekly X 3 weeks)	98
8. GW016-100 (sidX21 days) + Taxotere-50 (once weekly X 3 weeks)	103
9. GW016-200 (sidX 21 days) + Tax-25 (once weekly X 3 weeks)	109

Example 4
Clinical study of lapatinib in combination with trastuzumab

Patients (pts) with advanced or metastatic breast cancer that overexpress the erbB2 protein 2+ or 3+, confirmed by either immunohistochemistry and/or fluorescence in situ hybridization were enrolled. Escalating dose levels of lapatinib (750 - 1500 mg) were administered daily q4 weeks in combination with weekly, standard dosing of trastuzumab (4 mg/kg loading dose followed by weekly 2 mg/kg infusions). Three pts were treated at each dose level, with expansion to 6 in the event of dose-limiting toxicity. Limited pharmacokinetic samples were obtained to determine any correlation between peak concentrations and treatment-related toxicities. One incidence each of dose-limiting grade 3 fatigue and grade 3 nausea

was reported separately at the 1500 mg/d dose level. Grades 1-2 diarrhea, anorexia, fatigue and rash are the common toxicities. Assessments of clinical response per RECIST criteria were performed at week 8 and then every 8 weeks.

26 pts were treated (cohort 750 - 3; cohort 1000 - 10; cohort 1250 – 10, cohort 1500 - 3). Median age was 54 years (30-81). Seventy-five treatment periods (4 weeks = 1 treatment period) were completed: median 2. Twenty pts were evaluable for response: 4 PR, duration 1-4 months; 9 SD, duration 1-5 months, and 7 PD, within 1-6 months.

After 152 treatment periods response evaluation: 5 PR, duration 1.9, 2.6, 3.9, 5.0+, and 6.7+ months respectively and 1 CR of 7.7+ months.

CR - complete response defined as disappearance of target lesions
PR – partial response defined as reduction of at least 30 % in target lesions
SD – stable disease defined as no growth or some reduction in target lesion

Example 5
Clinical study of lapatinib in combination with letrozole

Patients (pts) with advanced breast cancer, ER or PR positive, or other tumors (e.g., ovarian, endometrial) that would be likely to respond to the combination therapy were enrolled. Escalating doses of lapatinib (1250-1500 mg) were administered q4 weeks in combination with the standard dose of letrozole (2.5 mg/d). Three patients (pts) were treated at each dose level, with expansion to 6 in the event of dose-limiting toxicity (DLT).

Seventeen pts (17 F, median age 50, range 32-74 years; median Karnofsky PS 90%) were enrolled at the 2 dose levels (1250 mg cohort –4 pts, 1500 mg cohort – 13 pts). Thirty-three treatment periods (4 weeks = 1 treatment period) were completed: median 2. One incidence of DLT (gr 3 diarrhea) was reported at the 1500 mg/d dose level. The optimally tolerated regimen was determined to be letrozole 2.5 mg + lapatinib 1500 mg/d. Grades 1-2 diarrhea, nausea, rash and fatigue were the common non-hematologic toxicities. Out of 16 evaluable patients, 3pts experienced SD for $\geq$ 2 months (breast – 1pt, bladder – 1 pt, endometrial – 1pt and cervical – 1 pt) and 4 patients have experienced PD within 2-4 months.

Example 6

Clinical study of lapatinib in combination with capecitabine

A 2-part Phase I study combining lapatinib with capecitabine was conducted in 45 patients (pts) with advanced solid tumors: (A) dose-escalation phase (24 pts) and (B) pharmacokinetic phase at the optimally tolerated regimen (OTR) (21 pts): M/F (23:22), median age 57 yrs (34-78), ECOG (0/1/2:29/13/3), heavily:lightly pretreated (23:22), tumor types (H&N (8); breast (8), colorectal (7), lung (6), others (16)) and median cycle 3 (1-9). Pts were treated with 14 days of capecitabine (C) (1500-2500 mg/m2) and daily lapatinib (L) (1250-1500 mg) every 3 weeks.

Dose-limiting toxicities (DLT) were: Grade 3 mucositis, fatigue and anorexia- 1250 L/2000 C (n=1); Grade 3 rash (n=1), Grade 3 diarrhea (n=1)- 1500 L/2000 C & Grade 2 bleeding stomatitis (n=1), Grade 3 diarrhea (n=1)- 1250 L/2500 C. Other toxicities included stomatitis (36%), nausea/vomiting (30%), diarrhea (45%), unconjugated hyperbilirubinemia (14%), fatigue (19%), rash (38%) and hand foot syndrome (29%). OTR was 1250 L/2000 C. Responses (RECIST criteria) included 1 CR in a woman with inflammatory breast cancer refractory to trastuzimab and chemotherapy. Her tumor overexpressed ErbB2 (3+) with low TS. In addition, 4 PRs (1 erlotinib-resistant H&N; taxane refractory-H&N; breast; gastric) and 6 SD >12 weeks were observed.

Example 7

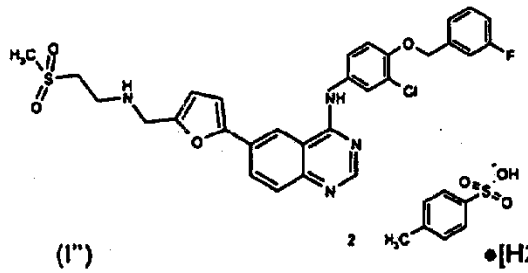
Combination of Lapatinib with a Bcl-2 Inhibitor.

The effect of a combination of lapatanib with a Bcl-2 inhibitor (HA14-1) on the growth of MCF-7 human breast cancer cells, a HER-2/neu transfected MCF-7 cell line and a tamoxifen (TAM) resistant MCF-7 cell line was examined. Cell growth was determined using the MTT tetrazolium dye assay. Cells were dosed with Lapatinib and HA14-1 as monotherapies. Both lapatinib (1-10 uM) and HA14-1 (1-10 uM) gave dose-dependent growth inhibition on each of the 3 cell lines. Treatment with the combination of EGFR/erbB-2 inhibitor lapatinib and the Bcl-2 inhibitor HA14-1 resulted in synergistic growth inhibition of all 3 cell lines.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of treating breast cancer in a mammal, comprising: administering to said mammal therapeutically effective amounts of

(i) a compound of formula (I")



(I") •[H2O] and

(ii) capecitabine.

2. A method according to claim 1, substantially as hereinbefore described.