

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 June 2010 (03.06.2010)

(10) International Publication Number
WO 2010/061208 A2

PCT

(51) International Patent Classification:

A61P 35/00 (2006.01) *A61K 31/337* (2006.01)
A61K 31/517 (2006.01) *A61K 45/06* (2006.01)

(21) International Application Number:

PCT/GB2009/051471

(22) International Filing Date:

2 November 2009 (02.11.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/110,710 3 November 2008 (03.11.2008) US

(71) Applicant (for all designated States except MG, US): **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(71) Applicant (for MG only): **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London Greater London W1K 1LN (GB).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **HICKINSON, Daniel, Mark** [GB/GB]; AstraZeneca Intellectual Property, AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB).

(74) Agent: **ASTRAZENECA INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: THERAPEUTIC TREATMENT 555

(57) Abstract: A combination, comprising 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-{{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, or a pharmaceutically acceptable salt thereof, and a taxane is described.



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THERAPEUTIC TREATMENT 555

The present invention relates to a combination comprising 4-(3-chloro-2-fluoroanilino)-7-methoxy-6- {[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline, or a pharmaceutically acceptable salt thereof, hereafter "Compound (I)", and a taxane.

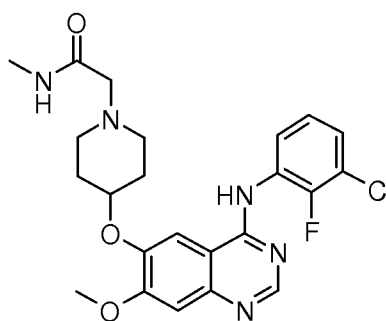
The combination is expected to be useful for the treatment or prophylaxis of cancer. The invention also relates to a pharmaceutical composition comprising such combinations and to the use thereof in the manufacture of a medicament for use in the treatment or prophylaxis of cancer, such as breast cancer.

The erbB family of receptor tyrosine kinases, which include EGFR, erbB2, erbB3 and erbB4, are frequently involved in driving the proliferation and survival of tumour cells and as such the erbB family of receptors is implicated in a number of epithelial cancers (reviewed in Olayioye *et al.*, EMBO J., 2000, 19, 3159), including for example breast cancer (Sainsbury *et al.*, Brit. J. Cancer, 1988, 58, 458; Guerin *et al.*, Oncogene Res., 1988, 3, 21; Slamon *et al.*, Science, 1989, 244, 707; Klijn *et al.*, Breast Cancer Res. Treat., 1994, 29, 73 and reviewed in Salomon *et al.*, Crit. Rev. Oncol. Hematol., 1995, 19, 183), non-small cell lung cancers (NSCLCs) including adenocarcinomas (Cerny *et al.*, Brit. J. Cancer, 1986, 54, 265; Reubi *et al.*, Int. J. Cancer, 1990, 45, 269; Rusch *et al.*, Cancer Research, 1993, 53, 2379; Brabender *et al.*, Clin. Cancer Res., 2001, 7, 1850) as well as other cancers of the lung (Hendler *et al.*, Cancer Cells, 1989, 7, 347; Ohsaki *et al.*, Oncol. Rep., 2000, 7, 603), bladder cancer (Neal *et al.*, Lancet, 1985, 366; Chow *et al.*, Clin. Cancer Res., 2001, 7, 1957, Zhau *et al.*, Mol Carcinog., 3, 254), oesophageal cancer (Mukaida *et al.*, Cancer, 1991, 68, 142), gastrointestinal cancer such as colon, rectal or stomach cancer (Bolen *et al.*, Oncogene Res., 1987, 1, 149; Kapitanovic *et al.*, Gastroenterology, 2000, 112, 1103; Ross *et al.*, Cancer Invest., 2001, 19, 554), cancer of the prostate (Visakorpi *et al.*, Histochem. J., 1992, 24, 481; Kumar *et al.*, 2000, 32, 73; Scher *et al.*, J. Natl. Cancer Inst., 2000, 92, 1866), leukaemia (Konaka *et al.*, Cell, 1984, 37, 1035, Martin-Subero *et al.*, Cancer Genet Cytogenet., 2001, 127, 174), ovarian (Hellstrom *et al.*, Cancer Res., 2001, 61, 2420), head and neck (Shiga *et al.*, Head Neck, 2000, 22, 599) or pancreatic cancer (Ovotny *et al.*, Neoplasma, 2001, 48, 188).

Accordingly it has been recognised that an inhibitor of erbB receptor tyrosine kinases should be of value as a selective inhibitor of the growth of certain carcinomas. A

number of erbB tyrosine kinase inhibitors have demonstrated clinical benefit and a number of erbB tyrosine kinase inhibitors have been approved for use in the treatment of cancer. For example, the EGFR tyrosine kinase inhibitors gefitinib and erlotinib for the treatment of advanced non-small cell lung cancer and lapatinib, which has erbB2 tyrosine kinase inhibitory activity, for use in metastatic breast cancer. Several other EGFR and erbB2 tyrosine kinase inhibitors are currently in development.

Compound (I) is disclosed in International Patent Application Publication number WO2005/028469 as Example 1 therein and is of the structure:



Compound (I)

In WO2005/028469 it is stated that compounds disclosed therein may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment.

WO2005/028469 then goes on to describe examples of such conjoint treatment including surgery, radiotherapy and many different types of chemotherapeutic agent.

Nowhere in WO2005/028469 is the specific combination of Compound (I) and a taxane disclosed.

Compound (I) is an erbB receptor tyrosine kinase inhibitor, in particular Compound (I) is a potent inhibitor of EGFR, erbB2 and erbB3 receptor signalling.

There is a growing body of pre- and clinical evidence suggesting that, in addition to signalling via EGFR and erbB2 homodimers, cell signalling mediated by EGFR, erbB2 & erbB3 heterodimers may be an important oncogenic signalling pathway (Sergina et al., Nature, 2007, 445, 437; Ritter et al., Clin Cancer Res. 2007, 13, 4909; Johnston et al., JCO, 2008, 26, 1066). Since erbB3 does not have an intrinsic tyrosine kinase activity, activation

of the erbB3 receptor is achieved only through the formation of heterodimeric receptor complexes with other kinase-active receptors including particularly EGFR and erbB2. EGFR and erbB2 heterodimers formed with erbB3 are thought to drive tumour growth in tumours where these receptors are expressed.

5 We have found in pre-clinical experiments that Compound (I) inhibits erbB3 mediated signalling through the inhibition of phosphorylation of erbB3 following ligand stimulated EGFR/erbB3 and/or erbB2/erbB3 heterodimerisation. Accordingly, Compound (I) exhibits a unique erbB tyrosine kinase inhibitory effect compared to other erbB tyrosine kinase inhibitors such as gefitinib or erlotinib that act primarily as EGFR tyrosine kinase
10 inhibitors and lapatinib which is primarily an erbB2 inhibitor with some EGFR inhibitory activity. We have carried out pre-clinical studies which suggest that Compound (I) exhibits improved anti-tumour effects compared to EGFR tyrosine kinase inhibitors such as gefitinib, erlotinib, herceptin and lapatinib. Without wishing to be bound by theory, it is thought that the improved properties may result from the inhibition of the erbB3 mediated
15 signalling by Compound (I).

Taxanes are anti-mitotic agents that bind to tubulin and act to stabilise microtubule polymerisation thereby disrupting the normal equilibrium involved in microtubule assembly and deconstruction and therefore retards microtubule functioning. Microtubules are essential to cell division and cells exposed to taxanes are arrested in the premitotic G2
20 phase and fail to divide. Cells treated with these drugs are held in mitosis, i.e. they interfere with the cell division process, this may eventually result in cell death due to unsuccessful mitosis.

Taxanes such as paclitaxel and docetaxel have been approved for use in the treatment of a number of cancers, including ovary, breast, lung, head and neck, prostate
25 and gastric carcinomas.

The present inventors have unexpectedly found that the combination of Compound (I) and a taxane can have a particular beneficial and/or synergistic anti-tumour effect and may therefore be useful in the treatment of cancer.

Therefore according to a first aspect of the present invention, there is provided a
30 combination, comprising Compound (I) and a taxane.

Herein where the term “taxane” is used it is to be understood that this refers to any chemical analogue which exerts its anticancer effect by stabilization of the tubulin microtubules involved in cell division.

Particular examples of taxanes include:

- 5 • (2aR,3aR,4aR,6R,9S,11S,12S,12aR,12bS)-6,12b-diacetoxy-9-[3(S)-(tert-butoxycarbonylamino)-2(R)-hydroxy-3-phenylpropionyloxy]-12-benzoyloxy-11-hydroxy-8,13,13-trimethyl-2a,3,3a,4,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]-cyclopropa[4,5]benz[1,2-b]oxet-5-one dihydrate;
- Paclitaxel (Taxol),
- 10 • BMS-184476 (7-methylthiomethylpaclitaxel);
- BMS-188797;
- BMS-275183;
- BMS-188797;
- BMS-109881;
- 15 • CYC-3204 (a penetratin-paclitaxel conjugate);
- Taxoprexin;
- DJ-927;
- Docetaxel (Taxotere);
- Larotaxel (XRP9881; RPR-109881A);
- 20 • XRP6258 (RPR112658);
- Milataxel (MAC-321);
- MST 997;
- MBT-206;
- NBT-287;
- 25 • Ortataxel;
- Protax-3;
- PG-TXL;
- PNU-166945;
- PNU-106258;
- 30 • Orataxel (BAY 59-8862; IDN 5109; semisynthetic taxane);
- TPI-287;

- Protaxel and
- MAC-321 (Taxalog).

The term “taxane” is also intended to include formulations of taxanes such as paclitaxel and docetaxel. Particular examples of such formulations include:

- 5 • conventional formulations of paclitaxel or docetaxel, for example the currently approved Taxol and Taxotere formulations;
- formulations with biocompatible polymers, particularly proteins such as albumin, more particularly nano-particle or micro-particle formulations of paclitaxel or docetaxel with albumin, for example Abraxane (described in US 5,439,686 and US 6,749,868) or
10 NAB-docetaxel (described in, for example US 20080161382, US20070117744 and US 20070082838);
- polymer conjugates, particularly polymer conjugates of paclitaxel or docetaxel, more particularly conjugates of docetaxel or paclitaxel with poly-L-glutamate, for example Opaxio (also known as Xyotax, paclitaxel poliglumex, CT-2103 and described in for
15 example Li C.; Poly (L -glutamic acid) – anticancer drug conjugates; Adv. Drug Deliv. Rev. 2002; 54 : 695 –713);
- conjugates of docetaxel or paclitaxel with a fatty acid, particularly conjugates of paclitaxel or docetaxel with docosahexaenoic acid (DHA), for example, Taxoprexin (DHA-paclitaxel, described in for example Bradley MO et al. Tumor targeting by
20 covalent conjugation of a natural fatty acid to paclitaxel; Clin. Cancer Res. 2001; 7: 3229 –38);
- microparticle compositions such as the porous microparticle formulations described in US 6,645,528, for example the microparticle formulation of paclitaxel AI-850, comprising paclitaxel nanoparticles in a porous, hydrophilic matrix, composed
25 primarily of a sugar; and
- emulsions of paclitaxel or docetaxel in vitamin E, for example Tocosol.

Further formulations of paclitaxel and docetaxel are also known, further examples of which are mentioned hereafter. Such formulations of taxanes may also be used as the taxane component of the combinations according to the present invention.

- 30 Particularly the taxane is selected from paclitaxel, docetaxel and Abraxane. In one embodiment the taxane is paclitaxel. In another embodiment the taxane is docetaxel. In a further embodiment the taxane is Abraxane.

Therefore according to a further aspect of the invention there is provided a combination comprising Compound (I) and a taxane selected from paclitaxel, docetaxel and Abraxane.

According to a further aspect of the invention there is provided a combination
5 comprising Compound (I) and paclitaxel.

According to a further aspect of the invention there is provided a combination comprising Compound (I) and docetaxel.

According to a further aspect of the invention there is provided a combination comprising Compound (I) and a Abraxane.

10 According to a further aspect of the invention there is provided a combination comprising Compound (I) and NAB-docetaxel.

References herein to “Compound (I)” unless stated otherwise include Compound (I) and pharmaceutically acceptable salts thereof. Similarly references to any of the taxanes described herein are intended to cover the agent and pharmaceutically acceptable
15 salts thereof unless specified otherwise.

Herein, where the term “combination” is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention “combination” refers to simultaneous administration. In another aspect of the invention “combination” refers to separate administration. In a further aspect of the invention
20 “combination” refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination.

In one aspect, where a compound or a pharmaceutically acceptable salt thereof, is referred to this refers to the compound only. In another aspect this refers to a
25 pharmaceutically acceptable salt of the compound.

Where cancer is referred to, it refers to, for example, tumours expressing one or more of the erbB family of receptors, such as EGFR, erbB2 and/or erbB3 receptors. Particularly cancer refers to oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer, Ewing’s tumour, neuroblastoma, Kaposi’s sarcoma, ovarian cancer, breast
30 cancer, colorectal cancer, prostate cancer, bladder cancer, melanoma, lung cancer - non small cell lung cancer (NSCLC), and small cell lung cancer (SCLC), gastric cancer, head and neck cancer, brain cancer, renal cancer, lymphoma and leukaemia. In another

embodiment cancer refers to breast cancer, lung cancer (for example NSCLC), gastric cancer, head and neck cancer, colorectal cancer and/or ovarian cancer. In another embodiment cancer refers to SCLC, NSCLC, colorectal cancer, ovarian cancer and/or breast cancer. In another embodiment cancer refers to SCLC. In addition, it refers to NSCLC. In addition, it refers to colorectal cancer. In addition it refers to head and neck cancer. In addition it refers to gastric cancer. In addition, it refers to ovarian cancer. In addition, more particularly it refers to breast cancer. In addition, more particularly it refers to hormone receptor positive breast cancer, especially to hormone receptor positive breast cancer in post-menopausal women. In one embodiment it refers to non-metastatic hormone receptor positive breast cancer, for example non-metastatic hormone receptor positive breast cancer in post-menopausal women. Still furthermore it refers to non-metastatic estrogen and/or progesterone receptor positive breast cancer, especially to non-metastatic estrogen and/or progesterone receptor positive breast cancer in post-menopausal women. In addition, more particularly it refers to metastatic hormone receptor positive breast cancer, especially to metastatic hormone receptor positive breast cancer in post-menopausal women. Still furthermore it refers to metastatic estrogen and/or progesterone receptor positive breast cancer, especially to metastatic estrogen and/or progesterone receptor positive breast cancer in post-menopausal women. Furthermore it refers to tumours with low over-expression of erbB2, more particularly breast cancer with low over-expression of erbB2. Furthermore it refers to advanced breast cancer with low over-expression of erbB2. Furthermore, it refers to bladder cancer, oesophageal cancer, gastric cancer, melanoma, cervical cancer and/or renal cancer. In addition it refers to endometrial, liver, stomach, thyroid, rectal and/or brain cancer. In another embodiment of the invention, particularly the cancer is in a non-metastatic state. In another embodiment of the invention, particularly the cancer is in a metastatic state. In a further embodiment of the invention, particularly the cancer is in a metastatic state, and more particularly the cancer produces skin metastases. In a further embodiment of the invention, particularly the cancer is in a metastatic state, and more particularly the cancer produces lymphatic metastases. In a further embodiment of the invention, particularly the cancer is in a metastatic state, and more particularly the cancer produces brain metastases. In a further embodiment of the invention, particularly the cancer is in a metastatic state, and more particularly the cancer produces bone metastases.

The term “low over-expression of erbB2” refers to tumours which express low levels of erbB2, for example those tumours that are not eligible for treatment with the drug Herceptin, more particularly tumours that are Her2 fluorescent in-situ hybridization (FISH) negative. Such tumours are those tumours which have non-amplified levels of erbB2.

5 Where the term “low over-expression of erbB2” is used herein it refers to tumours which have non-amplified levels of erbB2. Particular tumours that have “low over-expression of erbB2” include those that are:

- (i) Her2 + by immunohistochemistry (IHC); and/or
- (ii) Her2 ++ by IHC and Her2 fluorescent in-situ hybridization (FISH) negative.

10 Accordingly in a particular embodiment of the invention the cancer is a cancer with low over-expression of erbB2 selected from one or more of:

- (a) a breast cancer which is Her2 FISH negative;
- (b) a breast cancer which is Her2+ by IHC; and
- (c) a breast cancer which is Her2++by IHC and Her2 FISH negative.

15 Accordingly in another embodiment of the invention the cancer is a cancer with non-amplified levels of erbB2 selected from one or more of:

- (a) a breast cancer which is Her2 FISH negative;
- (b) a breast cancer which is Her2+ by IHC; and
- (c) a breast cancer which is Her2++by IHC and Her2 FISH negative.

20 The term “advanced cancer” refers to a cancer that is locally advanced (where the cancer has spread from the primary tumour to surrounding tissues) or metastatic cancer. Particularly “advanced cancer” refers to metastatic cancer. Testing for Her2 in breast cancer is described in the Journal of Clinical Oncology, Vol 25, No 1 (January 1), 2007, p118-145, A. C. Wolff et al.

25 The anti-cancer effect of the combination according to the invention may be measured in terms of one or more of an anti-tumour effect, the extent of the response (for example reduced tumour volume or reduced tumour burden), the response rate, the clinical benefit rate (the sum of complete response, partial response and stable disease) the time to disease progression, progression-free survival and the overall survival rate. Such clinical trial endpoints are well known and are described in for example the FDA publication
30 “Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics” May 2007 (www.fda.gov/CbER/gdlns/clintrialend.htm). The anti-tumour

effects of the combination according to the invention may be for example one or more of inhibition of tumour growth, tumour growth delay, regression of tumour, shrinkage of tumour, increased time to regrowth of tumour on cessation of treatment or slowing of disease progression.

5 The combination use of Compound (I) and a taxane may also have a beneficial effect in preventing the onset of cancer in warm-blooded animals, such as man.

Pharmaceutically-acceptable salts mentioned herein include, for example, salts with alkali metals (such as sodium, potassium or lithium), alkaline earth metals (such as calcium or magnesium), ammonium salts, and salts with organic bases affording physiologically acceptable cations, such as salts with methylamine, dimethylamine, trimethylamine, 10 piperidine and morpholine. In addition, for those compounds which are sufficiently basic, examples of pharmaceutically-acceptable salts include, pharmaceutically-acceptable acid-addition salts with hydrogen halides, sulphuric acid, phosphoric acid and with organic acids such as citric acid, maleic acid, methanesulphonic acid and p-toluenesulphonic acid.

15 Alternatively, the compounds may exist in zwitterionic form.

A particular pharmaceutically acceptable salt of Compound (I) is a di-fumarate salt of Compound (I).

Therefore according to the present invention, there is provided a combination, comprising Compound (I) and a taxane, for use as a medicament.

20 According to a further aspect of the present invention, there is provided a combination, comprising Compound (I) and a taxane, for use in the treatment of a cancer.

According to a further aspect of the present invention, there is provided a combination, comprising Compound (I) and a taxane, for use in the treatment of hormone receptor positive breast cancer, for example estrogen receptor positive breast cancer.

25 According to a further aspect of the present invention, there is provided a combination, comprising Compound (I) and a taxane, for use in the treatment of hormone receptor negative breast cancer, for example estrogen receptor negative breast cancer.

According to a further aspect of the present invention, there is provided a combination, comprising Compound (I) and a taxane, for use in the treatment of breast 30 cancer with low over-expression of erbB2.

According to a further aspect of the present invention, there is provided a combination, comprising Compound (I) and a taxane, for use in the treatment of advanced breast cancer with low over-expression of erbB2.

According to a further aspect of the present invention, there is provided a
5 combination, comprising Compound (I) and a taxane, for use in the first line treatment of advanced breast cancer with low over-expression of erbB2.

According to a still further aspect of the present invention, there is provided a combination, comprising Compound (I) and a taxane, for use in the treatment of advanced breast cancer with low over-expression of erbB2 in a patient that has not received prior chemotherapy.

10 According to a further aspect of the present invention, there is provided a combination, comprising Compound (I) and a taxane, for use in the treatment of hormone receptor positive (for example ER and/or PR receptor positive) breast cancer with low over-expression of erbB2.

According to a further aspect of the present invention, there is provided a
15 combination, comprising Compound (I) and a taxane, for use in the treatment of advanced hormone receptor positive (for example ER and/or PR receptor positive) breast cancer with low over-expression of erbB2.

According to a further aspect of the present invention, there is provided a
20 combination, comprising Compound (I) and a taxane, for use in the first-line treatment of advanced hormone receptor positive (for example ER and/or PR receptor positive) breast cancer with low over-expression of erbB2.

According to a still further aspect of the present invention, there is provided a
combination, comprising Compound (I) and a taxane, for use in the treatment of advanced
25 hormone receptor positive (for example ER and/or PR receptor positive) breast cancer with low over-expression of erbB2 in a patient that has not received prior chemotherapy.

According to a further aspect of the present invention, there is provided a
combination, comprising Compound (I) and a taxane, for use in the treatment of hormone
receptor negative (for example ER and/or PR receptor negative) breast cancer with low
over-expression of erbB2.

30 According to a further aspect of the present invention, there is provided a combination, comprising Compound (I) and a taxane, for use in the treatment of advanced

hormone receptor negative (for example ER and/or PR receptor negative) breast cancer with low over-expression of erbB2.

According to a further aspect of the present invention, there is provided a combination, comprising Compound (I) and a taxane, for use in the first-line treatment of advanced hormone receptor negative (for example ER and/or PR receptor negative) breast cancer with low over-expression of erbB2.

According to a still further aspect of the present invention, there is provided a combination, comprising Compound (I) and a taxane, for use in the treatment of advanced hormone receptor negative (for example ER and/or PR receptor negative) breast cancer with low over-expression of erbB2 in a patient that has not received prior chemotherapy.

As mentioned herein where it is referred to that a patient has “not received prior chemotherapy”, this refers to chemotherapy before the combination according to the present invention is used to treat the cancer. In other words the combination according to the invention is the first chemotherapy used to treat the patient. The patient may however have received other non-chemotherapeutic treatments of the cancer prior to, during or after use of the combination according to the invention. For example, the patient may undergo surgery to remove some or all of the tumour and/or radiotherapy prior to treatment with a combination according to the invention. References to use of the combination according to the invention as the “first-line treatment”, this refers to the first treatment of the cancer (In other words the combination is used as the primary therapy for the cancer.

Compound (I) and the taxane may be used as a single composition containing Compound (I) and the taxane. Accordingly, a further aspect of the invention provides a pharmaceutical composition which comprises Compound (I) and a taxane in association with a pharmaceutically acceptable diluent or carrier.

Suitably however, Compound (I) and the taxane may be used as two individual compositions, one containing Compound (I) and one containing the taxane, wherein the two compositions are administered simultaneously, separately or sequentially. Accordingly a further aspect of the invention provides a pharmaceutical composition which comprises Compound (I), in association with a pharmaceutically acceptable diluent or carrier, in combination with a pharmaceutical composition which comprises a taxane in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention, there is provided a method of treating cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of Compound (I) in combination with an effective amount of a taxane.

5 Therefore according to a further aspect of the present invention, there is provided a method of treating hormone receptor positive breast cancer, for example estrogen receptor positive breast cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of Compound (I) in combination with an effective amount of a taxane.

10 According to a further aspect of the present invention, there is provided a method of treating breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of Compound (I) in combination with an effective amount of a taxane.

15 According to a further aspect of the present invention, there is provided a method of treating advanced breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of Compound (I) in combination with an effective amount of a taxane.

20 According to a further aspect of the present invention, there is provided a method for the first-line treatment of advanced breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of Compound (I) in combination with an effective amount of a taxane.

25 According to a further aspect of the present invention, there is provided a method of treating advanced breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man, that has not received prior chemotherapy, in need of such treatment which comprises administering to said animal an effective amount of Compound (I) in combination with an effective amount of a taxane.

30 According to a further aspect of the present invention, there is provided a method of treating hormone receptor positive (for example ER and/or PR receptor positive) breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man, in

need of such treatment which comprises administering to said animal an effective amount of Compound (I) in combination with an effective amount of a taxane.

According to a further aspect of the present invention, there is provided a method of treating advanced hormone receptor positive (for example ER and/or PR receptor
5 positive) breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of Compound (I) in combination with an effective amount of a taxane.

According to a further aspect of the present invention, there is provided a method of treating advanced hormone receptor positive (for example ER and/or PR receptor
10 positive) breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man that has not received prior chemotherapy, in need of such treatment which comprises administering to said animal an effective amount of Compound (I) in combination with an effective amount of a taxane.

According to a further aspect of the present invention, there is provided a method
15 for the first-line treatment of advanced hormone receptor positive (for example ER and/or PR receptor positive) breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of Compound (I) in combination with an effective amount of a taxane.

According to a further aspect of the present invention, there is provided a method
20 of treating hormone receptor negative (for example ER and/or PR receptor negative) breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of Compound (I) in combination with an effective amount of a taxane.

According to a further aspect of the present invention, there is provided a method
25 of treating advanced hormone receptor negative (for example ER and/or PR receptor negative) breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of Compound (I) in combination with an effective amount of a taxane.

According to a further aspect of the present invention, there is provided a method
30 of treating advanced hormone receptor negative (for example ER and/or PR receptor negative) breast cancer with low over-expression of erbB2, in a warm-blooded animal,

such as man that has not received prior chemotherapy, in need of such treatment which comprises administering to said animal an effective amount of Compound (I) in combination with an effective amount of a taxane.

According to a further aspect of the present invention, there is provided a method
5 for the first-line treatment of advanced hormone receptor negative (for example ER and/or PR receptor negative) breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of Compound (I) in combination with an effective amount of a taxane.

10 For the avoidance of doubt, where the treatment of cancer is indicated, it is to be understood that this also refers to the prevention of metastases and the treatment of metastases, i.e. cancer spread. Therefore the combination of the present invention could be used to treat a patient who has no metastases to stop them occurring, or to lengthen the time period before they occur, and to a patient who already has metastases to treat the
15 metastases themselves. In one aspect of the invention the combination of the present invention could be used to treat a patient with a cancer where the cancer is either in a metastatic or a non-metastatic state. Furthermore the treatment of cancer also refers to treatment of an established primary tumour or tumours and developing primary tumour or tumours. In one aspect of the invention the treatment of cancer relates to the prevention of
20 metastases. In another aspect of the invention the treatment of cancer relates to the treatment of metastases. In another aspect of the invention the treatment of cancer relates to treatment of an established primary tumour or tumours or developing primary tumour or tumours. In one embodiment the treatment of cancer relates to an adjuvant treatment. In another embodiment the treatment of cancer refers to the neo-adjuvant treatment of cancer.
25 In one embodiment the treatment of cancer relates to first-line treatment of cancer. Accordingly in an embodiment of the invention the combination according to the invention is used as an adjuvant treatment of breast cancer which has a tumour with low over-expression of erbB2, for example as an adjuvant treatment of estrogen receptor positive breast cancer which has a tumour with low over-expression of erbB2.

30 In another embodiment of the invention the combination is used as a first line treatment of advanced breast cancer, which has a tumour with low over-expression of erbB2. In another embodiment of the invention the combination according to the invention

is used as a neo-adjuvant treatment of breast cancer, for example advanced breast cancer, which has a tumour with low over-expression of erbB2.

The term “adjuvant therapy” refers to a treatment given following removal of the primary tumour. Where the cancer is breast cancer, removal of the primary tumour may
5 be effected by, for example, surgery (for example lumpectomy or mastectomy) and/or radiotherapy.

The term “neo-adjuvant therapy” refers to a treatment given prior to removal of the primary tumour by surgery or radiotherapy.

In a further embodiment the treatment of the cancer refers to the first-line treatment
10 of the cancer. In another embodiment the treatment of the cancer refers to the second-line treatment of the cancer (a treatment administered following failure of the first-line treatment of the cancer).

Herein, the treatment of cancer also refers to the prevention of cancer *per se*.

The effect of a method of treatment of the present invention is expected to be at
15 least equivalent to the addition of the effects of each of the components of said treatment used alone, that is, of each of Compound (I) and the taxane used alone.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be greater than the addition of the effects of each of the components of said treatment used alone, that is, of each of Compound (I)
20 and the taxane used alone.

According to another aspect of the present invention the effect of a method of treatment of the present invention is expected to be a synergistic effect.

According to the present invention a treatment using the combination according to the invention is defined as affording a synergistic effect if the effect is therapeutically
25 superior, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, to that achievable on dosing one or other of the components of the combination treatment at its conventional dose. For example, the effect of the combination treatment is synergistic if the effect is therapeutically superior to the effect achievable with Compound (I) or the taxane alone. Further, the effect of the
30 combination treatment is synergistic if a beneficial effect is obtained in a group of patients that does not respond (or responds poorly) to Compound (I) or the taxane alone. In addition, the effect of the combination treatment is defined as affording a synergistic effect

if one of the components is dosed at its conventional dose and the other component(s) is/are dosed at a reduced dose and the therapeutic effect, as measured by, for example, the extent of the response, the response rate, the time to disease progression or the survival period, is equivalent to that achievable on dosing conventional amounts of the components of the combination treatment. In particular, synergy is deemed to be present if the conventional dose of Compound (I) or the taxane may be reduced without detriment to one or more of the extent of the response, the response rate, the time to disease progression and survival data, in particular without detriment to the duration of the response, but with fewer and/or less troublesome side-effects than those that occur when conventional doses of each component are used.

According to a further aspect of the present invention there is provided a kit comprising Compound (I) and a taxane; optionally with instructions for use.

According to a further aspect of the present invention there is provided a kit comprising:

- a) Compound (I), in a first unit dosage form;
- b) a taxane, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms; and optionally
- d) with instructions for use.

According to a further aspect of the present invention there is provided a kit comprising:

- a) Compound (I), together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) a taxane, together with a pharmaceutically acceptable diluent or carrier, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms; and optionally
- d) with instructions for use.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises Compound (I), in association with a pharmaceutically acceptable diluent or carrier, in combination with a pharmaceutical composition which comprises a taxane in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer.

The pharmaceutical compositions of compound (I) described herein may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. An example of a suitable dosage form for a taxane such as docetaxel or paclitaxel is for example a formulation suitable for parenteral, particularly intravenous administration. Such parenteral compositions of paclitaxel and docetaxel are well known in the art. In general the above compositions may be prepared in a conventional manner.

For example, Compound (I) is suitably formulated as a tablet using the following excipients:

Tablet Core:

Compound (I);
lactose;
microcrystalline cellulose;
crospovidone;
polyvidone (PVP); and
magnesium stearate

The tablet core may be coated with a conventional film-coating such as an HPMC based film coating which optionally contains one or more colorants and/or light protective agents. Suitably Compound (I) is used in the tablet as the Compound (I) difumarate salt, more specifically the Compound (I) difumarate salt. If required the Compound (I) may be milled prior to formulation into the tablet to provide a uniform particle size distribution of the Compound (I) in the tablet. For example Compound (I) difumarate may be milled to provide an average particle size of about 5µm. Suitable milling methods are well known.

The tablets may be prepared using conventional methods and as illustrated in the Examples.

The taxane may be formulated according to known procedures. For example various formulations of Paclitaxel are known, including the currently approved intravenous formulations of paclitaxel and docetaxel. Further examples of taxane formulations include

those mentioned hereinbefore, including Abraxane; AI-850; DO/NDR/02 (a cremophor-free paclitaxel formulation); EndoTag-1; liposome encapsulated paclitaxel; LPE/PLP Paclitaxel; MPI-5019; NK-105; OncoGel; Paclimer Microspheres; S-8184; ABI-007; NOVA-12005; SP-1010C-O; Pacligel; SP-1010C; Paxoral, Xorane; Genexol; Tocosol; 5 PacoExtra; Yewtaxan; Taxosomes; Atrigel; Xyotax (paclitaxel polyglumex; polyglutamated paclitaxel) and SP 1010C.

According to a further aspect of the present invention there is provided a kit comprising Compound (I) and a taxane; optionally with instructions for use; for use in the treatment of cancer.

10 According to another feature of the invention there is provided the use of Compound (I), in combination with a taxane, in the manufacture of a medicament for use in the treatment of cancer, in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of Compound (I), in combination with a taxane, in the manufacture of a medicament for use 15 in the treatment of hormone receptor positive breast cancer, for example estrogen receptor positive breast cancer, in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of Compound (I), in combination with a taxane, in the manufacture of a medicament for use in the treatment of breast cancer with low over-expression of erbB2, in a warm-blooded 20 animal, such as man.

According to another feature of the invention there is provided the use of Compound (I), in combination with a taxane, in the manufacture of a medicament for use in the treatment of advanced breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man.

25 According to another feature of the invention there is provided the use of Compound (I), in combination with a taxane, in the manufacture of a medicament for use as the first-line treatment of advanced breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of 30 Compound (I), in combination with a taxane, in the manufacture of a medicament for use in the treatment of advanced breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man that has not received prior chemotherapy.

According to another feature of the invention there is provided the use of Compound (I), in combination with a taxane, in the manufacture of a medicament for use in the treatment of hormone receptor positive (for example ER and/or PR receptor positive) breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man.

5 According to another feature of the invention there is provided the use of Compound (I), in combination with a taxane, in the manufacture of a medicament for use in the treatment of advanced hormone receptor positive (for example ER and/or PR receptor positive) breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man.

10 According to another feature of the invention there is provided the use of Compound (I), in combination with a taxane, in the manufacture of a medicament for use in the treatment of advanced hormone receptor positive (for example ER and/or PR receptor positive) breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man that has not received prior chemotherapy.

15 According to another feature of the invention there is provided the use of Compound (I), in combination with a taxane, in the manufacture of a medicament for use in the first-line treatment of advanced hormone receptor positive (for example ER and/or PR receptor positive) breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man.

20 According to another feature of the invention there is provided the use of Compound (I), in combination with a taxane, in the manufacture of a medicament for use in the treatment of hormone receptor negative (for example ER and/or PR receptor negative) breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man.

25 According to another feature of the invention there is provided the use of Compound (I), in combination with a taxane, in the manufacture of a medicament for use in the treatment of advanced hormone receptor negative (for example ER and/or PR receptor negative) breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man.

30 According to another feature of the invention there is provided the use of Compound (I), in combination with a taxane, in the manufacture of a medicament for use in the treatment of advanced hormone receptor negative (for example ER and/or PR

receptor negative) breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man that has not received prior chemotherapy.

According to another feature of the invention there is provided the use of Compound (I), in combination with a taxane, in the manufacture of a medicament for use
5 in the first-line treatment of advanced hormone receptor negative (for example ER and/or PR receptor negative) breast cancer with low over-expression of erbB2, in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of Compound
10 (I), optionally together with a pharmaceutically acceptable diluent or carrier, in combination with an effective amount of a taxane, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment, for use in the treatment of cancer.

The amount of Compound (I), or a pharmaceutically acceptable salt thereof,
15 administered would be that sufficient to provide the desired pharmaceutical effect. For instance, Compound (I) could be administered to a warm-blooded animal orally, at a unit dose less than 1g daily but more than 1mg. Particularly Compound (I) could be administered to a warm-blooded animal, at a unit dose of less than 250 mg per day. In another aspect of the invention, Compound (I) could be administered to a warm-blooded
20 animal, at a unit dose of less than 160 mg per day. In a further aspect of the invention, Compound (I) could be administered to a warm-blooded animal, at a unit dose of less than 50 mg per day. The dose of Compound (I) may be administered as a single daily dose or as multiple fractions of the total daily dose. For example, the total daily dose of Compound (I) may be administered as two doses, which may be the same or different.
25 Suitably however, each fraction of the total daily dose would be approximately equal. By way of example compound (I) may be administered as a one or more tablets containing, for example 1, 2.5, 10, 40 or 100mg of Compound (I).

The taxane will normally be administered in accordance with approval guidelines. Suitable doses are both species and schedule dependent with respect to their maximum
30 tolerated doses. For example when the taxane is paclitaxel, it may be administered intravenously on a 4-week cycle, wherein the paclitaxel is administered once a week for three weeks, followed by one week without treatment. The cycle may then be repeated as

required, for example to the point of disease progression or treatment failure. Suitably, the paclitaxel is intravenous infusion is administered over a 3 or 24 hour period.

For example, in one embodiment compound (I) is administered 2 times daily and paclitaxel is administered using the 4-week cycle described above.

5 However, as will be realised, the dose of compound (I) and the taxane will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly, the optimum dosage may be determined by the practitioner who is treating any particular patient. The dosage of each of the drugs and their proportions have to be composed so that the best
10 possible treatment effects, as defined by national and international guidelines (which are periodically reviewed and re-defined), will be met.

Compound (I) may be prepared as described in Example 1 of WO2005/028469. Alternatively Compound (I) may be prepared as described in the Examples.

When Compound (I) is used in the form of a di-fumarate salt, the salt may be
15 prepared as described in the Examples.

Legends to Figures

Figures 1, 2 and 3 show the effect on cell viability of treating MCF-7, SKBr3 and BT474c cells respectively with a combination of Compound (I) (0.2 μ M) + Taxol (20nM/1000nM) compared to either compound (I) alone or Taxol alone. The y-axis shows
20 the optical density (OD) measured using a spectrophotometer at a wavelength of 490nm. "NTC" in figures 1 to 3 refers to non-treatment control.

In Figure 1, "P=0.005" is the p value comparing Taxol alone (20nM) with the combination of Compound (I) (0.2 μ M) and Taxol (20nM). "P=0.09" is the p value comparing Compound (I) (0.2 μ M) alone with the combination of Compound (I) (0.2 μ M) and Taxol (20nM). "P=0.002" is the p value comparing Taxol alone (1000nM) with the
25 combination of Compound (I) (0.2 μ M) and Taxol (1000nM). "P=0.065" is the p value comparing Compound (I) (0.2 μ M) alone with the combination of Compound (I) (0.2 μ M) and Taxol (1000nM).

In Figure 2, "P=0.019" is the p-value comparing Taxol at its IC₅₀ with the
30 combination of Compound (I) and Taxol at their respective IC₅₀ concentrations in the SKBr3 cells. "P=0.08" is the p-value comparing Compound (I) at its IC₅₀ concentration

with the combination of Compound (I) and Taxol at their respective IC50 concentrations in the SKBr3 cells.

In Figure 3 “P=0.0002” is the p-value comparing Taxol at its IC50 with the combination of Compound (I) and Taxol at their respective IC50 concentrations in the BT474c cells. “P=0.3” is the p-value comparing Compound (I) at its IC50 concentration with the combination of Compound (I) and Taxol at their respective IC50 concentrations in the BT474c cells.

Figure 4 shows the combination index (CI) for MCF-7, SKBr3 and BT474c cell lines tested with a combination of Compound (I) and Taxol relative to the use of either Compound (I) or Taxol alone.

Figure 5 shows the results of an anti tumour study in a BT474c xenograft in female Swiss (nu/nu) mice. Animals were dosed as detailed below:

Group 1: Control A: 1% Polysorbate 80 p.o. twice daily and

Control B: 5% Cremaphor/5% Ethanol/90% PBS i.p. once weekly (trace with black squares).

Group 2: Compound (I) @ 12.5mg/kg p.o. twice daily (trace with circles)

Group 3: Taxol @ 15mg/kg i.p. once weekly (trace with triangles pointing up)

Group 4: Taxol @ 7.5mg/kg i.p. once weekly (trace with triangles pointing down)

Group 5: Compound (I) @ 12.5mg/kg p.o. twice daily + Taxol @ 15mg/kg i.p. once weekly (trace with triangle pointing left)

Group 6: Compound (I) @ 12.5mg/kg po twice daily + Taxol @ 7.5mg/kg i.p. once weekly (trace with triangle pointing right). The x-axis shows the days of dosing. The y-axis shows the mean tumour volume on cm^3 +/- the standard experimental measurement error (SEM).

Figure 6 shows an X-ray powder diffraction pattern (XRPD) for Compound (I) difumarate Form A. The x-axis shows the 2-theta value and the y-axis the counts.

Examples

The invention is further illustrated by way of the following examples, which are intended to elaborate several embodiments of the invention. These examples are not intended to, nor are they to be construed to, limit the scope of the invention. It will be clear that the invention may be practiced otherwise than as particularly described herein.

Numerous modifications and variations of the present invention are possible in view of the teachings herein and, therefore, are within the scope of the invention.

Example A

Preparation of 4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-[[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy]quinazoline (Compound (I) free base)

2-Chloro-N-methylacetamide (3.720 kg, 34.60 mol) and 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline (13.70 kg, 24.97 mol), were dissolved in acetonitrile (79.2 kg). To the stirred suspension, at ambient temperature, was added triethylamine (17.40 kg, 172.11 mol). The resulting clear solution was heated to reflux and held for 3 hours. The solution was cooled to 20°C (product crystallized at 50°C). Water (54.2 kg) was added to the reactor and the suspension was stirred for a further 2 hours at 20°C. The product was filtered and washed with water (34 kg) followed by cold (0°C) acetonitrile (13.0 kg). The product was recrystallised from acetonitrile (94.6 kg), isolated by filtration and washed with cold (0°C) acetonitrile (13.2 kg). A further recrystallisation of this product was then carried out as above from acetonitrile (75.2 kg). The solid was then dried under vacuum to give the title product as a white solid (6.50 kg, 55%); ¹H NMR Spectrum: (CDCl₃) 1.98 (m, 2H), 2.08 (m, 2H), 2.46 (-m, 2H), 2.85 (m, 2H), 2.87 (d, 3H), 3.07 (s, 2H), 4.02 (s, 3H), 4.49 (m, 1H), 7.16 (m, 4H), 7.31 (m, 2H), 8.49 (m, 1H), 8.71 (s, 1H); Mass spectrum: MH⁺ 474.

The 4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline used as the starting material was prepared as follows:

Step 1: 6-Acetoxy-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline hydrochloride 6-Acetoxy-4-hydroxy-7-methoxyquinazoline (21.4 kg, 89.3 mol) was suspended in toluene (150 kg). To this was added N-ethyldiisopropylamine (13.3 kg, 103 mol). The brown suspension was heated to 70°C then phosphorus oxychloride (36.0 kg, 228 mol) was charged. The reaction mixture was stirred at 70°C for 5 hours. Further toluene 84.0 kg) was added followed by 3-chloro-2-fluoraniline (14.88 kg, 102 mol). The reaction mixture was stirred at 70°C for 2 hours during which time a solid precipitated. The suspension was cooled to 25°C and held at this temperature for 93 hours. The reaction mixture was filtered and the filter cake washed with toluene (2 x 55.5 kg). The cake was further washed with a mixture of ethanol (24.5 kg) and water (32.0 kg) twice, then ethanol (50.5 kg) twice and the solid then dried under vacuum to give the title product as a beige solid (33.4 kg,

97.8%); ¹H NMR: 2.37 (s, 3H), 4.00 (s, 3H), 7.34 (ddd, 1H), 7.48 (s, 1H), 7.52 (ddd, 1H), 7.61 (ddd, 1H), 8.62 (s, 1H), 8.86 (s, 1H); Mass Spectrum: 362.4, 364.4. Step 2: 4-(3-Chloro-2-fluoroanilino)-6-hydroxy-7-methoxyquinazoline

6-Acetoxy-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline hydrochloride from step 1 (33.5 kg, 82.2 mol) was suspended in methanol (198 kg). To the stirred suspension at 25°C was added water (86 kg) and sodium hydroxide (31.5 kg, 32%). The resulting solution was stirred at 60°C for 4.5 hours and then cooled to 25°C. Acetic acid (approximately 16.0 kg) was added until a pH of 5.5-6.0 was achieved at which point the product precipitates from solution. After the addition of further methanol (5.5 kg) the suspension was stirred for 90 minutes. The product was filtered then washed with 25% aqueous methanol (39.0 kg MeOH + 17.0 kg Water) and then methanol (55.5 kg). The crude solid was dried under vacuum at 40°C. The crude solid was slurried with water (145 kg) and stirred for 2 hours at 65°C. The slurry was cooled to 20°C and filtered. The filter cake was washed with methanol (2 x 21.5 kg), then dried under vacuum at 40°C to give the title product as a light brown solid (21.85 kg, 81.2%); ¹H NMR: 3.95 (s, 3H), 7.19 (s, 1H), 7.23 (dd, 1H), 7.42 (dd, 1H), 7.50 (dd, 1H), 7.64 (s, 1H), 8.32 (s, 1H), 9.43 (s, 1H), 9.67 (br.s, 1H); Mass Spectrum: 320.4, 322.4.

Step 3: 6-([(1-tert-Butoxycarbonyl)piperidin-4-yl]oxy)-4-(3-chloro-2-fluoroanilino)-7-methoxy quinazoline

4-(3-Chloro-2-fluoroanilino)-6-hydroxy-7-methoxyquinazoline from Step 2 (15.591 kg, 48.77 mol), *tert*-Butyl (4-methanesulfonyloxy)piperidine-1-carboxylate (prepared as in Chemical & Pharmaceutical Bulletin 2001, **49**(7), 822-829; 16.20 kg, 57.99 mol) and potassium carbonate (7.978 kg, 57.73 mol) were dissolved in N-methylpyrrolidinone (114.2 kg), and the mixture was heated to 100°C with stirring.. Heating was continued at 100°C (95°C - 105°C) for 5 hours. The mixture was then cooled to 80°C and quenched by the addition of water (216.6 kg).

The batch was stirred at 80°C for a further 60 minutes then cooled to 20°C over 2 hours, during which time the product crystallized. The product was isolated by filtration. The product was dissolved in hot (reflux) methanol (200 L). To this mixture was added water (20 L), which induced crystallization. The suspension was cooled to 0°C and filtered. Vacuum drying at 50°C afforded the title product, 18.80 kg (77%, 97.9% wt/wt); ¹H NMR: 1.40 (s, 9H), 1.60-1.65 (m, 2H), 1.95-2.00 (m, 2H), 3.20-3.25 (m, 2H), 3.65-3.70 (m, 2H),

3.92 (s, 3H), 4.68 (m, 1H), 7.21 (s, 1H), 7.27 (dd, 1H), 7.47 (ddd, 1H), 7.51 (dd, 1H), 7.85 (s, 1H), 8.36 (s, 1H), 9.53 (s, 1H); Mass Spectrum: 503.5, 505.5.

Step 4: 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline

6-{[(1-*tert*-Butoxycarbonyl)piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline from step 3 (18.80 kg, 37.38 mol) was suspended in isopropanol (139.8 kg), and heated to 40°C with stirring. Hydrochloric acid (15.40 kg, ~156.3 mol) was charged to the vessel over 50 minutes, allowing an exotherm of approximately 9°C to occur. During the charging of the acid, the suspension dissolved to give a clear solution. The solution was heated slowly to reflux over approximately 90 minutes, and then held at reflux for a further 3 hours. The product crystallised out during this reflux period. The thick suspension was cooled to 0°C and filtered. The filter cake was washed twice with cold (0°C) isopropanol (2 X 20.6 kg). The product was dried under vacuum at 50°C to give the title product, 13.60 kg (66%, 80.1% wt/wt); ¹H NMR: 1.53-1.64 (m, 2H), 2.00-2.05 (m, 2H), 2.64-2.72 (m, 2H), 3.00-3.07 (m, 2H), 3.92 (s, 3H), 4.60 (m, 1H), 7.20 (s, 1H), 7.26 (ddd, 1H), 7.47 (dd, 1H), 7.50 (dd, 1H), 7.82 (s, 1H), 8.34 (s, 1H), 9.56 (s, 1H); Mass Spectrum: 403.2, 405.2.

Example B Preparation of 4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy}quinazoline (Compound (I) free base)

2-Chloro-N-methylacetamide (24.22 g, 223.1 mmol) and 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline dihydrochloride (86.00 g, 160.9 mmol), were slurried in acetonitrile (537 ml). To the stirred suspension, at ambient temperature, was added triethylamine (101 ml, 723.9 mmol). The reaction was heated to 75°C held for 5 hours. The solution was cooled to 70°C and ethanol (268 ml) added. The reaction was cooled to 45°C and water (9.6 ml) added. Compound (I) (0.42 g) was added to establish crystallisation and then the slurry cooled to 20°C over 2 hours. After stirring for a further 12 hours the product was isolated by filtration. The filter cake was washed twice with acetonitrile (102 ml): ethanol (51 ml): water (1.8 ml) and then with water (153 ml). The product was dried *in vacuo* at 60°C to give the title compound as a white solid (45.9g, 60%); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.76 - 1.87 (m, 2 H) 2.01 - 2.11 (m, 2 H) 2.35 - 2.44 (m, 2 H) 2.64 (d, *J*=4.74 Hz, 3 H) 2.72 - 2.80 (m, 2 H) 2.95 (s, 2 H) 3.95 (s, 3 H) 4.51 - 4.63 (m, 1 H) 7.23 (s, 1 H) 7.29 (td, *J*=8.08, 1.29 Hz, 1 H) 7.46 - 7.58 (m, 2

H) 7.75 (q, $J=4.60$ Hz, 1 H) 7.83 (s, 1 H) 8.38 (s, 1 H) 9.59 (s, 1 H) Mass spectrum: MH^+ 474.

The 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline dihydrochloride used as the starting material was prepared as follows:

5 **Step 1: 6-{[(1-*tert*-Butoxycarbonyl)piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxy quinazoline**

4-(3-Chloro-2-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (prepared as described in Step 2 of Example A; 60.00 g, 0.1828 mol), *tert*-Butyl (4-methanesulfonyloxy)piperidine-1-carboxylate (88.04 g, 0.3107 mol) and potassium carbonate (30.31 g, 0.2193 mol) were suspended in ethanol (584 ml) and water (58 ml), and the mixture was heated to reflux with stirring.. Heating was continued at reflux for 16.5 hours. The mixture was then cooled to 70°C and water (234 ml) was added over 60 minutes.

The batch was stirred at 65°C for a further 2 hours to establish crystallisation. The slurry was cooled to 20°C over 6 hours. The product was isolated by filtration. The filter cake was slurried with aqueous ethanol (ethanol 117 ml, water 58 ml) and then displacement washed with aqueous ethanol (ethanol 117 ml, water 58 ml). The filter cake was then slurried with water (175 ml) and then displacement washed with water (175 ml). The product was dried *in vacuo* at 40°C to give the title compound (81.5 g, 84%); 1H NMR (500 MHz, DMSO- d_6) δ ppm 1.42 (s, 9 H) 1.60 - 1.70 (m, 2 H) 1.96 - 2.04 (m, 2 H) 3.23 - 3.30 (m, 2 H) 3.65 - 3.75 (m, 2 H) 3.95 (s, 3 H) 4.68 - 4.75 (m, 1 H) 7.24 (s, 1 H) 7.29 (t, $J=8.06$ Hz, 1 H) 7.49 (t, $J=7.50$ Hz, 1 H) 7.54 (t, $J=7.19$ Hz, 1 H) 7.88 (s, 1 H) 8.39 (s, 1 H) 9.57 (s, 1 H); Mass Spectrum: 503.5, 505.5.

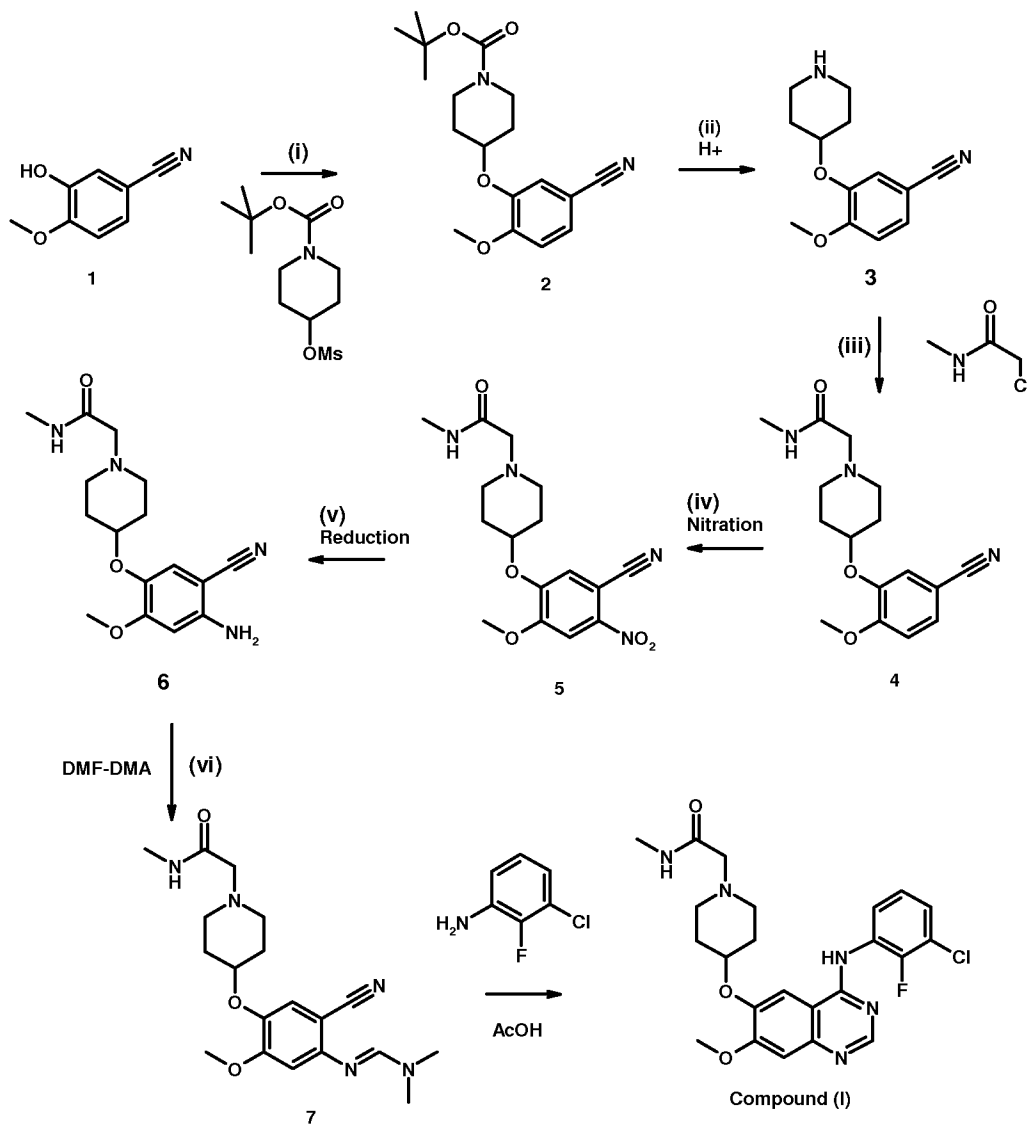
25 **Step 2: 4-(3-chloro-2-fluoroanilino)-7-methoxy-6-[(piperidin-4-yl)oxy]quinazoline dihydrochloride**

6-{[(1-*tert*-Butoxycarbonyl)piperidin-4-yl]oxy}-4-(3-chloro-2-fluoroanilino)-7-methoxyquinazoline (10.00 g, 0.1879 mol) was suspended in industrial methylated spirits (95 ml), and heated to 35°C with stirring. Hydrochloric acid (6.59 ml, approximately 0.7891 mol) was charged to the vessel allowing an exotherm of approximately 5.5°C to occur. During the charging of the acid, the suspension dissolved to give a clear solution. The solution was heated slowly to 70°C over approximately 90 minutes, and then held at 70°C for a further 1 hour. The reaction is then cooled to 0°C over 4 hours during which

time the product crystallises. The product was isolated by filtration and then filter cake was washed twice with industrial methylated spirits (2 x 14 ml). The product was dried *in vacuo* at 50°C to give the title product (9.04 g, 88%); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.91 - 2.01 (m, 2 H) 2.27 - 2.35 (m, 2 H) 3.15 - 3.26 (m, 2 H) 3.26 - 3.35 (m, 2 H) 4.02 (s, 3 H) 5.07 - 5.15 (m, 1 H) 7.35 (td, *J*=8.08, 1.29 Hz, 1 H) 7.46 (s, 1 H) 7.52 (ddd, *J*=8.03, 5.23 Hz, 1 H) 7.63 (ddd, *J*=8.22, 6.76, 1.62 Hz, 1 H) 8.83 (s, 1 H) 8.91 (s, 1 H) 9.02 - 9.13 (m, 1 H) 9.20 - 9.31 (m, 1 H) 12.51 (br. s., 1 H)); Mass Spectrum: 403.2, 405.2

Example C Preparation of 4-(3-Chloro-2-fluoroanilino)-7-methoxy-6-{{1-(N-methylcarbamoylmethyl)piperidin-4-yl}oxy}quinazoline (Compound (I))

Compound (I) was prepared according to the scheme shown below:



2-[4-(5-cyano-4-{{[(dimethylamino)methylene]amino}-2-methoxyphenoxy}piperidin-1-yl)-N-methylacetamide (**7**, 7.00g, 17.71mmoles), was suspended in methoxybenzene (35.8g). Acetic acid (16.6g) was charged and to the resulting solution was added 3-chloro-2-fluoroaniline (2.71g, 18.07mmoles). The reaction mixture was heated at 90°C for 20 hours then cooled to 20°C. Water (37.04g) was charged to the reaction mixture, and the organic

layer discarded. To the resulting aqueous mixture was charged isopropanol (39.00g), followed by aqueous ammonia (20.79g, 25%). The

reaction mixture was heated to 30°C and seeded with Compound (I), which induced crystallisation. The reaction was then cooled to 0°C and the product isolated by filtration.

The filter cake was washed twice with a mixture of water (7.28g) and isopropanol (4.68g), then dried to afford the Compound (I) (5.65g, 55% yield); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.79 (m, 2 H) 2.04 (m, 2 H) 2.38 (m, 2 H) 2.62 (d, *J*=4.5 Hz, 3 H) 2.74 (m, 2 H) 2.94 (s, 2 H) 3.93 (s, 3 H) 4.56 (tt, *J*=8.1, 3.8 Hz, 1 H) 7.21 (s, 1 H) 7.28 (m, 1 H) 7.50 (m, 2 H) 7.73 (q, *J*=4.5 Hz, 1 H) 7.81 (s, 1 H) 8.36 (s, 1 H) 9.56 (br.s, 1 H); Mass Spectrum: *m/z* (M + H)⁺ 474.2, 476.2.

The 2-[4-(5-cyano-4-{[(dimethylamino)methylene]amino}-2-methoxyphenoxy)piperidin-1-yl]-*N*-methyleacetamide (7), used as the starting material was prepared as follows:

Step 1. Preparation of tert-butyl 4-(5-cyano-2-methoxyphenoxy)piperidine-1-carboxylate (2)

3-hydroxy-4-methoxybenzonitrile (1, 6.00g, 39.62mmole), *tert*-butyl (4-methanesulfonyloxy)piperidine-1-carboxylate (16.6g, 59.44mmoles) (Chemical & Pharmaceutical Bulletin 2001, 49(7), 822-829); and potassium carbonate (6.71g, 47.55mmoles) were suspended in isopropanol (78.98g) and the mixture was heated at reflux with stirring. Additional *tert*-butyl (4-methanesulfonyloxy)piperidine-1-carboxylate (2.08g, 7.43mmoles) was added to push the reaction to completion. The mixture was then cooled and quenched by the addition of water (100.47g). Seeding with *tert*-butyl 4-(5-cyano-2-methoxyphenoxy)piperidine-1-carboxylate (2) followed by cooling to 0°C resulted in a crystalline product, which was isolated by filtration. The filter cake was washed with a mixture of water (8.86g) and isopropanol (6.97g), followed by water (23.64g) and then dried to give the title compound (10.75g, 80% yield); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.39 (s, 9 H) 1.48 (m, 2 H) 1.88 (m, 2 H) 3.13 (m, 2 H) 3.67 (m, 2 H) 3.83 (s, 3 H) 4.56 (tt, *J*=8.1, 3.8 Hz, 1 H) 7.13 (d, *J*=8.4 Hz, 1 H) 7.42 (dd, *J*=8.4, 1.9 Hz, 1 H) 7.51 (d, *J*=1.9 Hz, 1 H); Mass Spectrum: *m/z* (M + H)⁺ 333.1.

Step 2. Preparation of 4-methoxy-3-(piperidin-4-yloxy)benzonitrile (3)

Tert-butyl 4-(5-cyano-2-methoxyphenoxy)piperidine-1-carboxylate (2, 39.31g, 118.26mmoles) was suspended in ethanol (155.53g) and heated to 40°C. To this slurry was

slowly added HCl (46.61g, 573.04mmoles). The mixture was heated to 60°C and held for 3 hours. The reaction mixture was cooled to 20°C and seed was charged initiating crystallisation. The resulting solid was isolated by filtration at 0°C, washed twice with ethanol (62.21g) and then dried to give the title compound as the hydrochloride salt (29.84g, 77% yield); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.84 (m, 2 H) 2.09 (m, 2 H) 3.02 (ddd, *J*=12.7, 8.9, 3.4 Hz, 2 H) 3.20 (m, 2 H) 3.84 (s, 3 H) 4.63 (tt, *J*=7.7, 3.6 Hz, 1 H) 7.15 (d, *J*=8.5 Hz, 1 H) 7.45 (dd, *J*=8.5, 1.9 Hz, 1 H) 7.56 (d, *J*=1.9 Hz, 1 H) 9.16 (br. s, 2 H); Mass Spectrum: *m/z* (M + H)⁺ 233.2.

Step 3. Preparation of 2-[4-(5-cyano-2-methoxyphenoxy)piperidin-1-yl]-N-methylacetamide (4)

4-Methoxy-3-(piperidin-4-yloxy)benzonitrile hydrochloride salt (**3**, 28.36g, 95.82mmoles), 2-chloro-N-methylacetamide (12.37g, 114.98mmoles) and potassium carbonate (33.11g, 239.55mmoles) were suspended in acetonitrile (161.36g). The reaction mixture was heated at reflux for 3 hours. The reaction mixture was cooled to 20°C and water (386.26g) was charged. The reaction was heated to 75°C and the volume reduced by distillation. Upon cooling crystallisation occurred. The resulting solid was isolated by filtration, washed twice with water (77.25g and 128.75g) and then dried to give the title compound (27.95g, 94% yield); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.68 (m, 2 H) 1.91 (m, 2 H) 2.29 (m, 2 H) 2.61 (d, *J*=4.7 Hz, 3 H) 2.67 (m, 2 H) 2.88 (s, 2 H) 3.83 (s, 3 H) 4.41 (tt, *J*=8.3, 4.0 Hz, 1 H) 7.11 (d, *J*=8.4 Hz, 1 H) 7.40 (dd, *J*=8.4, 1.9 Hz, 1 H) 7.47 (d, *J*=1.9 Hz, 1 H) 7.68 (q, *J*=4.7 Hz, 1 H); Mass Spectrum: *m/z* (M + H)⁺ 304.2.

Step 4. Preparation of 2-[4-(5-cyano-2-methoxy-4-nitrophenoxy)piperidin-1-yl]-N-methylacetamide (5)

2-[4-(5-Cyano-2-methoxyphenoxy)piperidin-1-yl]-N-methylacetamide (**4**, 8.78g, 26.11mmoles) was suspended in acetic acid (22.82g, 364.87mmoles) and the resulting reaction mixture cooled to 5°C. To this was added sulfuric acid (23.64g, 234.95mmoles) maintaining the reaction temperature below 30°C. To the resulting solution was added nitric acid (2.40g, 26.63mmoles). The reaction mixture was then heated to 35°C and held for 3 hours. Additional nitric acid (117 mg, 1.31 mmoles) and sulphuric acid (1.31g 13.1 mmoles) were charged and the reaction mixture was heated at 35°C for 30 minutes. The solution was cooled to 20°C and quenched with aqueous ammonia (92.45g 1.36 moles), resulting in an increase in temperature to 50°C. To the resulting slurry was added,

propionitrile (61.58g 1.12 moles) and water (19g). The reaction mixture was heated to 80°C resulting in a clear solution, which upon settling gave two layers. The bottom layer was removed. The reaction mixture was cooled to 20°C resulting in a thick slurry. The solid was isolated by filtration, washed with propionitrile (6.16g 112.0 mmols) and dried to afford the title compound (7.44g, 82% yield); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.72 (m, 2 H) 1.97 (m, 2 H) 2.35 (m, 2 H) 2.61 (d, *J*=4.7 Hz, 3 H) 2.66 (m, 2 H) 2.90 (s, 2 H) 3.96 (s, 3 H) 4.73 (tt, *J*=8.4, 4.0 Hz, 1 H) 7.71 (q, *J*=4.7 Hz, 1 H) 7.82 (s, 1 H) 7.86 (s, 1 H). Mass Spectrum: *m/z* (M + H)⁺ 349.2

Step 5. Preparation of 2-[4-(4-amino-5-cyano-2-methoxyphenoxy)piperidin-1-yl]-N-methylacetamide (6)

2-[4-(5-Cyano-2-methoxy-4-nitrophenoxy)piperidin-1-yl]-N-methylacetamide (**5**, 7.42g, 19.38mmoles) was suspended in water (44.52g) and methanol (5.35g). To this was added sodium dithionite (11.91g, 58.15mmoles) and the resulting reaction mixture was heated to 60°C. To the reaction mixture was added hydrochloric acid (46.98g, 463.89mmoles)), resulting in a solution, which was held at 60°C for 3 hours. The reaction mixture was then allowed to cool to 20°C. Aqueous sodium hydroxide (15.51g 182.2 mmols) was charged followed by 2-methyltetrahydrofuran (58.0g). The reaction mixture was heated to 60°C, which upon settling gave two layers and the lower aqueous layer was discarded. The volume of the reaction mixture was reduced by vacuum distillation and methyl tert-butyl ether (18.54g) was added to give a slurry which was cooled to 10°C. and then the solid was collected by filtration. The solid was washed with 2-methyltetrahydrofuran (5.8g) and dried to give the title compound (5.4g, 78% yield); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.62 (m, 2 H) 1.82 (m, 2 H) 2.20 (m, 2 H) 2.60 (d, *J*=4.7 Hz, 3 H) 2.65 (m, 2 H) 2.86 (s, 2 H) 3.72 (s, 3 H) 4.00 (tt, *J*=8.3, 4.0 Hz, 1 H) 5.66 (br. s, 2 H) 6.39 (s, 1 H) 6.94 (s, 1 H) 7.65 (q, *J*=4.7 Hz, 1 H)

Mass Spectrum: *m/z* (M + H)⁺ 319.2

Step 6. Preparation of 2-[4-(5-cyano-4-[(dimethylamino)methylene]amino)-2-methoxyphenoxy)piperidin-1-yl]-N-methylacetamide (7)

2-[4-(4-Amino-5-cyano-2-methoxyphenoxy)piperidin-1-yl]-N-methylacetamide (**6**, 18.21g, 52.05mmoles) was suspended in 2-methyltetrahydrofuran (99.62g). To this was added acetic acid (162.79mg), and N,N-dimethylformamide dimethyl acetal (DMA) (8.63g, 70.27mmoles) and the resulting reaction mixture was heated at 76°C for 16hrs.

Additional N,N-dimethylformamide dimethyl acetal (639.41mg, 5.20mmoles) was added to the reaction mixture to ensure the reaction completed. The reaction mixture was cooled to 30°C during which time crystallisation occurred. The resulting solid was isolated by filtration, washed with 2-methyltetrahydrofuran (14.23g) and dried to afford the title compound (19.53g, 97% yield); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.65 (m, 2 H) 1.86(m, 2 H) 2.24 (m, 2 H) 2.60 (d, *J*=4.7 Hz, 3 H) 2.66 (m, 2 H) 2.87 (s, 2 H) 2.95 (s, 3 H) 3.04 (s, 3 H) 3.81 (s, 3 H) 4.19 (tt, *J*=8.2, 3.8 Hz, 1 H) 6.72 (s, 1 H) 7.15 (s, 1 H) 7.67 (q, *J*=4.7 Hz, 1 H) 7.90 (s, 1 H); Mass Spectrum: *m/z* (M + H)⁺ 374.2.

Example D

Preparation of Compound (I) Difumarate Form A: 2-[4-({4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]-N-methylacetamide di-[(2E)-but-2-enedioate] Form A

A solution of fumaric acid (2.7 g, 23.22mmol) in methanol (95 ml) was added to a mixture of 2-[4-({4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]-N-methylacetamide (Compound (I)) (5.62g at 89% w/w, 10.55 mmol) in isopropanol (100 ml) maintaining the temperature >65°C. The mixture was heated at reflux for one hour before clarification. The reaction mixture was cooled to 30°C over 90 minutes and held for 30 minutes to establish crystallisation. The reaction was cooled to 0°C over 2 hours and held for 1 hour before isolation by filtration. The filter cake was washed twice with cold isopropanol (2 x 10 ml) and dried *in vacuo* at 50°C to give the title compound as a white solid (5.84 g, 78%); ¹H NMR Spectrum: (DMSO) 1.85 (m, 1H), 2.08 (m, 1H), 2.50 (m, 1H), 2.66 (d, 3H), 2.83 (m, 1H), 3.05 (s, 2H), 3.96 (s, 3H), 4.58 (m, 1H), 6.64 (s, 4H), 7.23 (s, 1H), 7.28 (m, 1H), 7.46 (ddd, 1H), 7.55 (m, 1H), 7.70 (broad q, 1H), 7.85 (s, 1H), 8.38 (s, 1H).

Example E

Preparation of Compound (I) Difumarate Form A: 2-[4-({4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]-N-methylacetamide di-[(2E)-but-2-enedioate] Form A

A solution of fumaric acid (1.4 kg, 12.1mol) in methanol (26.6 kg) was added to a mixture of 2-[4-({4-[(3-chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}oxy)piperidin-1-yl]-N-methylacetamide (Compound (I)) (2.93 kg, 84.8% w/w, 5.24mol) in isopropanol (39 kg) maintaining the temperature >65°C. A line wash of

methanol (3.6 kg) was charged. The mixture was heated at reflux for one hour before clarification, followed by a line wash of methanol (7 kg). The reaction mixture was distilled at atmospheric pressure to remove 47 kg of distillates. Isopropanol (15.8 kg) was added and the reaction mixture distilled to remove 15.6 kg of distillates. Crystallisation occurred during the distillation. Isopropanol (21 kg) was added and the reaction cooled to 0°C over 8 hours and held for 1 hour before isolation by filtration. The filter cake was washed with cold 50:50 isopropanol:MeOH (4kg) followed by cold isopropanol (4kg) and dried *in vacuo* at 50°C to give the title compound as a white solid (3.64 kg, 98%); ¹H NMR Spectrum: (DMSO) 1.85 (m, 1H), 2.08 (m, 1H), 2.50 (m, 1H), 2.66 (d, 3H), 2.83 (m, 1H), 3.05 (s, 2H), 3.96 (s, 3H), 4.58 (m, 1H), 6.64 (s, 4H), 7.23 (s, 1H), 7.28 (m, 1H), 7.46 (ddd, 1H), 7.55 (m, 1H), 7.70 (broad q, 1H), 7.85 (s, 1H), 8.38 (s, 1H).

Example F

Preparation of Compound (I) Difumarate Form A: 2-[4-(4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl]-N-methylacetamide di-[(2E)-but-2-enedioate] Form A

2-[4-(4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl]-N-methylacetamide (Compound (I)) (60.19 g at 88% w/w, 111.8 mmol) was dissolved in ethyl acetate (1550 ml). The solution was clarified by filtration and the filter washed with ethyl acetate (53 ml). The solution was cooled to 40°C. A clarified solution of fumaric acid (26.60 g, 257.0mmol) in isopropanol (408 ml) was then added over 1 hour. The filter used to clarify the fumaric acid solution was then washed with isopropanol (37 ml). After holding for 1 hour at 40°C the reaction was cooled to 20°C over 1 hour. The reaction mixture was held for 13.5 hours before isolating the product by filtration. The filter cake was washed twice with ethyl acetate (82 ml) : isopropanol (24 ml) and then dried *in vacuo* at 40°C to give the title compound as a white solid (72.32 g, 90%); ¹H NMR Spectrum: (DMSO) 1.85 (m, 1H), 2.08 (m, 1H), 2.50 (m, 1H), 2.66 (d, 3H), 2.83 (m, 1H), 3.05 (s, 2H), 3.96 (s, 3H), 4.58 (m, 1H), 6.64 (s, 4H), 7.23 (s, 1H), 7.28 (m, 1H), 7.46 (ddd, 1H), 7.55 (m, 1H), 7.70 (broad q, 1H), 7.85 (s, 1H), 8.38 (s, 1H).

Example G**Preparation of Compound (I) Difumarate Form A: 2-[4-(4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl]-N-methylacetamide di-[(2E)-but-2-enedioate] Form A**

5 2-[4-(4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl]-N-methylacetamide (Compound (I)) (2.75 g at assumed 100% w/w, 5.80 mmol) was dissolved in ethyl acetate (94 ml) and isopropanol (14 ml). The solution was distilled such that 25.2 ml of distillates were collected. The solution was cooled to 40°C. A clarified solution of fumaric acid (1.38 g, 11.90 mmol) in isopropanol (21 ml)
10 was then added over 1 hour. Compound (I) difumarate Form A seed was added (3.7 mg, 5.3 µmol). The filter used to clarify the fumaric acid solution was then washed with isopropanol (2 ml). After holding for 1 hour at 40°C the reaction was cooled to 20°C over 2 hours. The reaction mixture was held for 15 hours before isolating the product by filtration. The filter cake was washed twice with ethyl acetate (4.3 ml): isopropanol (1.2
15 ml) and then dried *in vacuo* at 40°C to give the title compound as a white solid (72.32 g, 90%); ¹H NMR Spectrum: (DMSO) 1.85 (m, 1H), 2.08 (m, 1H), 2.50 (m, 1H), 2.66 (d, 3H), 2.83 (m, 1H), 3.05 (s, 2H), 3.96 (s, 3H), 4.58 (m, 1H), 6.64 (s, 4H), 7.23 (s, 1H), 7.28 (m, 1H), 7.46 (ddd, 1H), 7.55 (m, 1H), 7.70 (broad q, 1H), 7.85 (s, 1H), 8.38 (s, 1H).

Example H

20 **Preparation of Compound (I) Difumarate Form A: 2-[4-(4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl]-N-methylacetamide di-[(2E)-but-2-enedioate] Form A**

25 2-[4-(4-[(3-Chloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl)oxy)piperidin-1-yl]-N-methylacetamide (Compound (I)) (1g, 1.86mmoles) and fumaric acid (0.44g, 3.81mmoles) were suspended in water (4.4g) and heated to 85°C. The reaction mixture was cooled to 60°C at 1°C/minute and Compound (I) Form A seed was added when the temperature was 77°C. The resulting solid was isolated by filtration, washed twice with acetone (0.70g per wash) and dried in a vacuum oven at 40°C to afford the title
30 compound (0.89g, 68% yield), ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.84 (m, 2 H) 2.08 (m, 2 H) 2.55 (m, 2 H) 2.63 (d, J=4.7 Hz, 3 H) 2.86 (m, 2 H) 3.12 (s, 2 H) 3.93 (s, 3 H)

4.59 (tt, J=7.8, 3.7 Hz, 1 H) 6.62 (s, 4 H) 7.21 (s, 1 H) 7.27 (td, J=8.1, 1.3 Hz, 1 H) 7.49 (m, 2 H) 7.86 (m, 2 H) 8.36 (s, 1 H) 9.63 (br. s., 1 H).

Compound (I) difumarate Form A is a free flowing powder. X-ray powder diffraction of Compound (I) difumarate (Figure 6) indicates that the material is crystalline. The X-Ray Powder Diffraction analysis was carried out using a Siemens D5000 powder X-ray diffractometer fitted with a scintillation detector; the X-Ray source was Cu K α , giving a wavelength of 1.54Å; data were collected over the range 2-theta 2 - 40°, in increments of 2-theta 0.02°, with 1 second per increment and was categorised into the categories identified in the table below:

% Relative Intensity*	Definition
25 – 100	vs (very strong)
10 – 25	s (strong)
3 – 10	m (medium)
1 – 3	w (weak)

* The relative intensities are derived from diffractograms measured with fixed slits.

Persons skilled in the art of X-ray powder diffraction will realise that the relative intensity of peaks can be affected by, for example, grains above 30 microns in size and non-unitary aspect ratios, which may affect analysis of samples. The skilled person will also realise that the position of reflections can be affected by the precise height at which the sample sits in the diffractometer and the zero calibration of the diffractometer. The surface planarity of the sample may also have a small effect. Hence the diffraction pattern data presented are not to be taken as absolute values (see Jenkins, R & Snyder, R.L. 'Introduction to X-Ray Powder Diffractometry' John Wiley & Sons, 1996, for further information)

Tablet formulation of Compound (I)

Compound (I) tablets may be manufactured using, for example, a wet granulation, compression and film coating process. The powdered ingredients are charged to a mixer and mixed to produce a uniform distribution of drug substance. A binder solution is prepared and added to the powders with further mixing until a suitable wet mass is formed. The wet mass is passed through a screen and the resultant granules dried to an appropriate moisture content. The dried granules are passed through an appropriately sized screen and blended with magnesium stearate before compressing into tablet cores using conventional

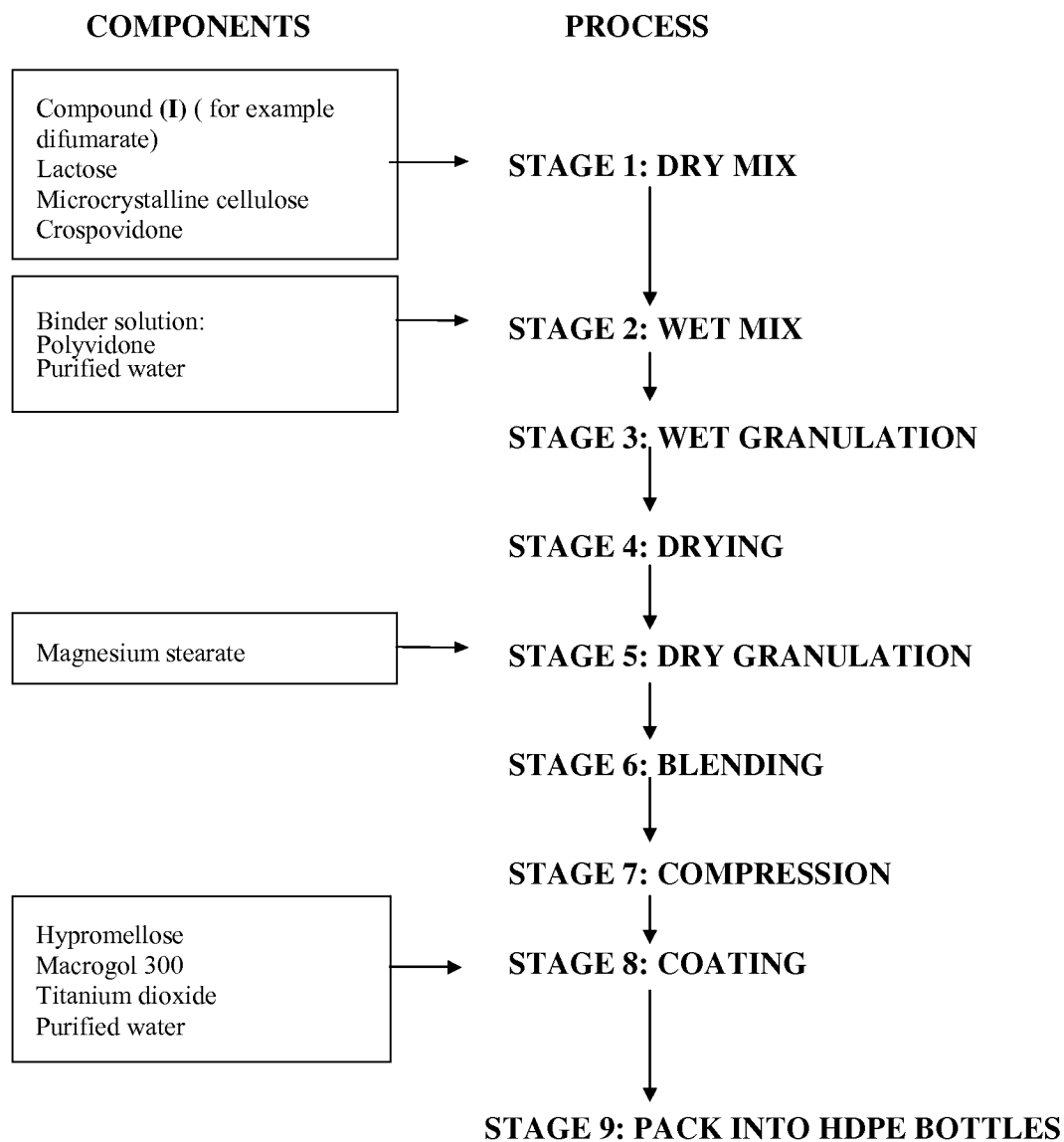
tableting equipment. The compressed cores are coated with an aqueous suspension of film coating components using a conventional perforated drum coater.

Suitable film-coated tablets containing the equivalent of 2.5, 10, 40 and 100 mg of Compound (I) free base are illustrated in the following table.

Tablet strength	2.5 mg	10 mg	40 mg	100mg
Ingredient	g/batch	g/batch	g/batch	g/batch
Tablet core				
Compound (I) Difumarate	37.25	149.0	448.1	448.1
Lactose (450 mesh)	782.75	671.0	371.9	371.9
Microcrystalline cellulose (PH101)	100.0	100.0	100.0	100.0
Crospovidone	50.0	50.0	50.0	50.0
Polyvidone	20.0	20.0	20.0	20.0
Magnesium stearate	10.0	10.0	10.0	10.0
Core tablet weight	100 mg	100 mg	133 mg	333 mg
Tablet coating				
Opadry White (03B28460)	23.0	23.0	23.3	23.0
Hypromellose ^a	15.0	15.0	15.0	15.0
Titanium dioxide ^a	5.0	5.0	5.3	5.0
Macrogol 300 ^a	3.0	3.0	3.0	3.0
Purified water ^b	177.0	177.0	176.7	177.0
Nominal coated tablet weight	102.1 mg	102.1 mg	136.1 mg	140.6 mg

- 5 a The hypromellose, macrogol 300 and titanium dioxide are included as Opadry White (03B28460), supplied by Colorcon.
- b Purified water is used as the solvent/carrier fluid during film-coating and is removed during the coating process.

A suitable manufacturing process is outlined below:



Preclinical Data Comparing Compound (I) and Gefitinib

The activity of Compound (I) was compared to that of gefitinib to assess its ability to:

- a) inhibit the activation (phosphorylation) of EGFR, ErbB2 and ErbB3 in ligand-stimulated cells; and
- b) inhibit the basal and ligand-stimulated proliferation of MCF-7 cells.

a) Comparison of Compound (I) With Gefitinib in Ligand Driven Assays**Methods:**

KB cells and MCF-7 cells were obtained from the American Type Culture Collection (ATCC) and routinely cultured in RPMI 1640 (Phenol red free) + 10% Foetal Bovine Serum + 2mM L-Glutamine.

Treatment and Lysis of Cells:

KB cells were seeded at 5000cells/well and MCF-7 cells at 4000cells/well in 96 well plates in RPMI 1640 media containing 10% FBS. Cells were incubated for 72 hours before replacing the media with serum-free RPMI 1640 media for 24 hrs. Cells were then treated with Compound (I) or gefitinib for 90 mins at concentrations ranging from 0-10 μ M. Immediately before cell lysis, MCF-7 and KB cells were incubated for 5 minutes with ligand (heregulin ("HRG")) for the MCF-7 cells and epidermal growth factor ("EGF") for the KB cells) at concentrations required to increase receptor phosphorylation to 90% of max (ED₉₀) to allow inter-assay comparison.

Measurement of p-EGFR, p-ErbB2 and p-ErbB3:

The p-EGFR status of KB cells was measured using the Human phospho-EGFR DuoSet ELISA kit (R&D systems, DYC1095). The p-ErbB2 and p-ErbB3 content of MCF-7 cells were measured using the Human phospho-ErbB2 DuoSet ELISA kit (R&D systems, DYC1768) and Human phospho-ErbB3 DuoSet ELISA kit (R&D systems, DYC1769) respectively. The kits measured whole cell tyrosine phosphorylation of EGFR, ErbB2 or ErbB3. Assays were performed according to the manufacturers instructions, with 50 μ l lysate added per well.

Results:

The results are summarised in Table 1

Table 1: Compound activity against p-EGFR (in KB cells) and p-ErbB2 and p-ErbB3 (in MCF-7 cells)

Compound	p-EGFR Geo Mean IC ₅₀ (95% CIR*)	p-ErbB2 Geo Mean IC ₅₀ (95% CIR)	p-ErbB3 Geo Mean IC ₅₀ (95% CIR)
Compound (I)	0.004 (1.377)	0.003 (1.817)	0.004 (1.89)
Gefitinib	0.011 (1.601)	0.024 (2.827)	0.095 (2.18)

* Confidence Interval Ratio

Table 1 shows that Compound (I) is a statistically significantly more potent inhibitor of phospho-EGFR, phospho-ErbB2 and phospho-ErbB3 in these cells than gefitinib.

b) Compound (I) compared to gefitinib in basal or HRG-stimulated MCF-7 cell proliferation assay

Methods:

MCF-7 cells were routinely cultured in DMEM (Phenol red free) + 10% Foetal Bovine Serum + 2mM L-Glutamine.

Cells were seeded at 4000 cells per well in 96 well plates in DMEM media containing 1% charcoal/dextran-treated FBS and 2mM glutamine and allowed to settle for 4 hours prior to treatment with Compound (I) or gefitinib at concentrations ranging from 0-3µM and 0-10µg/ml respectively. Two hours following treatment, cells were incubated with 10ng/ml HRG, a concentration required to increase MCF-7 cell proliferation to 90% of max (ED₉₀). Basal wells were unstimulated with ligand. After incubation for 4 days, cell viability was assessed using a 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay.

Prior to IC₅₀ determination of HRG-stimulated compound-treated cells, mean basal growth at 96 hours was subtracted from each of the readouts so that proliferation driven

through HRG-signalling was assessed. Basal IC₅₀ values are expressed as GI₅₀ i.e. the day 0 plate cell number (baseline reading) was subtracted from the readout at 96 hours later.

Results:

The results are summarised in Tables 2 and 3.

5

Table 2: HRG-stimulated proliferation IC₅₀ value

Compound	Geo Mean IC ₅₀	95% CIR
Compound (I)	0.061μM	2.421
Gefitinib	0.386μM	5.263

Table 3 Basal proliferation GI₅₀ values

Compound	Geo Mean GI ₅₀	95% CIR
Compound (I)	1.094μM	4.423
Gefitinib	> 3μM	

10 In the KB cells, stimulation with EGF, which specifically binds to EGFR, causes phosphorylation and therefore activation of this receptor. Similarly in the MCF-7 cells HRG, which binds specifically to ErbB3 causes it to form heterodimers with ErbB2 and both receptors become phosphorylated and activated. Tables 2 and 3 show that Compound (I) is a more potent inhibitor of HRG-stimulated MCF-7 proliferation than gefitinib. These
15 effects on proliferation are believed to be due to the activities of these compounds on ErbB2/ErbB3 heterodimers, with Compound (I) being a much more potent inhibitor of this heterodimer than the more EGFR-selective compound gefitinib.

The MCF-7 basal assays represent a situation where there no increased stimulation or activation of erbB2/erbB3 heterodimerisation. Table 3 shows that even in such
20 conditions Compound (I) is a more potent inhibitor of MCF-7 proliferation than gefitinib.

Example 1**In –Vitro Study on the Concurrent Combination of Paclitaxel and Compound (I) in MCF-7 &, SKBr3 and BT474c Cells****Methods:**

5 The MCF-7 and SKBr3 cells were obtained from the American Type Culture Collection (ATCC). The BT-474 tumour cell line (human mammary carcinoma) was obtained from Dr Baselga (at Laboratorio Recerca Oncologica, Paseo Vall D'Hebron 119-129, Barcelona 08035, Spain). This cell line was subcloned and a certain population referred herein to as BT474c was obtained

10 Cells were routinely cultured in growth medium containing 10% FBS and 2mM L-Glutamine. (For SKBr3 cells 20% of FBS was added).

 Compound (I) was used as the free base.

 Where “Taxol” is referred to in this example this was paclitaxel powder ex Sigma.

Treatment with compounds

15 SKBr3 cells were seeded at 4000cells/well, BT-474c cells were seeded at 5000 cells/well in complete growth medium (10%FCS). MCF-7 cells were seeded at 6000cells/well in serum free medium. Following 4/5-hour incubation, cells were treated with Compound (I), Taxol and combinations of Compound (I) and Taxol at the concentrations described below in the Results. Following treatment with compounds the

20 MCF-7 cells were stimulated with ligand (heregulin (HRG) at 30ng/ml) and all cells were incubated with compound for 96 hours and analysed by the MTS assay described below.

MTS cell proliferation assay

 The yellow tetrazolium salt ([3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt (MTS) is reduced in

25 metabolically active cells to form insoluble purple formazan crystals, which are solubilised by a detergent. The colour can be quantified by spectrophotometer, providing an estimation of cell number. The quantity of formazan product as measured by the amount of absorbance at 490nm is directly proportional to the number of living cells in culture.

Results:Results in MCF-7 Cells

The results in MCF-7 cells using Compound (I) (0.2 μ M) + Taxol (20nM/1000nM) compared to the use of either compound (I) alone or Taxol alone are shown in Figure 1. The p-values shown in Figure 1 illustrate the effect of the combination of Compound (I)+Taxol compared with the effect of either compound alone.

The data in Figure 1 is expressed as the mean value $\pm$ standard error (SE).

Figure 1 shows that treatment of the MCF-7 cells with combinations of Compound (I) (0.2 μ M) + Taxol (20nM and 1000nM) significantly reduces cell viability compared to Taxol monotherapy alone (*P<0.05).

Results in SKBr3 Cells

In the tests on the SKBr3 cells Compound (I) and the Taxol were used at the IC₅₀ concentration for each compound (Compound (I) geometric mean IC₅₀ 0.50 μ M, and Taxol geometric mean IC₅₀ 0.0036 μ M).

The results in SKBr3 cells of using Compound (I) (IC₅₀) + Taxol (IC₅₀) combinations compared with either monotherapy alone (IC₅₀) are shown in Figure 2 in which the data is expressed as mean $\pm$ SE.

The number of viable cells when treated with IC₅₀ concentrations of Compound (I) and Taxol monotherapy alone and combinations of Compound (I) (IC₅₀) + Taxol (IC₅₀) are illustrated in Figure 2. Figure 2 shows that the Compound (I) + Taxol combination at the IC₅₀ concentration significantly reduced cell viability compared to Taxol monotherapy at its IC₅₀ concentration (*P<0.05).

Results in BT474c Cells

In the tests on the BT474c cells Compound (I) and the Taxol were used at the IC₅₀ concentration for each compound (Compound (I) 0.67 μ M $\pm$ 0.07 μ M; Taxol = 0.005 μ M $\pm$ 0.001 μ M).

The results in BT474c cells for Compound (I) (IC₅₀) + Taxol (IC₅₀) combinations compared with either monotherapy alone (IC₅₀) are shown in Figure 3 in which the data is expressed as mean $\pm$ SE.

Figure 3 shows that the number of viable cells when treated with IC₅₀ concentrations of Compound (I) and Taxol significantly reduced cell viability compared to Taxol monotherapy at the IC₅₀ concentration (*P<0.05).

Combination Index Range for Individual Cell Lines

Figure 4 shows the combination index (CI) for each of the cell lines tested with the combination according to the invention.

The CI values were generated from the monotherapy and combination data using the method described in Chou and Talalay, 1984;Adv. Enzyme Regul. 22:27-55.

Figure 4 shows that in each of the cell lines tested, all have a combination index of less than 2, therefore demonstrating a beneficial effect for the combination of Compound (I) and Taxol in the cell lines tested.

Conclusions

The Compound (I) + Taxol combination has an overall benefit compared to either single monotherapy alone. All CI values resided in the 'benefit' range.

Proliferation in the heregulin stimulated MCF-7 cells is driven by ErbB2/3 heterodimers. In the SK-Br3 cells proliferation is driven by ErbB2 homodimerisation. In the BT-474c cells proliferation is driven by ErbB2 homodimerisation and EGFR/ErbB2 heterodimerisation.

Accordingly based upon this data, combining Compound (I) with Taxol appears to be beneficial to the activity of Taxol in cell lines driven by a range of erbB hetero + homo dimers.

Example 2

In-vivo BT 474c Xenograft Study

Tolerated Dose study:

A 28 day tolerated dose study was performed using 2 female Swiss (nu/nu) mice. Animals were perorally (p.o.) dosed twice daily with Compound (I) at 12.5mg/kg and Taxol, was administered once a week intra-peritoneally (i.p) at 20mg/kg on day 0 and day 7 of the study. Body weights were measured daily and body weight loss calculated.

Results:

The combination of Compound (I) (12.5mg/kg) + Taxol (20mg/kg) was boarder-line tolerated, with maximum body weight losses of 9.8% and 7.5% observed in the 2 mice. As increased body weight loss is associated with tumour bearing animals and with

the additional effects associated with the implanting of estrogen pellets in the xenograft study, the dose of Taxol was reduced to 15mg/kg for the anti-tumour study.

Anti Tumour Studies: BT474c Xenograft

An Anti-tumour study was performed using female Swiss (nu/nu) mice. Mice were implanted with 0.36mg 60 day estrogen pellets 24 hours before being implanted subcutaneously with 5×10^6 BT474c cells and 50% matrigel/mouse. The mice used for the study were selected on day 7, with a mean tumour volume of 0.3cm^3 . Body weights were measured for the first 7 days, then twice weekly thereafter. Tumours were measured twice-weekly using callipers. Animals were dosed as detailed below:

Group 1: Control A: 1% Polysorbate 80 p.o. twice daily and

Control B: 5% Cremaphor/5% Ethanol/90% PBS i.p. once weekly.

Group 2: Compound (I) @ 12.5mg/kg p.o. twice daily.

Group 3: Taxol @ 15mg/kg i.p. once weekly (on day 0 and day 7).

Group 4: Taxol @ 7.5mg/kg i.p. once weekly (on day 0 and day 7).

Group 5: Compound (I) @ 12.5mg/kg p.o. twice daily + Taxol @ 15mg/kg i.p. once weekly (on day 0 and day 7).

Group 6: Compound (I) @ 12.5mg/kg po twice daily + Taxol @ 7.5mg/kg i.p. once weekly (on day 0 and day 7).

Results:

The Mean Tumour Volume in each group in the study is shown in Figure 5. The “tumour inhibition” for each of the treatment groups is shown in Table 4. The tumour inhibition is the % difference between the geometric mean delta volume of the tumours from one of the treatment groups and the geometric mean delta volume of the control group. The geometric delta means are calculated as the $\log_{10}$ of the final tumour volume - the $\log_{10}$ of the initial tumour volume using a T-test analysis). Accordingly, the tumour inhibition value is a measure of the relative volume change from the start of the study to the last day of study, compared to the growth of the control tumours using a T test for each of the treatments groups. Table 4: End of study (day 14) percentage changes in geometric mean delta volume (T test analysis).

5

Treatment	Tumour Inhibition
Compound (I) @ 12.5mg/kg (twice daily)	63% (p<0.001)
Taxol @ 15mg/kg (weekly)	83% (p<0.001)
Taxol @ 7.5mg/kg (weekly)	41% (p<0.01)
Compound (I) @ 12.5mg(twice daily) + Taxol @ 15mg/kg (weekly)	96% (p<0.001)
Compound (I) @ 12.5mg (twice daily) + Taxol @ 7.5mg/kg (weekly)	95% (p<0.001)

A comparison of tumour inhibition using either Compound (I) or Taxol alone compared to the combination of compound (I) and Taxol (T test analysis) is shown in Table 5. In Table 5 the tumour inhibition is calculated based upon the geometric mean delta volumes of the two groups being compared.

10

Table 5: End of study (day 14) comparison of monotherapy compared to combinations (T test analysis).

Treatment	Difference in tumour inhibition
Compound (I) @ 12.5mg/kg (twice daily) compared to the combination of Compound (I) @ 12.5mg/kg (twice daily) + Taxol @15mg/kg (weekly)	49% (p<0.001)
Compound (I) @ 12.5mg/kg (twice daily) compared to the combination of Compound (I) @ 12.5mg/kg (twice daily) + Taxol @ 7.5mg/kg (weekly)	49% (p<0.05)
Taxol @ 15mg/kg (weekly) compared to the Combination of Compound (I) @ 12.5mg/kg (twice daily) + Taxol @15mg/kg (weekly)	29% (p<0.01)
Taxol @ 7.5mg/kg (twice daily) compared to the combination of Compound (I) @ 12.5mg/kg (twice daily) + Taxol @7.5mg/kg (weekly)	62% (p<0.001)

15

Conclusions from *In-vivo* Xenograft Study:

The Compound (I) and Taxol combination showed significantly enhanced tumour growth inhibition compared to either Compound (I) or Taxol monotherapy. No apparent antagonism was observed in these *in vivo* studies when both agents were combined.

20

Although weekly Taxol monotherapy at 7.5mg/kg and 15mg/kg showed dose-dependent inhibition of tumour growth, the combination of Compound (I) at 12.5mg/kg

twice daily with either 7.5mg/kg or 15mg/kg Taxol weekly, produced greater enhancement of tumour growth inhibition.

CLAIMS

1. A combination, comprising 4-(3-chloro-2-fluoroanilino)-7-methoxy-6- {[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy} quinazoline, or a pharmaceutically acceptable salt thereof, and a taxane.

5

2. The combination as claimed in claim 1 wherein the taxane is paclitaxel.

3. The combination as claimed in claim 1 wherein the taxane is docetaxel.

10

4. The combination according to claim 1 comprising 4-(3-chloro-2-fluoroanilino)-7-methoxy-6- {[1-(N-methylcarbamoylmethyl)piperidin-4-yl]oxy} quinazoline di-fumarate and paclitaxel.

5. The combination as claimed in any one of claims 1 to 4 for use as a medicament.

15

6. A pharmaceutical composition comprising a combination as claimed in any one of claims 1 to 4 in association with a pharmaceutically acceptable diluent or carrier.

20

7. A method of treating cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a combination as claimed in any one of claims 1 to 4.

25

8. The method as claimed in claim 7 wherein the cancer is selected from breast cancer, lung cancer, gastric cancer, head and neck cancer, colorectal cancer and ovarian cancer.

9. The method as claimed in claim 7 wherein the cancer is breast cancer.

30

10. The method according to claim 7 wherein the cancer is breast cancer with non-amplified levels of erbB2.

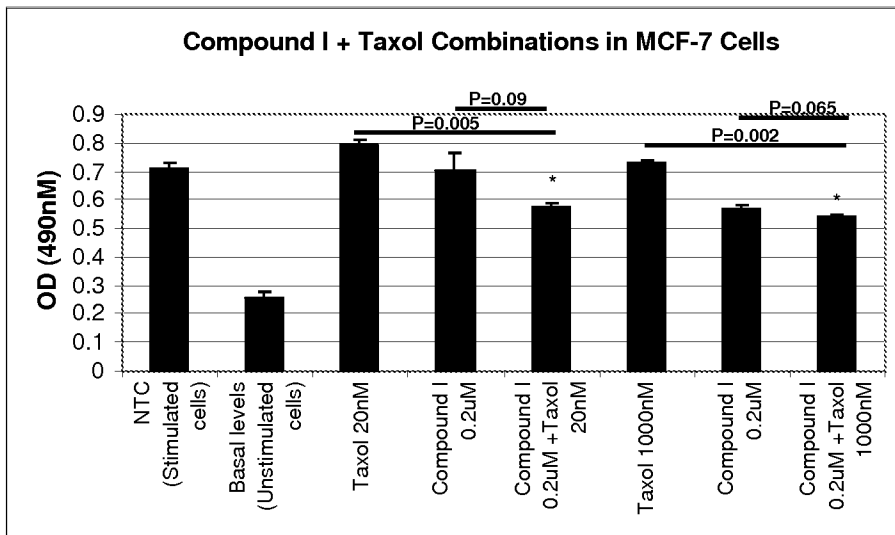
11. The method as claimed in any one of claims 7 to 10 wherein the combination is administered as the first-line treatment of the cancer.

12. The use of a combination as claimed in any one of claims 1 to 4 in the manufacture
5 of a medicament for use in the treatment of cancer, in a warm-blooded animal, such as man.

13. The use as claimed in claim 12 wherein the cancer is selected from breast cancer, lung cancer, gastric cancer, head and neck cancer, colorectal cancer and ovarian cancer.
10

14. The use according to claim 12 wherein the cancer is breast cancer with non-amplified levels of erbB2.

15. The use as claimed in any one of claims 12 to 14 wherein the combination is used
15 as the first-line treatment of the cancer.

**FIGURE 1**

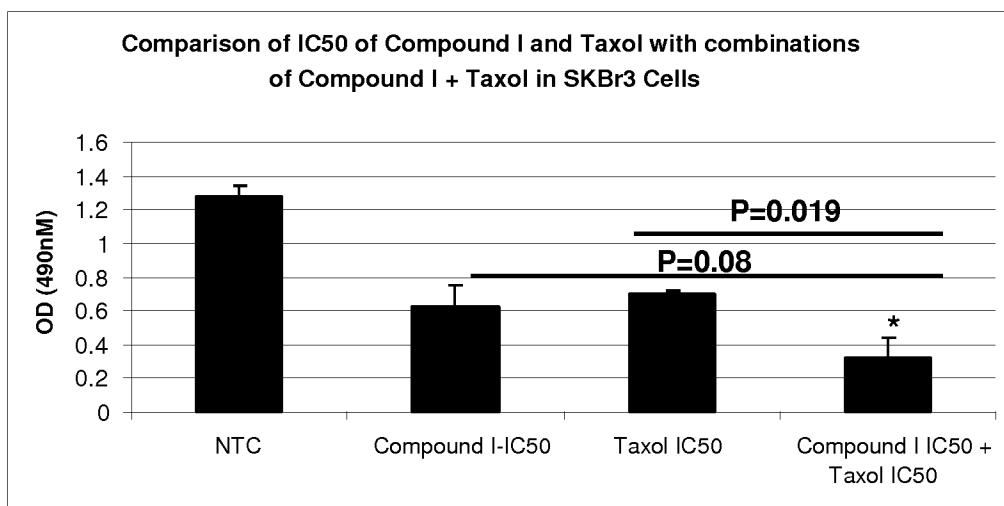


FIGURE 2

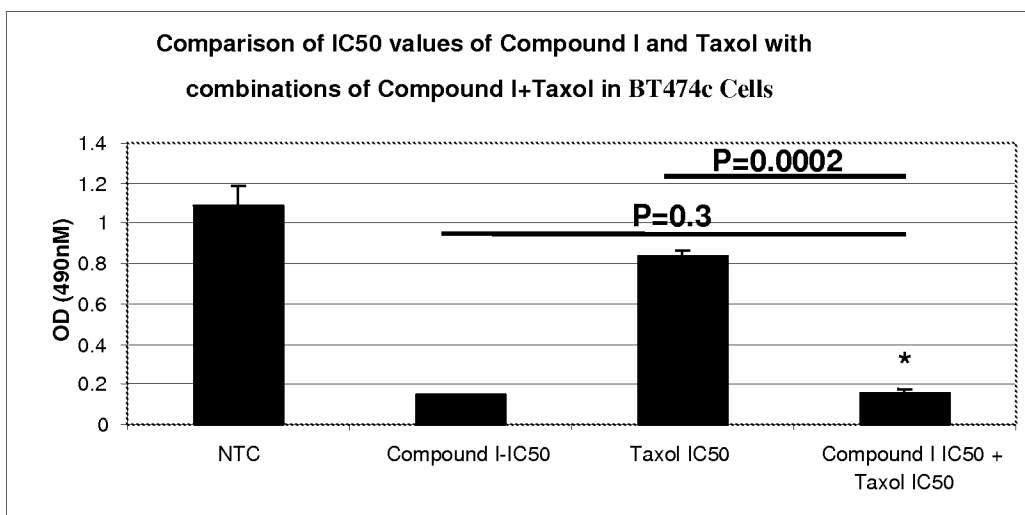


FIGURE 3

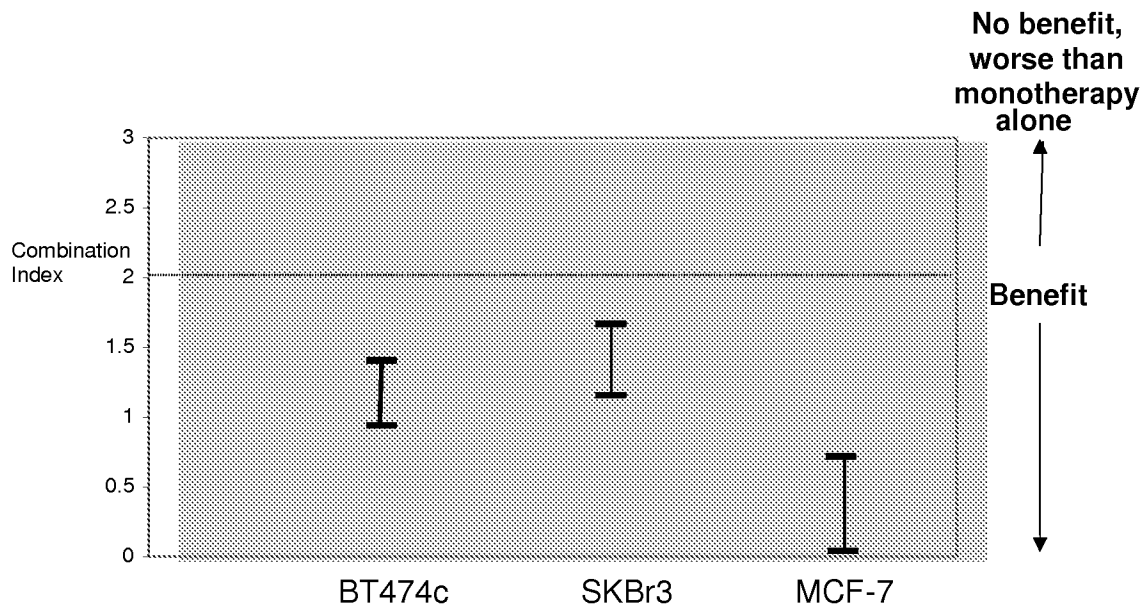


FIGURE 4

ERB0803 BT474c: Compound (I) + Taxol Combination Efficacy Study

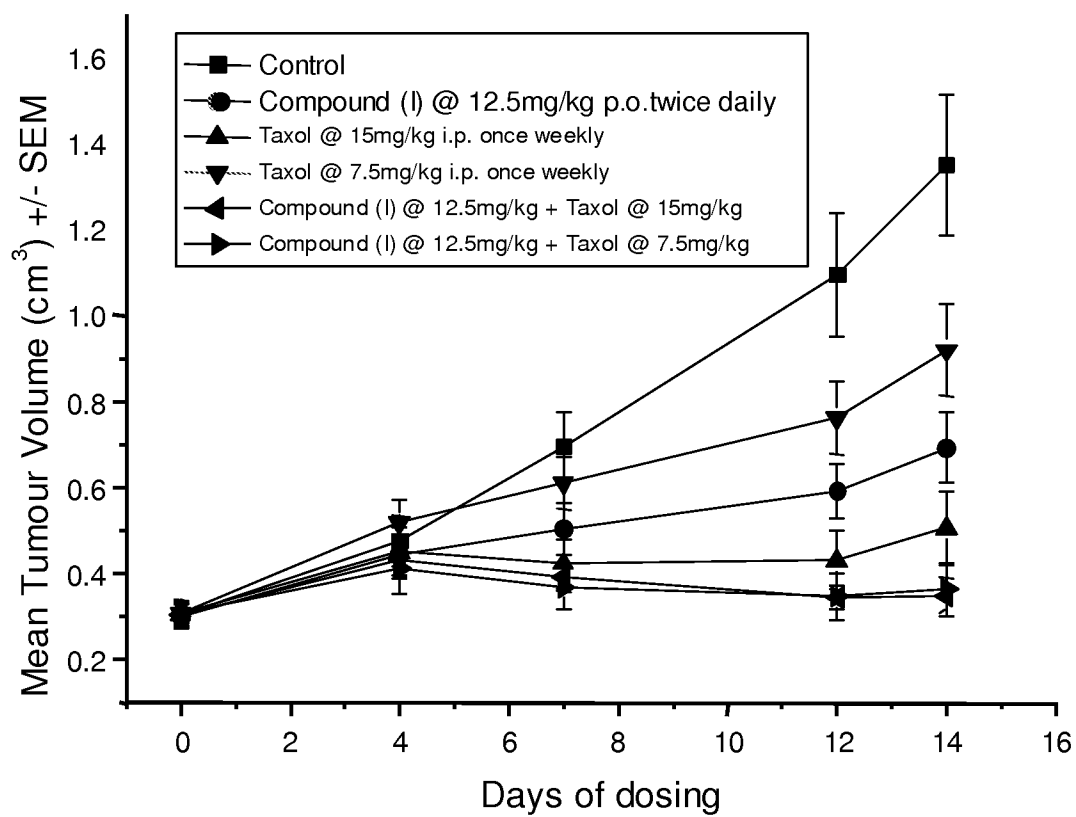
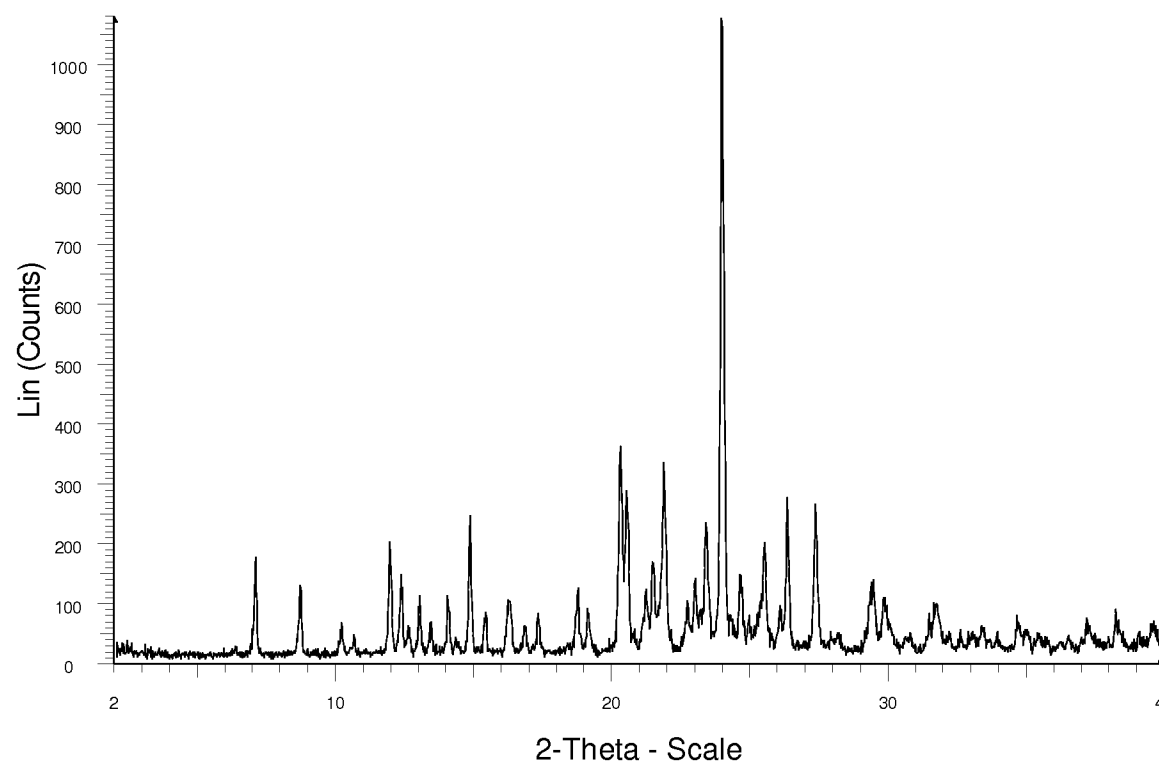


FIGURE 5

Powder X-ray diffraction pattern of Compound (I) difumarate Form A**FIGURE 6**