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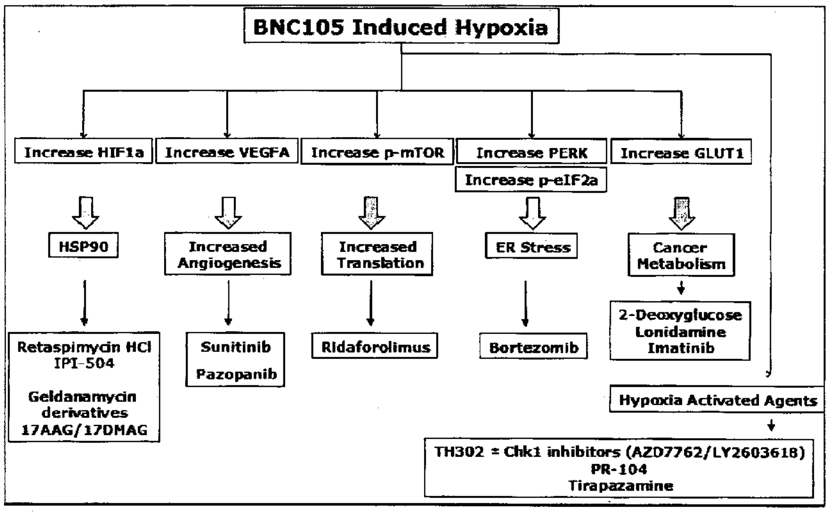
(54) Title: COMBINATION THERAPY INVOLVING A VASCULAR DISRUPTING AGENT AND AN AGENT WHICH TARGETS HYPOXIA

Figure 1



(57) **Abstract**: The present invention provides a method for treating a proliferative disease in a patient. The method comprises administering to a patient in need thereof: a) a vascular disrupting agent and (b) at least one hypoxia targeting agent. Preferred combinations are BNC105 and Pazopanib and BNC 105 and Bortezomib.

COMBINATION THERAPY INVOLVING A VASCULAR DISRUPTING AGENT AND AN AGENT WHICH TARGETS HYPOXIA

FILING DATA

[0001] This application is associated with and claims priority from Australian patent application no. 2012902291 filed on 1 June 2012 the entire contents of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates generally to new chemical combinations and methods for their use in the treatment of proliferative diseases and in particular cancer.

BACKGROUND OF THE INVENTION

[0003] Cancer is typically treated with either chemotherapy and/or radiation therapy. While often effective to destroy a significant amount of tumour cells, such therapies often leave behind a number of tumour cells that are resistant to the treatment. These resistant cells can proliferate to form new tumors that are then resistant to treatment. The use of known combinations of chemotherapeutic drugs has given rise to multidrug resistant ('MDR') tumour cells.

[0004] The mode of proliferative diseases, such as cancer, is multi-factorial. For instance, research over the last forty years has led to the realisation that cytotoxic agents (or anti-proliferative agents) includes anti-metabolic agents which interfere with microtubule formulation, alkylating agents which are able to cross-link DNA, platinum based agents which are able to interfere with DNA alkylation by blocking DNA replication, antitumor antibiotic agents, topoisomerase inhibitors, etc. In the treatment of such diseases drugs with different mechanisms may be combined (i.e, combination therapies) with beneficial effects including the effective treatment of MDR tumour cells and the minimisation of side effects such as undesirable cytotoxicity. The difficulty here is though that not all known antiproliferative agents provide useful or beneficial effects in combination and accordingly research in many laboratories is presently focused on developing new and useful anti-proliferative combination partners.

SUMMARY OF THE INVENTION

[0005] The present inventors have found that the use of a vascular disrupting agent (VDA), in particular BNC105, in conjunction with an agent which targets hypoxia, in particular Pazopanib or Bortezomib, provides a highly effective combination in the treatment of proliferative diseases. Indeed a synergistic effect has been shown with the combinations of BNC105 and Pazopanib and BNC105 and Bortezomib.

[0006] Accordingly, the present invention provides a pharmaceutical combination for treating a proliferative disease comprising: (a) a VDA, and (b) at least one other agent which targets hypoxia.

[0007] The present invention also provides a method for treating a proliferative disease including the step of administering to a patient in need thereof: (a) a VDA, and (b) at least one other agent which targets hypoxia.

[0008] The present invention also provides the use of: (a) a VDA, and (b) at least one other agent which targets hypoxia, in the manufacture of a medicament for the treatment of a proliferative disease.

[0009] The present invention also provides the use of: (a) a VDA in the manufacture of a medicament for the treatment of a proliferative disease to be used in combination with (b) at least one other agent which targets hypoxia.

[0010] The present invention also provides the use of: (b) at least one other agent which targets hypoxia in the manufacture of a medicament for the treatment of a proliferative disease to be used in combination with (a) a VDA.

[0011] The present invention further provides a pharmaceutical composition comprising (a) a VDA, and (b) at least one other agent which targets hypoxia.

[0012] It is believed that the effects in treating proliferative diseases with a combination which comprises: (a) a VDA, and (b) at least one other agent which targets hypoxia, are greater than the effects that can be achieved with either (a) or (b) alone. That is, the present combinations are believed to possess an additive or synergistic effect.

BRIEF DESCRIPTION OF THE FIGURES

[0013] **Figure 1** Rationale for therapy involving BNC105 in combination with tumor hypoxia targeting agents.

[0014] **Figure 2** Survival of mice bearing RENCA kidney tumours treated with BNC105P, Pazopanib or BNC105P + Pazopanib.

[0015] **Figure 3** Right kidney weight (mg) ± SEM of mice bearing RENCA kidney tumours treated with BNC105P, Pazopanib or BNC105P + Pazopanib.

DETAILED DESCRIPTION

[0016] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[0017] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Combination partner (a); vascular disrupting agent (VDA)

[0018] As used herein the term "vascular disrupting agents" refers to any and all compounds which are able to disrupt vasculature, in particular tumour vasculature..

[0019] Examples of suitable VDA's include:

Synthetic compounds

ABT-751 (E7010, Abbott)
MPC-6827 (Azixa^{TM}, Myriad Pharmaceuticals)
CYT997 (Cytopia)
MN-029 (Denibulin, MediciNova/Angiogene)
EPC2407 (EpiCept)

Natural products derivatives

Combretastatins
CA4 (Zybrestat™, OXiGENE)
Oxi4503 (OXiGENE)
AVE8062 (AC7700, Sanofi Aventis)
NPI-2358 (Nereus Pharmaceuticals)
TZT1027 (Soblidotin)

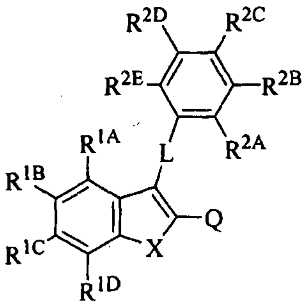
[0020] VDAs are important in the treatment of cancers primarily as a result of their capacity to selectively shut down blood flow through a tumour.

[0021] VDAs interfere with microtubule integrity, leading to cytoskeletal changes of the endothelial cells that line the blood vessels of the tumour. As a result, these usually flat cells become more rounded, and lose their cell to cell contact. These events lead to narrowing of tumour blood vessels and ultimately occlusion of blood flow through the vessels. The tumour selectivity associated with these agents results from the fact that tumour vasculature is weaker and more prone to collapse than normal vasculature. Nonetheless, a number of the dose limiting toxicities associated with VDAs are due to a reduction in blood flow in healthy tissues.

[0022] In an embodiment the VDA acts at the colchicine binding site and is based on annulated furans (e.g., benzofurans, furo[2,3-d]pyrimidin-2(1H)-ones, etc), benzothiophene and indole structural scaffolds, such as those disclosed in US 7,456,214, US 7,429,681, US 7,071,190, US 6,849,656, US 5,886,025, US 6,162,930, US 6,350,777, US 5,340,062, WO 06/084338, WO 02/060872, WO 07/087684, and WO 08/070908.

[0023] In an embodiment the VDA is selected from a agents disclosed in WO 06/084338, WO 07/087684, or WO 08/070908.

[0024] In an embodiment the VDA is selected from a compound of formula (I) and salts thereof



(I)

wherein;

X represents O, S, SO, SO_2, Se, SeO, SeO_2 or NR where R is selected from H, O, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted sulfonyl;

R^{1A} and R^{1B} each independently represents H, carboxy, cyano, dihalomethoxy, halogen, hydroxy, nitro, pentahaloethyl, phosphorylamino, phosphono, phosphinyl, sulfo, trihaloethenyl, trihalomethanethio, trihalomethoxy, trihalomethyl, optionally substituted acyl, optionally substituted acylamino, optionally substituted acylimino, optionally substituted acyliminoxy, optionally substituted acyloxy, optionally substituted arylalkyl, optionally substituted arylalkoxy, optionally substituted alkenyl, optionally substituted alkenyloxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted alkynyl, optionally substituted alkynyloxy, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted aminosulfonyl, optionally substituted aminothioacyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted oxyacyl, optionally substituted oxyacylamino, optionally substituted oxyacyloxy, optionally substituted oxyacylimino, optionally substituted oxysulfinylamino, optionally substituted oxysulfonylamino, optionally substituted oxythioacyl, optionally substituted oxythioacyloxy, optionally substituted sulfinyl, optionally substituted sulfinylamino, optionally substituted sulfonyl, optionally substituted sulphonylamino, optionally substituted thio, optionally substituted thioacyl, optionally substituted thioacylamino, or R^{1A} and R^{1B} together form an optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted cycloalkyl, or optionally substituted cycloalkenyl;

R^{1C} represents C_{1-3} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylamino, or C_{1-3} dialkylamino;

R^{1D} represents hydroxy or amino;

L represents C=O, O, S, SO, SO2, Se, SeO, SeO2, C=NZ', or NR' where Z' is H, optionally substituted alkyl, optionally substituted aryl or optionally substituted amino; and where R' is selected from H, O, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, or optionally substituted sulfonyl;

R^{2A}-R^{2E} each independently represents H, carboxy, cyano, dihalomethoxy, halogen, hydroxy, nitro, pentahaloethyl, phosphorylamino, phosphono, phosphinyl, sulfo, trihaloethenyl, trihalomethanethio, trihalomethoxy, trihalomethyl, optionally substituted acyl, optionally substituted acylamino, optionally substituted acylimino, optionally substituted acyliminoxy, optionally substituted acyloxy, optionally substituted arylalkyl, optionally substituted arylalkoxy, optionally substituted alkenyl, optionally substituted alkenyloxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted alkynyl, optionally substituted alkynyloxy, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted aminosulfonyl, optionally substituted aminothioacyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted oxyacyl, optionally substituted oxyacylamino, optionally substituted oxyacylimino, optionally substituted oxyacyloxy, optionally substituted oxysulfinylamino, optionally substituted oxysulfonylamino, optionally substituted oxythioacyl, optionally substituted oxythioacyloxy, optionally substituted sulfinyl, optionally substituted sulfinylamino, optionally substituted sulfonyl, optionally substituted sulphonylamino, optionally substituted thio, optionally substituted thioacyl, optionally substituted thioacylamino, or optionally substituted thioacyloxy; or any of R2A and R2B, R2B and R2C, R2C and R2D, and R2D and R2E, together form an optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted cycloalkyl, or optionally substituted cycloalkenyl; and

Q represents H, CN, halogen, trialkylsilyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted oxyacyl, optionally substituted acylamino, optionally substituted aminoacylamino, OR", SR" or NR"R", where each R" independently represents, H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted acyl and optionally substituted oxyacyl, or NR'"NR'", where each

R''' independently represents H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl and optionally substituted heteroaryl.

[0025] In some embodiments R^{1A}-R^{1B} and R^{2A}-R^{2E} are independently selected from the following groups:

alkyl group, preferably methyl and ethyl;

substituted alkyl group, preferably 1-hydroxyethyl, 1-thioethyl, methoxyiminomethyl, ethoxyiminomethyl, 1-(hydroxyimino)ethyl, 1-(hydroxyimino)propyl, 1-hydrazinoethyl, 1-hydrazinopropyl, hydroxyiminomethyl, 2-oxopropyl, 2-oxobutyl, 3-oxobutyl, 3-oxopentyl, nitromethyl, 1-nitromethyl, and 2-nitroethyl;

acyl group, preferably formyl acetyl, propionyl, benzoyl (optionally substituted with methyl, methoxy, halogen, nitro, trifluoromethyl or cyano);

alkoxy group, preferably methoxy and ethoxy;

oxyacyl group, preferably methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butyloxycarbonyl, isobutyloxycarbonyl;

acyloxy group, preferably acetoxy and propioxy;

substituted arylalkyl group, preferably 1-hydroxybenzyl, and 1-thiobenzyl;

sulfinyl group, preferably methylsulfinyl, ethylsulfinyl, benzene sulfinyl (optionally substituted with methyl, methoxy, halogen, nitro, trifluoromethane or cyano), methoxysulfinyl, ethoxysulfinyl;

sulfonyl group, preferably methylsulfonyl, ethylsulfonyl, benzenesulfonyl (optionally substituted with methyl, methoxy, halogen, nitro, trifluoromethane or cyano), methoxycarbo, trifluoromethane;

oxyacylamino group, preferably methoxycarbonylamido, and ethoxycarbonyl amido;

oxythioacyl group, preferably methoxythiocarbonyl and ethoxythiocarbonyl;

thioacyloxy group, preferably thionoacetoxy and thionopropionoxy;

sulphinylamino group, preferably methylsulfinylamino, ethylsulfinylamino, and benzenesulfinylamino (optionally substituted with methyl, methoxy, halogen, nitro, trifluoromethane or cyano);

amino group;

substituted amino groups, preferably residues of L-valine, D-valine, L-alanine, D-alanine, aspartic acid, and alanylserine, N-methylamino, and N,N'-dimethylamino;

sulphonylamino group, preferably methylsulfonylamino, ethylsulfonylamino and benzene sulfonylamino (optionally substituted with methyl, methoxy, halogen, nitro, trifluoromethane or cyano);

oxysulfinylamino group, preferably methoxysulfinylamino and ethoxysulfinylamino;

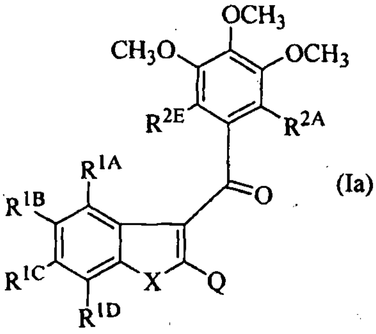
oxysulfonylamino group, preferably methoxysulfonylamino and ethoxysulfonylamino;

optionally substituted alkenyl group, preferably, 1-propenyl, vinyl, nitrovinyl, cyano vinyl, or trifluorovinyl and styryl (optionally substituted with methyl, methoxy, halogen, nitro, trifluoromethane or cyano);

alkynyl group, preferably 1-propynyl, ethynyl or trimethylsilylethynyl.

[0026] In one embodiment R^{2D}, R^{2C}, and R^{2B} are methoxy and L is a carbonyl group (C=O).

[0027] Accordingly, in this embodiment the VDAs of the present invention are represented by formula (Ia)



(Ia)

wherein;

X represents O, S, SO, SO_2, Se, SeO, SeO_2 or NR where R is selected from H, O, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted sulfonyl;

R^{1A} and R^{1B} each independently represents H, carboxy, cyano, dihalomethoxy, halogen, hydroxy, nitro, pentahaloethyl, phosphorylamino, phosphono, phosphinyl, sulfo, trihaloethenyl, trihalomethanethio, trihalomethoxy, trihalomethyl, optionally substituted acyl, optionally substituted acylamino, optionally substituted acylimino, optionally substituted acyliminoxy, optionally substituted acyloxy, optionally substituted arylalkyl, optionally substituted arylalkoxy, optionally substituted alkenyl, optionally substituted alkenyloxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted alkynyl, optionally substituted alkynyloxy, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted aminosulfonyl, optionally substituted aminothioacyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted oxyacyl, optionally substituted oxyacylamino, optionally substituted oxyacyloxy, optionally substituted oxyacylimino, optionally substituted oxysulfinylamino, optionally substituted oxysulfonylamino, optionally substituted oxythioacyl, optionally substituted oxythioacyloxy, optionally substituted sulfinyl, optionally substituted sulfinylamino, optionally substituted sulfonyl, optionally substituted sulphonylamino, optionally substituted thio, optionally substituted thioacyl, optionally substituted thioacylamino, or R^{1A} and R^{1B} together form an optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted cycloalkyl, or optionally substituted cycloalkenyl;

R^{1C} represents C_{1-3} alkoxy; C_{1-3} alkylthio, C_{1-3} alkylamino, or C_{1-3} dialkylamino;

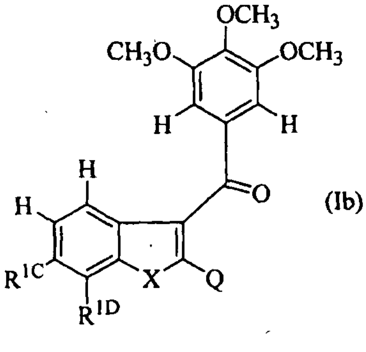
R^{1D} represents hydroxy or amino;

R^{2A} and R^{2E} independently represents H, carboxy, cyano, dihalomethoxy, halogen, hydroxy, nitro, pentahaloethyl, phosphorylamino, phosphono, phosphinyl, sulfo, trihaloethenyl, trihalomethanethio, trihalomethoxy, trihalomethyl, optionally substituted acyl, optionally substituted acylamino, optionally substituted acylimino, optionally substituted acyliminoxy, optionally substituted acyloxy, optionally substituted arylalkyl, optionally substituted arylalkoxy, optionally substituted alkenyl, optionally substituted alkenyloxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted alkynyl, optionally substituted alkynyloxy, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted aminosulfonyl, optionally substituted aminothioacyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted oxyacyl, optionally substituted oxyacylamino, optionally substituted oxyacyloxy, optionally substituted oxyacylimino, optionally substituted oxysulfinylamino, optionally substituted oxysulfonylamino, optionally substituted oxythioacyl, optionally substituted oxythioacyloxy, optionally substituted sulfinyl, optionally substituted sulfinylamino, optionally substituted sulfonyl, optionally substituted sulphonylamino, optionally substituted thio, optionally substituted thioacyl, optionally substituted thioacylamino, or optionally substituted thioacyloxy; and

Q represents H, CN, halogen, trialkylsilyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted oxyacyl, optionally substituted acylamino, optionally substituted aminoacylamino, OR", SR" or NR"R", where each R" independently represents, H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted acyl and optionally substituted oxyacyl, or NR'"NR'", where each R'" independently represents H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl and optionally substituted heteroaryl.

[0028] In another embodiment, R^{1A}, R^{1B}, R^{2A} and R^{2E} represent H and R^{1C} represents C_{1-3} alkoxy.

[0029] Accordingly, in this embodiment the VDA of the present invention is represented by formula (Ib)



(Ib)

wherein;

X represents O, S, SO, SO_2, Se, SeO, SeO_2 or NR where R is selected from H, O, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted sulfonyl;

R^{1C} represents C_{1-3} alkoxy;

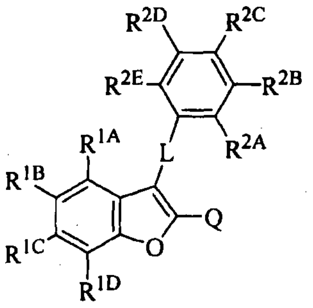
R^{1D} represents hydroxy or amino;

Q represents H, CN, halogen, trialkylsilyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted oxyacyl, optionally substituted acylamino, optionally substituted aminoacylamino, OR", SR" or NR"R", where each R" independently represents, H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted acyl and optionally substituted oxyacyl, or NR'"NR'", where each R'" independently represents H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl and optionally substituted heteroaryl.

[0030] In a preferred embodiment R^{1C} represents methoxy.

[0031] For the compounds represented by formulae I, Ia and Ib, X is preferably selected from O, S and NR. More preferably X is O or NR and most preferably X is O.

[0032] Accordingly, in another embodiment the VDA is represented by formula II:



(II)

wherein;

R^{1A} and R^{1B} each independently represents H, carboxy, cyano, dihalomethoxy, halogen, hydroxy, nitro, pentahaloethyl, phosphorylamino, phosphono, phosphinyl, sulfo, trihaloethenyl, trihalomethanethio, trihalomethoxy, trihalomethyl, optionally substituted acyl, optionally substituted acylamino, optionally substituted acylimino, optionally substituted acyliminoxy, optionally substituted acyloxy, optionally substituted arylalkyl, optionally substituted arylalkoxy, optionally substituted alkenyl, optionally substituted alkenyloxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted alkynyl, optionally substituted alkynyloxy, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted aminosulfonyl, optionally substituted aminothioacyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted oxyacyl, optionally substituted oxyacylamino, optionally substituted oxyacyloxy, optionally substituted oxyacylimino, optionally substituted oxysulfinylamino, optionally substituted oxysulfonylamino, optionally substituted oxythioacyl, optionally substituted oxythioacyloxy, optionally substituted sulfinyl, optionally substituted sulfinylamino, optionally substituted sulfonyl, optionally substituted sulphonylamino, optionally substituted thio, optionally substituted thioacyl, optionally substituted thioacylamino, or R^{1A} and R^{1B} together form an optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted cycloalkyl, or optionally substituted cycloalkenyl;

R^{1C} represents C_{1-3} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylamino, or C_{1-3} dialkylamino;

R^{1D} represents hydroxy or amino;

L represents C=O, O, S, SO, SO_2, Se, SeO, SeO_2, C=NZ', or NR' where Z' is H, optionally substituted alkyl, optionally substituted aryl or optionally substituted amino; and where R' is selected from H, O, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, or optionally substituted sulfonyl;

R^{2A}-R^{2E} each independently represents H, carboxy, cyano, dihalomethoxy, halogen, hydroxy, nitro, pentahaloethyl, phosphorylamino, phosphono, phosphinyl, sulfo, trihaloethenyl, trihalomethanethio, trihalomethoxy, trihalomethyl, optionally substituted acyl, optionally substituted acylamino, optionally substituted acylimino, optionally substituted acyliminoxy, optionally substituted acyloxy, optionally substituted arylalkyl, optionally substituted arylalkoxy, optionally substituted alkenyl, optionally substituted alkenyloxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted alkynyl, optionally substituted alkynyloxy, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted aminosulfonyl, optionally substituted aminothioacyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted oxyacyl, optionally substituted oxyacylamino, optionally substituted oxyacylimino, optionally substituted oxyacyloxy, optionally substituted oxysulfinylamino, optionally substituted oxysulfonylamino, optionally substituted oxythioacyl, optionally substituted oxythioacyloxy, optionally substituted sulfinyl, optionally substituted sulfinylamino, optionally substituted sulfonyl, optionally substituted sulphonylamino, optionally substituted thio, optionally substituted thioacyl, optionally substituted thioacylamino, or optionally substituted thioacyloxy; or any of R^{2A} and R^{2B}, R^{2B} and R^{2C}, R^{2C} and R^{2D}, and R^{2D} and R^{2E}, together form an optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted cycloalkyl, or optionally substituted cycloalkenyl; and

Q represents H, CN, halogen, trialkylsilyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted oxyacyl, optionally substituted acylamino, optionally substituted aminoacylamino, OR", SR" or NR"R", where each R" independently represents, H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted acyl and optionally substituted oxyacyl, or NR'"NR'", where each R'" independently represents H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl and optionally substituted heteroaryl.

[0033] In this embodiment it is preferred that L is a carbonyl group (C=O). Also, preferably at least one of R^{2D}, R^{2C} or R^{2B} represents a hydroxy or C_{1-3} alkoxy group. More preferably when X=O, L is a carbonyl group an R^{2D}, R^{2C} and R^{2B} represent methoxy. Even more preferably when X=O, L is a carbonyl group, R^{2D}, R^{2C}, and R^{2B} represent methoxy and R^{1A}, R^{1B}, R^{2A}, R^{2E} are H.

[0034] Furthermore, for the compounds of formula (I), (Ia), (Ib) and (II) it is preferred that Q represents H, CN, optionally substituted C_{2-4} alkynyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{1-4} alkyl, hydroxy, optionally substituted oxyacyl, NR"R", SR" (where each R" is independently H, optionally substituted C_{1-4}alkyl, optionally substituted heterocyclyl, optionally substituted heteroaryl), NR'''NR''' (where each R''' is independently H, C_{1-3} alkyl), optionally substituted acylamino, or halogen.

[0035] In some embodiments Q is independently selected from the following groups:

H;

CN;

halogen, preferably Br or Cl;

alkyl group, preferably methyl, ethyl, propyl, butyl;

substituted alkyl group, preferably amino, oxyacylaminoalkyl and oxysulphonylaminoalkyl;

optionally substituted alkenyl, preferably ethenyl, 2-alkylethenyl, 2-oxyacylethenyl, 2-aminoacylethenyl;

optionally substituted alkynyl, preferably ethynyl, 2-alkylethynyl;

optionally substituted oxyacyl;

OR'', preferably hydroxy, methoxy, ethoxy;

NR''R'', preferably NH_2, alkylamino, dialkylamino, heteroarylamino, aminoalkylamino, hydroxyalkylamino, alkoxyalkylamino, oxyacylalkylamino, oxyacylaminoalkylamino, guanidinoalkylamino;

SR'', preferably alkylthio, aminoalkylthio, heteroarylthio, aminoalkylthio, hydroxyalkylthio, alkoxyalkylthio, oxyacylalkylthio, oxyacylaminoalkylthio, guanidinoalkylthio;

hydrazine.

Chemical Definitions

[0036] "Alkyl" refers to monovalent alkyl groups which may be straight chained or branched and preferably have from 1 to 10 carbon atoms or more preferably 1 to 6 carbon atoms, and even more preferably 1 to 3 carbon atoms. Examples of such alkyl groups include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, and the like.

[0037] "Alkylene" refers to divalent alkyl groups preferably having from 1 to 10 carbon atoms and more preferably 1 to 6 carbon atoms, and even more preferably 1 to 3 carbon atoms. Examples of such alkylene groups include methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), and the propylene isomers (e.g., $-CH_2CH_2CH_2-$ and $–CH(CH_3)CH_2-$), and the like.

[0038] "Aryl" refers to an unsaturated aromatic carbocyclic group having a single ring (eg., phenyl) or multiple condensed rings (eg., naphthyl or anthryl), preferably having from 6 to 14 carbon atoms. Examples of aryl groups include phenyl, naphthyl and the like.

[0039] "Arylene" refers to a divalent aryl group wherein the aryl group is as described above.

[0040] "Aryloxy" refers to the group aryl-O- wherein the aryl group is as described above.

[0041] "Arylalkyl" refers to –alkylene-aryl groups preferably having from 1 to 10 carbon atoms in the alkylene moiety and from 6 to 10 carbon atoms in the aryl moiety. Such arylalkyl groups are exemplified by benzyl, phenethyl and the like.

[0042] "Arylalkoxy" refers to the group arylalkyl-O- wherein the arylalkyl group are as described above. Such arylalkoxy groups are exemplified by benzyloxy and the like.

[0043] "Alkoxy" refers to the group alkyl-O- where the alkyl group is as described above. Examples include, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

[0044] "Alkenyl" refers to a monovalent alkenyl group which may be straight chained or branched and preferably have from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and have at least 1 and preferably from 1-2, carbon to carbon, double bonds. Examples include ethenyl ($-CH=CH_2$), *n*-propenyl ($-CH_2CH=CH_2$), *iso*-propenyl ($-C(CH_3)=CH_2$), but-2-enyl ($-CH_2CH=CHCH_3$), and the like.

[0045] "Alkenyloxy" refers to the group alkenyl-O- wherein the alkenyl group is as described above.

[0046] "Alkenylene" refers to divalent alkenyl groups preferably having from 2 to 8 carbon atoms and more preferably 2 to 6 carbon atoms. Examples include ethenylene ($-CH=CH-$), and the propenylene isomers (e.g., $-CH_2CH=CH-$ and $-C(CH_3)=CH-$), and the like.

[0047] "Alkynyl" refers to alkynyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1, and preferably from 1-2, carbon to carbon, triple bonds. Examples of alkynyl groups include ethynyl ($-C\equiv CH$), propargyl ($-CH_2C\equiv CH$), pent-2-ynyl ($-CH_2C\equiv CCH_2-CH_3$), and the like.

[0048] "Alkynyloxy" refers to the group alkynyl-O- wherein the alkynyl groups is as described above.

[0049] "Alkynylene" refers to the divalent alkynyl groups preferably having from 2 to 8 carbon atoms and more preferably 2 to 6 carbon atoms. Examples include ethynylene ($-C\equiv C-$), propynylene ($-CH_2-C\equiv C-$), and the like.

[0050] "Acyl" refers to groups H-C(O)-, alkyl-C(O)-, cycloalkyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocyclyl-C(O)-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

[0051] "Oxyacyl" refers to groups HOC(O)-, alkyl-OC(O)-, cycloalkyl-OC(O)-, aryl-OC(O)-, heteroaryl-OC(O)-, and heterocyclyl-OC(O)-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

[0052] "Amino" refers to the group –NR*R* where each R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

[0053] "Aminoacyl" refers to the group –C(O)NR*R* where each R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

[0054] "Aminoacylamino" refers to the group –NR*C(O)NR*R* where each R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

[0055] "Acylamino" refers to the group –NR*C(O)R* where each R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

[0056] "Acyloxy" refers to the groups -OC(O)-alkyl, -OC(O)-aryl, -C(O)O-heteroaryl, and -C(O)O-heterocyclyl where alkyl, aryl, heteroaryl and heterocyclyl are as described herein.

[0057] "Aminoacyloxy" refers to the groups -OC(O)NR*-alkyl, -OC(O)NR*-aryl, -OC(O)NR*-heteroaryl, and -OC(O)NR*-heterocyclyl where R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

[0058] "Oxyacylamino" refers to the groups –NR*C(O)O-alkyl, -NR*C(O)O-aryl, -NR*C(O)O-heteroaryl, and NR*C(O)O-heterocyclyl where R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

[0059] "Oxyacyloxy" refers to the groups –OC(O)O-alkyl, -O-C(O)O-aryl, -OC(O)O-heteroaryl, and –OC(O)O-heterocyclyl where alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

[0060] "Acylimino" refers to the groups –C(NR*)-R* where each R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

[0061] "Acyliminoxy" refers to the groups –O-C(NR*)-R* where each R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

[0062] "Oxyacylimino" refers to the groups –C(NR*)-OR* where each R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

[0063] "Cycloalkyl" refers to cyclic alkyl groups having a single cyclic ring or multiple condensed rings, preferably incorporating 3 to 8 carbon atoms. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

[0064] "Cycloalkenyl" refers to cyclic alkenyl groups having a single cyclic ring and at least one point of internal unsaturation, preferably incorporating 4 to 8 carbon atoms. Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclohex-4-enyl, cyclooct-3-enyl and the like.

[0065] "Halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

[0066] "Heteroaryl" refers to a monovalent aromatic heterocyclic group which fulfils the Hückel criteria for aromaticity (ie. contains 4n + 2 π electrons) and preferably has from 2 to 10 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen, selenium, and sulfur within the ring (and includes oxides of sulfur, selenium and nitrogen). Such heteroaryl groups can have a single ring (eg., pyridyl, pyrrolyl or N-oxides thereof or furyl) or multiple condensed rings (eg., indolizinyl, benzoimidazolyl, coumarinyl, quinolinyl, isoquinolinyl or benzothienyl).

[0067] "Heterocyclyl" refers to a monovalent saturated or unsaturated group having a single ring or multiple condensed rings, preferably from 1 to 8 carbon atoms and from 1 to 4 heteroatoms selected from nitrogen, sulfur, oxygen, selenium or phosphorous within the ring. The most preferred heteroatom is nitrogen.

[0068] Examples of heterocyclyl and heteroaryl groups include, but are not limited to, oxazole, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, isothiazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiadiazoles, oxadiazole, oxatriazole, tetrazole, thiazolidine, thiophene, benzo[b]thiophene, morpholino, piperidinyl, pyrrolidine, tetrahydrofuranyl, triazole, and the like.

[0069] "Heteroarylene" refers to a divalent heteroaryl group wherein the heteroaryl group is as described above.

[0070] "Heterocyclylene" refers to a divalent heterocyclyl group wherein the heterocyclyl group is as described above.

[0071] "Thio" refers to groups H-S-, alkyl-S-, cycloalkyl-S-, aryl-S-, heteroaryl-S-, and heterocyclyl-S-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

[0072] "Thioacyl" refers to groups H-C(S)-, alkyl-C(S)-, cycloalkyl-C(S)-, aryl-C(S)-, heteroaryl-C(S)-, and heterocyclyl-C(S)-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

[0073] "Oxythioacyl" refers to groups HO-C(S)-, alkylO-C(S)-, cycloalkylO-C(S)-, arylO-C(S)-, heteroarylO-C(S)-, and heterocyclylO-C(S)-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

[0074] "Oxythioacyloxy" refers to groups HO-C(S)-O-, alkylO-C(S)-O-, cycloalkylO-C(S)-O-, arylO-C(S)-O-, heteroarylO-C(S)-O-, and heterocyclylO-C(S)-O-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

[0075] "Phosphorylamino" refers to the groups –NR*-P(O)(R**)(OR***) where R* represents H, alkyl, cycloalkyl, alkenyl, or aryl, R** represents OR*** or is hydroxy or amino and R*** is alkyl, cycloalkyl, aryl or arylalkyl, where alkyl, amino, alkenyl, aryl, cycloalkyl, and arylalkyl are as described herein.

[0076] "Thioacyloxy" refers to groups H-C(S)-O-, alkyl-C(S)-O-, cycloalkyl-C(S)-O-, aryl-C(S)-O-, heteroaryl-C(S)-O-, and heterocyclyl-C(S)-O-, where alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl are as described herein.

[0077] "Sulfinyl" refers to groups H-S(O)-, alkyl-S(O)-, cycloalkyl-S(O)-, aryl-S(O)-, heteroaryl-S(O)-, and heterocyclyl-S(O)-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

[0078] "Sulfonyl" refers to groups H-$S(O)_2$-, alkyl-$S(O)_2$-, cycloalkyl-$S(O)_2$-, aryl-$S(O)_2$-, heteroaryl-$S(O)_2$-, and heterocyclyl-$S(O)_2$-, where alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are as described herein.

[0079] "Sulfinylamino" refers to groups H-S(O)-NR*-, alkyl-S(O)-NR*-, cycloalkyl-S(O)-NR*-, aryl-S(O)-NR*-, heteroaryl-S(O)-NR*-, and heterocyclyl-S(O)-NR*-, where R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

[0080] "Sulfonylamino" refers to groups H-$S(O)_2$-NR*-, alkyl-$S(O)_2$-NR*-, cycloalkyl-$S(O)_2$-NR*-, aryl-$S(O)_2$-NR*-, heteroaryl-$S(O)_2$-NR*-, and heterocyclyl-$S(O)_2$-NR*-, where R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

[0081] "Oxysulfinylamino" refers to groups HO-S(O)-NR*-, alkylO-S(O)-NR*-, cycloalkylO-S(O)-NR*-, arylO-S(O)-NR*-, heteroarylO-S(O)-NR*-, and heterocyclylO-S(O)-NR*-, where R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

[0082] "Oxysulfonylamino" refers to groups HO-S$(O)_2$-NR*-, alkylO-S$(O)_2$-NR*-, cycloalkylO-S$(O)_2$-NR*-, arylO-S$(O)_2$-NR*-, heteroarylO-S$(O)_2$-NR*-, and heterocyclylO-S$(O)_2$-NR*-, where R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

[0083] "Aminothioacyl" refers to groups R*R*N-C(S)-, where each R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclic and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

[0084] "Thioacylamino" refers to groups H-C(S)-NR*-, alkyl-C(S)-NR*-, cycloalkyl-C(S)-NR*-, aryl-C(S)-NR*-, heteroaryl-C(S)-NR*-, and heterocyclyl-C(S)-NR*-, where R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

[0085] "Aminosulfinyl" refers to groups R*R*N-S(O)-, where each R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclic and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

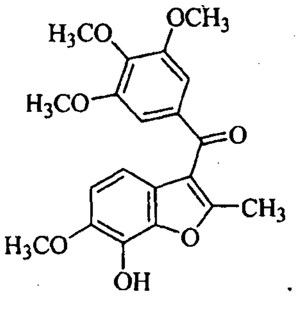
[0086] "Aminosulfonyl" refers to groups R*R*N-S$(O)_2$-, where each R* is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclic and where each of alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is as described herein.

[0087] In this specification "optionally substituted" is taken to mean that a group may or may not be further substituted or fused (so as to form a condensed polycyclic group) with one or more groups selected from hydroxy, acyl, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, alkynyloxy, amino, aminoacyl, thio, arylalkyl, arylalkoxy, aryl, aryloxy, acylamino, cyano, halogen, nitro, sulfo, phosphono, phosphorylamino, phosphinyl, heteroaryl, heteroaryloxy, heterocyclyl, heterocyclyloxy, oxyacyl, oxime, oxime ether, hydrazone, -NHC(NH)NH_2, oxyacylamino, oxysulfonylamino, aminoacyloxy, trihalomethyl, trialkylsilyl, pentafluoroethyl, trifluoromethoxy, difluoromethoxy, trifluoromethanethio, trifluoroethenyl, mono- and di-alkylamino, mono-and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclyl amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, aryl, heteroaryl and heterocyclyl, and the like.

[0088] An optionally substituted amino group may also include amino acid and peptide residues.

[0089] The VDA of formula I, Ia, Ib, or II may be prepared by known methods including those disclosed in WO 02/060872 and WO 07/087684 which are incorporated herein by reference.

[0090] In a further preferred embodiment the VDA for use in the present combination therapy is a compound of formula (III) or a salt, solvate or prodrug thereof



[0091] The compound of formula (III) (2-Methyl-7-hydroxy-3-(3,4,5-trimethoxybenzoyl)-6-methoxybenzofuran) can be prepared by the synthetic methodology described in PCT/AU2007/000101 (WO 07/087684).

[0092] The compounds of formula I, Ia, Ib, II or III have been observed to be potent tubulin polymerisation inhibitors (TPIs). An important aspect of the compounds of formulae I, Ia, Ib, II and III is the combination of the specific C-6 and C-7 substituents together with the C-2 Q-group (especially C-2 methyl) which appears to confer greater potency and selectivity when compared to other structurally related TPI compounds. In these compounds selectivity is not simply reliant on the predisposition of tumour vasculature towards collapse when challenged with the VDA but on a capacity of the VDA to distinguish between tumour endothelial cells and normal endothelial cells. Normal endothelial cells, found in healthy tissues, are in a "quiescent" state and tumour endothelial cells are in an "activated" state. Most VDAs do not distinguish between these two states, for example, Combretastatin A4 (CA4) is equally potent against quiescent and activated endothelial cells. However, the compounds of formulae I, Ia, Ib, II and particularly III show selectivity towards tumor endothelial cells (activated) over normal endothelial cells (quiescent).

[0093] It will be appreciated that the VDAs of the invention and compounds of formula I, Ia, Ib, II, or III can be administered to a subject as a pharmaceutically acceptable salt thereof. Suitable pharmaceutically acceptable salts include, but are not limited to salts of pharmaceutically acceptable inorganic acids such as hydrochloric, sulphuric, phosphoric, nitric, carbonic, boric, sulfamic, and hydrobromic acids, or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, hydroxymaleic, fumaric, maleic, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulphonic, toluenesulphonic, benezenesulphonic, salicyclic sulphanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic and valeric acids.

[0094] Base salts include, but are not limited to, those formed with pharmaceutically acceptable cations, such as sodium, potassium, lithium, calcium, magnesium, ammonium and alkylammonium. In particular, the present invention includes within its scope cationic salts eg sodium or potassium salts, or alkyl esters (eg methyl, ethyl) of the phosphate group.

[0095] It will also be appreciated that any compound that is a prodrug of a VDA of the invention or a compound of formula I, Ia, Ib, II, and III are also within the scope and spirit of the invention. The term "pro-drug" is used in its broadest sense and encompasses those derivatives that are converted *in vivo* to a compound of the invention (for instance, a compound of formulae I, Ia, Ib, II, and III). Such derivatives would readily occur to those skilled in the art, and include, for example, compounds where the free hydroxy group (for instance at C-7 position or R^{1D}) is converted into an ester, such as an acetate or phosphate ester, or where a free amino group (for instance at C-7 position or R^{1D}) is converted into an amide (e.g., α-aminoacid amide). Procedures for esterifying, eg. acylating, the compounds are well known in the art and may include treatment of the compound with an appropriate carboxylic acid, anhydride or chloride in the presence of a suitable catalyst or base. A particularly preferred prodrug is a disodium phosphate ester. The disodium phosphate ester (in particular a C-7 disodium phosphate ester of a compound of formula III) of the compound of the invention may be useful in increasing the solubility of the compounds. This would, for instance, may allow for delivery of the compound in a benign vehicle like saline. The disodium phosphate ester may be prepared in accordance with the methodology described in Pettit, G. R., *et al*, *Anticancer Drug Des.*, 1995, 10, 299. Other texts which generally describe prodrugs (and the preparation thereof) include: *Design of Prodrugs*, 1985, H. Bundgaard (Elsevier); *The Practice of Medicinal Chemistry*, 1996, Camille G. Wermuth *et al.*, Chapter 31 (Academic Press); and *A Textbook of Drug Design and Development*, 1991, Bundgaard *et al.*, Chapter 5, (Harwood Academic Publishers).

[0096] The compounds of formulae I, Ia, Ib, II, and III (or a salt or prodrug thereof) may be in crystalline form either as the free compound or as a solvate (e.g. hydrate) and it is intended that both forms are within the scope of the present invention. Methods of solvation are generally known within the art.

Combination partner (b): hypoxia targeting agent

[0097] The induction of hypoxia in a tumour results in upregulation of a number of molecules including CXCL12, MMP-9, Hif1a, VEGFA, p-mTOR, PERK, p-eIF2α, GLUT1 and other hypoxia activated agents.

[0098] Accordingly, any agent that inhibits or targets one or more molecules upregulated by tumour hypoxia is encompassed by the meaning of "hypoxia targeting agent" as used herein.

[0099] Suitable hypoxia targeting agents are preferably selected from the group consisting of Retaspimycin HCl, Geldanamycin derivatives, Sunitib, Pazopanib, Ridaforolimus, Bortezomib, 2-Deoxyglucose, Lonidamine, Imatinib, TH-302 with or without Chk1 inhibitors, PR-104, CXCR4-SDF-1 targeting agents, BMS-936564 and Tirapazamine.

[0100] The suitability of any hypoxia targeting combination partner will often depend on the mode of delivery, however, particularly preferred agents are Pazopanib and Bortezomib. The preferred combinations of agents are BNC105 and Pazopanib and BNC105 and Bortezomib. Typically the BNC105 will be used in the form of a phosphate salt.

Proliferative Diseases

[0101] As used herein the term "proliferative disease" broadly encompasses any neoplastic disease including those which are potentially malignant (pre-cancerous) or malignant (cancerous). The term therefore encompasses the treatment of tumours.

[0102] Accordingly, the term "tumour" is used generally to define any malignant cancerous or pre-cancerous cell growth, and may include leukaemias and carcinomas such as melanomas, colon, lung, ovarian, skin, breast, pancreas, pharynx, brain prostate, CNS, and renal cancers, as well as other cancers.

[0103] In a preferred embodiment the combination may be used in the treatment of tumours and in particular in the following tumours: breast adenocarcinoma, brain glioblastoma, colorectal adenocarcinoma, lung carcinoma, ovary adenocarcinoma, pancreatic adenocarcinoma, prostate carcinoma, renal cell adenocarcinoma, and pharynx squamous cell carcinoma.

[0104] In a preferred aspect the invention provides a combination of (a) and (b) for the treatment of renal cancer, and in particular metastatic renal cell carcinoma.

The combination of (a) and (b)

[0105] Without wishing to be bound to any particular theory it is postulated that VDA's induce hypoxia in highly vascularised tumors which can drive angiogenic/survival responses. Combination partners (b) target various hypoxia response pathways. Therefore inhibition using combination partner (b) directed against tumor hypoxia may yield a beneficial additive or synergistic effect through limiting the induction of the angiogenic/survival responses when combined with combination partner (a).

[0106] The present invention therefore provides a method of treating tumours comprising the administration of an effective amount of (a) a VDA in combination with an effective amount of (b) at least one hypoxia targeting agent.

[0107] An "effective amount" is intended to mean that the amount of each combination partner, when administered to a mammal (in particular a human) in need of such treatment, is sufficient to effect treatment for a particular proliferative disease. Thus, for example, a therapeutically effective amount of a compound of combination partner (a) (or a pharmaceutically acceptable salt, solvate, or prodrug thereof) is a quantity sufficient to synergise or potentiate the activity of the hypoxia targeting agent (or *vice versa*) such that a targeted disease is reduced or alleviated.

[0108] This may include at least partially attaining the desired effect, or delaying the onset of, or inhibiting the progression of, or halting or reversing altogether the onset or progression of the particular disease (e.g., tumour) being treated.

[0109] Clinical studies such as open-label, dose escalation studies in patients with proliferative diseases may include studies to prove the synergism of the active ingredients of the combination. The beneficial and/or synergistic effects can be determined directly through the results of these studies which are known as such to a person skilled in the art. These studies are also able to compare the effects of a monotherapy using the active ingredients and a combination of the invention. Preferably, the dose of combination partner (a) may be escalated until the Maximum Tolerated Dosage (MTD) is reached, and agent (b) is administered as a fixed dose. Alternatively, combination partner (a) is administered in a fixed dose and the dose of agent (b) is escalated. Each patient may receive doses of agent (a) either daily or intermittent. The efficacy of the treatment can be determined in such studies, e.g., after 6, 12, 18 or 24 weeks by evaluation of symptom scores every 9 weeks.

[0110] The administration of the pharmaceutical combination of the present invention may result not only in a beneficial effect, e.g., an additive or synergistic therapeutic effect, for instance, with regard to alleviating, delaying progression of or inhibiting the symptoms, but also in further surprising beneficial effects. Such other effects may include fewer side effects, an improved quality of life or a decreased morbidity, compared with a monotherapy applying only one of the pharmaceutically active ingredients used in the combination of the present invention.

[0111] A further benefit of the invention is that lower doses of the active ingredients of the combination can be used. The dosages need not only be smaller but may also be applied less frequently, which may diminish the incidence or severity of side effects.

[0112] The term "administration" relates to the co-administration of the combination partners to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. Accordingly, combination partners (a) and (b) may be administered together, one after the other or separately in one combined unit dosage form or in two separate unit dosage forms. The unit dosage form may also be a fixed combination such as a pharmaceutical composition which comprises both partner (a) (or a salt, solvate or prodrug thereof) and partner (b).

[0113] In particular, a therapeutically effective amount of each of the combination partner of the combination of the invention may be administered simultaneously or sequentially and in any order, and the components may be administered separately or as a fixed combination.

[0114] For example, the method of preventing or treating proliferative diseases according to the invention may comprise: (i) administration of partner (a) in free or pharmaceutically acceptable salt form; and (ii) administration of partner (b) in free or pharmaceutically acceptable salt form, simultaneously or sequentially in any order, in jointly therapeutically effective amounts, preferably in synergistically effective amounts, e.g., in daily or intermittent dosages corresponding to the amounts described herein. The individual combination partners of the combination of the invention may be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. Furthermore, the term administering also encompasses the use of a pro-drug of a combination partner that converts in vivo to the combination partner as such. The present invention is therefore to be understood as embracing all such regimens of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

[0115] As such it will be appreciated that the combination partners may be presented as a "kit of parts" for use in the treatment of a proliferative disease (e.g., tumour therapy). The kit may comprise a package where the combination partners are supplied separately for co-administration with instructions for use in the particular therapy.

[0116] The effective dosage of each of the combination partners employed in the combination of the invention may vary depending on the particular compound or pharmaceutical composition employed, the mode of administration, the condition being treated, the severity of the condition being treated. Thus, the dosage regimen of the combination of the invention is selected in accordance with a variety of factors including the route of administration and the renal and hepatic function of the patient. A physician of ordinary skill can readily determine and prescribe the effective amount of the single active ingredients required to alleviate, counter or arrest the progress of the condition.

[0117] Daily dosages for combination partners (a) and (b) will, of course, vary depending on a variety of factors, e.g., the compound chosen, the particular condition to be treated and the desired effect. In general, however, satisfactory results are achieved on administration of agent (a) at daily dosage rates of about 0.05 to 20 mg/kg per day, particularly 1 to 20 mg/kg per day, e.g. 0.4 to 16 mg/kg per day, as a single dose or in divided doses. Combination partner (a) and partner (b) may be administered by any conventional route, in particular enterally, e.g., orally, e.g., in the form of tablets, capsules, drink solutions or parenterally, e.g., in the form of injectable solutions or suspensions. Suitable unit dosage forms for oral administration comprise from about 0.02 to 50 mg active ingredient, usually 0.1 to 30 mg and 2 to 25 mg, 4 to 20 mg e.g. combination partner (a) or (b), together with one or more pharmaceutically acceptable diluents or carriers therefore.

[0118] Combination partner (b) may be administered to a human in a daily dosage range of 0.5 to 1000 mg. Suitable unit dosage forms for oral administration comprise from about 0.1 to 500 mg active ingredient, preferably 5-50 mg/day, more preferably 5-20 mg/day, and most preferably about 7-12 mg/day, together with one or more pharmaceutically acceptable diluents or carriers therefore. Methods and administration regimes for delivery known hypoxia targeting agents would be known to the skilled clinician.

[0119] For instance, an administration regime may include adding the TPI (e.g., compound of formula III) at an assigned dose level by I.V. on days 1 and 8 (of a 21 day cycle) where the hypoxia targeting agent is given as an oral daily dose (e.g., about 10 mg/day). In this embodiment the compound of formula (III) may be dosed at a level of between 4 to 16 mg/m^2.

[0120] The administration of a pharmaceutical combination of the invention results not only in a beneficial effect, e.g., an additive or synergistic therapeutic effect, e.g., with regard to inhibiting the growth of tumors, but also in further surprising beneficial effects, e.g., less side effects, an improved quality of life or a decreased morbidity, compared to a monotherapy applying only one of the pharmaceutically active ingredients used in the combination of the invention.

[0121] A further benefit is that lower doses of the active ingredients of the combination of the invention can be used, e.g., that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects. This is in accordance with the desires and requirements of the patients to be treated.

[0122] Combinations of partners (a) and (b) may be combined, independently or together, with one or more pharmaceutically acceptable carriers and, optionally, one or more other conventional pharmaceutical adjuvants and administered enterally, e.g., orally, in the form of tablets, capsules, caplets, etc. or parenterally, e.g., intraperitoneally or intravenously, in the form of sterile injectable solutions or suspensions. The enteral and parenteral compositions may be prepared by conventional means.

[0123] The pharmaceutical compositions for separate administration of combination partner (a) and partner (b) or for the administration in a fixed combination (i.e., a composition), according to the invention may be prepared in a manner known in the art and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), particularly humans, comprising a therapeutically effective amount of at least one pharmacologically active combination partner alone, e.g., as indicated above, or in combination with one or more pharmaceutically acceptable carriers or diluents, especially suitable for enteral or parenteral application.

[0124] Suitable pharmaceutical compositions contain, e.g., from about 0.1% to about 99.9%, preferably from about 1 % to about 60%, of the active ingredient(s).

[0125] The composition may contain any suitable carriers, diluents or excipients. These include all conventional solvents, dispersion media, fillers, solid carriers, coatings, antifungal and antibacterial agents, dermal penetration agents, surfactants, isotonic and absorption agents and the like. It will be understood that the compositions of the invention may also include other supplementary physiologically active agents.

[0126] The carrier must be pharmaceutically "acceptable" in the sense of being compatible with the other ingredients of the composition and not injurious to the subject. Compositions include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parental (including subcutaneous, intramuscular, intravenous and intradermal) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

[0127] Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0128] A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g inert diluent, preservative disintegrant (e.g. sodium starch glycolate, cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

[0129] Compositions suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured base, usually sucrose and acacia or tragacanth gum; pastilles comprising the active ingredient in an inert basis such as gelatine and glycerin, or sucrose and acacia gum; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0130] Compositions suitable for topical administration to the skin may comprise the compounds dissolved or suspended in any suitable carrier or base and may be in the form of lotions, gel, creams, pastes, ointments and the like. Suitable carriers include mineral oil, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. Transdermal patches may also be used to administer the compounds of the invention.

[0131] Compositions for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter, glycerin, gelatine or polyethylene glycol.

[0132] Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0133] Compositions suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, bactericides and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0134] Preferred unit dosage compositions are those containing a daily dose or unit, daily sub-dose, as herein above described, or an appropriate fraction thereof, of the active ingredient.

[0135] It should be understood that in addition to the active ingredients particularly mentioned above, the compositions of this invention may include other agents conventional in the art having regard to the type of composition in question, for example, those suitable for oral administration may include such further agents as binders, sweeteners, thickeners, flavouring agents disintegrating agents, coating agents, preservatives, lubricants and/or time delay agents. Suitable sweeteners include sucrose, lactose, glucose, aspartame or saccharine. Suitable disintegrating agents include cornstarch, methylcellulose, polyvinylpyrrolidone, xanthan gum, bentonite, alginic acid or agar. Suitable flavouring agents include peppermint oil, oil of wintergreen, cherry, orange or raspberry flavouring. Suitable coating agents include polymers or copolymers of acrylic acid and/or methacrylic acid and/or their esters, waxes, fatty alcohols, zein, shellac or gluten. Suitable preservatives include sodium benzoate, vitamin E, alpha-tocopherol, ascorbic acid, methyl paraben, propyl paraben or sodium bisulphite. Suitable lubricants include magnesium stearate, stearic acid, sodium oleate, sodium chloride or talc. Suitable time delay agents include glyceryl monostearate or glyceryl distearate.

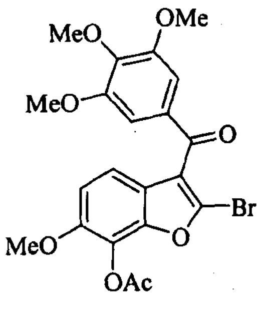
[0136] Those skilled in the art will appreciate that the invention described herein in susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications which fall within the spirit and scope. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

[0137] Certain embodiments of the invention will now be described with reference to the following examples which are intended for the purpose of illustration only and are not intended to limit the scope of the generality hereinbefore described.

EXAMPLES

Synthetic Protocols

Preparation of 2-Bromo-7-acetoxy-3-(3,4,5-trimethoxybenzoyl)-6-methoxybenzofuran.



Step 1: 2-*t*-Butyldimethylsilyl-3-(*t*-butyldimethylsilyloxymethylene)-6-methoxy-7-isopropoxybenzofuran (Larock coupling).

[0138] A suspension of 2-isopropoxy-3-methoxy-5-iodophenol (4.41 mmol), 1-(*tert*-butyldimethylsilyl)-3-(*tert*-butyldimethylsilyloxy)propyne (1.5 g, 5.28 mmol), lithium chloride (189 mg, 4.45 mmol) and sodium carbonate (2.34 g, 22.08 mmol) in dry dimethylformamide (5 mL) at 100 °C was deoxygenated 4 times by evacuation and backfilling with nitrogen. Palladium acetate (135 mg, 0.60 mmol) was added and the reaction vessel was degassed twice with nitrogen. The reaction mixture was then stirred at this temperature for 4 hours (tlc) and the solvent was removed by distillation under vacuum. The residue was dissolved in ethyl acetate (75 mL), stirred well, filtered and treated with triethylamine (5 mL). The solution was concentrated onto silica gel (10 g) and purified by flash chromatography (silica gel, eluent = hexane/diethyl ether/triethylamine; 95:5:1%) to afforded the title compound as a yellow oil (1.45 g, 96 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24(d, 1H, J = 8.45 Hz), 6.88(d, 1H, J = 8.47 Hz), 4.80(s, 2H, CH_2), 4.73(m, 1H), 3.88(s, 3H, OMe), 1.36(d, 6H, J = 6.17 Hz), 0.94(s, 9H), 0.92(s, 9H), 0.35(s, 6H), 0.12(s, 6H).

Step 2: 2-*t*-Butyldimethylsilyl-3-formyl-6-methoxy-7-isopropoxybenzofuran

[0139] To a solution of 2-*t*-butyldimethylsilyl-3-(*t*-butyldimethylsilyloxymethylene)-6-methoxy-7-isopropoxybenzofuran (2.69 mmol) in methanol (100 mL) was added concentrated hydrochloric acid (200 μL) and the reaction was stirred for 30 minutes (monitored by tlc), quenched with triethylamine (2 mL) and the solvent removed by distillation under vacuum. The residue was dissolved in dichloromethane (20 mL), washed with water (10 mL), dried over magnesium sulfate, concentrated under vacuum and co-distilled with toluene (20 mL). The crude product was dissolved in dry dichloromethane (4 mL) and added to a stirred solution of Collin's reagent (chromium trioxide (1.01 g), pyridine (1.65 mL) in dry dichloromethane (30 mL)). The suspension was stirred for 10 minutes, filtered and the residue washed with diethyl ether (20 mL). The filtrate was concentrated onto silica (10 g) and purified by flash chromatography (silica gel, eluent = hexane/diethyl-ether/triethylamine (90:9:1) to afford the title compound as a light yellow oil (503 mg, 48%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.25(s, 1H, CHO), 7.79(d, 1H, J = 8.45 Hz), 6.98(d, 1H, J = 8.46 Hz), 4.65(m, 1H), 3.89(s, 3H, OMe), 1.35(d, 6H, J = 6.17 Hz), 0.97(s, 9H), 0.45(s, 6H).

Step 3: 2-*t*-Butyldimethylsilyl-3-(3,4,5-trimethoxybenzoyl)-6-methoxy-7-isopropoxybenzofuran

[0140] To a stirred solution of 3,4,5-trimethoxyiodobenzene (377 mg, 1.27 mmol) in dry tetrahydrofuran (1 mL) at -78 °C under nitrogen was added *n*-butyllithium (795 μL, 1.59 mmol, 2M solution in cyclohexane) and the reaction mixture was stirred at this temperature for 40 minutes. After this time a solution of 2-*t*-butyldimethylsilyl-3-formyl-6-methoxy-7-isoproxybenzofuran (1.07 mmol) in dry tetrahydrofuran (1 mL) was added to the reaction dropwise via syringe pipette. The reaction mixture was stirred at -60 °C for 20 minutes and then allowed to warm to 0°C, stirred for 10 minutes, quenched with saturated ammonium chloride solution (2 mL) and diluted with ethyl acetate (20 mL). The organic layer was washed with water (10 mL), dried over magnesium sulfate and the solvent was removed under vacuum to give a residue that was co-distilled with toluene. The crude product (908 mg) was dissolved in dry tetrahydrofuran (10 mL) and treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (900 mg, 1.59 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours (monitored by tlc) and then loaded onto silica (10 g) and purified by flash chromatography (silica gel, eluent = hexane/diethyl ether/triethylamine, 90:9:1) to afford the title compound as a light yellow oil (498 mg, 69%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14(s, 2H, benzoyl Hs), 6.81(d, 1H, J = 8.64 Hz), 6.77(d, 1H, J = 8.64 Hz) 4.74(m, 1H), 3.93(s, 3H, OMe), 3.86(s, 3H, OMe), 3.78(s, 6H, 2 x OMe), 1.39(d, 6H, J = 6.14 Hz), 1.01(s, 9H), 0.26(s, 6H).

Step 4: 2-(*tert*-butyldimethylsilyloxy)-7-acetoxy-3-(3,4,5-trimethoxybenzoyl)-6-methoxybenzofuran

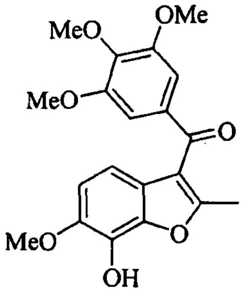
[0141] To a stirred solution of 2-(*t*-butyldimethylsilyloxy)-7-isopropoxy-3-(3,4,5-trimethoxybenzoyl)-6-methoxy-benzofuran (160 mg, 0.31 mmol) in dry DCM (2 mL) at room temperature under nitrogen was added solid aluminium trichloride (83 mg, 0.62 mmol) and the reaction mixture was stirred for 15 minutes (monitored by tlc). The reaction was quenched with a saturated solution of ammonium chloride, extracted with dichloromethane and dried over magnesium sulfate. The solvent was removed by distillation and residue was dried by azeotropic removal of water with toluene. The crude product was dissolved in pyridine (2 mL), acetic anhydride (1 mL) was added and reaction mixture was stirred for 2 hours at room temperature. The solvent was distilled under vacuum and the residue was loaded onto silica gel (1 g) and purified by column chromatography (silica gel, eluent, hexane:diethyl-ether; 80:20) (134 mg, 84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14(s, 2H, benzoyl Hs), 6.98(d, 1H, J = 8.72 Hz), 6.85(d, 1H, J = 8.72 Hz), 3.93(s, 3H, OMe), 3.86(s, 3H, OMe), 3.80(s, 6H, 2 x OMe), 2.41(s, 3H), 0.99(s, 9H), 0.25(s, 6H).

Step 5: 2-Bromo-7-acetoxy-3-(3,4,5-trimethoxybenzoyl)-6-methoxybenzofuran

[0142] To a stirred solution of 2-t-butyldimethylsilyl-7-acetoxy-3-(3,4,5-trimethoxybenzoyl)-6-methoxybenzofuran (120 mg, 0.44 mmol) in 1,2-dichloroethane (1 mL) at room temperature under nitrogen was added bromine (12 μl, 0.44 mmol) dropwise and the reaction mixture was stirred at this temperature for 10 minutes. After this time the reaction was quenched with saturated sodium thiosulfate solution, extracted with ethyl acetate (20 mL), dried over magnesium sulfate and the solvent removed by distillation under vacuum. The crude product was purified by silica gel column chromatography (eluent = Hexane:diethyl ether; 8:2 - 7:3) to afford the title compound as a colourless crystalline solid (91 mg, 81%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40(d, 1H, J = 8.70 Hz), 7.14(s, 2H, benzoyl-Hs), 6.98(d, 1H, J = 8.75 Hz), 3.94(s, 3H, OMe), 3.89(s, 3H, OMe), 3.86(s, 6H, 2 x OMe), 2.43(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.95(CO), 167.71, 152.75, 149.54, 147.49, 142.59, 131.92, 131.80, 123.91, 121.84, 119.89, 117.72, 109.89, 106.92, 60.69, 56.61, 56.00, 20.09.

Example 1

Preparation of 2-Methyl-7-hydroxy-3-(3,4,5-trimethoxybenzoyl)-6-methoxybenzofuran (BNC105)



Preparation A

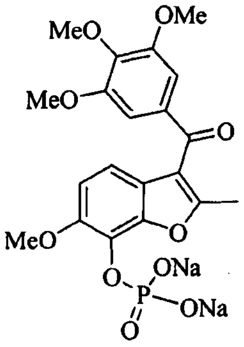
[0143] To a stirred solution of 2-Bromo-7-acetoxy-3-(3,4,5-trimethoxybenzoyl)-6-methoxybenzofuran (20 mg, 0.042 mmol), methyl-boronic acid (40 mg, 0.67 mmol), in 1,4-dioxane (2 mL) at 90 °C was added *tetrakis*-triphenylphosphine palladium (11 mg, 0.01 mmol) followed by the addition of a solution of sodium bicarbonate (40 mg, 0.48 mmol) in distilled water (0.5 mL). The reaction mixture turned red after 5 minutes. After 2 hours (tlc) the reaction mixture was brought to room temperature and was added saturated ammonium chloride (2 mL) and diluted with dichloromethane (20 mL). The organic layer was separated and washed with water, dried over magnesium sulfate and the solvent was removed by distillation under vacuum. The residue was purified by PTLC (eluent = Dichloromethane/Methanol, 1:1) to give the title compound (acetate cleaved during reaction) as a fluffy white solid; (3 mg, 19%).

Preparation B (Negishi Coupling)

[0144] To a stirred solution of zinc-bromide (592 mg, 2.63 mmol) in dry THF(1.5 mL) at 0°C was added the solution of methyl lithium (1.6 M solution in diethyl-ether, 2.6 mL, 4.15 mmol) and the reaction mixture was stirred for 2 hours. Solid 2-bromo-7-acetoxy-3-(3,4,5-trimethoxybenzoyl)-6-methoxy-benzofuran (300 mg, 0.63 mmol) was added and the ether was removed under vacuum and to the rest suspension was added dichlorobis(triphenylphosphine)palladium catalyst (21 mg) and catalytic amount of copper (I) iodide. The reaction mixture was stirred at room temperature for 36 hours (monitored by tlc), quenched with saturated ammonium chloride solution and extracted with dichloromethane (10 mL), dried over magnesium sulfate and solvent distilled under vacuum and the product was purified by silica gel column (eluent = hexane/ethyl acetate; 8:2). The product was crystallized in methanol (106 mg, 46%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09(s, 2H, benzoyl Hs), 6.93(d, 1H, J = 8.54 Hz), 6.83(d, 1H, J = 8.56 Hz), 5.70(bs, 1H, OH), 3.93(s, 3H, OMe), 3.92(s, 3H, OMe), 3.83(s, 6H, 2 x OMe), 2.54(s, 3H, 2-Me)

Example 2

Preparation of Disodium 6-methoxy-2-methyl-3-(3,4,5-trimethoxybenzoyl)benzofuran-7-yl phosphate



Step 1: Dibenzyl 6-methoxy-2-methyl-3-(3,4,5-trimethoxybenzoyl)benzofuran-7-yl phosphate:

[0145] To a mixture of 0.081 g (0.22 mmol) of (7-hydroxy-6-methoxy-2-methylbenzofuran-3-yl)(3,4,5-trimethoxyphenyl)methanone, 0.086 g (0.261 mmol) of carbon tetrabromide and 0.063 ml (0.283 mmol) of dibenzylphosphite in 2.5 ml of anhydrous acetonitrile 0.046 ml of anhydrous triethylamine was added dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 2h at room temperature, then diluted to 20 ml with ethyl acetate, washed with water brine, dried over anhydrous magnesium sulfate, filtered off and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography (dichloromethane/ ethyl acetate, 9:1) to give the title compound as a colorless foam (0.13g, 94%); ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H, Me-2); 3.83 (s, 1H, OMe); 3.93 (s, 3H, OMe); 5.33 (m, 4H, CH_2Ph); 6.89 (d, CH aromatic, J = 8.7 Hz); 7.21 (dd, 1H, CH aromatic, J = 8.72 Hz; J = 1.2 Hz); 7.08 (s, 2H, CH aromatic); 7.29 – 7.43 (m, 10 H, CH aromatic).

Step 2: Disodium 6-methoxy-2-methyl-3-(3,4,5-trimethoxybenzoyl)benzofuran-7-yl phosphate:

[0146] To a stirred solution of 0.122 g (0.193 mmol) of the product from Step 1 in 1 ml of anhydrous acetonitrile 0.075 ml (0.58 mmol) of bromotrimethylsilane was added at –5°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at 0°C, then evaporated to dryness *in vacuo*. The residue was diluted to 5 ml with anhydrous methanol and pH of the solution was brought up about 10 by the addition of sodium methoxide. After evaporation of the resulting mixture under reduced pressure the solid residue was washed with anhydrous isopropanol (4 x 1.5 ml) and anhydrous ethanol (3 x 1.5 ml) and dried under vacuum to give 0.062 g (65 % yield) of title compound as an colorless solid; ^{1}H NMR (D_2O) δ 2.37 (s, 3H, Me-2); 3.76 (s, 6H, OMe); 3.79 (s, 3H, OMe); 3.82 (s, 3H, OMe); 4.66 (s, H_2O); 6,93 (d, 1H, CH aromatic, J = 8.6 Hz); 7.04 (d, 1H, CH aromatic, J = 8.6 Hz); 7.10 (s, 2H, CH aromatic).

Biological data

[0147] BNC105P was shown to increase tumour hypoxia by disruption of tumour vasculature. This effect was demonstrated in a wide range of tumours including MDA-MB-231 breast carcinoma, Calu-6 lung carcinoma, Colo205 colon carcinoma and DU-145 prostate carcinoma. With MDA-MB-231 tumours BNC105P was shown to cause release of the angiogenic growth factor VEGF, destruction of tumour endothelial cells, damage of blood vessel integrity and an increase in apoptotic cells.

[0148] BNC105 induced vascular shutdown in RENCA renal tumours with an increase GLUT1, HIF-1a, PERK, eIF2a and VEGF. In vascular shutdown in RENCA renal tumours induced by BNC105 BNC105 induced hypoxia with an increase in CXCL12 and

MMP-9 with an inflammatory immuno-response and induced chemotaxis.

[0149] These findings lead to the present inventors to examine combination therapies involving BNC105 and a range of tumour hypoxia targeting agents. The rationale behind this approach is summarised in Figure 1.

Combination therapy of BNC105 with Pazopanib

[0150] Based on investigations on the histological changes caused by BNC105 anti-tumor action, it was established that >95% of the tumor mass becomes necrotic, while peripheral regions remain viable. Increased expression of a number of proteins that drive tumor recovery were observed in the viable regions. Among these is the angiogenesis growth factor VEGF. The present inventors sought to investigate the potential therapeutic benefit of combining BNC105 with an inhibitor of the VEGF/VEGFR2 signalling pathway.

[0151] Pazopanib is a Tyrosine Kinase Inhibitor that suppresses signalling through the VEGF family receptors and has been approved by the FDA for first line therapy use in renal cancer. Following establishment of a safe treatment regimen, the present inventors examined the anti-cancer effects of co-administering BNC105 and Pazopanib in the RENCA model involving mice carrying kidney tumors. Mice were treated with one cycle of BNC105 (16 mg/kg/dose on Day 2 and Day 9 in a 21 day cycle) while receiving daily oral administrations of Pazopanib (Days 1–21; 30 mg/kg). Treatment was discontinued at the 21-Day mark and the animals monitored for overall survival. Based on the data obtained combining BNC105 treatment with Pazopanib resulted in a considerable and statistically significant increase in animal survival (Figure 2).

[0152] RENCA (VHL wildtype) orthotopic tumour bearing kidneys from Balb/c mice were weighed on Day 10 day of treatment (Pazopanib 30mg/kg, p.o. Daily, BNC105 16mg/kg i.v. Days 2 and 9). Concurrent treatment with BNC105 and Pazopanib resulted in 47% tumour growth inhibition compared to 21 or 19% inhibition with BNC105 or Pazopanib treatment alone respectively. These results are shown in Figure 3.

[0153] As is demonstrated by these results treatment of RENCA orthotopic tumours with

BNC105 + Pazopanib resulted in tumour growth inhibition and an overall survival greater than in animals treated with Pazopanib or BNC105 alone. This shows that the combination therapy of BNC105 and Pazopanib is much more effective than BNC105 or Pazopanib monotherapy.

Combination therapy of BNC105 with Bortezomib:

[0154] Formalin fixed paraffin embedded RENCA (VHL wildtype) orthotopic tumour sections from tumour bearing Balb/c mice collected 24 hours after a single dose i.v. 32mg/kg BNC105P showed upregulation of unfolded protein response markers PERK (Cell signalling #5683) and phosphorylation of eIF2α (Cell Signalling #5324). (Fast Red detection on hematoxylin)

[0155] RENCA orthotopic tumour bearing kidneys from Balb/c mice were photographed 4 hours after dosing BNC105 on Day 9 of treatment (Bortezomib 0.5mg/kg iv Days 1, 5, 8, BNC105 32mg/kg iv Days 2 and 9). Formalin fixed and paraffin embedded sections were stained using a TUNEL assay (Roche) to visualize cell necrosis. Very little tumor necrosis was seen with each of the drugs used as monotherapies. Clearly increased necrosis, visualised as increased TUNEL staining, was seen in tumors extracted from mice treated with the combination of Bortezomib+BNC105.

[0156] Treatment of RENCA tumours with BNC105 + Bortezomib resulted in increased tumour necrosis compared to animals treated with Bortezomib or BNC105 alone. This demonstrates a clear advantage in the use of the BNC105 Bortezomib combination therapy over BNC105 or Bortezomib monotherapy.

CLAIMS:

1. A method for treating a proliferative disease comprising the step of administering to a patient in need thereof: a) a vascular disrupting agent and (b) at least one hypoxia targeting agent.

2. A pharmaceutical combination for treating a proliferative disease comprising: (a) a vascular disrupting agent and (b) at least one hypoxia targeting agent.

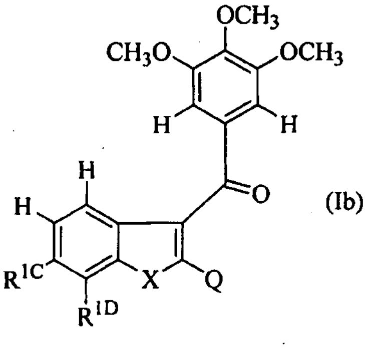
3. The use of: (a) a vascular disrupting agent and (b) at least one hypoxia targeting agent, in the manufacture of a medicament for the treatment of a proliferative disease.

4. The use of: (a) a vascular disrupting agent in the manufacture of a medicament for the treatment of a proliferative disease to be used in combination with (b) at least one hypoxia targeting agent.

5. The use of: (b) at least one hypoxia targeting agent in the manufacture of a medicament for the treatment of a proliferative disease to be used in combination with (a) a vascular disrupting agent.

6. A pharmaceutical composition comprising (a) a vascular disrupting agent and (b) at least one hypoxia targeting agent.

7. A combination, method, use or composition according to any one of claims 1 to 6 wherein the VDA is a compound of formula (Ib) or a salt, solvate or prodrug thereof



(Ib)

wherein;

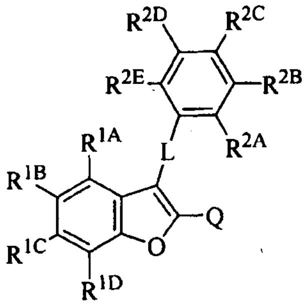
X represents O, S, SO, SO_2, Se, SeO, SeO_2 or NR where R is selected from H, O, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, and optionally substituted sulfonyl;

R^{1C} represents C_{1-3} alkoxy;

R^{1D} represents hydroxy or amino;

Q represents H, CN, halogen, trialkylsilyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted oxyacyl, optionally substituted acylamino, optionally substituted aminoacylamino, OR", SR" or NR"R", where each R" independently represents, H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted acyl and optionally substituted oxyacyl, or NR'"NR'", where each R'" independently represents H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl and optionally substituted heteroaryl.

8. A combination, method, use or composition according to any one of claims 1 to 6 wherein the VDA is a compound of formula (II) or a salt, solvate or prodrug thereof



(II)

wherein;

R^{1A} and R^{1B} each independently represents H, carboxy, cyano, dihalomethoxy, halogen, hydroxy, nitro, pentahaloethyl, phosphorylamino, phosphono, phosphinyl, sulfo, trihaloethenyl, trihalomethanethio, trihalomethoxy, trihalomethyl, optionally substituted acyl, optionally substituted acylamino, optionally substituted acylimino, optionally substituted acyliminoxy, optionally substituted acyloxy, optionally substituted arylalkyl, optionally substituted arylalkoxy, optionally substituted alkenyl, optionally substituted alkenyloxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted alkynyl, optionally substituted alkynyloxy, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted aminosulfonyl, optionally substituted aminothioacyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted oxyacyl, optionally substituted oxyacylamino, optionally substituted oxyacyloxy, optionally substituted oxyacylimino, optionally substituted oxysulfinylamino, optionally substituted oxysulfonylamino, optionally substituted oxythioacyl, optionally substituted oxythioacyloxy, optionally substituted sulfinyl, optionally substituted sulfinylamino, optionally substituted sulfonyl, optionally substituted sulphonylamino, optionally substituted thio, optionally substituted thioacyl, optionally substituted thioacylamino, or R^{1A} and R^{1B} together form an optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted cycloalkyl, or optionally substituted cycloalkenyl;

R^{1C} represents C_{1-3} alkoxy, C_{1-3} alkylthio, C_{1-3} alkylamino, or C_{1-3} dialkylamino;

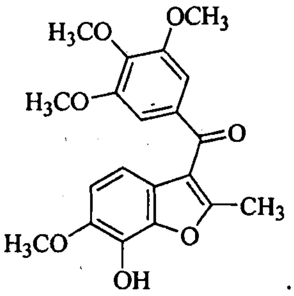
R^{1D} represents hydroxy or amino;

L represents C=O, O, S, SO, SO_2, Se, SeO, SeO_2, C=NZ', or NR' where Z' is H, optionally substituted alkyl, optionally substituted aryl or optionally substituted amino; and where R' is selected from H, O, optionally substituted acyl, optionally substituted alkenyl, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, or optionally substituted sulfonyl;

R^{2A}-R^{2E} each independently represents H, carboxy, cyano, dihalomethoxy, halogen, hydroxy, nitro, pentahaloethyl, phosphorylamino, phosphono, phosphinyl, sulfo, trihaloethenyl, trihalomethanethio, trihalomethoxy, trihalomethyl, optionally substituted acyl, optionally substituted acylamino, optionally substituted acylimino, optionally substituted acyliminoxy, optionally substituted acyloxy, optionally substituted arylalkyl, optionally substituted arylalkoxy, optionally substituted alkenyl, optionally substituted alkenyloxy, optionally substituted alkoxy, optionally substituted alkyl, optionally substituted alkynyl, optionally substituted alkynyloxy, optionally substituted amino, optionally substituted aminoacyl, optionally substituted aminoacyloxy, optionally substituted aminosulfonyl, optionally substituted aminothioacyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted cycloalkenyl, optionally substituted cycloalkyl, optionally substituted heteroaryl, optionally substituted heterocyclyl, optionally substituted oxyacyl, optionally substituted oxyacylamino, optionally substituted oxyacylimino, optionally substituted oxyacyloxy, optionally substituted oxysulfinylamino, optionally substituted oxysulfonylamino, optionally substituted oxythioacyl, optionally substituted oxythioacyloxy, optionally substituted sulfinyl, optionally substituted sulfinylamino, optionally substituted sulfonyl, optionally substituted sulphonylamino, optionally substituted thio, optionally substituted thioacyl, optionally substituted thioacylamino, or optionally substituted thioacyloxy; or any of R^{2A} and R^{2B}, R^{2B} and R^{2C}, R^{2C} and R^{2D}, and R^{2D} and R^{2E}, together form an optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted cycloalkyl, or optionally substituted cycloalkenyl; and

Q represents H, CN, halogen, trialkylsilyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted oxyacyl, optionally substituted acylamino, optionally substituted aminoacylamino, OR", SR" or NR"R", where each R" independently represents, H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted acyl and optionally substituted oxyacyl, or NR'"NR'", where each R'" independently represents H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl and optionally substituted heteroaryl.

9. A combination, method, use or composition according to any one of claims 1 to 6 wherein the VDA is a compound of formula (III) or a salt, solvate or prodrug thereof



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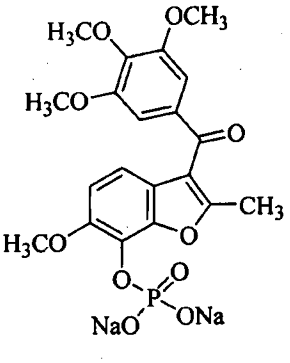
10. A combination, method, use or composition according to claim 9 wherein the compound of formula (III) is a compound of formula

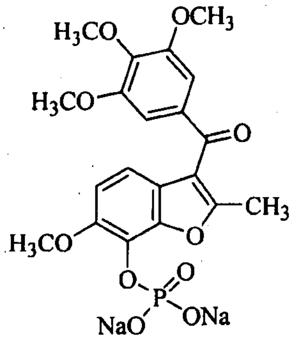


11. A combination, method, use or composition according to any one of claims 1 to

10 wherein the hypoxia targeting agent is selected from the group consisting of Retaspimycin HCl, Geldanamycin derivatives, Sunitib, Pazopanib, Ridaforolimus, Bortezomib, 2-Deoxyglucose, Lonidamine, Imatinib, TH-302 with or without Chk1 inhibitors, PR-104, CXCR4-SDF-1 targeting agents, BMS-936564 and Tirapazamine.

12. A combination, method, use or composition according to claim 11 wherein the hypoxia targeting agent is Pazopanib or Bortezomib.

13. A method for treating a proliferative disease comprising the step of administering to a patient in need thereof a compound of the following formula



and Pazopanib or Bortezomib.

14. A combination, method, use or composition according to any one of claims 1 to 13 wherein the proliferative disease is selected from renal cancer, ovarian cancer, and lung cancer.

15. A combination, method, use or composition according to claim 14 wherein the proliferative disease is renal cancer.

Figure 1

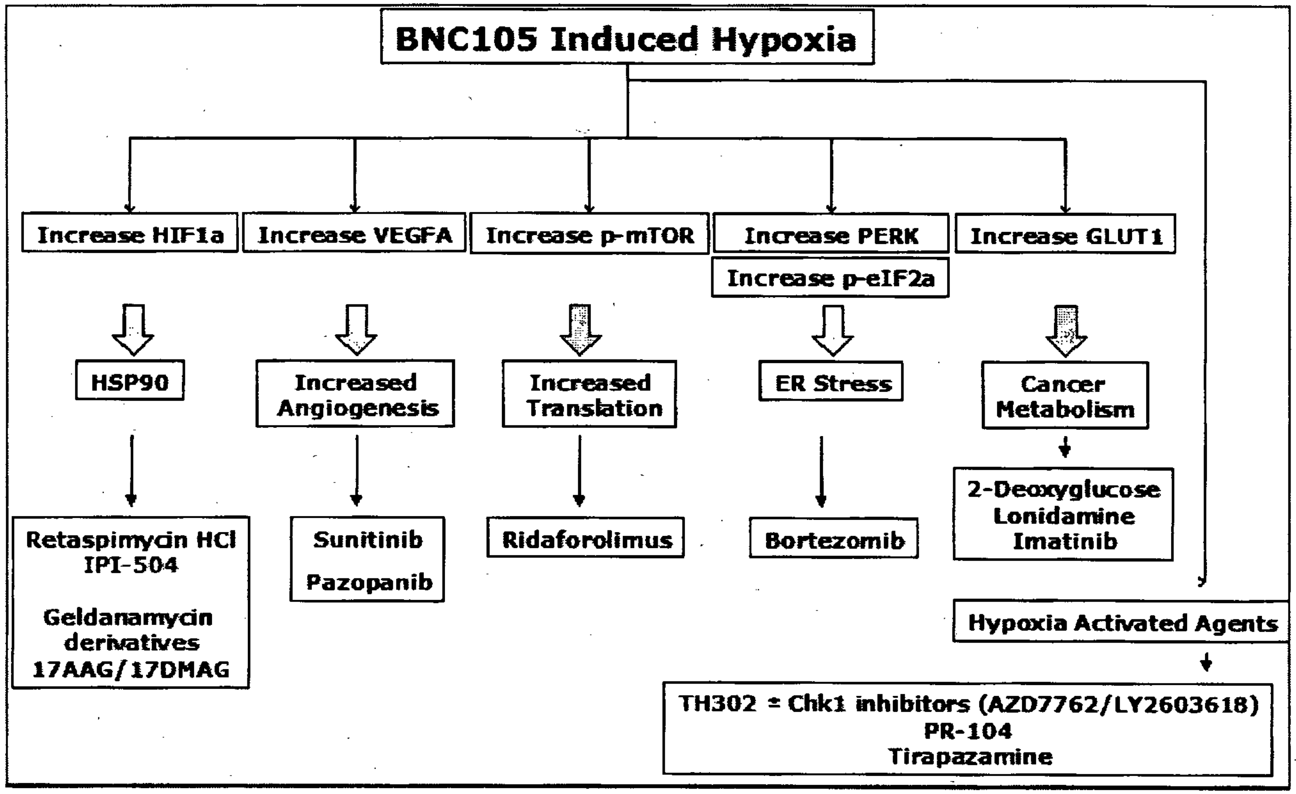

BNC105 Induced Hypoxia
Increase HIF1a
Increase VEGFA
Increase p-mTOR
Increase PERK
Increase p-eIF2a
Increase GLUT1
HSP90
Increased Angiogenesis
Increased Translation
ER Stress
Cancer Metabolism
Retaspimycin HCl
IPI-504
Geldanamycin derivatives
17AAG/17DMAG
Sunitinib
Pazopanib
Ridaforolimus
Bortezomib
2-Deoxyglucose
Lonidamine
Imatinib
Hypoxia Activated Agents
TH302 ± Chk1 inhibitors (AZD7762/LY2603618)
PR-104
Tirapazamine

Figure 2

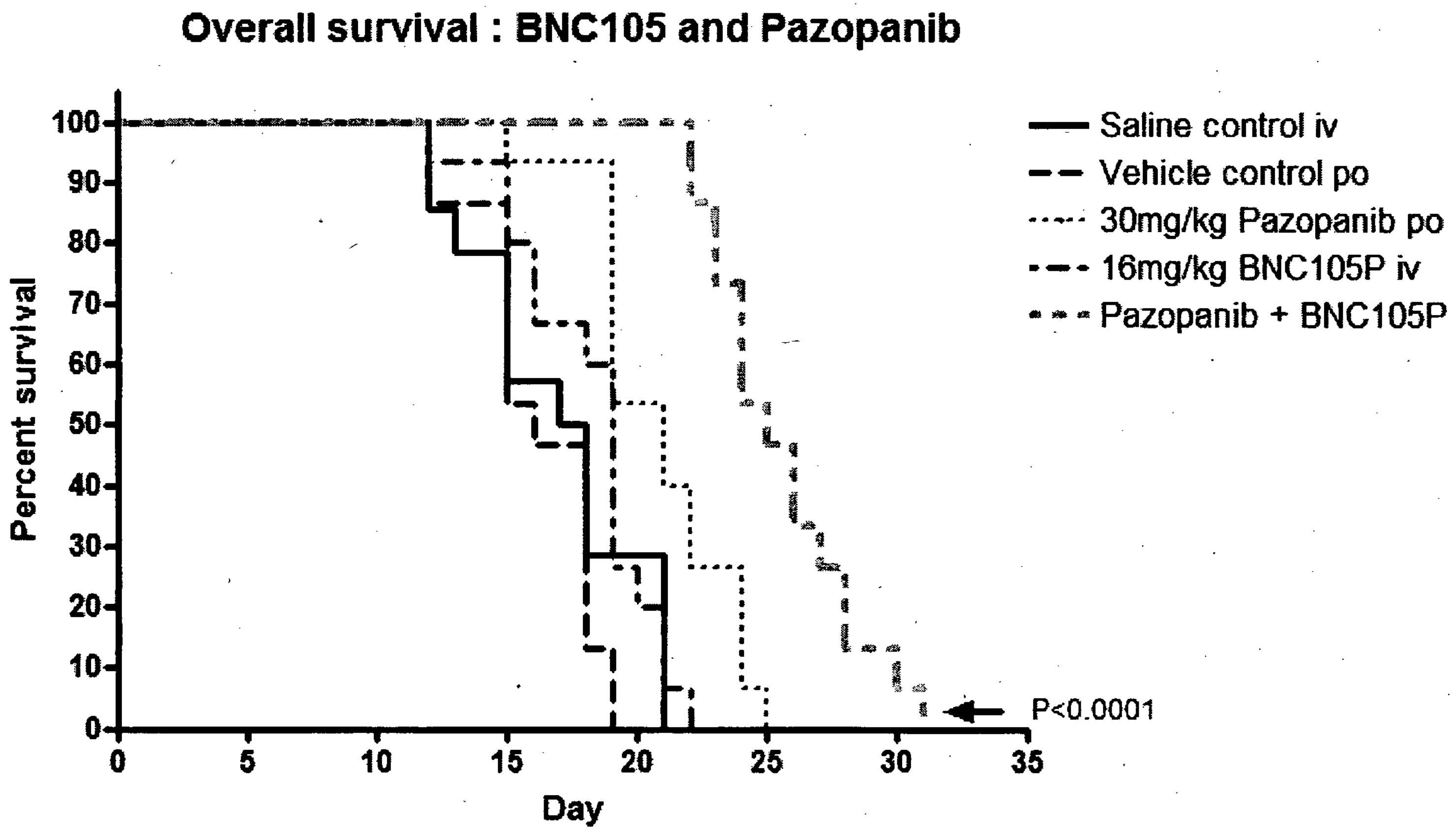
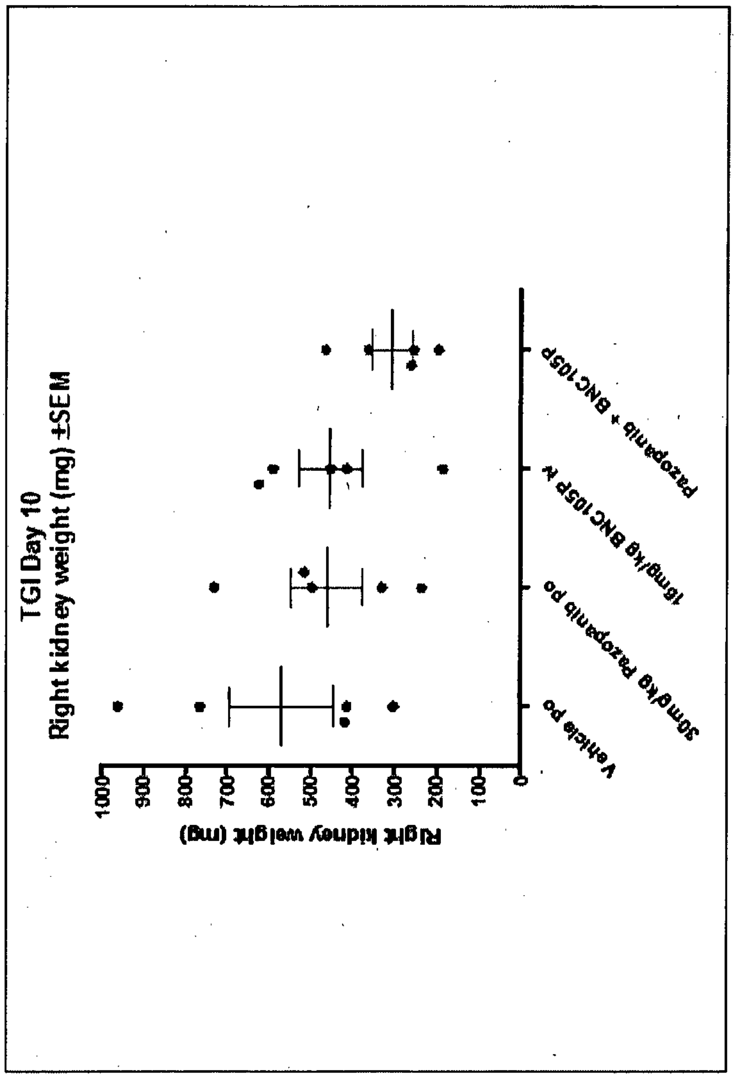

Overall survival : BNC105 and Pazopanib
Percent survival
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
Day
Saline control iv
Vehicle control po
30mg/kg Pazopanib po
16mg/kg BNC105P iv
Pazopanib + BNC105P
P<0.0001

Figure 3


TGI Day 10
Right kidney weight (mg) ±SEM
Right kidney weight (mg)
1000
900
800
700
600
500
400
300
200
100
0
Vehicle po
30mg/kg Pazopanib po
16mg/kg BNC105P iv
Pazopanib + BNC105P

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU2013/000581

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/343 (2006.01) A61K 31/381 (2006.01) A61K 31/404 (2006.01) A61K 31/44 (2006.01) A61K 31/506 (2006.01) A61K 31/53 (2006.01) A61K 31/69 (2006.01) A61K 31/661 (2006.01) A61P 35/00 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Chemical Abstracts, Medline, EPODOC and WPI: Vascular, venous, blood, interfering, damaging, vascular targeting, vascular disrupting, vadimezan, ASA404, ZD6126, AVE8062, OXI4503, combrestatin, microtubule destabil , VDA , VTA, ABT751, E7010, MPC6827, Azixa, CYT997, MN029, denibulin, EPC2407, zybrestat, NPI2358, TZT1027, BNC105, 945771 74 4, hypoxia targeting, retaspimycin, geldanamycin, sunitib, pazopanib, ridaforolimus, bortezomib, deoxy glucose, lonidamine, imatinib, TH302, CHK1 inhibitor, PR104, CXCR4 SDF 1, BMS936564, tirapazamine, proliferative, cancer, sarcoma, carcinoma, neoplasm, melanoma, tumour, tumor and similar terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

☒ Further documents are listed in the continuation of Box C ☒ See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 5 July 2013	Date of mailing of the international search report 05 July 2013
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au Facsimile No.: +61 2 6283 7999	**Authorised officer** Grant McNeice AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262832617

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012/0087913 A1 (LEE, R. et al) 12 April 2012 Paras 0005, 0014-0020, 0038 and 0041	1-6, 11, 12, 14 and 15
X	WO 2012/009288 A2 (THRESHOLD PHARMACEUTICALS, INC.) 19 January 2012 Paras 0009, 0040, 0043, 0044, 0058-0060 and 0069-0071	1-6, 11, 12, 14 and 15
X	CA 2686587 A1 (BIONOMICS LIMITED) 27 May 2011 Pages 2 and 6-8, page 9, lines 12-14 and page 12, combinations 21 and 25-28,	1-10 and 13-15
X	MONAGHAN, K. et al, "CYT997 causes apoptosis in human multiple myeloma." Invest New Drugs. Apr 2011; 29(2): (Epub 12 Nov 2009), pages 232-8. Page 236, col. 1, last paragraph to col. 2, first paragraph	1-6, 14 and 15
X	MASUNAGA, S. et al, "Dependency of the effect of a vascular disrupting agent on sensitivity to tirapazamine and gamma-ray irradiation upon the timing of its administration and tumor size, with reference to the effect on intratumor quiescent cells." J Cancer Res Clin Oncol. Jan 2007;133(1): (Epub 22 Aug 2006) pages 47-55. Page 54, col. 2	1-6, 14 and 15
X	MASUNAGA, S, et al, "Combination of the antivascular agent ZD6126 with hypoxic cytotoxin treatment, with reference to the effect on quiescent tumor cells and the dependency on p53 status of tumor cells." Oncol Rep. Aug 2005; 14(2): pages 393-400. Page 399, col. 2, lines 30-32 and 41-45	1-6, 14 and 15
X	KENDREW, J. et al, "Anti-tumour and anti-vascular effects of cediranib (AZD2171) alone and in combination with other anti-tumour therapies." Cancer Chemother Pharmacol. Apr 2013; 71(4): (Epub 26 Jan 2013), pages 1021-32. Page 1029, col. 1, lines 21-31	1-6, 14 and 15
X	US 2011/0130367 A1 (KREMMIDIOTIS, G. et al) 02 June 2011 Paras 0006-0028, 0030, 0038, 0047, 0070-0074 and Examples 1 and 2	1-10 and 13-15

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2013/000581**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
US 2012/0087913 A1	12 Apr 2012	None	
WO 2012/009288 A2	19 Jan 2012	EP 2593139 A2	22 May 2013
		KR 20130045341 A	03 May 2013
		WO 2012009288 A2	19 Jan 2012
CA 2686587 A1	27 May 2011	None	
US 2011/0130367 A1	02 Jun 2011	None	

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.