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(54) Title: USE OF PI3K-INHIBITORS

(57) Abstract: The present invention relates to inhibitors of PI3K kinase for the treatment or prophylaxis of a disease, particularly for the treatment of cancers and their metastases.

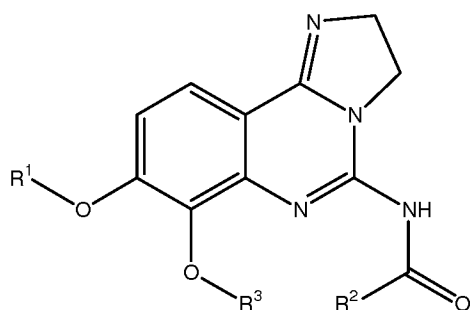


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Use of PI3K-Inhibitors

The present invention relates to the use of a compound of general formula (I),

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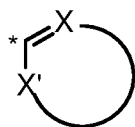


(I)

in which :

10 R^1 represents $-(CH_2)_n-(CHR^4)-(CH_2)_m-N(R^5)(R^{5'})$;

R^2 represents a heteroaryl of structure :



optionally substituted with 1, 2 or 3 R^6 groups,

in which :

15 * represents the point of attachment of said heteroaryl with the rest of the compound of general formula (I),

X represents N or C- R^6 ,

X' represents O, S, NH, N- R^6 , N or C- R^6 ,

with the proviso that when X and X' are both C- R^6 , then one C- R^6 is C-H ;

20 R^3 is methyl ;

R^4 is hydroxy ;

R^5 and $R^{5'}$ are the same or different and are, independently of each other, a hydrogen atom, or a C₁-C₆-alkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, or C₁-C₆-alkoxy-C₁-C₆-alkyl,

25 or

R^5 and $R^{5'}$, taken together with the nitrogen atom to which they are bound, represent a 3- to 7-membered nitrogen containing heterocyclic ring optionally

containing at least one additional heteroatom selected from oxygen, nitrogen or sulfur and which may be optionally substituted with 1 or more $R^{6'}$ groups ;

each occurrence of R^6 may be the same or different and is independently a
 5 hydrogen atom, a halogen atom, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, aryl, aryl- C_1 - C_6 -alkyl, heteroaryl, heteroaryl- C_1 - C_6 -alkyl, 3- to 8-membered heterocyclic ring, 3- to 8-membered heterocyclyl- C_1 - C_6 -alkyl, - C_1 - C_6 -alkyl- OR^7 , - C_1 - C_6 -alkyl- SR^7 , - C_1 - C_6 -alkyl- $N(R^7)(R^7)$, - C_1 - C_6 -alkyl- $C(=O)R^7$, -CN, - $C(=O)OR^7$, - $C(=O)N(R^7)(R^7)$, - OR^7 , - SR^7 ,
 10 - $N(R^7)(R^7)$, or - $NR^7C(=O)R^7$ each of which may be optionally substituted with 1 or more R^8 groups ;

each occurrence of $R^{6'}$ may be the same or different and is independently C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, or C_1 - C_6 -alkyl- OR^7 ;

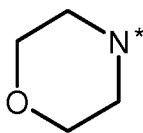
15 each occurrence of R^7 and $R^{7'}$ may be the same or different and is independently a hydrogen atom, or a C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkenyl, aryl, aryl- C_1 - C_6 -alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, 3- to 8-membered heterocyclyl- C_1 - C_6 -alkyl, or heteroaryl- C_1 - C_6 -alkyl ;

each occurrence of R^8 is independently a halogen atom, or nitro, hydroxy, cyano, formyl, acetyl, amino, C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, C_1 - C_6 -cycloalkenyl, aryl,
 25 aryl- C_1 - C_6 -alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, heterocyclyl- C_1 - C_6 -alkyl, or heteroaryl- C_1 - C_6 -alkyl ;

n is an integer of 1 and m is an integer of 1 ;

30 with the proviso that when :

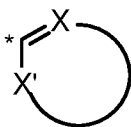
- said R^5 and $R^{5'}$, taken together with the nitrogen atom to which they are bound, represent :



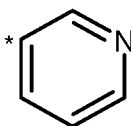
in which * represents the point of attachment with the rest of the structure of general formula (I),

then

- 5 - said R² heteroaryl of structure :



is not :



- 10 in which * represents the point of attachment with the rest of the structure of general formula (I),

as a sole active agent, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt,

- 15 for the preparation of a medicament for the treatment or prophylaxis of cancer, particularly breast cancer, prostate cancer, multiple myeloma, hepatocyte carcinoma, lung cancer, in particular non-small cell lung carcinoma, colorectal cancer, melanoma, pancreatic cancer and/or metastases thereof.

- 20 Another aspect of the present invention relates to the use of the compounds of formula (I) as described herein for the preparation of a medicament for the treatment or prophylaxis of breast cancer or prostate cancer and/or metastases thereof. According to another aspect of the invention the metastases are bone metastases.

25

The present invention further relates to a combination of

a) a compound of formula(I) as described herein, and

- b) one or more further active agents selected from the group consisting of:
anti-angiogenesis, anti-hyper-proliferative, anti-inflammatory, analgesic,
immunoregulatory, diuretic, antiarrhythmic, anti-hypercholesterolemia, anti-
dyslipidemia, anti-diabetic or antiviral agents, and/or admixtures or combinations
5 thereof.

Another aspect of the invention relates to a pharmaceutical composition which
comprises a combination as described *supra*.

- 10 Yet another aspect of the invention relates to the use of a combination or of a
pharmaceutical composition as described *supra*
and
one or more further active agents as described herein or a pharmaceutical
composition containing such a combination,
15 for the preparation of a medicament for the treatment or prophylaxis of a cancer,
particularly breast cancer, prostate cancer, multiple myeloma, hepatocyte
carcinoma, lung cancer, in particular non-small cell lung carcinoma, colorectal
cancer, melanoma, pancreatic cancer and/or metastases thereof.
- 20 Another aspect of the present invention relates to a method of treatment or
prophylaxis of a cancer, particularly multiple myeloma, hepatocyte carcinoma,
lung cancer, in particular non-small cell lung carcinoma, colorectal cancer,
melanoma, pancreatic cancer, prostate cancer, breast cancer and/or
metastases thereof, in a subject, comprising administering to said subject a
25 therapeutically effective amount of a compound as described herein.

- Further, the present invention relates to a kit comprising a combination of :
one or more compounds as described herein; and,
one or more further active agents selected from the group consisting of :
30 anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic,
immunoregulatory, diuretic, antiarrhythmic, anti-hypercholesterolemia, anti-
dyslipidemia, anti-diabetic or antiviral agents, and/or admixtures or combinations
thereof, in which optionally both or either of said compounds as described herein

and further active agents are in the form of a pharmaceutical formulation which is ready for use to be administered simultaneously, concurrently, separately or sequentially.

5

BACKGROUND

Cancer is the second most prevalent cause of death in the United States, causing 450,000 deaths per year. While substantial progress has been made in
10 identifying some of the likely environmental and hereditary causes of cancer, there is a need for additional therapeutic modalities that target cancer and related diseases. In particular there is a need for therapeutic methods for treating diseases associated with dysregulated growth / proliferation.

Cancer is a complex disease arising after a selection process for cells with
15 acquired functional capabilities like enhanced survival / resistance towards apoptosis and a limitless proliferative potential. Thus, it is preferred to develop drugs for cancer therapy addressing distinct features of established tumors.

The PI3K/AKT/mTOR pathway, which is constitutively activated in many types of cancers, is one of the prominent pathway that promote tumor cell survival. Initial
20 activation of the PI3K/AKT/mTOR pathway occurs at the cell membrane, where the signal for pathway activation is propagated through class IA PI3K. Activation of PI3K can occur through tyrosine kinase growth factor receptors (e.g. platelet-derived growth factor receptor (PDGF-R), human epidermal growth factor 1/2/3 receptor (EGFR, HER2/3), or the insulin-like growth factor 1 receptor (IGF-1R)),
25 cell adhesion molecules through integrin-linked kinase (ILK), Ca²⁺/calmodulin-dependent kinase kinase (CaMKK), nuclear DNA-dependent protein kinase (DNA-PK), G-protein-coupled receptors, and oncogenic proteins, such as Ras. Once PI3K is activated, it catalyzes phosphorylation of the D-3 position on phosphoinositides to generate the biologically-active phosphatidylinositol-3,4,5-
30 triphosphate [PI(3,4,5)P₃, PIP₃] and phosphatidylinositol-3,4-bisphosphate [PI(3,4)P₂, PIP₂]. PIP₃ binds to the pleckstrin homology (PH) domains of phosphoinositide-dependent kinase 1 (PDK-1), AKT, and other PH-domain containing proteins, such as Rho and PLC. As the consequence of binding to

PIP₃, the proteins are translocated to the cell membrane and are subsequently activated. The tumour suppressor PTEN (phosphatase and tensin homolog deleted on chromosome 10) antagonizes PI3K by dephosphorylating PIP₃, thereby preventing translocation and activation of PDK1, AKT and other
5 signaling proteins.^{1,2}

AKT is the major effector of PI3K, which elicits a broad range of downstream signaling events. It recognizes and phosphorylates the consensus sequence
10 RXRXX(S/T) when surrounded by hydrophobic residues. As this sequence is present in many proteins, about 50 AKT substrates have been identified and validated.^{3, 4} These substrates control key cellular processes such as apoptosis, cell cycle progression, transcription, and translation, stress adaptation, metabolism, and metastasis of tumor cells. For instance, AKT phosphorylates
15 the FOXO subfamily of forkhead family transcription factors, which inhibits transcription of several pro-apoptotic genes, e.g. Fas-L, IGFBP1 and Bim.^{5, 6} Additionally, AKT can directly regulate apoptosis by phosphorylating and inactivating pro-apoptotic proteins such as Bad, which control the release of cytochrome c from mitochondria, and apoptosis signal-regulating kinase-1, a
20 mitogen-activated protein kinase kinase involved in stress-induced and cytokine-induced cell death.⁷ In contrast, AKT can phosphorylate I κ B kinase, which indirectly increases the activity of nuclear factor κ B and stimulates the transcription of pro-survival genes.⁸ Cell cycle progression can also be affected at the G1/S transition by AKT through its inhibitory phosphorylation of the cyclin
25 dependent kinase inhibitors, p21WAF1/CIP1 and p27KIP1. In addition AKT can phosphorylate mouse double minute 2 (MDM2) leading to its nuclear translocation and promotion of degradation of p53. This in consequence leads to an decrease in p21Cip1mRNA.⁹ Furthermore AKT has also an important function in the control of the G2/M transition by e.g. phosphorylation of Myt1 and
30 FOXO3a.^{10, 11}

The best-studied downstream substrate of AKT is the serine/threonine kinase mTOR. AKT can directly phosphorylate and activate mTOR, as well as cause indirect activation of mTOR by phosphorylating and inactivating TSC2 (tuberous

sclerosis complex 2, also called tuberin), which normally inhibits mTOR through the GTP-binding protein Rheb (Ras homolog enriched in brain). When TSC2 is inactivated by phosphorylation, the GTPase Rheb is maintained in its GTP-bound state, allowing for increased activation of mTOR. mTOR exists in two
5 complexes: the TORC1 complex, in which mTOR is bound to Raptor, and the TORC2 complex, in which mTOR is bound to Rictor.¹² In the TORC1 complex, mTOR phosphorylates its downstream effectors S6 kinase (S6K1) and 4EBP-1. S6K1 can then phosphorylate its substrate, a ribosomal protein called S6. 4EBP-1, when phosphorylated cannot bind effectively to its binding partner,
10 eIF4E. The cumulative effect is to increase protein translation, especially of highly structured, capped mRNA species.¹³ Although mTOR is generally considered a downstream substrate of AKT, mTOR in complex with Rictor can also phosphorylate AKT at S473, thereby providing a level of positive feedback on the pathway.¹⁴ Finally, S6K1 can also regulate the pathway by catalyzing an
15 inhibitory phosphorylation on insulin receptor substrate proteins (IRS). This prevents IRS from activating PI3K, which indirectly lowers activation of AKT. This feedback pathway is very important for developing PI3K/AKT/mTOR pathway inhibitors, as the re-activation of PI3K has to be taken into consideration during the evaluation of the anti-tumor efficacy of the PI3K
20 pathway inhibitors.^{15, 16}

In addition to the well described PI3K/AKT/mTOR axis of the PI3K signaling pathway, PI3K, AKT and mTOR also receive and branch differential signaling events that are independent from the axis. For example, mTOR has the crosstalk with and is activated by MAPK pathway through ERK and RSK
25 regulated phosphorylation of TSC2.¹⁷ There are collective data describing the AKT/mTOR-independent PI3K-mediated signaling events. First of all, PI3K downstream signaling molecule PDK1 responds to increased levels of PIP3 and activates not only AKT, but also a group of AGC kinases comprising S6K, RSK, SGK and PKC isoforms, which play essential roles in regulating tumor cell
30 growth, proliferation, survival and metabolism.¹⁸ Furthermore, many PIK3CA mutant cancer cell lines and human breast tumors exhibit only minimal AKT activation and a diminished reliance on AKT for anchorage-independent growth. Instead, these cells retain robust PDK1 activation and membrane localization

and exhibit dependency on the PDK1 substrate SGK3. SGK3 undergoes PI3K- and PDK1-dependent activation in PIK3CA mutant cancer cells. Thus, PI3K may promote cancer through both AKT-dependent and AKT-independent mechanisms.¹⁹ In addition to PDK1 and AGC kinases, PI3Ks regulate also other
5 cancer related signaling proteins such as PLC, Rac, Rho, ITK and BTK, etc.

In humans, class I PI3K has four isoforms of the p110 catalytic subunits, p110 α , p110 β , p110 γ and p110 δ . p110 α and p110 β are present in all cell types, while p110 δ and p110 γ are highly enriched in leukocytes. p110 subunits are divided
10 into a class IA group (p110 α , p110 β and p110 δ), which bind the p85 regulatory subunit, and a class IB group (p110 γ), which does not. The p85 regulatory subunits contain Src homology 2 (SH2) domains and bind phosphorylated tyrosine (pTyr), which lead to the activation of the class IA p110 catalytic subunits. On the other hand, p110 γ is activated directly through G protein
15 coupled receptors (GPCRs). Recent data indicated that p110 β was also activated by GPCRs directly through G $\beta\gamma$ protein.²⁰

The signaling inputs to each class I PI3Ks are diverse and well depicted in genetic analyses. Thus, activation of AKT was impaired in p110 α -deficient MEFs upon stimulation by classical RTK ligands (EGF, insulin, IGF-1, and PDGF).²¹
20 On the other hand, MEFs in which p110 β is ablated or replaced by a kinase-dead allele of p110 β respond normally to growth factor stimulation via RTKs.²² Instead, p110 β catalytic activity is actually required for AKT activation in response to GPCR ligands (such as LPA). As such, p110 α appears to carry the majority of the PI3K signal in classic RTK signaling and is responsible for tumor
25 cell growth, proliferation, survival, angiogenesis and metabolism whereas p110 β mediates GPCR signaling from mitogens and chemokines and therefore may regulate tumor cell proliferation, metabolism, inflammation and invasion.^{23, 24}

30 Although the differences in signaling outputs from the four class I PI3K isoforms are still largely unknown, it seems that PI3K β together with PTEN determines the basal levels of PIP3 in tumor cells, while RTK stimulated elevation of PIP3 is controlled mainly by PI3K α . The potential for differential signaling outputs

downstream of specific PI3K isoforms, in parallel with a possibly more universal Akt activation are yet to be discovered.

5 Activation of PI3K/AKT kinases promotes increased nutrient uptake, converting cells to a glucose-dependent metabolism that redirects lipid precursors and amino acids to anabolic processes that support cell growth and proliferation. These metabolic phenotype with overactivated AKT lead to malignancies that display a metabolic conversion to aerobic glycolysis (the Warburg effect). In that respect the PI3K/AKT pathway is discussed to be central for survival despite unfavourable growth conditions such as glucose depletion or hypoxia.

10 A further aspect of the activated PI3K/AKT pathway is to protect cells from programmed cell death ("apoptosis") and is hence considered to transduce a survival signal. By acting as a modulator of anti-apoptotic signalling in tumor cells, the PI3K/AKT pathway, particular PI3K itself is a target for cancer therapy.

15 Activated PI3K/AKT phosphorylates and regulates several targets, e.g. BAD, GSK3 or FKHRL1, that affect different signalling pathways like cell survival, protein synthesis or cell movement. This PI3K/AKT pathway also plays a major part in resistance of tumor cells to conventional anti-cancer therapies. Blocking the PI3K/AKT pathway could therefore simultaneously inhibit the proliferation of tumor cells (e.g. via the inhibition of the metabolic effect) and sensitize towards pro-apoptotic agents. PI3K inhibition selectively sensitized tumor cells to apoptotic stimuli like Trail, Camptothecin and Doxorubicin.

25 The resistance of many types of cancer to chemo- and targeted therapeutics represents the major hurdle in successful cancer treatment. Cancer cells can escape the effect of most commonly used drugs despite their different chemical structure and intracellular targets. Many mechanisms underlying the failure of therapeutic drugs have been well studied. Activation of PI3K/AKT pathway plays a key role in different cellular functions such as growth, migration, survival and differentiation. Data accumulated in the last decade have established that this pathway plays also a key role in resistance to both chemo-, radiation- and targeted therapeutics. Collective data describing constitutive or residual pathway activation in cells that have developed resistance to conventional chemotherapy

and radiation, as well as to other targeted therapies such as EGFR antagonism. For example, experiments in doxorubicin-resistant CML cell lines demonstrated high levels of PI3K/ AKT activity; importantly, doxorubicin resistance could be overcome by decreasing PI3K/ AKT activity. Further experimental evidence was
5 observed in two pancreatic cancer cell lines in which decreased levels of phosphorylated AKT can increase gemcitabine-induced apoptosis. Synergistic antitumor activity with cisplatin was also demonstrated in xenograft models of lung cancer.

The PI3K/AKT pathway is linked to resistance to both chemo- and targeted
10 therapeutics. The Inhibition of PI3K β might present a promising strategy to overcome the resistance to radiation and DNA targeting therapy. Nuclear PI3K β can induce nuclear AKT phosphorylated on both T308 and S473 in response to either IR or the DNA-damaging agent doxorubicin.

15 In summary, PI3K plays central role downstream of many cancer related signaling pathways that are critical for tumorigenesis, tumor growth / proliferation and survival, tumor cell adhesion, invasion and metastasis, as well as tumor angiogenesis. In addition, gain-function mutation of PIK3CA is common in several human cancers and the link between tumor suppressor gene PTEN and
20 PI3K β has been observed in some tumors such as prostate cancer. An increased expression of the p110 β and p110 δ isoforms has been observed in some colon and bladder tumors, and in glioblastoma. In addition, nuclear PI3K β plays roles in DNA synthesis and repair.³⁵ Furthermore, p110 δ controls proliferation in acute myeloid leukemia (AML) and migration of breast cancer
25 cells,³⁶ whereas p110 γ plays roles in tumor angiogenesis, drug resistance of CML cells, and pancreatic tumor growth and survival.³⁷ Thus, developing PI3K inhibitors for treatment in mono- and combination therapy is a promising strategy to treat cancer and overcome cancer treatment resistance.

30

Thus inhibitors of PI3K represent valuable compounds that should complement therapeutic options as single agents and also in combination with other drugs, e.g. DNA targeting agent and radiation therapy.

It has been surprisingly found, that the compounds of general formula (I) as described herein are effective in the treatment or prophylaxis of cancer, particularly breast cancer, prostate cancer, multiple myeloma, hepatocyte carcinoma, lung cancer, in particular non-small cell lung carcinoma, colorectal cancer, melanoma, pancreatic cancer, particularly where such cancers show metastases. Furthermore, the compounds of general formula (I) are effective in the treatment or prophylaxis of cancer, particularly breast cancer, prostate cancer, multiple myeloma, hepatocyte carcinoma, lung cancer, in particular non-small cell lung carcinoma, colorectal cancer, melanoma, pancreatic cancer with bone metastases.

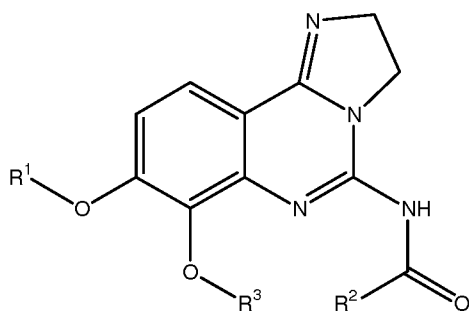
Surprisingly it was observed that by administering a PI3K inhibitor of general formula (I) or a physiologically acceptable salt, solvate, hydrate or stereoisomer as a sole agent showed a statistically significant reduction in whole body tumor burden. Further, a reduction in total tumor-induced osteolytic and osteoblast lesion area in bone was also observed. Moreover, a significant reduction in kidney metastases was observed with a PI3K inhibitor of the present invention as monotherapy.

20

SUMMARY of the INVENTION

Therefore, in accordance with a first aspect, the present invention provides the use of a compound of general formula (I),

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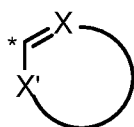


(I)

in which :

R¹ represents $-(CH_2)_n-(CHR^4)-(CH_2)_m-N(R^5)(R^{5'})$;

- 5 R² represents a heteroaryl of structure :

optionally substituted with 1, 2 or 3 R⁶ groups,

in which :

- * represents the point of attachment of said heteroaryl with the rest of the
10 compound of general formula (I),

X represents N or C-R⁶,X' represents O, S, NH, N-R⁶, N or C-R⁶,with the proviso that when X and X' are both C-R⁶, then one C-R⁶ is C-H ;R³ is methyl ;

- 15 R⁴ is hydroxy ;

R⁵ and R^{5'} are the same or different and are, independently of each other, a hydrogen atom, or a C₁-C₆-alkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, or C₁-C₆-alkoxy-C₁-C₆-alkyl,

or

- 20 R⁵ and R^{5'}, taken together with the nitrogen atom to which they are bound, represent a 3- to 7-membered nitrogen containing heterocyclic ring optionally containing at least one additional heteroatom selected from oxygen, nitrogen or sulfur and which may be optionally substituted with 1 or more R^{6'} groups ;

- 25 each occurrence of R⁶ may be the same or different and is independently a hydrogen atom, a halogen atom, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, aryl, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, 3- to 8-membered heterocyclic ring, 3- to 8-membered heterocyclyl-C₁-C₆-alkyl, -C₁-C₆-alkyl-OR⁷, -C₁-C₆-alkyl-SR⁷, -C₁-C₆-alkyl-
30 N(R⁷)(R^{7'}), -C₁-C₆-alkyl-C(=O)R⁷, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)(R^{7'}), -OR⁷, -SR⁷, -N(R⁷)(R^{7'}), or -NR⁷C(=O)R⁷ each of which may be optionally substituted with 1 or more R⁸ groups ;

each occurrence of R^6 may be the same or different and is independently C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, or C_1 - C_6 -alkyl- OR^7 ;

- 5 each occurrence of R^7 and $R^{7'}$ may be the same or different and is independently a hydrogen atom, or a C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkenyl, aryl, aryl- C_1 - C_6 -alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, 3- to 8-membered heterocycl- C_1 - C_6 -alkyl, or heteroaryl- C_1 - C_6 -alkyl ;

10

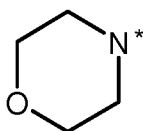
each occurrence of R^8 is independently a halogen atom, or nitro, hydroxy, cyano, formyl, acetyl, amino, C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, C_1 - C_6 -cycloalkenyl, aryl, aryl- C_1 - C_6 -alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, heterocycl- C_1 -

- 15 C_6 -alkyl, or heteroaryl- C_1 - C_6 -alkyl ;

n is an integer of 1 and m is an integer of 1 ;

with the proviso that when :

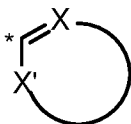
- 20 - said R^5 and $R^{5'}$, taken together with the nitrogen atom to which they are bound, represent :



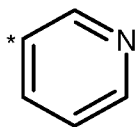
in which * represents the point of attachment with the rest of the structure of general formula (I),

- 25 then

- said R^2 heteroaryl of structure :



is not :



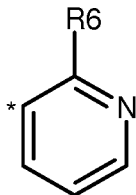
in which * represents the point of attachment with the rest of the structure of general formula (I),

- 5 as a sole active agent, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt, for the preparation of a medicament for the treatment or prophylaxis of cancer, particularly breast cancer, prostate cancer, multiple myeloma, hepatocyte carcinoma, lung cancer, in particular non-small cell lung carcinoma, colorectal
10 cancer, melanoma, pancreatic cancer and/or metastases thereof.

According to an embodiment of the invention,

R^1 represents $-(CH_2)_n-(CHR^4)-(CH_2)_m-N(R^5)(R^{5'})$;

R^2 represents a heteroaryl of structure :



15

in which :

* represents the point of attachment of said heteroaryl with the rest of the structure of general formula (I) ;

R^3 is methyl ;

- 20 R^4 is hydroxy ;

R^5 and $R^{5'}$ are the same or different and are, independently of each other, a hydrogen atom, or a C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, or C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl,

or

- 25 R^5 and $R^{5'}$, taken together with the nitrogen atom to which they are bound, represent a 3- to 7-membered nitrogen containing heterocyclic ring optionally containing at least one additional heteroatom selected from oxygen, nitrogen or sulfur and which may be optionally substituted with 1 or more R^6 groups ;

each occurrence of R^6 may be the same or different and is independently a hydrogen atom, a halogen atom, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, aryl, aryl- C_1 - C_6 -alkyl, heteroaryl, heteroaryl- C_1 - C_6 -alkyl, 3- to 8-membered heterocyclic ring, 3- to 8-membered heterocyclyl- C_1 - C_6 -alkyl, $-C_1$ - C_6 -alkyl- OR^7 , $-C_1$ - C_6 -alkyl- SR^7 , $-C_1$ - C_6 -alkyl- $N(R^7)(R^{7'})$, $-C_1$ - C_6 -alkyl- $C(=O)R^7$, $-CN$, $-C(=O)OR^7$, $-C(=O)N(R^7)(R^{7'})$, $-OR^7$, $-SR^7$, $-N(R^7)(R^{7'})$, or $-NR^7C(=O)R^7$ each of which may be optionally substituted with 1 or more R^8 groups ;

10

each occurrence of $R^{6'}$ may be the same or different and is independently C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, or C_1 - C_6 -alkyl- OR^7 ;

each occurrence of R^7 and $R^{7'}$ may be the same or different and is independently a hydrogen atom, or a C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkenyl, aryl, aryl- C_1 - C_6 -alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, 3- to 8-membered heterocyclyl- C_1 - C_6 -alkyl, or heteroaryl- C_1 - C_6 -alkyl ;

each occurrence of R^8 is independently a halogen atom, or nitro, hydroxy, cyano, formyl, acetyl, amino, C_1 - C_6 -alkyl, C_1 - C_6 -alkoxy, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, C_1 - C_6 -cycloalkenyl, aryl, aryl- C_1 - C_6 -alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, heterocyclyl- C_1 - C_6 -alkyl, or heteroaryl- C_1 - C_6 -alkyl ;

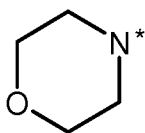
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n is an integer of 1 and m is an integer of 1 ;

with the proviso that when :

- said R^5 and $R^{5'}$, taken together with the nitrogen atom to which they are bound, represent :

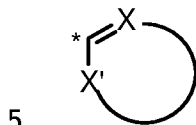
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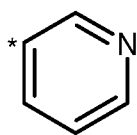
in which * represents the point of attachment with the rest of the structure of general formula (I),

then

- said R² heteroaryl of structure :



is not :



10 in which * represents the point of attachment with the rest of the structure of general formula (I),

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt.

15

According to one embodiment, the compound of general formula (I) is selected from the group consisting of :

- 20 N-(8-[[[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide
- N-(8-[[[(2S)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide
- N-[8-({(2R)-3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-hydroxypropyl}oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide
- N-(8-[[[(2R)-2-hydroxy-3-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide
- N-{8-[2-hydroxy-3-(thiomorpholin-4-yl)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide

N-(8-([(2R)-3-(azetidin-1-yl)-2-hydroxypropyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-(8-([(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-(8-([(2R)-2-hydroxy-3-(piperidin-1-yl)propyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-{8-[3-(dimethylamino)-2-hydroxypropoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyridine-3-carboxamide

N-(8-([(2R)-3-(dimethylamino)-2-hydroxypropyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-(8-([(2R)-3-(dipropan-2-ylamino)-2-hydroxypropyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-(8-([(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-(8-([(2R)-3-(azetidin-1-yl)-2-hydroxypropyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-[8-([(2R)-3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-hydroxypropyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-(8-([(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-(8-([(2R)-2-hydroxy-3-(piperidin-1-yl)propyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-(8-([(2R)-3-(dipropan-2-ylamino)-2-hydroxypropyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

6-amino-N-{8-[2-hydroxy-3-(morpholin-4-yl)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyridine-3-carboxamide

6-amino-N-(8-([(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy)-7-

methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide

2-amino-N-{8-[2-hydroxy-3-(morpholin-4-yl)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide

2-amino-N-[8-({(2R)-3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-hydroxypropyl}oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide

2-amino-N-(8-{{(2R)-2-hydroxy-3-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)propyl}oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide dihydrochloride

2-amino-N-(8-{{(2R)-3-(dimethylamino)-2-hydroxypropyl}oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-thiazole-5-carboxamide

N-[8-({(2R)-3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-hydroxypropyl}oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-thiazole-5-carboxamide

N-(8-[[[(2R)-3-(azetidin-1-yl)-2-hydroxypropyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-thiazole-5-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-thiazole-5-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(piperidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-thiazole-5-carboxamide

N-(8-[[[(2R)-2-Hydroxy-3-(pyrrolidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-4-methyl-1,3-thiazole-5-carboxamide

2-amino-N-(8-[[[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-

methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-4-methyl-1,3-thiazole-5-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-oxazole-5-carboxamide

N-(8-[[[(2R)-3-(dipropylamino)-2-hydroxypropyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-thiazole-5-carboxamide,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt.

According to another embodiment the compound of general formula (I) is selected from the group consisting of :

5

N-(8-[[[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide

N-[8-[[[(2R)-3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-hydroxypropyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide

N-(8-[[[(2R)-3-(azetidin-1-yl)-2-hydroxypropyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(piperidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide

N-(8-[[[(2R)-3-(dimethylamino)-2-hydroxypropyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide

N-(8-[[[(2R)-3-(dipropylamino)-2-hydroxypropyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-(8-[[[(2R)-3-(azetidin-1-yl)-2-hydroxypropyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methylpyridine-3-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methylpyridine-3-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(piperidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methylpyridine-3-carboxamide

N-(8-[[[(2R)-3-(dipropan-2-ylamino)-2-hydroxypropyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methylpyridine-3-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-thiazole-5-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(piperidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-thiazole-5-carboxamide

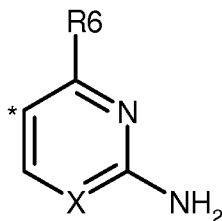
N-(8-[[[(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-oxazole-5-carboxamide,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt.

According to another embodiment,

R¹ represents $-(CH_2)_n-(CHR^4)-(CH_2)_m-N(R^5)(R^{5'})$;

R² represents a heteroaryl of structure :



in which :

* represents the point of attachment of said heteroaryl with the rest of the structure of general formula (I), and

X represents N or C-R⁶ ;

R³ is methyl ;

R⁴ is hydroxy ;

R⁵ and R^{5'} are the same or different and are, independently of each other, a
 5 hydrogen atom, or a C₁-C₆-alkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, or C₁-C₆-alkoxy-
 C₁-C₆-alkyl,

or

R⁵ and R^{5'}, taken together with the nitrogen atom to which they are bound,
 represent a 3- to 7-membered nitrogen containing heterocyclic ring optionally
 10 containing at least one additional heteroatom selected from oxygen, nitrogen or
 sulfur and which may be optionally substituted with 1 or more R^{6'} groups ;

each occurrence of R⁶ may be the same or different and is independently a
 hydrogen atom, a halogen atom, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-
 15 C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, aryl, aryl-C₁-C₆-alkyl, heteroaryl,
 heteroaryl-C₁-C₆-alkyl, 3- to 8-membered heterocyclic ring, 3- to 8-membered
 heterocyclyl-C₁-C₆-alkyl, -C₁-C₆-alkyl-OR⁷, -C₁-C₆-alkyl-SR⁷, -C₁-C₆-alkyl-
 N(R⁷)(R⁷), -C₁-C₆-alkyl-C(=O)R⁷, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)(R⁷), -OR⁷, -SR⁷,
 -N(R⁷)(R⁷), or -NR⁷C(=O)R⁷ each of which may be optionally substituted with 1
 20 or more R⁸ groups ;

each occurrence of R^{6'} may be the same or different and is independently C₁-C₆-
 alkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, or C₁-C₆-alkyl-OR⁷;

25 each occurrence of R⁷ and R^{7'} may be the same or different and is
 independently a hydrogen atom, or a C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl,
 C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, C₃-C₆-cycloalkenyl, aryl, aryl-C₁-
 C₆-alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, 3- to 8-membered
 heterocyclyl-C₁-C₆-alkyl, or heteroaryl-C₁-C₆-alkyl ;

30

each occurrence of R⁸ is independently a halogen atom, or nitro, hydroxy,
 cyano, formyl, acetyl, amino, C₁-C₆-alkyl, C₁-C₆-alkoxy, C₂-C₆-alkenyl, C₂-C₆-
 alkynyl, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, C₁-C₆-cycloalkenyl, aryl,

aryl-C₁-C₆-alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, heterocycl-C₁-C₆-alkyl, or heteroaryl-C₁-C₆-alkyl ;

n is an integer of 1 and m is an integer of 1 ;

5

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt.

According to another embodiment the compound of general formula (I) is
10 selected from the group consisting of :

- 6-amino-N-{8-[2-hydroxy-3-(morpholin-4-yl)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyridine-3-carboxamide
6-Amino-N-(8-[[[(2S)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide
15 6-Amino-N-(8-[[[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methylpyridine-3-carboxamide
2-Amino-N-{8-[2-hydroxy-3-(morpholin-4-yl)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide
20 2-Amino-N-(8-[[[(2S)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide
2-amino-N-[8-({(2R)-3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-hydroxypropyl}oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide
25 2-Amino-N-(8-[[[(2R)-2-hydroxy-3-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide dihydrochloride
2-Amino-N-(8-[[[(2R)-3-(dimethylamino)-2-hydroxypropyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide,
30 or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt.

According to a preferred embodiment the compound of general formula (I) is

N-(8-{[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt.

5

According to a more preferred embodiment the compound of general formula (I) is

N-(8-{[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide or a
10 physiologically acceptable salt thereof.

According to a even more preferred embodiment the compound of general formula (I) is

N-(8-{[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide.
15

According to an embodiment, the invention encompasses the use of a compound of general formula (I), as described *supra*, for the preparation of a medicament for the treatment or prophylaxis of cancer.

20

According to a preferred embodiment, the invention encompasses the use of a compound of general formula (I), as described *supra*, for the preparation of a medicament for the treatment or prophylaxis of breast cancer or prostate cancer and/or metastases thereof. In a more preferred embodiment, the metastases are
25 bone metastases.

In an embodiment, the compound of general formula (I) is selected from the group of PI3K inhibitors generically or specifically disclosed in WO2012062748 A1, which are incorporated by reference herein.

30

The compounds of general formula (I), as described and defined herein, are also referred to as “compounds of the present invention”, “compounds of the invention” or “compounds of this invention”.

In accordance with a second aspect, the present invention covers a combination of :

- 5 a) a compound of general formula (I) as described *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt; or a pharmaceutical composition containing such a compound or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt,
- 10 and
- b) one or more further active agents selected from the group consisting of: anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhythmic, anti-hypercholesterolemia, anti-dyslipidemia, anti-diabetic or antiviral agents, and/or admixtures or combinations
- 15 thereof.

In accordance with a third aspect, the present invention comprises a pharmaceutical composition which comprises a combination of :

- a) a compound of general formula (I) as described *supra*, or a stereoisomer, a
- 20 tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt; and
- b) one or more further active agents selected from the group consisting of : anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhythmic, anti-hypercholesterolemia, anti-
- 25 dyslipidemia, anti-diabetic or antiviral agents, and/or admixtures or combinations thereof.

In accordance with a fourth aspect, the present invention relates to the use of a combination of :

- 30 a) a compound of general formula (I) as described *supra*, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt;

- or of a pharmaceutical composition containing such a compound or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt,
and
- 5 b) one or more further active agents selected from the group consisting of:
anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhythmic, anti-hypercholesterolemia, anti-dyslipidemia, anti-diabetic or antiviral agents, and/or admixtures or combinations thereof,
- 10 or a pharmaceutical composition containing such a combination,
for the preparation of a medicament for the treatment or prophylaxis of a cancer, particularly breast cancer, prostate cancer, multiple myeloma, hepatocyte carcinoma, lung cancer, in particular non-small cell lung carcinoma, colorectal cancer, melanoma, pancreatic cancer and/or metastases thereof.
- 15 According to an embodiment the use of the combination as described *supra* is for the preparation of a medicament for the treatment or prophylaxis of breast cancer or prostate cancer and/or metastases thereof. In a more preferred embodiment the metastases are bone metastases.
- 20 In accordance with a fifth aspect, the present invention relates to a method of treatment or prophylaxis of a cancer, particularly multiple myeloma, hepatocyte carcinoma, lung cancer, in particular non-small cell lung carcinoma, colorectal cancer, melanoma, pancreatic cancer, prostate cancer, breast cancer and/or
- 25 metastases thereof, in a subject, comprising administering to said subject a therapeutically effective amount of a compound of general formula (I) as described herein. In one embodiment the method is for the treatment or prophylaxis of breast cancer or prostate cancer and/or metastases thereof. In a preferred embodiment the metastases are bone metastases.
- 30 Further, the present invention relates to :
A kit comprising a combination of :
one or more compounds of general formula (I) as described *supra*;

one or more further active agents selected from the group consisting of :
anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic,
immunoregulatory, diuretic, antiarrhythmic, anti-hypercholesterolemia, anti-
dyslipidemia, anti-diabetic or antiviral agents, and/or admixtures or combinations
5 thereof, in which optionally both or either of said compounds of general formula
(I) and further active agents are in the form of a pharmaceutical formulation
which is ready for use to be administered simultaneously, concurrently,
separately or sequentially.

10

DETAILED DESCRIPTION OF THE INVENTION

A. Definitions

15 The terms as mentioned in the present text have preferably the following
meanings :

The term "halogen atom" or "halo" is to be understood as meaning a fluorine,
chlorine, bromine or iodine atom.

20

The term "C₁-C₆-alkyl" is to be understood as preferably meaning a linear or
branched, saturated, monovalent hydrocarbon group having 1, 2, 3, 4, 5 or 6
carbon atoms, *e.g.* a methyl, ethyl, propyl, butyl, pentyl, hexyl, iso-propyl, iso-
butyl, sec-butyl, tert-butyl, iso-pentyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl,
25 1,2-dimethylpropyl, neo-pentyl, 1,1-dimethylpropyl, 4-methylpentyl, 3-
methylpentyl, 2-methylpentyl, 1-methylpentyl, 2-ethylbutyl, 1-ethylbutyl, 3,3-
dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-dimethylbutyl, 1,3-
dimethylbutyl, or 1,2-dimethylbutyl group, or an isomer thereof. Particularly, said
group has 1, 2 or 3 carbon atoms ("C₁-C₃-alkyl"), methyl, ethyl, n-propyl- or iso-
30 propyl.

The term "C₁-C₆-alkoxy" is to be understood as preferably meaning a linear or
branched, saturated, monovalent, hydrocarbon group of formula -O-alkyl, in

which the term "alkyl" is defined *supra*, e.g. a methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, tert-butoxy, sec-butoxy, pentoxy, iso-pentoxy, or n-hexoxy group, or an isomer thereof.

- 5 The term "C₁-C₆-alkoxy-C₁-C₆-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a C₁-C₆-alkoxy group, as defined *supra*, e.g. methoxyalkyl, ethoxyalkyl, propyloxyalkyl, iso-propoxyalkyl, butoxyalkyl, iso-butoxyalkyl, tert-butoxyalkyl, sec-butoxyalkyl, pentyloxyalkyl, iso-pentyloxyalkyl, hexyloxyalkyl group, in which
10 the term "C₁-C₆-alkyl" is defined *supra*, or an isomer thereof.

The term "C₂-C₆-alkenyl" is to be understood as preferably meaning a linear or branched, monovalent hydrocarbon group, which contains one or more double
15 bonds, and which has 2, 3, 4, 5, or 6 carbon atoms, particularly 2 or 3 carbon atoms ("C₂-C₃-alkenyl"), it being understood that in the case in which said alkenyl group contains more than one double bond, then said double bonds may be isolated from, or conjugated with, each other. Said alkenyl group is, for example, a vinyl, allyl, (E)-2-methylvinyl, (Z)-2-methylvinyl, homoallyl, (E)-but-2-
20 enyl, (Z)-but-2-enyl, (E)-but-1-enyl, (Z)-but-1-enyl, pent-4-enyl, (E)-pent-3-enyl, (Z)-pent-3-enyl, (E)-pent-2-enyl, (Z)-pent-2-enyl, (E)-pent-1-enyl, (Z)-pent-1-enyl, hex-5-enyl, (E)-hex-4-enyl, (Z)-hex-4-enyl, (E)-hex-3-enyl, (Z)-hex-3-enyl, (E)-hex-2-enyl, (Z)-hex-2-enyl, (E)-hex-1-enyl, (Z)-hex-1-enyl, isopropenyl, 2-methylprop-2-enyl, 1-methylprop-2-enyl, 2-methylprop-1-enyl, (E)-1-methylprop-
25 1-enyl, (Z)-1-methylprop-1-enyl, 3-methylbut-3-enyl, 2-methylbut-3-enyl, 1-methylbut-3-enyl, 3-methylbut-2-enyl, (E)-2-methylbut-2-enyl, (Z)-2-methylbut-2-enyl, (E)-1-methylbut-2-enyl, (Z)-1-methylbut-2-enyl, (E)-3-methylbut-1-enyl, (Z)-3-methylbut-1-enyl, (E)-2-methylbut-1-enyl, (Z)-2-methylbut-1-enyl, (E)-1-methylbut-1-enyl, (Z)-1-methylbut-1-enyl, 1,1-dimethylprop-2-enyl, 1-ethylprop-
30 1-enyl, 1-propylvinyl, 1-isopropylvinyl, 4-methylpent-4-enyl, 3-methylpent-4-enyl, 2-methylpent-4-enyl, 1-methylpent-4-enyl, 4-methylpent-3-enyl, (E)-3-methylpent-3-enyl, (Z)-3-methylpent-3-enyl, (E)-2-methylpent-3-enyl, (Z)-2-methylpent-3-enyl, (E)-1-methylpent-3-enyl, (Z)-1-methylpent-3-enyl, (E)-4-

methylpent-2-enyl, (Z)-4-methylpent-2-enyl, (E)-3-methylpent-2-enyl, (Z)-3-
 methylpent-2-enyl, (E)-2-methylpent-2-enyl, (Z)-2-methylpent-2-enyl, (E)-1-
 methylpent-2-enyl, (Z)-1-methylpent-2-enyl, (E)-4-methylpent-1-enyl, (Z)-4-
 methylpent-1-enyl, (E)-3-methylpent-1-enyl, (Z)-3-methylpent-1-enyl, (E)-2-
 5 methylpent-1-enyl, (Z)-2-methylpent-1-enyl, (E)-1-methylpent-1-enyl, (Z)-1-
 methylpent-1-enyl, 3-ethylbut-3-enyl, 2-ethylbut-3-enyl, 1-ethylbut-3-enyl, (E)-3-
 ethylbut-2-enyl, (Z)-3-ethylbut-2-enyl, (E)-2-ethylbut-2-enyl, (Z)-2-ethylbut-2-
 enyl, (E)-1-ethylbut-2-enyl, (Z)-1-ethylbut-2-enyl, (E)-3-ethylbut-1-enyl, (Z)-3-
 ethylbut-1-enyl, 2-ethylbut-1-enyl, (E)-1-ethylbut-1-enyl, (Z)-1-ethylbut-1-enyl, 2-
 10 propylprop-2-enyl, 1-propylprop-2-enyl, 2-isopropylprop-2-enyl, 1-isopropylprop-
 2-enyl, (E)-2-propylprop-1-enyl, (Z)-2-propylprop-1-enyl, (E)-1-propylprop-1-enyl,
 (Z)-1-propylprop-1-enyl, (E)-2-isopropylprop-1-enyl, (Z)-2-isopropylprop-1-enyl,
 (E)-1-isopropylprop-1-enyl, (Z)-1-isopropylprop-1-enyl, (E)-3,3-dimethylprop-1-
 enyl, (Z)-3,3-dimethylprop-1-enyl, 1-(1,1-dimethylethyl)ethenyl, buta-1,3-dienyl,
 15 penta-1,4-dienyl, hexa-1,5-dienyl, or methylhexadienyl group. Particularly, said
 group is vinyl or allyl.

The term "C₂-C₆-alkynyl" is to be understood as preferably meaning a linear or
 branched, monovalent hydrocarbon group which contains one or more triple
 20 bonds, and which contains 2, 3, 4, 5, or 6 carbon atoms, particularly 2 or 3
 carbon atoms ("C₂-C₃-alkynyl"). Said C₂-C₆-alkynyl group is, for example,
 ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, pent-1-ynyl,
 pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, hex-1-ynyl, hex-2-ynyl, hex-3-ynyl, hex-4-
 ynyl, hex-5-ynyl, 1-methylprop-2-ynyl, 2-methylbut-3-ynyl, 1-methylbut-3-ynyl, 1-
 25 methylbut-2-ynyl, 3-methylbut-1-ynyl, 1-ethylprop-2-ynyl, 3-methylpent-4-ynyl, 2-
 methylpent-4-ynyl, 1-methylpent-4-ynyl, 2-methylpent-3-ynyl, 1-methylpent-3-
 ynyl, 4-methylpent-2-ynyl, 1-methylpent-2-ynyl, 4-methylpent-1-ynyl, 3-
 methylpent-1-ynyl, 2-ethylbut-3-ynyl, 1-ethylbut-3-ynyl, 1-ethylbut-2-ynyl, 1-
 propylprop-2-ynyl, 1-isopropylprop-2-ynyl, 2,2-dimethylbut-3-ynyl, 1,1-
 30 dimethylbut-3-ynyl, 1,1-dimethylbut-2-ynyl, or 3,3-dimethylbut-1-ynyl group.
 Particularly, said alkynyl group is ethynyl, prop-1-ynyl, or prop-2-ynyl.

The term "C₃-C₆-cycloalkyl" is to be understood as preferably meaning a saturated, monovalent, mono-, or bicyclic hydrocarbon ring which contains 3, 4, 5, or 6 carbon atoms. Said C₃-C₆-cycloalkyl group is for example, a monocyclic hydrocarbon ring, *e.g.* a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl group, or a bicyclic hydrocarbon ring, *e.g.* a perhydropentalenylene or decalin ring. Said cycloalkyl ring can optionally contain one or more double bonds *e.g.* cycloalkenyl, such as a cyclopropenyl, cyclobutenyl, cyclopentenyl or cyclohexenyl group, wherein the bond between said ring with the rest of the molecule may be to any carbon atom of said ring, be it saturated or unsaturated.

10 The term "alkylene" is understood as preferably meaning an optionally substituted hydrocarbon chain (or "tether") having 1, 2, 3, 4, 5, or 6 carbon atoms, *i.e.* an optionally substituted -CH₂- ("methylene" or "single membered tether" or, for example -C(Me)₂-), -CH₂-CH₂- ("ethylene", "dimethylene", or "two-membered tether"), -CH₂-CH₂-CH₂- ("propylene", "trimethylene", or "three-membered tether"), -CH₂-CH₂-CH₂-CH₂- ("butylene", "tetramethylene", or "four-membered tether"), -CH₂-CH₂-CH₂-CH₂-CH₂- ("pentylene", "pentamethylene" or "five-membered ether"), or -CH₂-CH₂-CH₂-CH₂-CH₂-CH₂- ("hexylene", "hexamethylene", or six-membered tether") group. Particularly, said alkylene tether has 1, 2, 3, 4, or 5 carbon atoms, more particularly 1 or 2 carbon atoms.

20

The term "3- to 8-membered heterocycloalkyl", is to be understood as meaning a saturated, monovalent, mono- or bicyclic hydrocarbon ring which contains 2, 3, 4, 5, 6 or 7 carbon atoms, and one or more heteroatom-containing groups selected from C(=O), O, S, S(=O), S(=O)₂, NR^a, in which R^a represents a hydrogen atom, or a C₁-C₆-alkyl- or halo-C₁-C₆-alkyl- group ; it being possible for said heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, the nitrogen atom.

Particularly, said 3- to 8-membered heterocycloalkyl can contain 2, 3, 4, 5, 6 or 7 carbon atoms, and one or more of the above-mentioned heteroatom-containing groups (a "3- to 8-membered heterocycloalkyl"), more particularly said heterocycloalkyl can contain 4 or 5 carbon atoms, and one or more of the

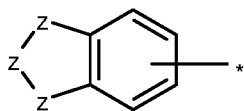
above-mentioned heteroatom-containing groups (a "5- to 7-membered heterocycloalkyl").

Particularly, without being limited thereto, said heterocycloalkyl can be a 4-membered ring, such as an azetidiny, oxetanyl, or a 5-membered ring, such as tetrahydrofuranyl, dioxolinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, pyrrolinyl, or a 6-membered ring, such as tetrahydropyranyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, or trithianyl, or a 7-membered ring, such as a diazepanyl ring, for example. Optionally, said heterocycloalkyl can be benzo fused.

Said heterocyclyl can be bicyclic, such as, without being limited thereto, a 5,5-membered ring, e.g. a hexahydrocyclopenta[c]pyrrol-2(1H)-yl ring, or a 5,6-membered bicyclic ring, e.g. a hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl ring, or 8-oxa-3-azabicyclo[3.2.1]oct-3-yl ring, for example.

As mentioned *supra*, said nitrogen atom-containing ring can be partially unsaturated, *i.e.* it can contain one or more double bonds, such as, without being limited thereto, a 2,5-dihydro-1H-pyrrolyl, 4H-[1,3,4]thiadiazinyl, 4,5-dihydrooxazolyl, or 4H-[1,4]thiazinyl ring, for example, or, it may be benzo-fused, such as, without being limited thereto, a dihydroisoquinolinyl ring, for example.

The term "aryl" is to be understood as preferably meaning a monovalent, aromatic or partially aromatic, mono-, or bi- or tricyclic hydrocarbon ring having 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms (a "C₆-C₁₄-aryl" group), particularly a ring having 6 carbon atoms (a "C₆-aryl" group), *e.g.* a phenyl group; or a biphenyl group, or a ring having 9 carbon atoms (a "C₉-aryl" group), *e.g.* an indanyl or indenyl group, or a ring having 10 carbon atoms (a "C₁₀-aryl" group), *e.g.* a tetralinyl, dihydronaphthyl, or naphthyl group, or a ring having 13 carbon atoms, (a "C₁₃-aryl" group), *e.g.* a fluorenyl group, or a ring having 14 carbon atoms, (a "C₁₄-aryl" group), *e.g.* an anthranyl group. A particular example of an aryl group is one of the following possible structures :



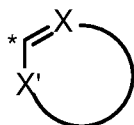
in which z represents O, S, NH or N(C₁-C₆-alkyl), and * indicates the point of attachment of said aryl group with the rest of the molecule.

5

The term “heteroaryl” is understood as preferably meaning a monovalent, monocyclic-, bicyclic- or tricyclic aromatic ring system having 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring atoms (a “5- to 14-membered heteroaryl” group), particularly 5 or 6 or 9 or 10 atoms, and which contains at least one heteroatom which may be identical or different, said heteroatom being such as oxygen, nitrogen or sulfur, and in addition in each case can be benzocondensed.

10

Particularly, said heteroaryl is of structure :



15

optionally substituted with 1, 2 or 3 R⁶ groups,

in which :

* represents the point of attachment of said heteroaryl with the rest of the compound of general formula (I) as defined *supra*,

X represents N or C-R⁶,

20

X' represents O, S, NH, N-R⁶, N or C-R⁶,

- each occurrence of R⁶ may be the same or different and is independently a hydrogen atom, a halogen atom, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, aryl, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, 3- to 8-membered heterocyclic ring, 3- to 8-membered heterocycl-C₁-C₆-alkyl, -C₁-C₆-alkyl-OR⁷, -C₁-C₆-alkyl-SR⁷, -C₁-C₆-alkyl-N(R⁷)(R⁷), -C₁-C₆-alkyl-C(=O)R⁷, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)(R⁷), -OR⁷, -SR⁷, -N(R⁷)(R⁷), or -NR⁷C(=O)R⁷ each of which may be optionally substituted with 1 or more R⁸ groups ;

25

- each occurrence of R⁷ and R⁷' may be the same or different and is independently a hydrogen atom, or a C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl,

30

- C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, C₃-C₆-cycloalkenyl, aryl, aryl-C₁-C₆-alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, 3- to 8-membered heterocyclyl-C₁-C₆-alkyl, or heteroaryl-C₁-C₆-alkyl ;
- each occurrence of R⁸ is independently a halogen atom, or nitro, hydroxy,
- 5 cyano, formyl, acetyl, amino, C₁-C₆-alkyl, C₁-C₆-alkoxy, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, C₁-C₆-cycloalkenyl, aryl, aryl-C₁-C₆-alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, heterocyclyl-C₁-C₆-alkyl, or heteroaryl-C₁-C₆-alkyl.
- 10 More particularly, said heteroaryl is selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, thia-4H-pyrazolyl *etc.*, and benzo derivatives thereof, such as, for example, benzofuranyl, benzothienyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, benzotriazolyl, indazolyl, indolyl, isoindolyl, *etc.*; or pyridyl,
- 15 pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, *etc.*, and benzo derivatives thereof, such as, for example, quinolinyl, quinazolinyl, isoquinolinyl, *etc.*; or azocinyl, indoliziny, purinyl, *etc.*, and benzo derivatives thereof; or cinnoliny, phthalazinyl, quinazolinyl, quinoxalinyl, naphthpyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, xanthenyl, or oxepinyl, *etc.*.
- 20
- In general, and unless otherwise mentioned, the heteroarylic or heteroarylenic radicals include all the possible isomeric forms thereof, e.g. the positional isomers thereof. Thus, for some illustrative non-restricting example, the term pyridinyl or pyridinylene includes pyridin-2-yl, pyridin-2-ylene, pyridin-3-yl, pyridin-3-ylene, pyridin-4-yl and pyridin-4-ylene; or the term thienyl or thienylene includes thien-2-yl, thien-2-ylene, thien-3-yl and thien-3-ylene.
- 25

The term "C₁-C₆", as used throughout this text, *e.g.* in the context of the definition of "C₁-C₆-alkyl" or "C₁-C₆-alkoxy" is to be understood as meaning an

30 alkyl group having a finite number of carbon atoms of 1 to 6, *i.e.* 1, 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "C₁-C₆" is to be interpreted as any sub-range comprised therein, *e.g.* C₁-C₆, C₂-C₅, C₃-C₄, C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆; particularly C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆;

more particularly C₁-C₄ ; in the case of "C₁-C₆-haloalkyl" or "C₁-C₆-haloalkoxy"
even more particularly C₁-C₂.

Similarly, as used herein, the term "C₂-C₆", as used throughout this text, *e.g.* in
5 the context of the definitions of "C₂-C₆-alkenyl" and "C₂-C₆-alkynyl", is to be
understood as meaning an alkenyl group or an alkynyl group having a finite
number of carbon atoms of 2 to 6, *i.e.* 2, 3, 4, 5, or 6 carbon atoms. It is to be
understood further that said term "C₂-C₆" is to be interpreted as any sub-range
comprised therein, *e.g.* C₂-C₆ , C₃-C₅ , C₃-C₄ , C₂-C₃ , C₂-C₄ , C₂-C₅ ; particularly
10 C₂-C₃.

Further, as used herein, the term "C₃-C₆", as used throughout this text, *e.g.* in
the context of the definition of "C₃-C₆-cycloalkyl", is to be understood as meaning
a cycloalkyl group having a finite number of carbon atoms of 3 to 6, *i.e.* 3, 4, 5 or
15 6 carbon atoms. It is to be understood further that said term "C₃-C₆" is to be
interpreted as any sub-range comprised therein, *e.g.* C₃-C₆ , C₄-C₅ , C₃-C₅ , C₃-C₄
, C₄-C₆ , C₅-C₆ ; particularly C₃-C₆.

The term "substituted" means that one or more hydrogens on the designated
20 atom is replaced with a selection from the indicated group, provided that the
designated atom's normal valency under the existing circumstances is not
exceeded, and that the substitution results in a stable compound. Combinations
of substituents and/or variables are permissible only if such combinations result
in stable compounds.

25 The term "optionally substituted" means optional substitution with the specified
groups, radicals or moieties.

Ring system substituent means a substituent attached to an aromatic or
30 nonaromatic ring system which, for example, replaces an available hydrogen on
the ring system.

As used herein, the term "one or more times", *e.g.* in the definition of the substituents of the compounds of the present invention, is understood as meaning "one, two, three, four or five times, particularly one, two, three or four times, more particularly one, two or three times, even more particularly one or
5 two times".

Where the plural form of the word components, compounds, salts, polymorphs, hydrates, solvates and the like, is used herein, this is taken to mean also a single component, compound, salt, polymorph, isomer, hydrate, solvate or the
10 like.

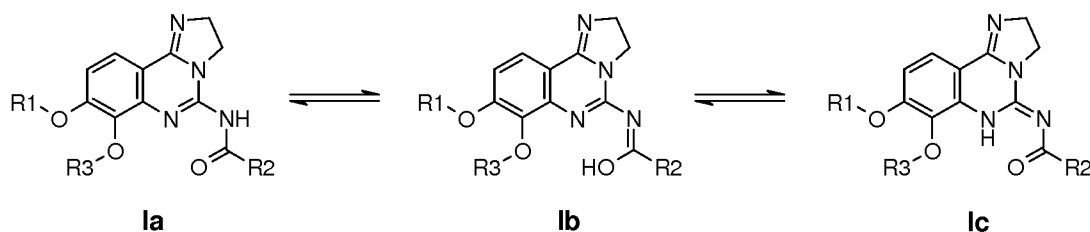
By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

15 The term "carbonyl" refers to an oxygen atom bound to a carbon atom of the molecule by a double bond.

The compounds of this invention may contain one or more asymmetric centers, depending upon the location and nature of the various substituents desired. Asymmetric carbon atoms may be present in the (*R*)- and/or (*S*)-configuration, resulting in racemic mixtures in the case of a single asymmetric center, and diastereomeric mixtures in the case of multiple asymmetric centers. In certain instances, asymmetry may also be present due to restricted rotation about a
20 given bond, for example, the central bond adjoining two substituted aromatic rings of the specified compounds. Substituents on a ring may also be present in either cis or trans form. It is intended that all such configurations (including enantiomers and diastereomers), are included within the scope of the present invention. Preferred compounds are those, which produce the more desirable
25 biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The
30

purification and the separation of such materials can be accomplished by standard techniques known in the art.

Tautomers, sometimes referred to as proton-shift tautomers, are two or more compounds that are related by the migration of a hydrogen atom accompanied by the switch of one or more single bonds and one or more adjacent double bonds. The compounds of this invention may exist in one or more tautomeric forms. For example, a compound of Formula I may exist in tautomeric form **la**, tautomeric form **lb**, or tautomeric form **lc**, or may exist as a mixture of any of these forms. It is intended that all such tautomeric forms are included within the scope of the present invention.



The present invention also relates to useful forms of the compounds as disclosed herein, such as pharmaceutically acceptable salts, co-precipitates, metabolites, hydrates, solvates and prodrugs of all the compounds of examples. The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," *J. Pharm. Sci.* 1977, 66, 1-19. Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid and citric acid. Pharmaceutically acceptable salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and choline salts. Those skilled in the art will further recognize that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a

number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

- 5 Representative salts of the compounds of this invention include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate,
10 camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, chloride, bromide, iodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate,
15 pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, sulfate, tartrate, thiocyanate, tosylate, and undecanoate.

- Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium
20 salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, or butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl sulfate, or diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl
25 chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

- A solvate for the purpose of this invention is a complex of a solvent and a compound of the invention in the solid state. Exemplary solvates would include,
30 but are not limited to, complexes of a compound of the invention with ethanol or methanol. Hydrates are a specific form of solvate wherein the solvent is water.

Constituents which are optionally substituted as stated herein, may be substituted, unless otherwise noted, one or more times, independently from one another at any possible position. When any variable occurs more than one time in any constituent, each definition is independent.

5

The heteroaryl, or heterocyclic groups mentioned herein can be substituted by their given substituents or parent molecular groups, unless otherwise noted, at any possible position, such as e.g. at any substitutable ring carbon or ring nitrogen atom. Analogously it is being understood that it is possible for any heteroaryl or heterocyclyl group to be attached to the rest of the molecule via any suitable atom if chemically suitable. Unless otherwise noted, any heteroatom of a heteroaryl ring with unsatisfied valences mentioned herein is assumed to have the hydrogen atom(s) to satisfy the valences. Unless otherwise noted, rings containing quaternizable amino- or imino-type ring nitrogen atoms (-N=) may be preferably not quaternized on these amino- or imino-type ring nitrogen atoms by the mentioned substituents or parent molecular groups.

Preferred compounds are those which produce the more desirable biological activity. Separated, pure or partially purified isomers and stereoisomers or racemic or diastereomeric mixtures of the compounds of this invention are also included within the scope of the present invention. The purification and the separation of such materials can be accomplished by standard techniques already known in the art.

The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A

different process for separation of optical isomers involves the use of chiral chromatography (*e.g.*, chiral HPLC columns), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, *e.g.*, Chiracel OD
5 and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without derivatisation, are also useful. The optically active compounds of this invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

10 If in the context of the invention "embodiment" is mentioned it should be understood to include a plurality of possible combinations.

In order to limit different types of isomers from each other reference is made to IUPAC Rules Section E (Pure Appl Chem 45, 11-30, 1976).

15

The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually or
20 predominantly found in nature. Examples of isotopes that can be incorporated into a compound of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine, chlorine, bromine and iodine, such as ^2H (deuterium), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{18}F , ^{36}Cl , ^{82}Br , ^{123}I , ^{124}I , ^{129}I and ^{131}I , respectively. Certain isotopic variations of a
25 compound of the invention, for example, those in which one or more radioactive isotopes such as ^3H or ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated and carbon-14, *i.e.*, ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium may afford certain therapeutic
30 advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of a compound of the invention can generally be prepared by conventional procedures known by a person skilled in

the art such as by the illustrative methods or by the preparations described in the examples hereafter using appropriate isotopic variations of suitable reagents.

- 5 The present invention includes all possible stereoisomers of the compounds of the present invention as single stereoisomers, or as any mixture of said stereoisomers, in any ratio. Isolation of a single stereoisomer, *e.g.* a single enantiomer or a single diastereomer, of a compound of the present invention may be achieved by any suitable state of the art method, such as
10 chromatography, especially chiral chromatography, for example.

The present invention includes all possible tautomers of the compounds of the present invention as single tautomers, or as any mixture of said tautomers, in any ratio.

15

Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorphs, or as a mixture of more than one polymorphs, in any ratio.

- 20 In some embodiments, the asymmetric carbon to which R⁴ is bonded has the (*R*)-configuration in the compound of formula (I), as described herein.

In other embodiments, the asymmetric carbon to which R⁴ is bonded has the (*S*)-configuration in the compound of formula (I), as described herein.

25

- In other embodiment, the PI3K inhibitor is selected from the group of PI3K inhibitors consisting of buparlisib, idelalisib, BYL-719, dactolisib, PF-05212384, pictilisib, copanlisib, copanlisib dihydrochloride, ZSTK-474, GSK-2636771, duvelisib, GS-9820, PF-04691502, SAR-245408, SAR-245409, sonolisib,
30 Archexin, GDC-0032, GDC-0980, apitolisib, pilaralisib, DLBS 1425, PX-866, voxtalisib, AZD-8186, BGT-226, DS-7423, GDC-0084, GSK-2126458, INK-1117, SAR-260301, SF-1126, AMG-319, BAY-1082439, CH-5132799, GSK-2269557, P-7170, PWT-33597, CAL-263, RG-7603, LY-3023414, RP-5264, RV-1729,

taselisib, TGR-1202, GSK-418, INCB-040093, Panulisib, GSK-1059615, CNX-1351, AMG-511, PQR-309, 17beta-Hydroxywortmannin, AEZS-129, AEZS-136, HM-5016699, IPI-443, ONC-201, PF-4989216, RP-6503, SF-2626, X-339, XL-499, PQR-401, AEZS-132, CZC-24832, KAR-4141, PQR-311, PQR-316, RP-5090, VS-5584, X-480, AEZS-126, AS-604850, BAG-956, CAL-130, CZC-24758, ETP-46321, ETP-47187, GNE-317, GS-548202, HM-032, KAR-1139, LY-294002, PF-04979064, PI-620, PKI-402, PWT-143, RP-6530, 3-HOI-BA-01, AEZS-134, AS-041164, AS-252424, AS-605240, AS-605858, AS-606839, BCCA-621C, CAY-10505, CH-5033855, CH-5108134, CUDC-908, CZC-19945, D-106669, D-87503, DPT-NX7, ETP-46444, ETP-46992, GE-21, GNE-123, GNE-151, GNE-293, GNE-380, GNE-390, GNE-477, GNE-490, GNE-493, GNE-614, HMPL-518, HS-104, HS-106, HS-116, HS-173, HS-196, IC-486068, INK-055, KAR 1141, KY-12420, Wortmannin, Lin-05, NPT-520-34, PF-04691503, PF-06465603, PGNX-01, PGNX-02, PI 620, PI-103, PI-509, PI-516, PI-540, PIK-75, PWT-458, RO-2492, RP-5152, RP-5237, SB-2015, SB-2312, SB-2343, SHBM-1009, SN 32976, SR-13179, SRX-2523, SRX-2558, SRX-2626, SRX-3636, SRX-5000, TGR-5237, TGX-221, UCB-5857, WAY-266175, WAY-266176, EI-201, AEZS-131, AQX-MN100, KCC-TGX, OXY-111A, PI-708, PX-2000, WJD-008.

20

Compounds of formula (I) as described and defined herein can be prepared according to the preparation methods contained in WO2012062748 which is incorporated herein by reference in its entirety.

25 The PI3K-inhibitors mentioned in the prior art as well as in the lists above have been disclosed for the treatment or prophylaxis of different diseases, especially cancer.

The beneficial effect of the present invention is demonstrated herein with one of the PI3K inhibitors specifically disclosed in the Examples section, as example 30 14, of WO 2012/062748, referred to as Compound A1 (or as Compd A1) below.

The compounds of the present invention may be administered, independently of one another when in combination, by the oral, intravenous, topical, local installations, intraperitoneal or nasal route.

- 5 Compounds of general formula (I) are administered intravenously, intraperitoneally, preferably they are administered orally.

Other active agents being administered as the case may be.

- 10 The term "pharmaceutically acceptable" is used synonymously to the term "physiologically acceptable".

The term "pharmaceutically or physiologically acceptable salt" of a compound refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," *J. Pharm. Sci.* 1977, 66, 1-19. Pharmaceutically acceptable salts include those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid and citric acid. Pharmaceutically acceptable salts also include those in which the main compound functions as an acid and is reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and choline salts. Those skilled in the art will further recognize that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

30 Representative salts of a compound of this invention include the conventional non-toxic salts and the quaternary ammonium salts which are formed, for example, from inorganic or organic acids or bases by means well known in the

art. For example, such acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cinnamate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, 5 glycerophosphate, hemisulfate, heptanoate, hexanoate, chloride, bromide, iodide, 2-hydroxyethanesulfonate, itaconate, lactate, maleate, mandelate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfonate, sulfate, tartrate, thiocyanate, tosylate, and undecanoate.

10

Base salts include alkali metal salts such as potassium and sodium salts, alkaline earth metal salts such as calcium and magnesium salts, and ammonium salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine. Additionally, basic nitrogen containing groups may be quaternized with such 15 agents as lower alkyl halides such as methyl, ethyl, propyl, or butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl sulfate, or diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

20

A solvate for the purpose of this invention is a complex of a solvent and a compound of the invention in the solid state. Exemplary solvates would include, but are not limited to, complexes of a compound of the invention with ethanol or methanol. Hydrates are a specific form of solvate wherein the solvent is water.

25

Compounds of this invention can be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatin, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, 30 alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, coloring agents, and

flavoring agents such as peppermint, oil of wintergreen, or cherry flavoring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

10

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those sweetening, flavoring and coloring agents described above, may also be present.

15

Compounds of this invention can also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

20

25

Oily suspensions can be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate; one or more coloring agents; one or more

30

flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

5 Syrups and elixirs can be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavoring and coloring agents.

10 Compounds of this invention can also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the compound in preferably a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl
15 alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as
20 pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

25 Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali
30 metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates,

and sulfosuccinates; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quaternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) preferably of from about 12 to about 17. The quantity of surfactant in such formulation preferably ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions can be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene

oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

5 The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic
10 mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

Compounds of the invention can also be administered in the form of suppositories for rectal administration of the drug. These components can be
15 prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are, for example, cocoa butter and polyethylene glycol.

20 Another formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in
25 the art (see, e.g., US Patent No. 5,023,252, issued June 11, 1991, incorporated herein by reference). Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Controlled release formulations for parenteral administration include liposomal,
30 polymeric microsphere and polymeric gel formulations that are known in the art.

It can be desirable or necessary to introduce a compound of the present invention to the patient via a mechanical delivery device. The construction and

use of mechanical delivery devices for the delivery of pharmaceutical agents is well known in the art. Direct techniques for, for example, administering a drug directly to the brain usually involve placement of a drug delivery catheter into the patient's ventricular system to bypass the blood-brain barrier. One such
5 implantable delivery system, used for the transport of agents to specific anatomical regions of the body, is described in US Patent No. 5,011,472, issued April 30, 1991.

The compositions of the invention can also contain other conventional
10 pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired. Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized. Such ingredients and procedures include those described in the following references, each of which is incorporated herein by reference: Powell, M.F. *et al*,
15 "Compendium of Excipients for Parenteral Formulations" *PDA Journal of Pharmaceutical Science & Technology* 1998, 52(5), 238-311; Strickley, R.G "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)-Part-1" *PDA Journal of Pharmaceutical Science & Technology*
1999, 53(6), 324-349; and Nema, S. *et al*, "Excipients and Their Use in
20 Injectable Products" *PDA Journal of Pharmaceutical Science & Technology* 1997, 51(4), 166-171.

Commonly used pharmaceutical ingredients that can be used as appropriate to formulate the composition for its intended route of administration include:

25

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);

alkalinizing agents (examples include but are not limited to ammonia solution,
30 ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine);

- adsorbents** (examples include but are not limited to powdered cellulose and activated charcoal);
- aerosol propellants** (examples include but are not limited to carbon dioxide,
5 CCl₂F₂, F₂ClC-CClF₂ and CClF₃)
- air displacement agents** (examples include but are not limited to nitrogen and argon);
- 10 **antifungal preservatives** (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);
- antimicrobial preservatives** (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium
15 chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);
- antioxidants** (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus
20 acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite);
- binding materials** (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones,
25 polysiloxanes and styrene-butadiene copolymers);
- buffering agents** (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)
30
- carrying agents** (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil,

mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

chelating agents (examples include but are not limited to edetate disodium and edetic acid)

colorants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);

10

clarifying agents (examples include but are not limited to bentonite);

emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate);

15

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate)

flavorants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);

20

humectants (examples include but are not limited to glycerol, propylene glycol and sorbitol);

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levigating agents (examples include but are not limited to mineral oil and glycerin);

oils (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);

30

- ointment bases** (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);
- 5 **penetration enhancers (transdermal delivery)** (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono-or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)
- 10 **plasticizers** (examples include but are not limited to diethyl phthalate and glycerol);
- solvents** (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);
- 15 **stiffening agents** (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);
- 20 **suppository bases** (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures));
- 25 **surfactants** (examples include but are not limited to benzalkonium chloride, nonoxynol 10, octoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate);
- 30 **suspending agents** (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);

- sweetening agents** (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);
- 5 **tablet anti-adherents** (examples include but are not limited to magnesium stearate and talc);
- tablet binders** (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin,
10 liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch);
- tablet and capsule diluents** (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose,
15 powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);
- tablet coating agents** (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose,
20 methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac);
- tablet direct compression excipients** (examples include but are not limited to dibasic calcium phosphate);
- 25 **tablet disintegrants** (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch);
- 30 **tablet glidants** (examples include but are not limited to colloidal silica, corn starch and talc);

- tablet lubricants** (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);
- 5 **tablet/capsule opaquants** (examples include but are not limited to titanium dioxide);
- tablet polishing agents** (examples include but are not limited to carnuba wax and white wax);
- 10 **thickening agents** (examples include but are not limited to beeswax, cetyl alcohol and paraffin);
- tonicity agents** (examples include but are not limited to dextrose and sodium chloride);
- 15 **viscosity increasing agents** (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth); and
- 20 **wetting agents** (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

25 Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile IV Solution: A 5 mg/mL solution of the desired compound of this invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1 – 2 mg/mL with sterile
30 5% dextrose and is administered as an IV infusion over about 60 minutes.

Lyophilized powder for IV administration: A sterile preparation can be prepared with (i) 100 - 1000 mg of the desired compound of this invention as a

lypholized powder, (ii) 32- 327 mg/mL sodium citrate, and (iii) 300 – 3000 mg Dextran 40. The formulation is reconstituted with sterile, injectable saline or dextrose 5% to a concentration of 10 to 20 mg/mL, which is further diluted with saline or dextrose 5% to 0.2 – 0.4 mg/mL, and is administered either IV bolus or
5 by IV infusion over 15 – 60 minutes.

Intramuscular suspension: The following solution or suspension can be prepared, for intramuscular injection:

50 mg/mL of the desired, water-insoluble compound of this invention
10 5 mg/mL sodium carboxymethylcellulose
4 mg/mL TWEEN 80
9 mg/mL sodium chloride
9 mg/mL benzyl alcohol

15 **Hard Shell Capsules:** A large number of unit capsules are prepared by filling standard two-piece hard galantine capsules each with 100 mg of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate.

20 **Soft Gelatin Capsules:** A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into molten gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules are washed and dried. The active ingredient can be dissolved in a mixture of polyethylene glycol,
25 glycerin and sorbitol to prepare a water miscible medicine mix.

Tablets: A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 mg of active ingredient, 0.2 mg. of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11
30 mg. of starch, and 98.8 mg of lactose. Appropriate aqueous and non-aqueous coatings may be applied to increase palatability, improve elegance and stability or delay absorption.

Immediate Release Tablets/Capsules: These are solid oral dosage forms made by conventional and novel processes. These units are taken orally without water for immediate dissolution and delivery of the medication. The active ingredient is mixed in a liquid containing ingredient such as sugar, gelatin, pectin and sweeteners. These liquids are solidified into solid tablets or caplets by freeze drying and solid state extraction techniques. The drug compounds may be compressed with viscoelastic and thermoelastic sugars and polymers or effervescent components to produce porous matrices intended for immediate release, without the need of water.

10

Commercial utility

The compounds of formula (I) and the stereoisomers thereof have valuable pharmaceutical properties, which make them commercially utilizable. In particular, they inhibit the PI3K/AKT pathway and exhibit cellular activity. They are expected to be commercially applicable in the therapy of diseases (e.g. diseases dependent on overactivated PI3K/AKT). An abnormal activation of the PI3K/AKT pathway is an essential step towards the initiation and maintenance of human tumors and thus its inhibition, for example with PI3K inhibitors, is understood to be a valid approach for treatment of human tumors. For a recent review see Garcia-Echeverria et al (Oncogene, 2008, 27, 551-5526).

The compounds of the present invention can be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, or diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, such as, for example, haematological tumours, solid tumours, and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the

thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

5

One embodiment relates to the use of a compound of general formula (I) according to any one of claims 1 to 9 for the preparation of a medicament for the treatment or prophylaxis of a cancer, particularly breast cancer, prostate cancer, multiple myeloma, hepatocyte carcinoma, lung cancer, in particular non-small
10 cell lung carcinoma, colorectal cancer, melanoma, pancreatic cancer and/or metastases thereof.

In one embodiment the invention relates to the use in the treatment of cancer indications particularly for such cancer types which are known to form
15 metastases in bone.

Such cancer types include, but are not limited to, breast, prostate, multiple myeloma, lung, kidney or thyroid cancer.

20 Another embodiment relates to the use of a compound of general formula (I) according to the present invention for the preparation of a medicament for the treatment or prophylaxis of breast cancer or prostate cancer and/or metastases thereof, especially wherein the metastases are bone metastases.

25 Another embodiment relates to the use of a compound of general formula (I) according to the present invention for the preparation of a medicament for the treatment or prophylaxis of breast cancer, multiple myeloma or prostate cancer and/or metastases thereof, especially wherein the metastases are bone metastases.

30

In one embodiment the invention relates to a method of treatment or prophylaxis of a cancer, particularly hepatocyte carcinoma, lung cancer, in particular non-small cell lung carcinoma, colorectal cancer, melanoma, pancreatic cancer,

prostate cancer, multiple myeloma, breast cancer and/or metastases thereof, in a subject, comprising administering to said subject a therapeutically effective amount of a compound according to any one of claims 1 to 9.

- 5 Another embodiment relates to a compound of general formula (I) according to the present invention for use in the treatment of a cancer, particularly hepatocyte carcinoma, lung cancer, in particular non-small cell lung carcinoma, colorectal cancer, melanoma, pancreatic cancer, prostate cancer, multiple myeloma, breast cancer and/or metastases thereof, more particularly breast cancer,
10 multiple myeloma or prostate cancer and/or metastases thereof, especially wherein the metastases are bone metastases.

Preferred uses of the compounds of the invention are the treatment of breast and prostate cancer, especially castration-resistant prostate cancer (CRPC),
15 and bone metastases thereof.

One preferred embodiment is the use of the compounds of the invention for the treatment of prostate cancer, especially castration-resistant prostate cancer (CRPC) and bone metastases thereof.
20

One preferred embodiment is the use of the compounds of the invention for the treatment of breast cancer and bone metastases thereof.

One preferred embodiment is the use of the compounds of the invention for the treatment of multiple myeloma and bone metastases thereof.
25

The term "inappropriate" within the context of the present invention, in particular in the context of "inappropriate cellular immune responses, or inappropriate cellular inflammatory responses", as used herein, is to be understood as preferably meaning a response which is less than, or greater than normal, and
30 which is associated with, responsible for, or results in, the pathology of said diseases.

Compounds of the present invention might be utilized to inhibit, block, reduce, decrease, etc., cell proliferation and/or cell division, and/or produce apoptosis.

This invention includes a method comprising administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a
5 pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof ; etc. which is effective to treat the disorder.

Hyper-proliferative disorders include but are not limited, e.g., psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), as well as malignant neoplasia. Examples of malignant neoplasia treatable with the
10 compounds according to the present invention include solid and hematological tumors. Solid tumors can be exemplified by tumors of the breast, bladder, bone, brain, central and peripheral nervous system, colon, anus, endocrine glands (e.g. thyroid and adrenal cortex), esophagus, endometrium, germ cells, head and neck, kidney, liver, lung, larynx and hypopharynx, mesothelioma, ovary,
15 pancreas, prostate, rectum, renal, small intestine, soft tissue, testis, stomach, skin, ureter, vagina and vulva. Malignant neoplasias include inherited cancers exemplified by Retinoblastoma and Wilms tumor. In addition, malignant neoplasias include primary tumors in said organs and corresponding secondary tumors in distant organs ("tumor metastases"). Hematological tumors can be
20 exemplified by aggressive and indolent forms of leukemia and lymphoma, namely non-Hodgkins disease, chronic and acute myeloid leukemia (CML / AML), acute lymphoblastic leukemia (ALL), Hodgkins disease, multiple myeloma and T-cell lymphoma. Also included are myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, and cancers of unknown primary site as
25 well as AIDS related malignancies.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-
30 cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophthalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

- 5 Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

- 10 Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

- 15 Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

- 20 Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

- 25 Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

10 The term "treating" or "treatment" as stated throughout this document is used conventionally, *e.g.*, the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, *etc.*, of a disease or disorder, such as a carcinoma.

Compounds of the present invention might also be used for treating disorders and diseases associated with excessive and/or abnormal angiogenesis.

Inappropriate and ectopic expression of angiogenesis can be deleterious to an organism. A number of pathological conditions are associated with the growth of extraneous blood vessels. These include, *e.g.*, diabetic retinopathy, ischemic retinal-vein occlusion, and retinopathy of prematurity [Aiello et al. *New Engl. J. Med.* **1994**, 331, 1480 ; Peer et al. *Lab. Invest.* **1995**, 72, 638], age-related macular degeneration [AMD ; see, Lopez et al. *Invest. Ophthalmol. Vis. Sci.* **1996**, 37, 855], neovascular glaucoma, psoriasis, retrolental fibroplasias, angiofibroma, inflammation, rheumatoid arthritis (RA), restenosis, in-stent restenosis, vascular graft restenosis, etc. In addition, the increased blood supply associated with cancerous and neoplastic tissue, encourages growth, leading to rapid tumor enlargement and metastasis. Moreover, the growth of new blood and lymph vessels in a tumor provides an escape route for renegade cells, encouraging metastasis and the consequence spread of the cancer. Thus, combinations of the present invention can be utilized to treat and/or prevent any of the aforementioned angiogenesis disorders, *e.g.*, by inhibiting and/or reducing

blood vessel formation ; by inhibiting, blocking, reducing, decreasing, etc. endothelial cell proliferation or other types involved in angiogenesis, as well as causing cell death or apoptosis of such cell types.

5 Dose and administration

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders and angiogenic disorders, by standard toxicity tests and by standard pharmacological assays for
10 the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredients to be administered in the treatment of one
15 of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The total amount of the active ingredients to be administered will generally
20 range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules of a compound will range from one to three times a day dosing to once every four weeks dosing. In addition, "drug holidays" in which a patient is not dosed with a drug for a certain period of time, may be
25 beneficial to the overall balance between pharmacological effect and tolerability. A unit dosage may contain from about 0.5 mg to about 1500 mg of active ingredient, and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of
30 infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will

preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average
5 daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

Combinations of the present invention

The combinations of the present invention can be used in particular in therapy
10 and prevention, i.e. prophylaxis, of tumour growth and metastases, especially in solid tumours of all indications and stages with or without pre-treatment of the tumour growth, more especially those tumor types spreading into bones.

Methods of testing for a particular pharmacological or pharmaceutical property
15 are well known to persons skilled in the art.

The compounds of this invention can be administered as the sole pharmaceutical agent or in combination with one or more further pharmaceutical agents where the resulting combination of compounds causes no unacceptable
20 adverse effects. For example, the compounds of this invention can be combined with one or more further pharmaceutical agents, such as known anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhythmic, anti-hypercholesterolemia, anti-dyslipidemia, anti-diabetic or antiviral agents, and the like, as well as with
25 admixtures and combinations thereof.

In one embodiment the one or more further pharmaceutical agents are selected from anti-angiogenesis, anti-hyper-proliferative and/or admixtures or combinations thereof.
30

In one embodiment the one or more further pharmaceutical agents are selected from antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhythmic, anti-

hypercholesterolemia, anti-dyslipidemia, anti-diabetic or antiviral agents, and/or admixtures or combinations thereof.

- 5 Further pharmaceutical agents can be one or more pharmaceutical agents such as ¹³¹I-chTNT, abarelix, abiraterone, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, aminoglutethimide, amrubicin, amsacrine, anastrozole, arglabin, arsenic trioxide, asparaginase, azacitidine, basiliximab, belotecan, bendamustine, bevacizumab, bexarotene, bicalutamide, bisantrene, bleomycin,
 - 10 bortezomib, buserelin, busulfan, cabazitaxel, calcium folinate, calcium levofolinate, capecitabine, carboplatin, carmofur, carmustine, catumaxomab, celecoxib, celmoleukin, cetuximab, chlorambucil, chlormadinone, chlormethine, cisplatin, cladribine, clodronic acid, clofarabine, copanlisib, crisantaspase, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin,
 - 15 darbepoetin alfa, dasatinib, daunorubicin, decitabine, degarelix, denileukin diftitox, denosumab, deslorelin, dibrospidium chloride, docetaxel, doxifluridine, doxorubicin, doxorubicin + estrone, eculizumab, edrecolomab, elliptinium acetate, eltrombopag, endostatin, enocitabine, enzalutamide, epirubicin, epitioctanol, epoetin alfa, epoetin beta, eptaplatin, eribulin, erlotinib, estradiol,
 - 20 estramustine, etoposide, everolimus, exemestane, fadrozole, filgrastim, fludarabine, fluorouracil, flutamide, formestane, fotemustine, fulvestrant, gallium nitrate, ganirelix, gefitinib, gemcitabine, gemtuzumab, glutoxim, goserelin, histamine dihydrochloride, histrelin, hydroxycarbamide, I-125 seeds, ibandronic acid, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib, imiquimod,
 - 25 improsulfan, interferon alfa, interferon beta, interferon gamma, ipilimumab, irinotecan, ixabepilone, lanreotide, lapatinib, lenalidomide, lenograstim, lentinan, letrozole, leuprorelin, levamisole, lisuride, lobaplatin, lomustine, lonidamine, masoprocol, medroxyprogesterone, megestrol, melphalan, mepitiostane, mercaptopurine, methotrexate, methoxsalen, Methyl aminolevulinate,
 - 30 methyltestosterone, mifamurtide, miltefosine, miriplatin, mitobronitol, mitoguazone, mitolactol, mitomycin, mitotane, mitoxantrone, nedaplatin, nelarabine, nilotinib, nilutamide, nimotuzumab, nimustine, nitracrine, ofatumumab, omeprazole, oprelvekin, oxaliplatin, p53 gene therapy, paclitaxel,

palifermin, palladium-103 seed, pamidronic acid, panitumumab, pazopanib, pegaspargase, PEG-epoetin beta (methoxy PEG-epoetin beta), pegfilgrastim, peginterferon alfa-2b, pemetrexed, pentazocine, pentostatin, peplomycin, perfosfamide, picibanil, pirarubicin, plerixafor, plicamycin, poliglusam, 5 polyestradiol phosphate, polysaccharide-K, porfimer sodium, pralatrexate, prednimustine, procarbazine, quinagolide, radium-223 chloride, raloxifene, raltitrexed, ranimustine, razoxane, refametinib, regorafenib, risedronic acid, rituximab, romidepsin, romiplostim, roniciclib, sargramostim, sipuleucel-T, sizofiran, sobuzoxane, sodium glycididazole, sorafenib, streptozocin, sunitinib, 10 talaporfin, tamibarotene, tamoxifen, tasonermin, teceleukin, tegafur, tegafur + gimeracil + oteracil, temoporfin, temozolomide, temsirolimus, teniposide, testosterone, tetrafosmin, thalidomide, thiotepa, thymalfasin, tioguanine, tocilizumab, topotecan, toremifene, tositumomab, trabectedin, trastuzumab, treosulfan, tretinoin, trilostane, triptorelin, trofosfamide, tryptophan, ubenimex, 15 valrubicin, vandetanib, vapreotide, vemurafenib, vinblastine, vincristine, vindesine, vinflunine, vinorelbine, vorinostat, vorozole, yttrium-90 glass microspheres, zinostatin, zinostatin stimalamer, zoledronic acid, zorubicin or combinations thereof.

20 Alternatively, said further pharmaceutical agents can be one or more further pharmaceutical agents selected from gemcitabine, paclitaxel, cisplatin, carboplatin, sodium butyrate, 5-FU, doxorubicin, tamoxifen, etoposide, trastumazab, gefitinib, intron A, rapamycin, 17-AAG, U0126, insulin, an insulin derivative, a PPAR ligand, a sulfonylurea drug, an α -glucosidase inhibitor, a 25 biguanide, a PTP-1B inhibitor, a DPP-IV inhibitor, a 11-beta-HSD inhibitor, GLP-1, a GLP-1 derivative, GIP, a GIP derivative, PACAP, a PACAP derivative, secretin or a secretin derivative.

Optional anti-hyper-proliferative agents which can be added as further 30 pharmaceutical agents to the compounds of the present invention include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the *Merck Index*, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine,

chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna,
5 methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-hyper-proliferative agents suitable for use further pharmaceutical
10 agents with the compounds the present invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 1225-1287, (1996), which is hereby incorporated by reference, such as aminoglutethimide,
15 L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyl adenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine mono-phosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone
20 acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-hyper-proliferative agents suitable for use as further pharmaceutical
25 agents with the compounds of the present invention include but are not limited to other anti-cancer agents such as epothilone and its derivatives, irinotecan, raloxifen and topotecan.

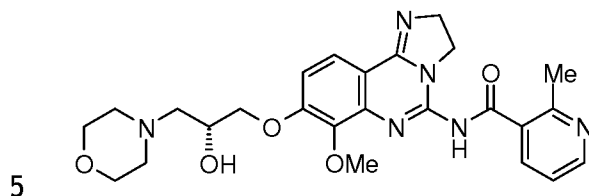
Generally, the use of cytotoxic and/or cytostatic agents as further
30 pharmaceutical agents in combination with a compound of the present invention will serve to:

- (1) yield better efficacy in reducing the growth of a tumor and/or metastasis or even eliminate the tumor and/ or metastasis as compared to administration of either agent alone,
- 5 (2) provide for the administration of lesser amounts of the administered chemotherapeutic agents,
- (3) provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than
10 observed with single agent chemotherapies and certain other combined therapies,
- (4) provide for treating a broader spectrum of different cancer types in mammals, especially humans,
- 15 (5) provide for a higher response rate among treated patients,
- (6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,
- 20 (8) provide a longer time for tumor progression, and/or
- (9) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer
25 agent combinations produce antagonistic effects.

EXPERIMENTAL SECTION

- 30 The schemes and procedures described in the art as cited in the present application (see introductory part) disclose general synthetic routes and specific procedures within their experimental sections to arrive at the PI3K- compounds of the present invention.

Compound A1 is a PI3K inhibitor as disclosed in the experimental section of WO2012/062748 in example 14 (N-(8-[[[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methylpyridine-3-carboxamide).



Compound A1

Examples demonstrating the activity of Compound A1 of the present invention

10

The monotherapy of compound A1 was tested in a syngeneic animal model that resembles the characteristics of breast cancer bone metastatic disease in humans. This model can be effectively used for testing the effects of cancer drug candidates on the metastasis of breast cancer cells to bone.

15 To this extend, 4T1-GFP-fluorescent mouse breast cancer cells were inoculated into the left cardiac ventricle of 4-5 weeks old female Balb/c mice. Within one-two weeks after the inoculation, the animals developed osteolytic bone metastases that can be visualized by GFP-fluorescence and X-ray radiography.

20 On day 7 post tumor cell inoculation, animals were randomized according to radiography and presence of tumor metastases. On day 7, animals were dosed with a daily dose of PI3K inhibitor. Half of the animals (n=10) from the treatment group were sacrificed on day 13 after inoculation, or earlier when they were moribund, half of the animals (N=10) were sacrificed when they became
25 moribund. The osteolytic lesions and whole body tumor burden were measured by x-ray and fluorescence imaging at sacrifice. Furthermore, tissue samples from the left and right tibia and femur were collected for further histomorphometric analysis. Tissue was embedded in paraffin for histomorphometric analysis of bone and tumor area.

30

The effects of PI3K inhibitor Compound A1 in MCF-7 and 4T1 breast cancer cells and PC-3 and LNCaP prostate cancer cells were investigated in vitro. The effects were studied by measuring cell proliferation and apoptosis. The PI3K inhibitor(s) was added at day -1 and at day 4. The following two concentrations
 5 of the inhibitors were tested:

		MCF-7	4T1	PC-3	LNCaP
Compd A1	D1	250 nM	500 nM	250 nM	500 nM
	D2	5000 nM	5000 nM	5000 nM	5000 nM

10

The effects on cell proliferation were studied using a WST-1 based proliferation assay and the effects on apoptosis were studied in parallel plates by measuring caspase 3/7 activity. The measurements were performed at 4 different time
 15 points, days 1, 2, 3 and 5. Caspase activity was normalized to the cell number obtained with the WST-1 assay in parallel plates.

The reference compound doxorubicin inhibited proliferation in all tested cell lines; MCF-7, 4T1, PC-3 and LNCaP, describing that the assays were performed
 20 successfully and the results obtained are reliable.

Further study in multiple myeloma

The following seven multiple myeloma cell lines are tested: 5TGM1, JJN3, LP-1, L363, MOLP-8, RPMI8226, OPM-2. The effects of Ra-223 and PI3K inhibitor
 25 compound A1 and their combinations on proliferation and apoptosis of the multiple myeloma cell lines are studied. Proliferation is measured using WST-1 based proliferation assay and apoptosis by measuring caspase 3/7 activity.

The following groups are tested for each of the 7 cell lines in both the WST-1 and caspase 3/7 measurements:

- 30
1. Baseline group with vehicle
 2. Control group with 0.1 μ M doxorubicin
 3. Test group receiving dose 1 of PI3Ki Compound A1
 4. Test group receiving dose 2 of PI3Ki Compound A1

A beneficial therapeutic effect is observed with the use of the PI3Ki compound A1.

Description of the Figures

5

Table 1. Day of sacrifice of the survival animals. Criteria for euthanasia were weight loss over 20%, severe breathing difficulties or overall morbidity (kyphotic posture, unresponsive, cold feet and tail). Treatment of Compound A1 increased average survival days to 6.6 compared to vehicle control group 5.7 days. Statistical significance could not be reached likely due to the short treatment time (aggressive model with average survival of 5.7 days in the vehicle group) and a small sample number.

10

Animal	Vehicle	Compound A1
1	8	6
2	4	4
3	4	6
4	6	8
5	6	8
6	6	8
7	8	8
8	1	6
9	8	6
10	6	6
Average	5.7	6.6
SD	2.1	1.3

Figure 1: Whole body tumor burden based on fluorescence imaging at sacrifice (mm², median $\pm$ IQR25% $\pm$ min/max). Animals were sacrificed on day 13 after tumor inoculation and 6 days after the treatment of Compound A1. PI3K inhibitor compound A1 decreased whole body tumor burden as a single agent. Statistical analysis was performed using Kruskal-Wallis test. As statistical differences were observed ($p < 0.001$), the pairwise comparison against the control group was performed using Mann-Whitney U-test. Notation: *** = statistically significant difference with p -value ≤ 0.001 , ** = p -value ≤ 0.01 , * = p -value ≤ 0.05 , and NS = Non-Significant.

Groups: Control group received vehicle and PI3K group was given 75 mg/kg of Compound A1 and vehicle.

- 5 Whole body tumor burden was significantly decreased by PI3K inhibitor Compound A1 alone ($p=0.00156$). Statistical analysis was performed using Kruskal-Wallis test. The pairwise comparison against the control group was performed using Mann-Whitney U-test. Notation: ** = statistically significant difference with $p\text{-value} \leq 0.01$, and NS = Non-Significant.

10

Figure 2: Total osteolytic area at sacrifice (mm², median $\pm$ IQR25% $\pm$ min /max).

- 15 Treatment with PI3K inhibitor Compound A1 showed trend of decreasing the total osteolytic area ($p=0.0305$, T-test).

Groups: Control group received vehicle and PI3K group was given 75 mg/kg of Compound A1 and vehicle.

20

Figure 3. Mean osteolytic area at sacrifice (mm², median $\pm$ IQR25% $\pm$ min /max).

- 25 Treatment with PI3K inhibitor Compound A1 showed trend of decreasing the mean osteolytic area. Statistical significance could not be reached likely due to the short treatment time (aggressive model with average survival of 5.7 days in the vehicle group) and a small sample number.

Groups: Control group received vehicle and PI3Ki group was given 75 mg/kg of Compound A1 and vehicle.

30

Figure 4. Relative tumor area in bone marrow area. Trends of inhibition of tumor cells in bone marrow area by PI3Ki Compound A1. Statistical significance

could not be reached likely due to the short treatment time (aggressive model with average survival of 5.7 days in the vehicle group) and a small sample number.

Groups: Control group received vehicle and PI3Ki group was given 75 mg/kg of Compound A1 and vehicle.

5

Table 2. Metastases in soft tissues/organs. Percentage of organs with metastasis as analyzed by macroscopic findings and fluorescence imaging from non-survival animals sacrificed at day 12 or 13. PI3Ki Compound A1 significantly decreased kidney metastases as single agent treatment. Trends of decreasing metastases in adrenal glands and ovaries by PI3Ki Compound A1 were observed. Statistical significance could not be reached likely due to the short treatment time (aggressive model with average survival of 5.7 days in the vehicle group) and a small sample number.

Groups: Control group received vehicle and PI3Ki group was given 75 mg/kg of Compound A1 and vehicle.

15

Organ	Control n=8	Compound A1 n=9
Kidneys (%)	63	17
p-value		0.012*
Adrenal glands, %	88	61
p-value		0.125
Ovaries, %	81	56
p-value		0.152

Table 3. The characteristics of the cell lines used to obtain the data underlying the figures below:

20

Cell line	Description	Derived from	Pathway Mutation
-----------	-------------	--------------	---------------------

MCF-7	human mammary gland adenocarcinoma	pleural effusion	PIK3CA
4T1	mouse mammary gland adenocarcinoma	mammary tumor	
PC-3	human prostate adenocarcinoma	bone	PTEN-del
LNCaP	human prostate carcinoma	left supraclavicular lymph node	PTEN-del

Figure 5.**The effects of Compound A1 on MCF-7 cell proliferation at days 1-5 and**

5 **apoptosis induction at day 2.** The results of the control group doxorubicin (C) and Compound A1 groups (D1 = 250 nM and D2 = 5000 nM) are depicted. (A) The results are shown as Absorbance (450 nm) measured in the WST-1 proliferation assay (MEAN). (B) The results are shown as Caspase 3/7 / WST-1 values (MEAN + SEM).

10

Figure 6.**The effects of Compound A1 on 4T1 breast tumor cell proliferation at days**

1-5. The results of the control group doxorubicin (C) and Compound A1 groups (D1 = 250 nM and D2 = 5000 nM) are depicted and shown as Absorbance (450
15 nm) measured in the WST-1 proliferation assay (MEAN).

Figure 7.**The effects of Compound A1 on PC3 prostate tumor cell proliferation at**

days 1-5. The results of the control group doxorubicin (C) and Compound A1
20 groups (D1 = 250 nM and D2 = 5000 nM) are depicted and shown as Absorbance (450 nm) measured in the WST-1 proliferation assay (MEAN).

Figure 8.**The effects of Compound A1 on LNCaP prostate tumor cell proliferation at**

25 **days 1-5 and apoptosis induction at day 2.** The results of the control group doxorubicin (C) and Compound A1 groups (D1 = 250 nM and D2 = 5000 nM) are depicted. (A) The results are shown as Absorbance (450 nm) measured in the WST-1 proliferation assay (MEAN). (B) The results are shown as Caspase 3/7 / WST-1 values (MEAN + SEM).

Figure 9.***In vitro* anti-tumor effects of Compound A1 as single agent on 4T1 and PC3 cells - Effects on apoptosis induction**

- 5 The effects on apoptosis were studied by measuring caspase 3/7 activity on the indicated day. Caspase3/7 activity was normalized to the value obtained with the WST-1 assay in the parallel plates. The following drug concentrations were used, Compd A1: D2 = 5000 nM; D1 = 500 nM for 4T1 and PC3 cells.

10 **Figure 10.**

Inhibition of 4T1-GFP tumor burden in mice treated with Compound A1 -

Image of whole body tumor burden in the representative mice.

Figure 11.

- 15 **Inhibition of osteolysis by Compound A1 measured by radiograph.** X-ray of representative animals from each treatment groups.

Figure 12.**Effect Reduced total tumor area by the treatment of compound A1.** Total

- 20 tumor area was analyzed from Masson-Goldner Trichrome (MGT) stained sections. One section from each sample was analyzed using MetaMorph image analysis software. Treatment of compound A1 decreased total tumor area. Statistical analysis was performed using Kruskal-Wallis test. As statistical differences were observed ($p=0.00928$, the pairwise comparison was
- 25 performed using Mann-Whitney U-test.

Notation: *** = statistically significant difference with $p\text{-value} \leq 0.001$, ** = $p\text{-value} \leq 0.01$, * = $p\text{-value} \leq 0.05$, a = $p\text{-value} \leq 0.1$, and NS = Non-Significant.

Figure 13.

- 30 **Reduction of lesion areas by compound A1.** The formation of osteoblastic lesions was assessed at indicated time point in vivo by x-ray radiography with Faxitron Specimen Radiographic System MX-20 D12 (Faxitron Corp. Illinois, USA) using Faxitron Dicom 3.0 –software. At least one

radiograph (both hind limbs) per animal was taken on each x-ray occasion (34 kV, 7 seconds, magnification 2x). The lesion area was determined from the images by using MetaMorph image analysis software. The growth of osteoblastic lesions was inhibited significantly by treatment of compound A1.

- 5 Statistical analysis was performed using linear mixed effect model and contrasts and indicated in Table 4.

Table 4

Comparison	Adjusted p-value	Significance
Vehicle vs Compd A1	0.00224	**
Vehicle vs Compd A1 on day 45	0.001	***

Notation: *** = statistically significant difference with p-value ≤ 0.001 , ** = p-value ≤ 0.01 .

10

Figure 14.

Inhibition of bone formation marker P1NP by Compound A1. Serum concentration of P1NP was measured by an ELISA kit (IDS, Boldon, UK, in ng/ml, mean $\pm$ SD). Treatment of compound A1 induced a decrease in serum

15 P1NP. Statistical analysis was performed using linear mixed effect model and contrasts: Compd A1 vs Vehicle (p-value <0.001).

Figure 15. Inhibition of the number of osteoblasts by Compound A1. The number of osteoblasts were counted from MGT –stained sections based on morphology and location. Two microscope fields at 10x magnification were

20 analyzed. The number of osteoblasts was reduced with the treatment of compound A1. Statistical analysis was performed using Kruskal-Wallis test. As statistical differences were observed (p <0.001), the pairwise comparison was performed using Mann-Whitney U-test. Notation: *** = statistically significant

25 difference with p-value ≤ 0.001 , ** = p-value ≤ 0.01 , * = p-value ≤ 0.05 .

Figure 16. Inhibition of osteoclasts by Compound A1.

The number of osteoclasts were studied by staining one section from each sample for TRAP (tartrate resistant acid phosphatase) activity. Only stained,

30 multinucleated cells on tumor-bone interface were counted. Whole section was analyzed. Treatment of compound A1 reduced the osteoclasts counted at tumor-

bone interface (TBI) (n, median $\pm$ IQR25% $\pm$ min/max). Statistical analysis was performed using Kruskal-Wallis test. As statistical differences were observed (p=0.01047), the pairwise comparison was performed using Mann-Whitney U-test. Notation: * = statistically significant difference with p-value $\leq$ 0.05.

5

Conclusions:

The pharmacological inhibition of PI3K kinase by Compound A1 significantly decreased whole body tumor burden as single agent (67% reduction, p=0.00156) in the 4T1 mouse syngenic breast cancer model. Furthermore, Compound A1 inhibited tumor-induced osteolysis measured by radiography and led to 53.2% reduction in total osteolytic area as single agent. The frequency of kidney metastases was also significantly decreased by treatment with Compound A1 alone (e.g. 73% reduction in kidney, p=0.012). These results suggest that treatment of tumors and their metastases with PI3K inhibitor Compound A1 has therapeutic activity as single agent.

15

In LNCaP CRPC model, PI3Ki compound A1 potently inhibited tumor growth (p-value vs vehicle group is 0.00878). In addition, PI3Ki compound A1 significantly inhibited the progression of osteoblastic lesions as single agent (P= 0.00878). This result is further supported by the enhanced inhibition of bone formation marker PINP in serum and reduction of osteoblasts observed. Finally, PI3Ki compound A1 decreased the number of osteoclasts.

20

In MCF7, a breast cancer cell line with ER+ and activating PIK3CA mutation, Compound A1 showed potent anti-proliferative activity and at high dose induced tumor cell apoptosis.

25

In 4T1, a triple negative metastatic breast cancer cell line, Compound A1 showed inhibition of 4T1 tumor cell proliferation upto day 2.

30

In PC3, a AR-negative CRPC cell line with loss-of-function of tumor suppressor PTEN, potent anti-proliferative activity was observed with Compound A1.

In LNCaP, a AR-positive CRPC cell line with loss-of-function of tumor suppressor PTEN, Compound A1 showed strong anti-proliferative effects. At high dose, Compound A1 induced LNCaP tumor cell death assessed with a caspase 3/7 activation assay.

5

Taken together, Compound A1 demonstrated direct anti-tumor activity in all 4 breast and prostate tumor cell lines tested, and induced tumor cell death in hormone receptor positive MCF7 (ER+) breast cancer and LNCaP (AR+) prostate tumor cell lines.

10

In summary, our data indicate anti-tumor activity of the PI3K inhibitor Compound A1 as single agent in inhibiting tumor cell proliferation, survival, total tumor burden, and tumor-induced osteolysis, with good tolerability and warrant further clinical evaluation of Compound A1 for the treatment of cancer and the

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1. Marone, R.; Cmiljanovic, V.; Giese, B.; Wymann, M. P. Targeting phosphoinositide 3-kinase - moving towards therapy. *Biochim. Biophys. Acta, Proteins Proteomics* **2008**, *1784*, 159-185.
- 5 2. Yuan, T. L.; Cantley, L. C. PI3K pathway alterations in cancer: variations on a theme. *Oncogene* **2008**, *27*, 5497-5510.
3. Manning, B. D.; Cantley, L. C. AKT/PKB signaling: navigating downstream. *Cell* **2007**, *129*, 1261-1274.
- 10 4. Obenauer, J. C.; Cantley, L. C.; Yaffe, M. B. Scansite 2.0: proteome-wide prediction of cell signaling interactions using short sequence motifs. *Nucleic Acids Res.* **2003**, *31*, 3635-3641.
5. Nicholson, K. M.; Anderson, N. G. The protein kinase B/Akt signalling pathway in human malignancy. *Cell. Signalling* **2002**, *14*, 381-395.
- 15 6. Datta, S. R.; Dudek, H.; Tao, X.; Masters, S.; Fu, H.; Gotoh, Y.; Greenberg, M. E. Akt phosphorylation of BAD couples survival signals to the cell-intrinsic death machinery. *Cell* **1997**, *91*, 231-241.
7. Zha, J.; Harada, H.; Yang, E.; Jockel, J.; Korsmeyer, S. J. Serine phosphorylation of death agonist BAD in response to survival factor results in binding to 14-3-3 not BCL-XL. *Cell* **1996**, *87*, 619-628.
- 20 8. Romashkova, J. A.; Makarov, S. S. Nf-kB is a target of Akt in anti-apoptotic PDGF signalling. *Nature* **1999**, *401*, 86-90.
9. Zhou, B. P.; Liao, Y.; Xia, W.; Spohn, B.; Lee, M.-H.; Hung, M.-C. Cytoplasmic localization of p21Cip1/WAF1 by Akt-induced phosphorylation in HER-2/neu-overexpressing cells. *Nat. Cell Biol.* **2001**, *3*, 245-252.
- 25 10. Tran, H.; Brunet, A.; Grenier, J. M.; Datta, S. R.; Fornace, A. J., Jr.; DiStefano, P. S.; Chiang, L. W.; Greenberg, M. E. DNA repair pathway stimulated by the Forkhead Transcription Factor FOXO3a through the Gadd45 protein. *Science* **2002**, *296*, 530-534.
11. Okumura, E.; Fukuhara, T.; Yoshida, H.; Hanada, S.-I.; Kozutsumi, R.; Mori, M.; Tachibana, K.; Kishimoto, T. Akt inhibits Myt1 in the signalling pathway that leads to meiotic G2/M-phase transition. *Nat. Cell Biol.* **2002**, *4*, 111-116.
- 30 12. Alessi, D. R.; Pearce, L. R.; Garcia-Martinez, J. M. New insights into mTOR signaling: mTORC2 and beyond. *Sci. Signal.* **2009**, *2*, pe27.
13. Yang, Q.; Guan, K.-L. Expanding mTOR signaling. *Cell Res.* **2007**, *17*, 666-681.
14. Sarbassov, D. D.; Guertin, D. A.; Ali, S. M.; Sabatini, D. M. Phosphorylation and Regulation of Akt/PKB by the Rictor-mTOR Complex. *Science* **2005**, *307*, 1098-1101.
- 35 15. Harrington, L. S.; Findlay, G. M.; Gray, A.; Tolkacheva, T.; Wigfield, S.; Rebholz, H.; Barnett, J.; Leslie, N. R.; Cheng, S.; Shepherd, P. R.; Gout, I.; Downes, C. P.; Lamb, R. F. The TSC1-2 tumor suppressor controls insulin-PI3K signaling via regulation of IRS proteins. *J. Cell Biol.* **2004**, *166*, 213-223.

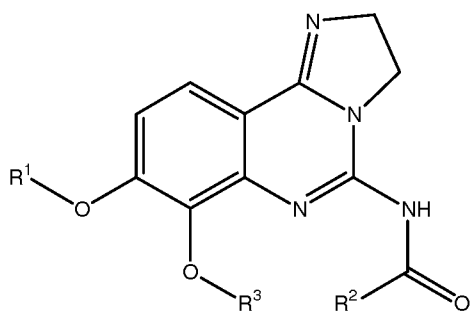
16. Barone, I.; Cui, Y.; Herynk, M. H.; Corona-Rodriguez, A.; Giordano, C.; Selever, J.; Beyer, A.; Ando, S.; Fuqua, S. A. W. Expression of the K303R estrogen receptor- α breast cancer mutation induces resistance to an aromatase inhibitor via addiction to the PI3K/Akt kinase pathway. *Cancer Res.* **2009**, *69*, 4724-4732.
- 5 17. Jozwiak, J.; Jozwiak, S.; Wlodarski, P. Possible mechanisms of disease development in tuberous sclerosis. *Lancet Oncol.* **2008**, *9*, 73-79.
18. Pearce, L. R.; Komander, D.; Alessi, D. R. The nuts and bolts of AGC protein kinases. *Nat. Rev. Mol. Cell Biol.* **2010**, *11*, 9-22.
- 10 19. Vasudevan, K. M.; Barbie, D. A.; Davies, M. A.; Rabinovsky, R.; McNear, C. J.; Kim, J. J.; Hennessy, B. T.; Tseng, H.; Pochanard, P.; Kim, S. Y.; Dunn, I. F.; Schinzel, A. C.; Sandy, P.; Hoersch, S.; Sheng, Q.; Gupta, P. B.; Boehm, J. S.; Reiling, J. H.; Silver, S.; Lu, Y.; Stemke-Hale, K.; Dutta, B.; Joy, C.; Sahin, A. A.; Gonzalez-Angulo, A. M.; Lluch, A.; Rameh, L. E.; Jacks, T.; Root, D. E.; Lander, E. S.; Mills, G. B.; Hahn, W. C.; Sellers, W. R.; Garraway, L. A. AKT-independent signaling downstream of oncogenic PIK3CA mutations in human cancer. *Cancer Cell* **2009**, *16*, 21-32.
- 15 20. Vanhaesebroeck, B.; Guillermet-Guibert, J.; Graupera, M.; Bilanges, B. The emerging mechanisms of isoform-specific PI3K signaling. *Nat. Rev. Mol. Cell Biol.* **2010**, *11*, 329-341.
- 20 21. Zhao, J. J.; Cheng, H.; Jia, S.; Wang, L.; Gjoerup, O. V.; Mikami, A.; Roberts, T. M. The p110 α isoform of PI3K is essential for proper growth factor signaling and oncogenic transformation. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 16296-16300.
22. Jia, S.; Liu, Z.; Zhang, S.; Liu, P.; Zhang, L.; Lee, S. H.; Zhang, J.; Signoretti, S.; Loda, M.; Roberts, T. M.; Zhao, J. J. Essential roles of PI(3)K-p110b in cell growth, metabolism and tumorigenesis. *Nature* **2008**, *454*, 776-779.
- 25 23. Vogt, P. K.; Gymnopoulos, M.; Hart, J. R. PI 3-kinase and cancer: changing accents. *Curr. Opin. Genet. Dev.* **2009**, *19*, 12-17.
24. Jia, S.; Roberts, T. M.; Zhao, J. J. Should individual PI3 kinase isoforms be targeted in cancer? *Curr. Opin. Cell Biol.* **2009**, *21*, 199-208.
25. Sanger Institute. Sanger Database.
- 30 26. Tannock, I. F.; de Wit, R.; Berry, W. R.; Horti, J.; Pluzanska, A.; Chi, K. N.; Oudard, S.; Theodore, C.; James, N. D.; Turesson, I.; Rosenthal, M. A.; Eisenberger, M. A. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N. Engl. J. Med.* **2004**, *351*, 1502-1512.
- 35 27. Benistant, C.; Chapuis, H.; Roche, S. A specific function for phosphatidylinositol 3-kinase α (p85 α -p110 α) in cell survival and for phosphatidylinositol 3-kinase β (p85 α -p110 β) in de novo DNA synthesis of human colon carcinoma cells. *Oncogene* **2000**, *19*, 5083-5090.
28. Brugge, J.; Hung, M.-C.; Mills, G. B. A new mutational activation in the PI3K pathway. *Cancer Cell* **2007**, *12*, 104-107.

29. Lee, S. H.; Poulogiannis, G.; Pyne, S.; Jia, S.; Zou, L.; Signoretti, S.; Loda, M.; Cantley, L. C.; Roberts, T. M. A constitutively activated form of the p110b isoform of PI3-kinase induces prostatic intraepithelial neoplasia in mice. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 11002-11007, S11002/11001-S11002/11050.
- 5 30. Wee, S.; Wiederschain, D.; Maira, S.-M.; Loo, A.; Miller, C.; de Beaumont, R.; Stegmeier, F.; Yao, Y.-M.; Lengauer, C. PTEN-deficient cancers depend on PIK3CB. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 13057-13062.
31. Liu, P.; Cheng, H.; Roberts, T. M.; Zhao, J. J. Targeting the phosphoinositide 3-kinase pathway in cancer. *Nat. Rev. Drug Disc.* **2009**, *8*, 627-644.
- 10 32. Byun, D.-S.; Cho, K.; Ryu, B.-K.; Lee, M.-G.; Park, J.-I.; Chae, K.-S.; Kim, H.-J.; Chi, S.-G. Frequent monoallelic deletion of PTEN and its reciprocal association with PIK3CA amplification in gastric carcinoma. *Int. J. Cancer* **2003**, *104*, 318-327.
- 15 33. Oki, E.; Kakeji, Y.; Baba, H.; Tokunaga, E.; Nakamura, T.; Ueda, N.; Futatsugi, M.; Yamamoto, M.; Ikebe, M.; Maehara, Y. Impact of loss of heterozygosity of encoding phosphate and tensin homolog on the prognosis of gastric cancer. *J. Gastroenterol. Hepatol.* **2006**, *21*, 814-818.
34. Li, Y.-L.; Tian, Z.; Wu, D.-Y.; Fu, B.-Y.; Xin, Y. Loss of heterozygosity on 10q23.3 and mutation of tumor suppressor gene PTEN in gastric cancer and precancerous lesions. *World J. Gastroenterol.* **2005**, *11*, 285-288.
- 20 35. Marques, M.; Kumar, A.; Poveda, A. M.; Zuluaga, S.; Hernandez, C.; Jackson, S.; Pasero, P.; Carrera, A. C. Specific function of phosphoinositide 3-kinase beta in the control of DNA replication. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 7525-7530.
- 25 36. Sujobert, P.; Bardet, V.; Cornillet-Lefebvre, P.; Hayflick, J. S.; Prie, N.; Verdier, F.; Vanhaesebroeck, B.; Muller, O.; Pesce, F.; Ifrah, N.; Hunault-Berger, M.; Berthou, C.; Villemagne, B.; Jourdan, E.; Audhuy, B.; Solary, E.; Witz, B.; Harousseau, J. L.; Himberlin, C.; Lamy, T.; Lioure, B.; Cahn, J. Y.; Dreyfus, F.; Mayeux, P.; Lacombe, C.; Bouscary, D. Essential role for the p110d isoform in phosphoinositide 3-kinase activation and cell proliferation in acute myeloid leukemia. *Blood* **2005**, *106*, 1063-1066.
- 30 37. Bruland O. S., Nilsson S., Fisher D.R., et al., High-linear energy transfer irradiation targeted to skeletal metastases by the alpha-emitter ²²³Ra: adjuvant or alternative to conventional modalities?, *Clin. Cancer Res.* 2006; 12: 6250s-7s

CLAIMS

1. Use of a compound of general formula (I),

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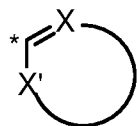


(I)

in which :

10 R¹ represents $-(CH_2)_n-(CHR^4)-(CH_2)_m-N(R^5)(R^{5'})$;

R² represents a heteroaryl of structure :



optionally substituted with 1, 2 or 3 R⁶ groups,

in which :

15 * represents the point of attachment of said heteroaryl with the rest of the compound of general formula (I),

X represents N or C-R⁶,

X' represents O, S, NH, N-R⁶, N or C-R⁶,

with the proviso that when X and X' are both C-R⁶, then one C-R⁶ is C-H ;

20 R³ is methyl ;

R⁴ is hydroxy ;

R⁵ and R⁵' are the same or different and are, independently of each other, a hydrogen atom, or a C₁-C₆-alkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, or C₁-C₆-alkoxy-C₁-C₆-alkyl,

25 or

R⁵ and R^{5'}, taken together with the nitrogen atom to which they are bound, represent a 3- to 7-membered nitrogen containing heterocyclic ring optionally containing at least one additional heteroatom selected from oxygen, nitrogen or sulfur and which may be optionally substituted with 1 or more R^{6'} groups ;

5

each occurrence of R⁶ may be the same or different and is independently a hydrogen atom, a halogen atom, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, aryl, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, 3- to 8-membered heterocyclic ring, 3- to 8-membered
 10 heterocyclyl-C₁-C₆-alkyl, -C₁-C₆-alkyl-OR⁷, -C₁-C₆-alkyl-SR⁷, -C₁-C₆-alkyl-N(R⁷)(R^{7'}), -C₁-C₆-alkyl-C(=O)R⁷, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)(R^{7'}), -OR⁷, -SR⁷, -N(R⁷)(R^{7'}), or -NR⁷C(=O)R⁷ each of which may be optionally substituted with 1 or more R⁸ groups ;

15 each occurrence of R^{6'} may be the same or different and is independently C₁-C₆-alkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, or C₁-C₆-alkyl-OR⁷;

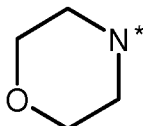
each occurrence of R⁷ and R^{7'} may be the same or different and is independently a hydrogen atom, or a C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl,
 20 C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, C₃-C₆-cycloalkenyl, aryl, aryl-C₁-C₆-alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, 3- to 8-membered heterocyclyl-C₁-C₆-alkyl, or heteroaryl-C₁-C₆-alkyl ;

each occurrence of R⁸ is independently a halogen atom, or nitro, hydroxy,
 25 cyano, formyl, acetyl, amino, C₁-C₆-alkyl, C₁-C₆-alkoxy, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, C₁-C₆-cycloalkenyl, aryl, aryl-C₁-C₆-alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, heterocyclyl-C₁-C₆-alkyl, or heteroaryl-C₁-C₆-alkyl ;

30 n is an integer of 1 and m is an integer of 1 ;

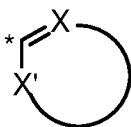
with the proviso that when :

- said R^5 and $R^{5'}$, taken together with the nitrogen atom to which they are bound, represent :



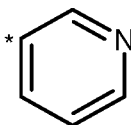
in which * represents the point of attachment with the rest of the structure of
 5 general formula (I),
 then

- said R^2 heteroaryl of structure :



is not :

10



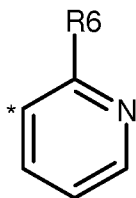
in which * represents the point of attachment with the rest of the structure of
 general formula (I),

15 as a sole active agent, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt,
 for the preparation of a medicament for the treatment or prophylaxis of cancer,
 particularly breast cancer, prostate cancer, multiple myeloma, hepatocyte
 carcinoma, lung cancer, in particular non-small cell lung carcinoma, colorectal
 20 cancer, melanoma, pancreatic cancer and/or metastases thereof.

2. Use according to claim 1, wherein

R^1 represents $-(CH_2)_n-(CHR^4)-(CH_2)_m-N(R^5)(R^{5'})$;

R^2 represents a heteroaryl of structure :



in which :

* represents the point of attachment of said heteroaryl with the rest of the structure of general formula (I) ;

5 R^3 is methyl ;

R^4 is hydroxy ;

R^5 and $R^{5'}$ are the same or different and are, independently of each other, a hydrogen atom, or a C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, or C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl,

10 or

R^5 and $R^{5'}$, taken together with the nitrogen atom to which they are bound, represent a 3- to 7-membered nitrogen containing heterocyclic ring optionally containing at least one additional heteroatom selected from oxygen, nitrogen or sulfur and which may be optionally substituted with 1 or more $R^{6'}$ groups ;

15

each occurrence of R^6 may be the same or different and is independently a hydrogen atom, a halogen atom, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, aryl, aryl- C_1 - C_6 -alkyl, heteroaryl, heteroaryl- C_1 - C_6 -alkyl, 3- to 8-membered heterocyclic ring, 3- to 8-membered

20 heterocyclyl- C_1 - C_6 -alkyl, $-C_1$ - C_6 -alkyl- OR^7 , $-C_1$ - C_6 -alkyl- SR^7 , $-C_1$ - C_6 -alkyl- $N(R^7)(R^7)$, $-C_1$ - C_6 -alkyl- $C(=O)R^7$, $-CN$, $-C(=O)OR^7$, $-C(=O)N(R^7)(R^7)$, $-OR^7$, $-SR^7$, $-N(R^7)(R^7)$, or $-NR^7C(=O)R^7$ each of which may be optionally substituted with 1 or more R^8 groups ;

25 each occurrence of $R^{6'}$ may be the same or different and is independently C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, or C_1 - C_6 -alkyl- OR^7 ;

each occurrence of R^7 and $R^{7'}$ may be the same or different and is independently a hydrogen atom, or a C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl,

30 C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkyl- C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkenyl, aryl, aryl- C_1 -

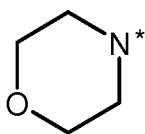
C₆-alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, 3- to 8-membered heterocyclyl-C₁-C₆-alkyl, or heteroaryl-C₁-C₆-alkyl ;

each occurrence of R⁸ is independently a halogen atom, or nitro, hydroxy,
 5 cyano, formyl, acetyl, amino, C₁-C₆-alkyl, C₁-C₆-alkoxy, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, C₁-C₆-cycloalkenyl, aryl, aryl-C₁-C₆-alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, heterocyclyl-C₁-C₆-alkyl, or heteroaryl-C₁-C₆-alkyl ;

10 n is an integer of 1 and m is an integer of 1 ;

with the proviso that when :

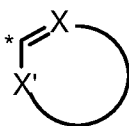
- said R⁵ and R^{5'}, taken together with the nitrogen atom to which they are bound, represent :



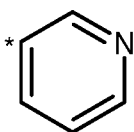
in which * represents the point of attachment with the rest of the structure of general formula (I),

then

- said R² heteroaryl of structure :



is not :



in which * represents the point of attachment with the rest of the structure of
 25 general formula (I),

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt.

- 5 **3.** Use according to claim 1 or 2, wherein the compound of general formula (I) is selected from the group consisting of :

N-(8-[[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-(8-[[(2S)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-[8-((2R)-3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-hydroxypropyl)oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide

N-(8-[[(2R)-2-hydroxy-3-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-{8-[2-hydroxy-3-(thiomorpholin-4-yl)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyridine-3-carboxamide

N-(8-[[(2R)-3-(azetidin-1-yl)-2-hydroxypropyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-(8-[[(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-(8-[[(2R)-2-hydroxy-3-(piperidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-{8-[3-(dimethylamino)-2-hydroxypropoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyridine-3-carboxamide

N-(8-[[(2R)-3-(dimethylamino)-2-hydroxypropyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-(8-[[(2R)-3-(dipropylamino)-2-hydroxypropyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-(8-[[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-(8-([(2R)-3-(azetidin-1-yl)-2-hydroxypropyl]oxy))-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-[8-([(2R)-3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-hydroxypropyl]oxy))-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methylpyridine-3-carboxamide

N-(8-([(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy))-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-(8-([(2R)-2-hydroxy-3-(piperidin-1-yl)propyl]oxy))-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-(8-([(2R)-3-(dipropan-2-ylamino)-2-hydroxypropyl]oxy))-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

6-amino-N-{8-[2-hydroxy-3-(morpholin-4-yl)propoxy]pyridine-3-carboxamide

6-amino-N-(8-([(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy))-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-(8-([(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy))-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide

2-amino-N-{8-[2-hydroxy-3-(morpholin-4-yl)propoxy]pyrimidine-5-carboxamide

2-amino-N-[8-([(2R)-3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-hydroxypropyl]oxy))-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide

2-amino-N-(8-([(2R)-2-hydroxy-3-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)propyl]oxy))-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide dihydrochloride

2-amino-N-(8-([(2R)-3-(dimethylamino)-2-hydroxypropyl]oxy))-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide

N-(8-([(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-3H-imidazo[4,5-b]pyridine-6-carboxamide

N-(8-([(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-thiazole-5-carboxamide

N-[8-([(2R)-3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-hydroxypropyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-1,3-thiazole-5-carboxamide

N-(8-([(2R)-3-(azetidin-1-yl)-2-hydroxypropyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-thiazole-5-carboxamide

N-(8-([(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-thiazole-5-carboxamide

N-(8-([(2R)-2-hydroxy-3-(piperidin-1-yl)propyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-thiazole-5-carboxamide

N-(8-([(2R)-2-Hydroxy-3-(pyrrolidin-1-yl)propyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-4-methyl-1,3-thiazole-5-carboxamide

2-amino-N-(8-([(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-4-methyl-1,3-thiazole-5-carboxamide

N-(8-([(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-oxazole-5-carboxamide

N-(8-([(2R)-3-(dipropylamino)-2-hydroxypropyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-thiazole-5-carboxamide,

or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt.

4. Use according to any of claims 1 to 3, wherein the compound of general formula (I) is selected from the group consisting of :

- 5 N-(8-([(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-[8-({(2R)-3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-hydroxypropyl}oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide

N-(8-{[(2R)-2-hydroxy-3-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)propyl]oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-(8-{[(2R)-3-(azetidin-1-yl)-2-hydroxypropyl]oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-(8-{[(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-(8-{[(2R)-2-hydroxy-3-(piperidin-1-yl)propyl]oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-(8-{[(2R)-3-(dimethylamino)-2-hydroxypropyl]oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-(8-{[(2R)-3-(dipropan-2-ylamino)-2-hydroxypropyl]oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyridine-3-carboxamide

N-(8-{[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-(8-{[(2R)-3-(azetidin-1-yl)-2-hydroxypropyl]oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-(8-{[(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-(8-{[(2R)-2-hydroxy-3-(piperidin-1-yl)propyl]oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

N-(8-{[(2R)-3-(dipropan-2-ylamino)-2-hydroxypropyl]oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-2-methylpyridine-3-carboxamide

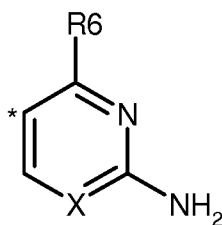
N-(8-{[(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy}-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide

N-(8-[[[(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-thiazole-5-carboxamide
 N-(8-[[[(2R)-2-hydroxy-3-(piperidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-thiazole-5-carboxamide
 N-(8-[[[(2R)-2-hydroxy-3-(pyrrolidin-1-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)-1,3-oxazole-5-carboxamide,
 or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt.

5. Use according to claim 1, wherein

R¹ represents $-(CH_2)_n-(CHR^4)-(CH_2)_m-N(R^5)(R^{5'})$;

R² represents a heteroaryl of structure :



5

in which :

* represents the point of attachment of said heteroaryl with the rest of the structure of general formula (I), and

X represents N or C-R⁶ ;

10 R³ is methyl ;

R⁴ is hydroxy ;

R⁵ and R^{5'} are the same or different and are, independently of each other, a hydrogen atom, or a C₁-C₆-alkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, or C₁-C₆-alkoxy-C₁-C₆-alkyl,

15 or

R⁵ and R^{5'}, taken together with the nitrogen atom to which they are bound, represent a 3- to 7-membered nitrogen containing heterocyclic ring optionally containing at least one additional heteroatom selected from oxygen, nitrogen or sulfur and which may be optionally substituted with 1 or more R^{6'} groups ;

20

each occurrence of R⁶ may be the same or different and is independently a hydrogen atom, a halogen atom, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-

C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, aryl, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, 3- to 8-membered heterocyclic ring, 3- to 8-membered heterocyclyl-C₁-C₆-alkyl, -C₁-C₆-alkyl-OR⁷, -C₁-C₆-alkyl-SR⁷, -C₁-C₆-alkyl-N(R⁷)(R^{7'}), -C₁-C₆-alkyl-C(=O)R⁷, -CN, -C(=O)OR⁷, -C(=O)N(R⁷)(R^{7'}), -OR⁷, -SR⁷,
 5 -N(R⁷)(R^{7'}), or -NR⁷C(=O)R⁷ each of which may be optionally substituted with 1 or more R⁸ groups ;

each occurrence of R^{6'} may be the same or different and is independently C₁-C₆-alkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, or C₁-C₆-alkyl-OR⁷;

10

each occurrence of R⁷ and R^{7'} may be the same or different and is independently a hydrogen atom, or a C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, C₃-C₆-cycloalkenyl, aryl, aryl-C₁-C₆-alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, 3- to 8-membered
 15 heterocyclyl-C₁-C₆-alkyl, or heteroaryl-C₁-C₆-alkyl ;

each occurrence of R⁸ is independently a halogen atom, or nitro, hydroxy, cyano, formyl, acetyl, amino, C₁-C₆-alkyl, C₁-C₆-alkoxy, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₃-C₆-cycloalkyl, C₃-C₆-cycloalkyl-C₁-C₆-alkyl, C₁-C₆-cycloalkenyl, aryl, aryl-C₁-C₆-alkyl, heteroaryl, 3- to 8-membered heterocyclic ring, heterocyclyl-C₁-C₆-alkyl, or heteroaryl-C₁-C₆-alkyl ;

20

n is an integer of 1 and m is an integer of 1 ;

25 or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt.

6. Use according to any of claims 1, 3 or 5, wherein the compound of general formula (I) is selected from the group consisting of :

30

6-amino-N-{8-[2-hydroxy-3-(morpholin-4-yl)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyridine-3-carboxamide

- 6-Amino-N-(8-[[[(2S)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyridine-3-carboxamide
- 6-Amino-N-(8-[[[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methylpyridine-3-carboxamide
- 5 2-Amino-N-{8-[2-hydroxy-3-(morpholin-4-yl)propoxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide
- 2-Amino-N-(8-[[[(2S)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide
- 2-amino-N-[8-({(2R)-3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-2-hydroxypropyl}oxy)-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide
- 10 dihydrochloride
- 2-Amino-N-(8-[[[(2R)-2-hydroxy-3-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide
- 15 2-Amino-N-(8-[[[(2R)-3-(dimethylamino)-2-hydroxypropyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide,
- or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt.
- 20 7. Use according to any of claims 1 to 4, wherein the compound of general formula (I) is
- N-(8-[[[(2R)-2-hydroxy-3-(morpholin-4-yl)propyl]oxy]-7-methoxy-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]-2-methylpyridine-3-carboxamide,
- or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof,
- 25 in particular a physiologically acceptable salt.
8. Use according to any of claims 1 to 7, for the preparation of a medicament for the treatment or prophylaxis of breast cancer, multiple myeloma or prostate cancer and/or metastases thereof.
- 30 9. Use according to any of claims claim 1 to 8, wherein the metastases are bone metastases.

10. A combination of :

- 5 a) a compound according to any one of claims 1 to 9, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt; or a pharmaceutical composition containing such a compound or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt, and
- 10 b) one or more further active agents selected from the group consisting of:
anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhythmic, anti-hypercholesterolemia, anti-dyslipidemia, anti-diabetic or antiviral agents, and/or admixtures or combinations thereof.

15 **11.** A pharmaceutical composition which comprises a combination of :

- 20 a) a compound according to any one of claims 1 to 9, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt; and
- b) one or more further active agents selected from the group consisting of :
anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic, immunoregulatory, diuretic, antiarrhythmic, anti-hypercholesterolemia, anti-dyslipidemia, anti-diabetic or antiviral agents, and/or admixtures or combinations thereof.
- 25

12. Use of a combination of :

- 30 a) a compound according to any one of claims 1 to 9, or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt;

or of a pharmaceutical composition containing such a compound or a stereoisomer, a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, in particular a physiologically acceptable salt, and

- 5 b) one or more further active agents selected from the group consisting of:
anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic,
immunoregulatory, diuretic, antiarrhythmic, anti-hypercholesterolemia, anti-
dyslipidemia, anti-diabetic or antiviral agents, and/or admixtures or
combinations thereof,

10

or a pharmaceutical composition containing such a combination,
for the preparation of a medicament for the treatment or prophylaxis of a cancer,
particularly breast cancer, prostate cancer, multiple myeloma, hepatocyte
carcinoma, lung cancer, in particular non-small cell lung carcinoma, colorectal
15 cancer, melanoma, pancreatic cancer and/or metastases thereof.

13. Use according to claim 12, for the preparation of a medicament for the
treatment or prophylaxis of breast cancer, multiple myeloma or prostate cancer
and/or metastases thereof.

20

14. Use according to claim 12 or 13, wherein the metastases are bone
metastases.

15. A method of treatment or prophylaxis of a cancer, particularly multiple
25 myeloma, hepatocyte carcinoma, lung cancer, in particular non-small cell lung
carcinoma, colorectal cancer, melanoma, pancreatic cancer, prostate cancer,
breast cancer and/or metastases thereof, in a subject, comprising administering
to said subject a therapeutically effective amount of a compound according to
any one of claims 1 to 9.

30

16. A method according to claim 15, for the treatment or prophylaxis of breast
cancer, multiple myeloma or prostate cancer and/or metastases thereof.

17. Method according to claim 15 or 16, wherein the metastases are bone metastases.

18. A kit comprising a combination of :

- 5 one or more compounds as defined in any one of the claims 1 to 9;
one or more further active agents selected from the group consisting of :
anti-angiogenesis, anti-hyper-proliferative, antiinflammatory, analgesic,
immunoregulatory, diuretic, antiarrhythmic, anti-hypercholesterolemia, anti-
dyslipidemia, anti-diabetic or antiviral agents, and/or admixtures or combinations
10 thereof, in which optionally both or either of said compounds as defined in any
one of the claims 1 to 9 and further active agents are in the form of a
pharmaceutical formulation which is ready for use to be administered
simultaneously, concurrently, separately or sequentially.

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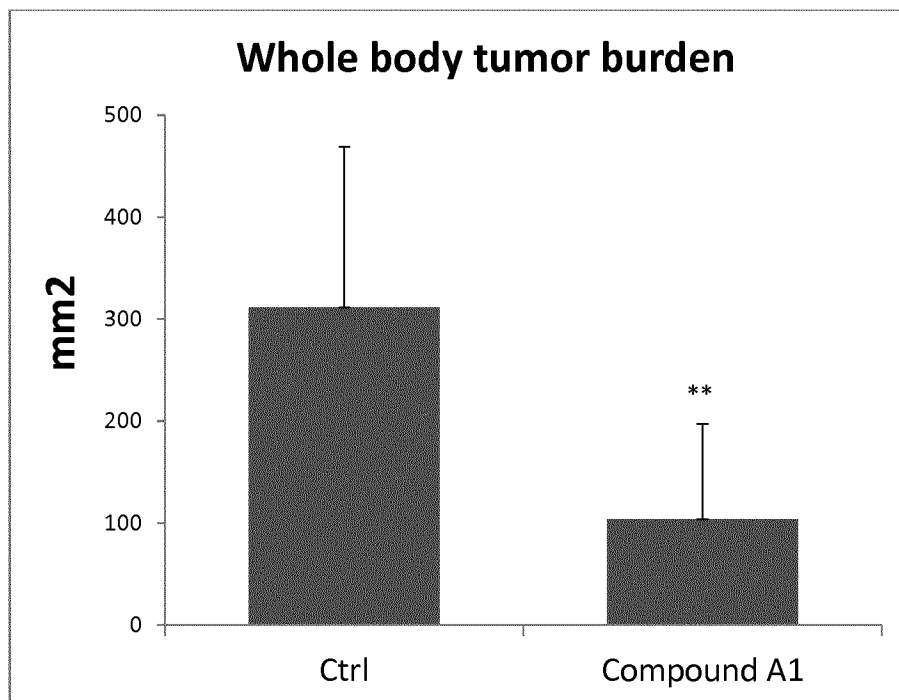
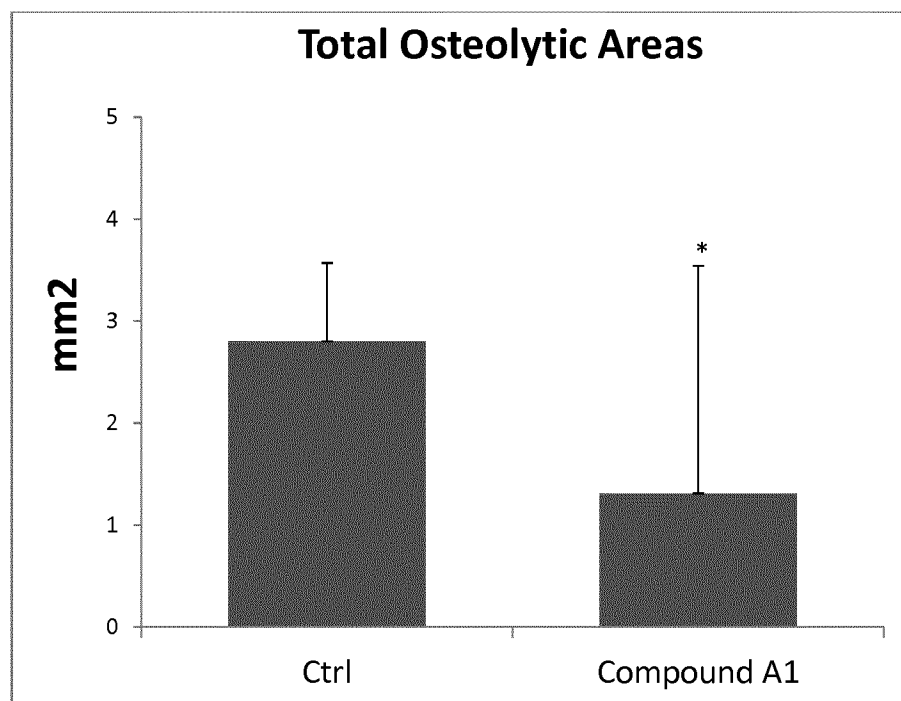


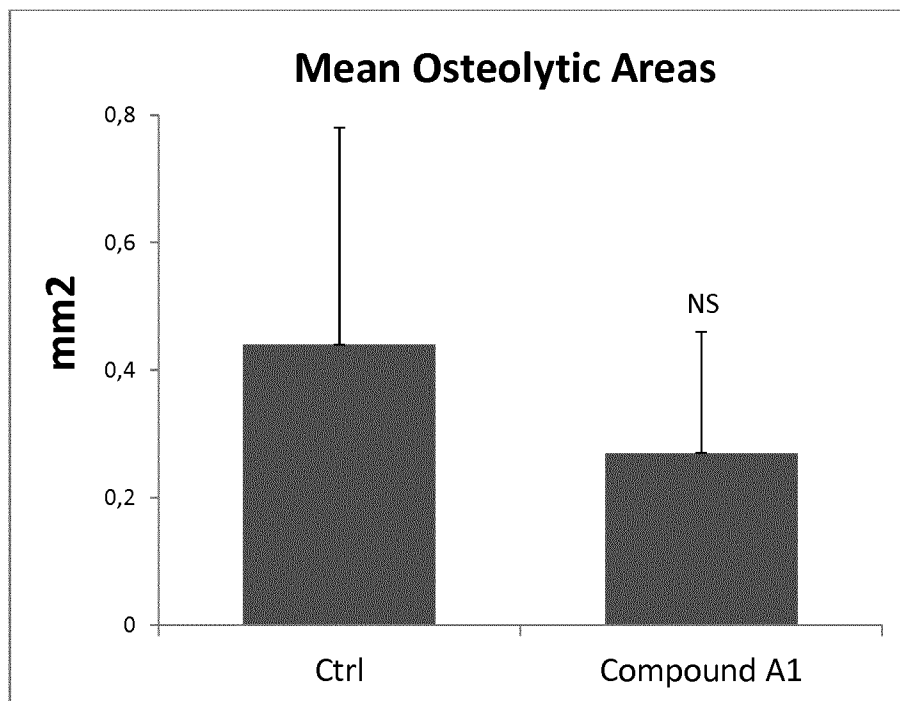
Figure 1



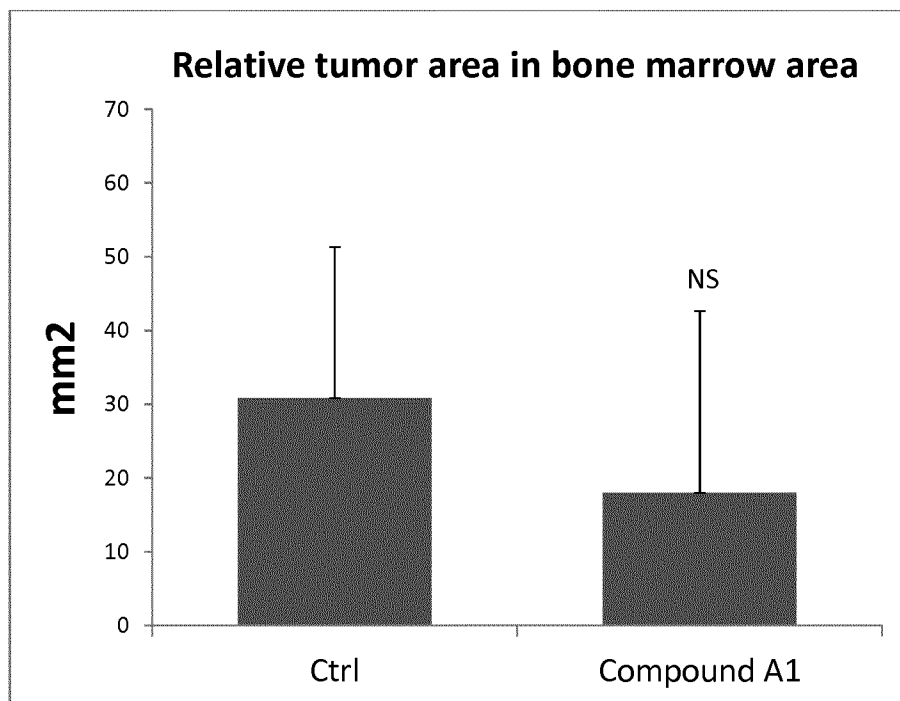
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Figure 2

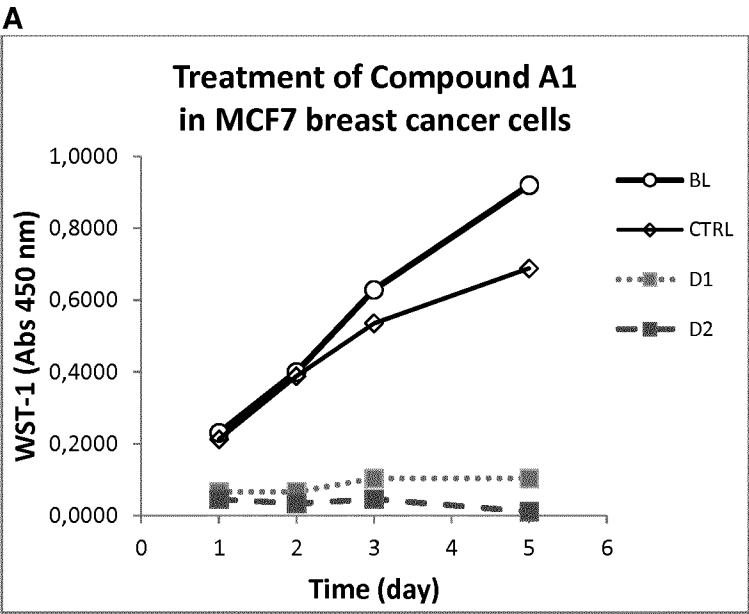
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**Figure 3**

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**Figure 4**

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5 **B**

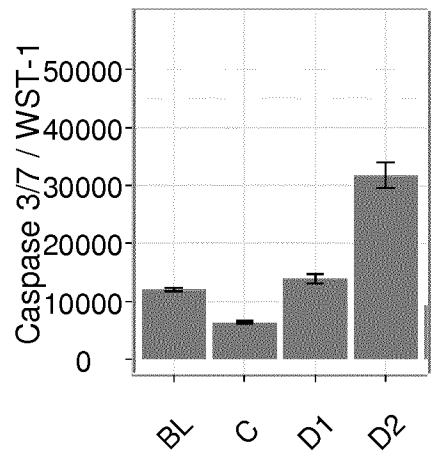
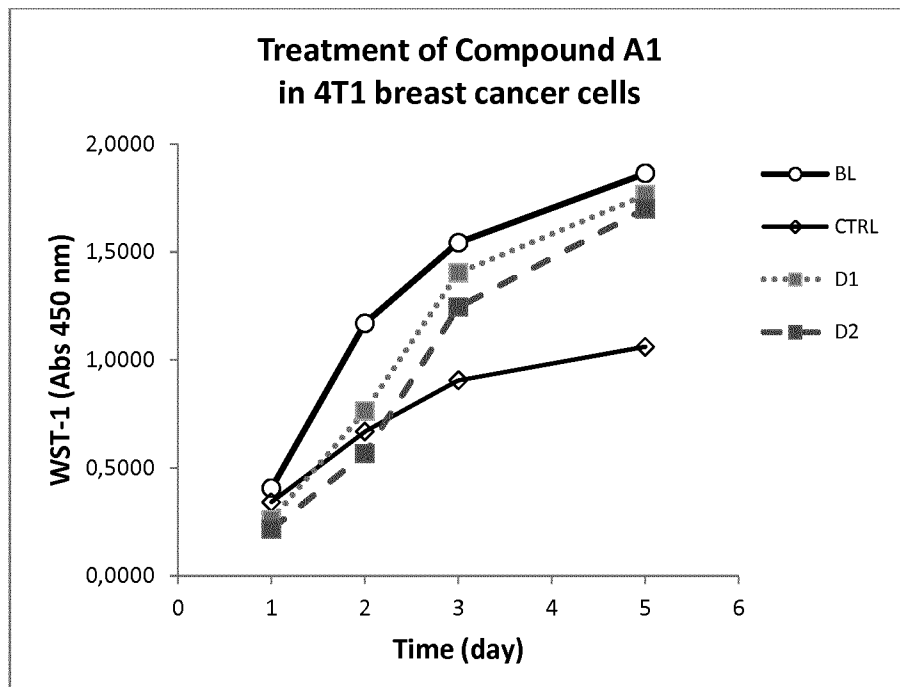


Figure 5.

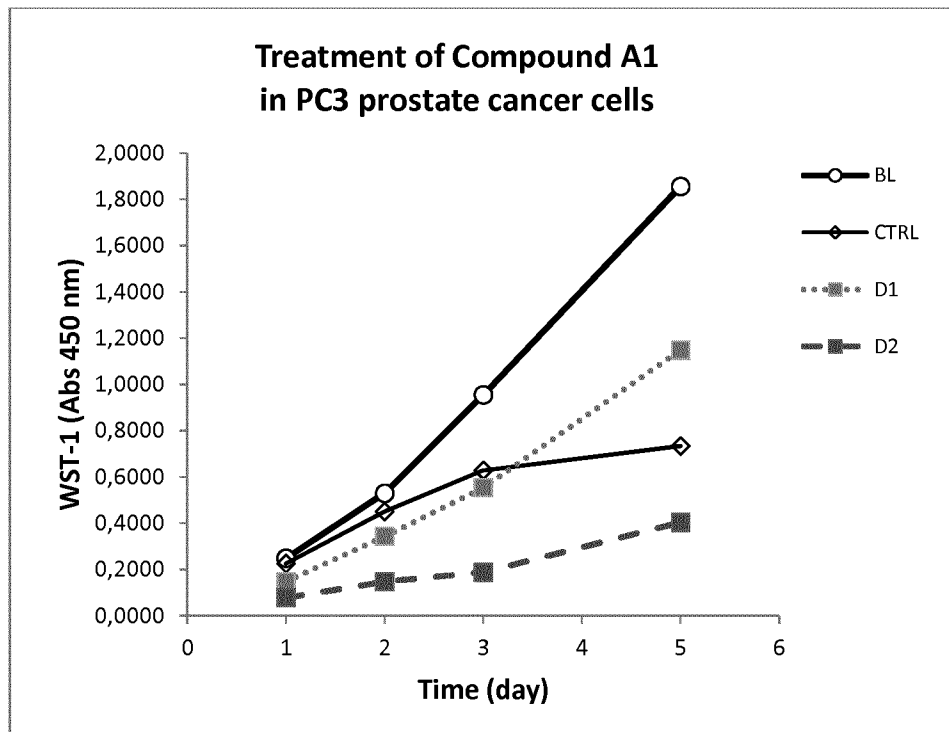
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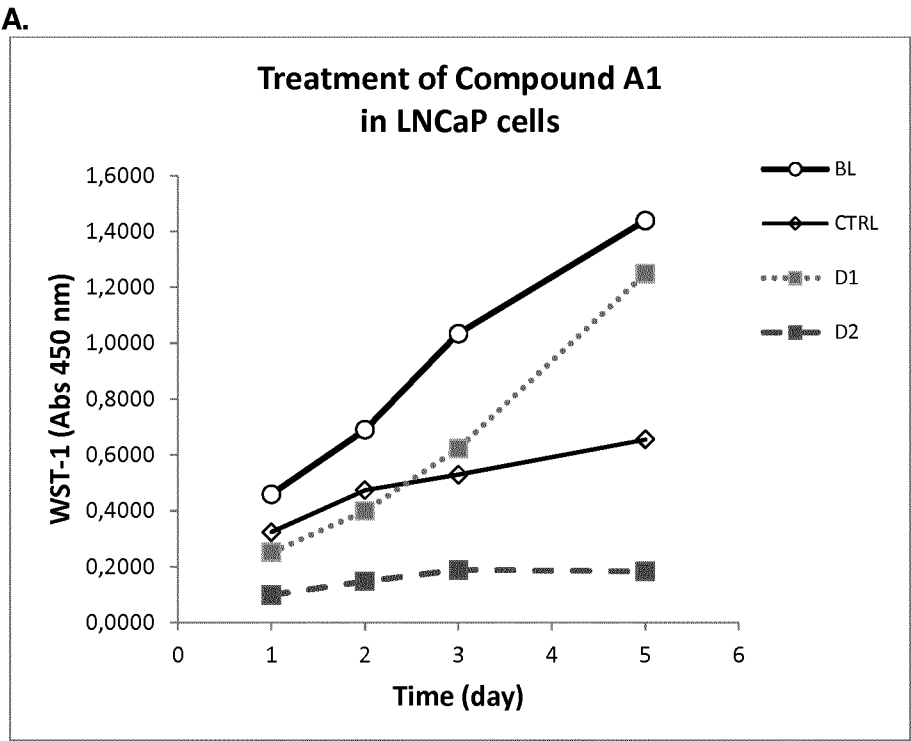
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Figure 6.

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**Figure 7.**

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B.

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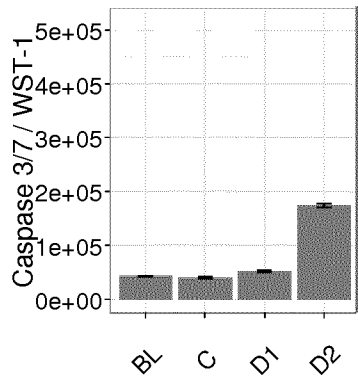


Figure 8.

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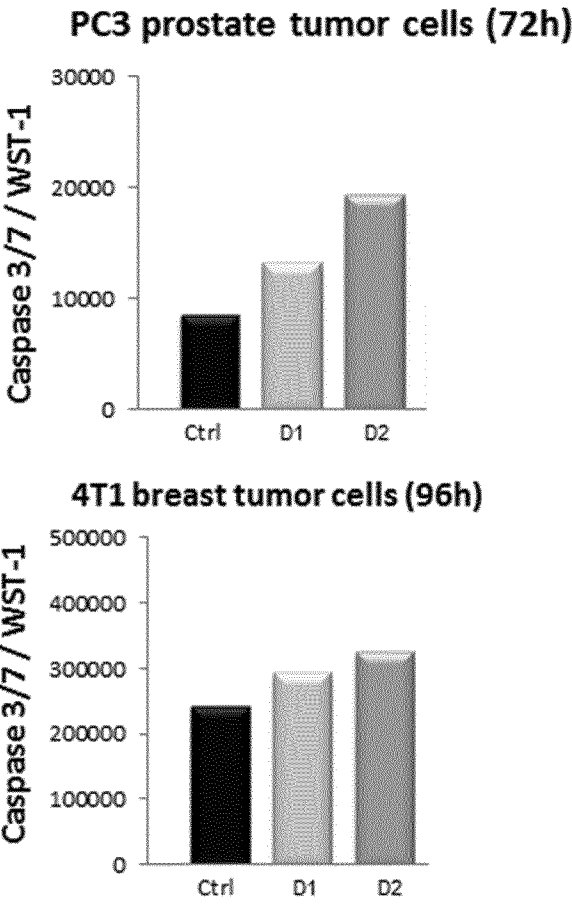


Figure 9.

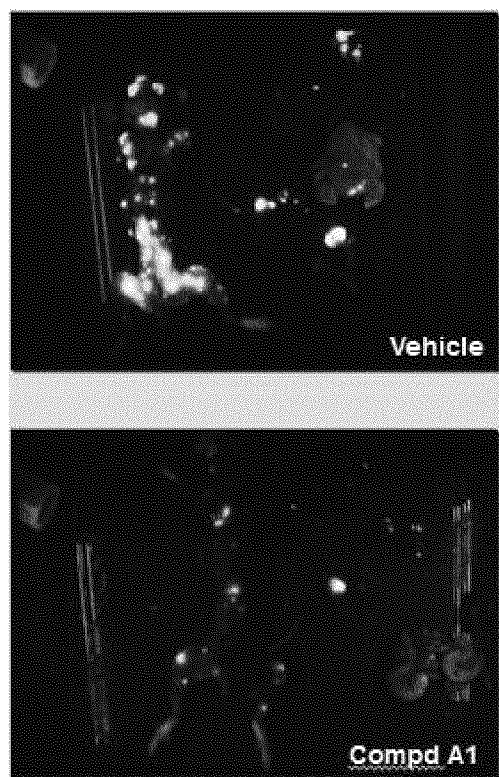
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5 **Figure 10.**

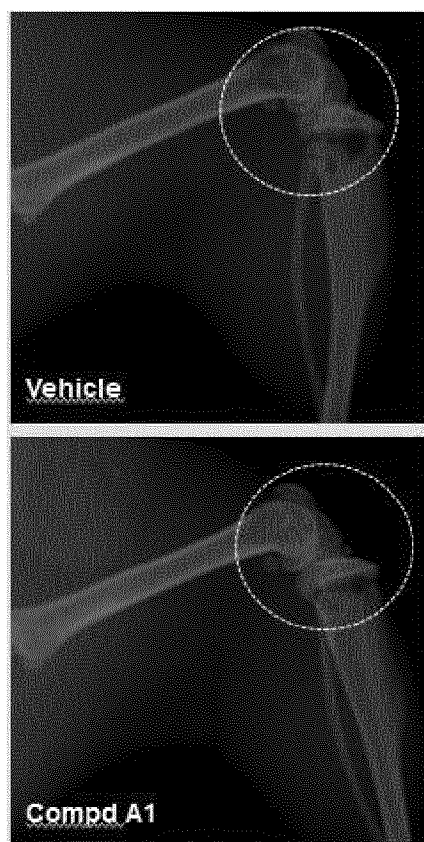
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5 **Figure 11.**

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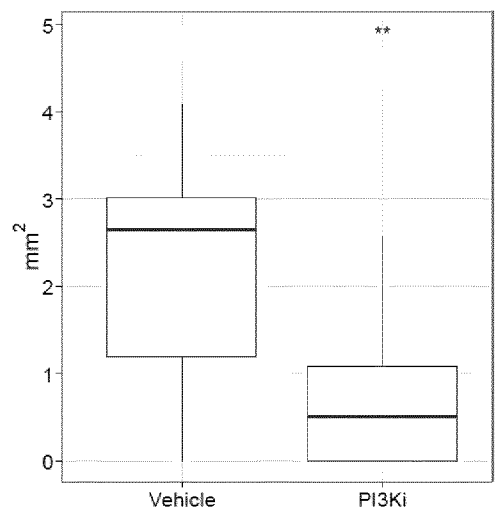


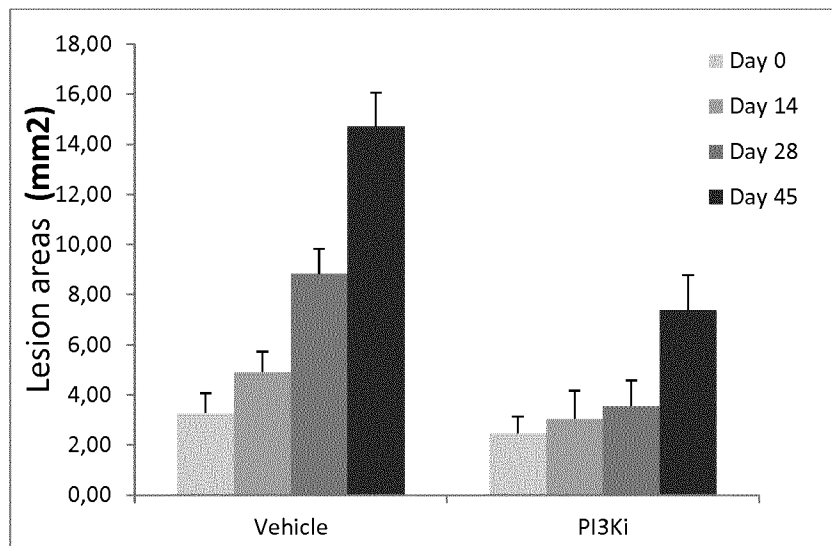
Figure 12

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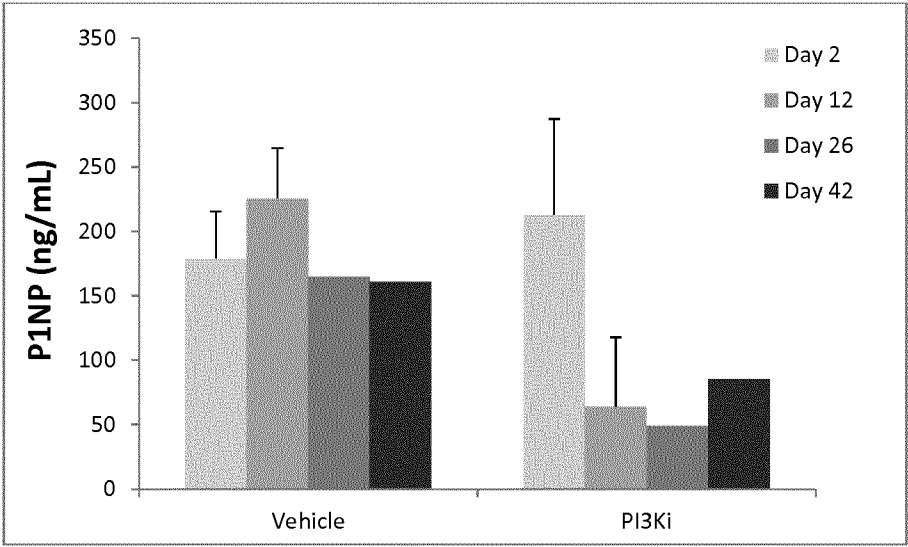


5 Figure 13

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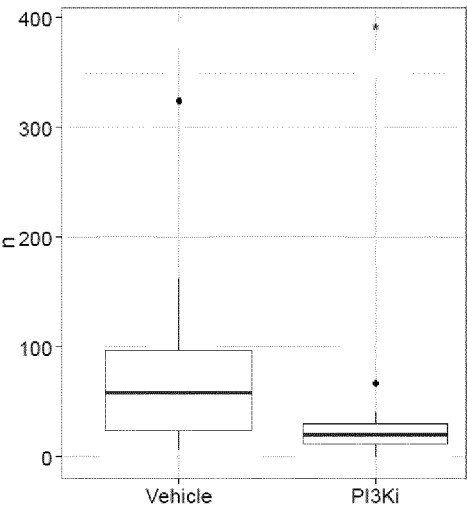


5 Figure 14

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5 Figure 15