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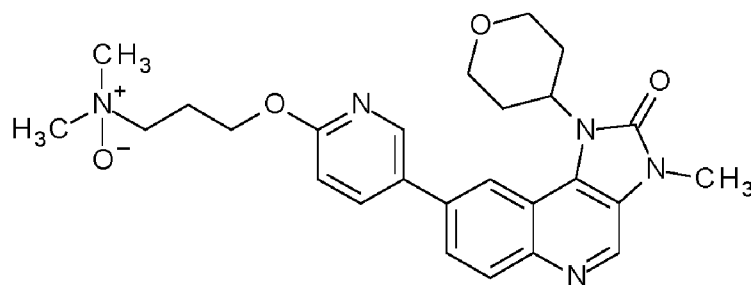
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(54) Title: N,N-DIMETHYL-3-[[5-(3-METHYL-2-OXO-1-TETRAHYDROPYRAN-4-YL-IMIDAZO[4,5-C]QUINOLIN-8-YL)-2-PYRIDYL]OXY]PROPAN-1-AMINE OXIDE AS ATM (ATAXIA TELANGIECTASIA MUTATED) KINASE MODULATOR FOR TREATING CANCER



(I)

(57) Abstract: The specification generally relates to the compound of Formula (I), i.e. to N,N-dimethyl-3-[[5-(3-methyl-2-oxo-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-8-yl)-2-pyridyl]oxy]propan-1-amine oxide as ATM (ataxia telangiectasia mutated) kinase modulator for treating cancer.

N,N-DIMETHYL-3-[[5-(3-METHYL-2-OXO-1-TETRAHYDROPYRAN-4-YL-IMIDAZO[4,5-C]QUINOLIN-8-YL)-2-PYRIDYL]OXY]PROPAN-1-AMINE OXIDE AS ATM (ATAXIA TELANGIECTASIA MUTATED) KINASE MODULATOR FOR TREATING CANCER

FIELD

5 This specification relates to *N,N*-dimethyl-3-[[5-(3-methyl-2-oxo-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-8-yl)-2-pyridyl]oxy]propan-1-amine oxide and pharmaceutically acceptable salts thereof. This compound selectively modulates ataxia telangiectasia mutated (“ATM”) kinase, and the specification therefore also relates to the use of *N,N*-dimethyl-3-[[5-(3-methyl-2-oxo-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-8-yl)-2-pyridyl]oxy]propan-1-amine
10 oxide and pharmaceutically acceptable salts thereof to treat or prevent ATM mediated disease, including cancer. The specification further relates to pharmaceutical compositions comprising *N,N*-dimethyl-3-[[5-(3-methyl-2-oxo-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-8-yl)-2-pyridyl]oxy]propan-1-amine
15 oxide and pharmaceutically acceptable salts thereof and the use of such compositions in therapy; kits comprising *N,N*-dimethyl-3-[[5-(3-methyl-2-oxo-1-tetrahydropyran-4-yl-imidazo[4,5-c]quinolin-8-yl)-2-pyridyl]oxy]propan-1-amine oxide and pharmaceutically acceptable salts thereof; and methods of manufacture of such compounds and salts.

20

BACKGROUND

ATM kinase is a serine threonine kinase originally identified as the product of the gene mutated in ataxia telangiectasia. Ataxia telangiectasia is located on
25 human chromosome 11q22-23 and codes for a large protein of about 350 kDa, which is characterized by the presence of a phosphatidylinositol (“PI”) 3-kinase-like serine/threonine kinase domain flanked by FRAP-ATM-TRRAP and FATC domains which modulate ATM kinase activity and function. ATM kinase has been identified as a major player of the DNA damage response elicited by double strand
30 breaks. It primarily functions in S/G2/M cell cycle transitions and at collapsed replication forks to initiate cell cycle checkpoints, chromatin modification, HR

repair and pro-survival signalling cascades in order to maintain cell integrity after DNA damage (Lavin, M. F.; *Rev. Mol. Cell Biol.* **2008**, 759-769).

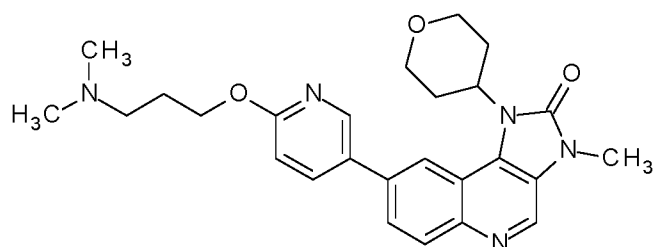
ATM kinase signalling can be broadly divided into two categories: a canonical pathway, which signals together with the Mre11-Rad50-NBS1 complex from double strand breaks and activates the DNA damage checkpoint, and several
5 non-canonical modes of activation, which are activated by other forms of cellular stress (Cremona *et al.*, *Oncogene* **2013**, 3351-3360).

ATM kinase is rapidly and robustly activated in response to double strand breaks and is reportedly able to phosphorylate in excess of 800 substrates
10 (Matsuoka *et al.*, *Science* **2007**, 1160-1166), coordinating multiple stress response pathways (Kurz and Lees Miller, *DNA Repair* **2004**, 889-900). ATM kinase is present predominantly in the nucleus of the cell in an inactive homodimeric form but autophosphorylates itself on Ser1981 upon sensing a DNA double strand break (canonical pathway), leading to dissociation to a monomer with full kinase activity
15 (Bakkenist *et al.*, *Nature* **2003**, 499-506). This is a critical activation event, and ATM phospho-Ser1981 is therefore both a direct pharmacodynamic and patient selection biomarker for tumour pathway dependency.

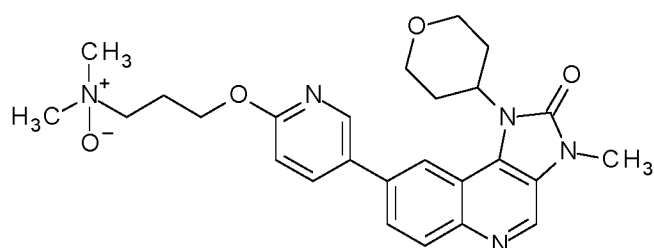
ATM kinase responds to direct double strand breaks caused by common anti-cancer treatments such as ionising radiation and topoisomerase-II inhibitors
20 (doxorubicin, etoposide) but also to topoisomerase-I inhibitors (for example irinotecan and topotecan) *via* single strand break to double strand break conversion during replication. ATM kinase inhibition can potentiate the activity of any these agents, and as a result ATM kinase inhibitors are expected to be of use in the treatment of cancer.

25 WO2015/170081 discloses various compounds which selectively inhibit ATM kinase. Among the compounds specifically described in WO2015/170081 is 8-[6-(3-dimethylaminopropoxy)pyridin-3-yl]-3-methyl-1-(oxan-4-yl)imidazo[5,4-c]quinolin-2-one, a compound having the structure:

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It has been found that when 8-[6-(3-Dimethylaminopropoxy)pyridin-3-yl]-3-methyl-1-(oxan-4-yl)imidazo[5,4-c]quinolin-2-one is metabolised an *N*-oxide metabolite of Formula **(I)** is produced:



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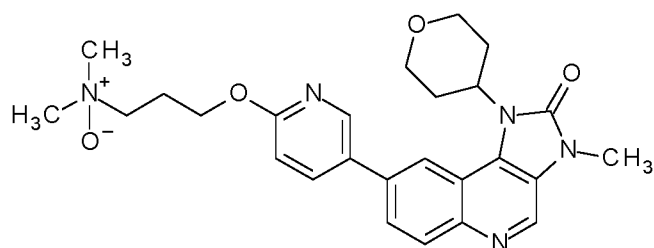
(I)

This *N*-oxide has surprisingly also been found to be a selective inhibitor of ATM kinase, and as such has potential applications in therapy, for example in the treatment of cancer.

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SUMMARY

This specification describes, in part, a compound of Formula **(I)**:



15

(I)

or a pharmaceutically acceptable salt thereof.

This specification also describes, in part, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in therapy.

This specification also describes, in part, a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

This specification also describes, in part, the use of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a
5 medicament for the treatment of cancer.

This specification also describes, in part, a method of treating cancer in a warm blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof.

10 This specification also describes, in part, a pharmaceutical composition which comprises a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

This specification also describes, in part, a pharmaceutical composition which comprises a compound of Formula **(I)**, or a pharmaceutically acceptable salt
15 thereof, and at least one pharmaceutically acceptable excipient, for use in therapy.

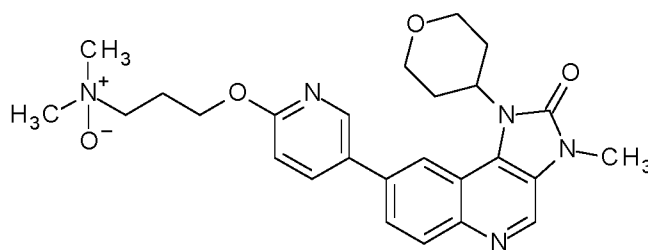
This specification also describes, in part, a pharmaceutical composition which comprises a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, for use in the treatment of cancer.

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ILLUSTRATIVE EMBODIMENTS

Many embodiments are detailed in this specification and will be apparent to a reader skilled in the art. The embodiments are not to be interpreted as being
25 limiting.

In the first embodiment there is provided a compound of Formula **(I)**:



(I)

or a pharmaceutically acceptable salt thereof.

The term “pharmaceutically acceptable” is used to specify that an object (for example a salt, dosage form or excipient) is suitable for use in patients. An example list of pharmaceutically acceptable salts can be found in the *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, P. H. Stahl and C. G. Wermuth, editors, Weinheim/zürich: Wiley-VCH/VHCA, 2002. A suitable pharmaceutically acceptable salt of a compound of Formula (I) is, for example, an acid-addition salt. An acid addition salt of a compound of Formula (I) may be formed by bringing the compound into contact with a suitable inorganic or organic acid under conditions known to the skilled person. An acid addition salt may for example be formed using an inorganic acid selected from hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid. An acid addition salt may also be formed using an organic acid selected from trifluoroacetic acid, citric acid, maleic acid, oxalic acid, acetic acid, formic acid, benzoic acid, fumaric acid, succinic acid, tartaric acid, lactic acid, pyruvic acid, methanesulfonic acid, benzenesulfonic acid and *para*-toluenesulfonic acid.

Therefore, in one embodiment there is provided a compound of Formula (I) or a pharmaceutically acceptable salt thereof, where the pharmaceutically acceptable salt is a hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, trifluoroacetic acid, citric acid, maleic acid, oxalic acid, acetic acid, formic acid, benzoic acid, fumaric acid, succinic acid, tartaric acid, lactic acid, pyruvic acid, methanesulfonic acid, benzenesulfonic acid or *para*-toluenesulfonic acid salt. In one embodiment there is provided a compound of Formula (I) or a pharmaceutically acceptable salt thereof, where the pharmaceutically acceptable salt is a methanesulfonic acid salt. In one embodiment there is provided a compound of Formula (I) or a pharmaceutically acceptable salt thereof, where the pharmaceutically acceptable salt is a *mono*-methanesulfonic acid salt, *i.e.* the stoichiometry of the compound of the compound of Formula (I) to methanesulfonic acid is 1:1.

Compounds and salts described in this specification may exist in solvated forms and unsolvated forms. For example, a solvated form may be a hydrated form, such as a hemi-hydrate, a mono-hydrate, a di-hydrate, a tri-hydrate or an alternative

quantity thereof. The invention encompasses all such solvated and unsolvated forms of compounds of Formula **(I)**, particularly to the extent that such forms possess ATM kinase inhibitory activity, as for example measured using the tests described herein.

5 Atoms of the compounds and salts described in this specification may exist as their isotopes. The invention encompasses all compounds of Formula **(I)** where an atom is replaced by one or more of its isotopes (for example a compound of Formula **(I)** where one or more carbon atom is an ^{11}C or ^{13}C carbon isotope, or where one or more hydrogen atoms is a ^2H or ^3H isotope).

10 Compounds and salts described in this specification may exist as a mixture of tautomers. "Tautomers" are structural isomers that exist in equilibrium resulting from the migration of a hydrogen atom. The invention includes all tautomers of compounds of Formula **(I)** particularly to the extent that such tautomers possess ATM kinase inhibitory activity.

15 In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, where the compound is in isolated form.

A compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof in an "isolated form" is one which is substantially free of other components, for example organic components found in a living organism.

20 In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, where the compound has been produced *ex-vivo*.

"*Ex-vivo*" means outside a living organism, for example a human patient being treated for cancer.

25 In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, where the compound has been produced by organic synthesis.

"Organic synthesis" means the execution of synthetic reactions in a laboratory or manufacturing setting to obtain a product..

30 As a result of their ATM kinase inhibitory activity, the compound of Formula **(I)**, and pharmaceutically acceptable salts thereof are expected to be useful

in therapy, for example in the treatment of diseases or medical conditions mediated at least in part by ATM kinase, including cancer.

Where “cancer” is mentioned, this includes both non-metastatic cancer and also metastatic cancer, such that treating cancer involves treatment of both primary
5 tumours and also tumour metastases.

“ATM kinase inhibitory activity” refers to a decrease in the activity of ATM kinase as a direct or indirect response to the presence of a compound of Formula (I), or pharmaceutically acceptable salt thereof, relative to the activity of ATM kinase in the absence of a compound of Formula (I), or pharmaceutically
10 acceptable salt thereof. Such a decrease in activity may be due to the direct interaction of the compound of Formula (I), or pharmaceutically acceptable salt thereof with ATM kinase, or due to the interaction of the compound of Formula (I), or pharmaceutically acceptable salt thereof with one or more other factors that in turn affect ATM kinase activity. For example, the compound of Formula (I), or
15 pharmaceutically acceptable salt thereof may decrease ATM kinase by directly binding to the ATM kinase, by causing (directly or indirectly) another factor to decrease ATM kinase activity, or by (directly or indirectly) decreasing the amount of ATM kinase present in the cell or organism.

The term “therapy” is intended to have its normal meaning of dealing with a
20 disease in order to entirely or partially relieve one, some or all of its symptoms, or to correct or compensate for the underlying pathology. The term “therapy” also includes “prophylaxis” unless there are specific indications to the contrary. The terms “therapeutic” and “therapeutically” should be interpreted in a corresponding manner.

25 The term “prophylaxis” is intended to have its normal meaning and includes primary prophylaxis to prevent the development of the disease and secondary prophylaxis whereby the disease has already developed and the patient is temporarily or permanently protected against exacerbation or worsening of the disease or the development of new symptoms associated with the disease.

30 The term “treatment” is used synonymously with “therapy”. Similarly the term “treat” can be regarded as “applying therapy” where “therapy” is as defined herein.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in therapy.

In one embodiment there is provided the use of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament.

5 In one embodiment there is provided the use of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, where the medicament is manufactured *ex-vivo*.

In any embodiment where the manufacture of a medicament is mentioned in a general sense, a further embodiment exists where the medicament is
10 manufactured *ex-vivo*.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease mediated by ATM kinase.

In one embodiment there is provided a compound of Formula **(I)**, or a
15 pharmaceutically acceptable salt thereof, for use in the treatment of a disease mediated by ATM kinase, where the disease mediated by ATM kinase is cancer.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease mediated by ATM kinase, where the disease mediated by ATM kinase is colorectal
20 cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer or non-small cell lung cancer.

In one embodiment there is provided a compound of Formula **(I)**, or a
25 pharmaceutically acceptable salt thereof, for use in the treatment of a disease mediated by ATM kinase, where the disease mediated by ATM kinase is colorectal cancer.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer.

30 In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma,

chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer or non-small cell lung cancer.

In one embodiment there is provided a compound of Formula (I), or a
5 pharmaceutically acceptable salt thereof, for use in the treatment of colorectal cancer.

In one embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of Huntingdon's disease.

10 In one embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use as a neuroprotective agent.

A "neuroprotective agent" is an agent that preserves neuronal structure and/or function.

In one embodiment there is provided the use of a compound of Formula (I),
15 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by ATM kinase.

In one embodiment there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by ATM kinase, where the medicament is
20 manufactured *ex-vivo*.

In one embodiment there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by ATM kinase, where the disease mediated by ATM kinase is cancer.

25 In one embodiment there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by ATM kinase, where the disease mediated by ATM kinase is colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid
30 leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer and non-small cell lung cancer.

In one embodiment there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by ATM kinase, where the disease mediated by ATM kinase is colorectal cancer.

5 In one embodiment there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer.

In one embodiment there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament
10 for the treatment of cancer, where the medicament is manufactured *ex-vivo*.

In one embodiment there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid
15 leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer or non-small cell lung cancer.

In one embodiment there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of colorectal cancer.

20 In one embodiment there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of Huntington's disease.

In one embodiment there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament
25 for use as a neuroprotective agent.

In one embodiment there is provided a method of treating a disease in which inhibition of ATM kinase is beneficial in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula (I), or a
30 pharmaceutically acceptable salt thereof.

The term "therapeutically effective amount" refers to an amount of a compound of Formula (I) as described in any of the embodiments herein which is

effective to provide “therapy” in a subject, or to “treat” a disease or disorder in a subject. In the case of cancer, the therapeutically effective amount may cause any of the changes observable or measurable in a subject as described in the definitions of “therapy”, “treatment” and “prophylaxis” above. For example, the effective
5 amount can reduce the number of cancer or tumour cells; reduce the overall tumour size; inhibit or stop tumour cell infiltration into peripheral organs including, for example, the soft tissue and bone; inhibit and stop tumour metastasis; inhibit and stop tumour growth; relieve to some extent one or more of the symptoms associated with the cancer; reduce morbidity and mortality; improve quality of life; or a
10 combination of such effects. An effective amount may be an amount sufficient to decrease the symptoms of a disease responsive to inhibition of ATM kinase activity. For cancer therapy, efficacy *in-vivo* can, for example, be measured by assessing the duration of survival, time to disease progression (TTP), the response rates (RR), duration of response, and/or quality of life. As recognized by those
15 skilled in the art, effective amounts may vary depending on route of administration, excipient usage, and co-usage with other agents. For example, where a combination therapy is used, the amount of the compound of formula **(I)** or pharmaceutically acceptable salt described in this specification and the amount of the other pharmaceutically active agent(s) are, when combined, jointly effective to treat a
20 targeted disorder in the animal patient. In this context, the combined amounts are in a “therapeutically effective amount” if they are, when combined, sufficient to decrease the symptoms of a disease responsive to inhibition of ATM activity as described above. Typically, such amounts may be determined by one skilled in the art by, for example, starting with the dosage range described in this specification
25 for the compound of formula **(I)** or pharmaceutically acceptable salt thereof and an approved or otherwise published dosage range(s) of the other pharmaceutically active compound(s).

“Warm-blooded animals” include, for example, humans.

In one embodiment there is provided a method of treating a disease in which
30 inhibition of ATM kinase is beneficial in a warm-blooded animal in need of such treatment, which comprises directly administering to said warm-blooded animal a

therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof.

“Directly administering” means that the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof is dosed to the patient directly rather than being indirectly dosed by administration of a precursor molecule. For any embodiment where administering a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof to a warm blooded animal is mentioned in a general sense, a further embodiment is provided where said compound or salt is directly administered.

In one embodiment there is provided a method of treating a disease in which inhibition of ATM kinase is beneficial in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and where the disease in which inhibition of ATM kinase is beneficial is cancer.

In one embodiment there is provided a method of treating a disease in which inhibition of ATM kinase is beneficial in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and where the disease in which inhibition of ATM kinase is beneficial is colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer or non-small cell lung cancer.

In one embodiment there is provided a method of treating a disease in which inhibition of ATM kinase is beneficial in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and where the disease in which inhibition of ATM kinase is beneficial is colorectal cancer.

In one embodiment there is provided a method of treating a disease in which inhibition of ATM kinase is beneficial in a warm-blooded animal in need of such

treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and where the disease in which inhibition of ATM kinase is beneficial is Huntingdon's disease.

5 In one embodiment there is provided a method of treating cancer in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

 In one embodiment there is provided a method of treating colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer or non-small cell lung cancer in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically
15 effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

 In one embodiment there is provided a method of treating colorectal cancer in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a
20 compound of Formula (I), or a pharmaceutically acceptable salt thereof.

 In one embodiment there is provided a method of treating Huntingdon's disease in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

25 In one embodiment there is provided a method of effecting neuroprotection in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

 In one embodiment there is provided a method of treating cancer in a
30 warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In one embodiment, said

cancer is selected from colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer and non-small cell lung cancer. In one embodiment, said cancer is selected from colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, head and neck squamous cell carcinoma and lung cancer. In one embodiment, said cancer is colorectal cancer.

In any embodiment where cancer is mentioned in a general sense, said cancer may be selected from colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer and non-small cell lung cancer.

In any embodiment where “cancer” is mentioned in a general sense the following embodiments may apply:

- In one embodiment the cancer is colorectal cancer.
- In one embodiment the cancer is glioblastoma.
- In one embodiment the cancer is gastric cancer.
- In one embodiment the cancer is oesophageal cancer.
- In one embodiment the cancer is ovarian cancer.
- In one embodiment the cancer is endometrial cancer.
- In one embodiment the cancer is cervical cancer.
- In one embodiment the cancer is diffuse large B-cell lymphoma.
- In one embodiment the cancer is chronic lymphocytic leukaemia.
- In one embodiment the cancer is acute myeloid leukaemia.
- In one embodiment the cancer is head and neck squamous cell carcinoma.
- In one embodiment the cancer is breast cancer. In one embodiment the cancer is triple negative breast cancer.

“Triple negative breast cancer” is any breast cancer that does not test positive for the oestrogen receptor, progesterone receptor and Her2/neu. Test methods to determine a positive test with respect to each of these receptors are well known in the art.

In one embodiment the cancer is hepatocellular carcinoma.

In one embodiment the cancer is lung cancer. In one embodiment the lung cancer is small cell lung cancer. In one embodiment the lung cancer is non-small cell lung cancer.

5 In one embodiment the cancer is metastatic cancer. In one embodiment the metastatic cancer comprises metastases of the central nervous system. In one embodiment the metastases of the central nervous system comprise brain metastases. In one embodiment the metastases of the central nervous system comprise leptomeningeal metastases.

10 “Leptomeningeal metastases” occur when cancer spreads to the meninges, the layers of tissue that cover the brain and the spinal cord. Metastases can spread to the meninges through the blood or they can travel from brain metastases, carried by the cerebrospinal fluid (CSF) that flows through the meninges. In one embodiment the cancer is non-metastatic cancer.

15 The anti-cancer treatment described in this specification may be useful as a sole therapy, or may involve, in addition to administration of the compound of Formula (I), conventional surgery, radiotherapy or chemotherapy; or a combination of such additional therapies. Such conventional surgery, radiotherapy or chemotherapy may be administered simultaneously, sequentially or separately to
20 treatment with the compound of Formula (I).

Radiotherapy may include one or more of the following categories of therapy:

- i. External radiation therapy using electromagnetic radiation, and intraoperative radiation therapy using electromagnetic radiation;
- 25 ii. Internal radiation therapy or brachytherapy; including interstitial radiation therapy or intraluminal radiation therapy;
- iii. Systemic radiation therapy, including iodine 131 and strontium 89; or
- iv. Proton therapy.

30 In one embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in combination with radiotherapy. In one embodiment the

radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iv) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of glioblastoma, lung cancer (for example small cell lung cancer or non-small cell lung cancer), breast cancer (for example triple negative breast cancer), head and neck squamous cell carcinoma, oesophageal cancer, cervical cancer or endometrial cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered in combination with radiotherapy. In one embodiment the radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iv) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of glioblastoma, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered in combination with radiotherapy. In one embodiment the radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iv) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of metastatic cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered in combination with radiotherapy. In one embodiment the radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iv) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of metastases of the central nervous system, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered in combination with radiotherapy. In one embodiment the radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iv) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of leptomeningeal metastases, where the compound of Formula **(I)**, or a pharmaceutically acceptable

salt thereof, is administered in combination with radiotherapy. In one embodiment the radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iv) above.

In one embodiment there is provided a compound of Formula **(I)**, or a
5 pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with radiotherapy. In one embodiment the radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iv) above.

10 In one embodiment there is provided a method of treating cancer in a warm-blooded animal who is in need of such treatment, which comprises administering to said warm-blooded animal a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof and radiotherapy, wherein the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and radiotherapy are jointly effective in
15 producing an anti-cancer effect. In one embodiment the cancer is selected from glioblastoma, lung cancer (for example small cell lung cancer or non-small cell lung cancer), breast cancer (for example triple negative breast cancer), head and neck squamous cell carcinoma, oesophageal cancer, cervical cancer and endometrial cancer. In one embodiment the cancer is glioblastoma. In one
20 embodiment, the cancer is metastatic cancer. In one embodiment the metastatic cancer comprises metastases of the central nervous system. In one embodiment the metastases of the central nervous system comprise brain metastases. In one embodiment the metastases of the central nervous system comprise leptomeningeal metastases. In any embodiment the radiotherapy is selected from one or more of the
25 categories of radiotherapy listed under points (i) - (iv) above.

In one embodiment there is provided a method of treating cancer in a warm-blooded animal who is in need of such treatment, which comprises administering to said warm-blooded animal a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof and simultaneously, separately or sequentially administering
30 radiotherapy, wherein the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and radiotherapy are jointly effective in producing an anti-cancer effect. In one embodiment the cancer is glioblastoma. In one embodiment,

the cancer is metastatic cancer. In one embodiment the metastatic cancer comprises metastases of the central nervous system. In one embodiment the metastases of the central nervous system comprise brain metastases. In one embodiment the metastases of the central nervous system comprise leptomeningeal metastases. In
5 any embodiment the radiotherapy is selected from one or more of the categories of radiotherapy listed under points (i) - (iv) above.

Chemotherapy may include one or more of the following categories of anti-tumour substance:

- i. Antineoplastic agents and combinations thereof, such as DNA alkylating
10 agents (for example cisplatin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustards like ifosfamide, bendamustine, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas like carmustine); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside,
15 and hydroxyurea); anti-tumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, liposomal doxorubicin, pirarubicin, daunomycin, valrubicin, epirubicin, idarubicin, mitomycin-C, dactinomycin, amrubicin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids
20 like taxol and taxotere and polokine inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, irinotecan, topotecan and camptothecin); inhibitors of DNA repair mechanisms such as CHK kinase; DNA-dependent protein kinase inhibitors; inhibitors of poly (ADP-ribose) polymerase (PARP inhibitors,
25 including olaparib); and Hsp90 inhibitors such as tanespimycin and retaspimycin, inhibitors of ATR kinase (such as AZD6738); and inhibitors of WEE1 kinase (such as AZD1775/MK-1775);
- ii. Antiangiogenic agents such as those that inhibit the effects of vascular
30 endothelial growth factor, for example the anti-vascular endothelial cell growth factor antibody bevacizumab and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib (ZD6474), sorafenib, vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW

- 786034) and cediranib (AZD2171); compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354; and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiostatin), or inhibitors of angiopoietins and their receptors (Tie-1 and Tie-2), inhibitors of PLGF, inhibitors of delta-like ligand (DLL-4);
- 5 iii. Immunotherapy approaches, including for example *ex-vivo* and *in-vivo* approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or
- 10 granulocyte-macrophage colony stimulating factor; approaches to decrease T-cell anergy or regulatory T-cell function; approaches that enhance T-cell responses to tumours, such as blocking antibodies to CTLA4 (for example ipilimumab and tremelimumab), B7H1, PD-1 (for example BMS-936558 or AMP-514), PD-L1 (for example MEDI4736) and agonist antibodies to
- 15 CD137; approaches using transfected immune cells such as cytokine-transfected dendritic cells; approaches using cytokine-transfected tumour cell lines, approaches using antibodies to tumour associated antigens, and antibodies that deplete target cell types (e.g., unconjugated anti-CD20 antibodies such as Rituximab, radiolabeled anti-CD20 antibodies
- 20 Bexxar and Zevalin, and anti-CD54 antibody Campath); approaches using anti-idiotypic antibodies; approaches that enhance Natural Killer cell function; and approaches that utilize antibody-toxin conjugates (e.g. anti-CD33 antibody Mylotarg); immunotoxins such as moxetumumab pasudotox; agonists of toll-like receptor 7 or toll-like receptor 9;
- 25 iv. Efficacy enhancers, such as leucovorin.

In one embodiment there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is administered in combination with at least one additional anti-tumour substance. In

30 one embodiment there is one additional anti-tumour substance. In one embodiment there are two additional anti-tumour substances. In one embodiment there are three or more additional anti-tumour substances. In any embodiment the additional anti-

tumour substance is selected from one or more of the anti-tumour substances listed under points (i) - (iv) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where
5 the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance. In one embodiment there is one additional anti-tumour substance. In one embodiment there are two additional anti-tumour substances. In one embodiment there are three or more additional anti-tumour substances. In any
10 embodiment the additional anti-tumour substance is selected from one or more of the anti-tumour substances listed under points (i) - (iv) above.

In one embodiment there is provided a method of treating cancer in a warm-blooded animal who is in need of such treatment, which comprises administering to said warm-blooded animal a compound of Formula **(I)**, or a pharmaceutically
15 acceptable salt thereof and at least one additional anti-tumour substance, wherein the amounts of the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and the additional anti-tumour substance are jointly effective in producing an anti-cancer effect. In any embodiment the additional anti-tumour substance is selected from one or more of the anti-tumour substances listed under points (i) - (iv)
20 above.

In one embodiment there is provided a method of treating cancer in a warm-blooded animal who is in need of such treatment, which comprises administering to said warm-blooded animal a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and simultaneously, separately or sequentially administering
25 at least one additional anti-tumour substance to said warm-blooded animal, wherein the amounts of the compound of Formula **(I)**, or pharmaceutically acceptable salt thereof, and the additional anti-tumour substance are jointly effective in producing an anti-cancer effect. In any embodiment the additional anti-tumour substance is selected from one or more of the anti-tumour substances listed under points (i) - (iv)
30 above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one anti-neoplastic agent for

use in the treatment of cancer. In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered in combination with at least one anti-neoplastic agent.

5 In one embodiment the anti-neoplastic agent is selected from the list of antineoplastic agents in point (i) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one anti-neoplastic agent for use in the simultaneous, separate or sequential treatment of cancer. In one
10 embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one anti-neoplastic agent. In one embodiment the antineoplastic agent is selected from the list of antineoplastic
15 agents in point (i) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional
20 anti-tumour substance selected from cisplatin, oxaliplatin, carboplatin, valrubicin, idarubicin, doxorubicin, pirarubicin, irinotecan, topotecan, amrubicin, epirubicin, etoposide, mitomycin, bendamustine, chlorambucil, cyclophosphamide, ifosfamide, carmustine, melphalan, bleomycin, olaparib, MEDI4736, AZD1775 and AZD6738.

In one embodiment there is provided a compound of Formula **(I)**, or a
25 pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from cisplatin, oxaliplatin, carboplatin, doxorubicin, pirarubicin, irinotecan, topotecan, amrubicin, epirubicin, etoposide, mitomycin,
30 bendamustine, chlorambucil, cyclophosphamide, ifosfamide, carmustine, melphalan, bleomycin, olaparib, AZD1775 and AZD6738.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional
5 anti-tumour substance selected from doxorubicin, irinotecan, topotecan, etoposide, mitomycin, bendamustine, chlorambucil, cyclophosphamide, ifosfamide, carmustine, melphalan, bleomycin and olaparib.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where
10 the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from doxorubicin, irinotecan, topotecan, etoposide, mitomycin, bendamustine, chlorambucil, cyclophosphamide, ifosfamide, carmustine, melphalan and bleomycin.

15 In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from doxorubicin, pirarubicin, amrubicin and
20 epirubicin.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of acute myeloid leukaemia, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with at least
25 one additional anti-tumour substance selected from doxorubicin, pirarubicin, amrubicin and epirubicin.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of breast cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof,
30 is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from doxorubicin, pirarubicin, amrubicin and epirubicin.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of triple negative breast cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially
5 with at least one additional anti-tumour substance selected from doxorubicin, pirarubicin, amrubicin and epirubicin.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of hepatocellular carcinoma, where the compound of Formula **(I)**, or a pharmaceutically acceptable
10 salt thereof, is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from doxorubicin, pirarubicin, amrubicin and epirubicin.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where
15 the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with irinotecan.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of colorectal cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt
20 thereof, is administered simultaneously, separately or sequentially with irinotecan.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of colorectal cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt
thereof, is administered simultaneously, separately or sequentially with FOLFIRI.

25 FOLFIRI is a dosage regime involving a combination of leucovorin, 5-fluorouracil and irinotecan.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is
30 administered simultaneously, separately or sequentially with olaparib.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of gastric cancer,

where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with olaparib.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where
5 the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with topotecan.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of lung cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof,
10 is administered simultaneously, separately or sequentially with topotecan.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of small cell lung cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with topotecan.

15 In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with immunotherapy. In one embodiment the immunotherapy is one or more of the agents listed under point
20 (iii) above.

In one embodiment there is provided a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, where the compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, is administered simultaneously, separately or sequentially with an anti-PD-L1
25 antibody (for example MEDI4736).

According to a further embodiment there is provided a kit comprising:

- a) A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, in a first unit dosage form;
- b) A further additional anti-tumour substance in a further unit dosage form;
- 30 c) Container means for containing said first and further unit dosage forms; and optionally
- d) Instructions for use. In one embodiment the anti-tumour substance

comprises an anti-neoplastic agent.

In any embodiment where an anti-neoplastic agent is mentioned, the anti-neoplastic agent is one or more of the agents listed under point (i) above.

The compounds of Formula **(I)**, and pharmaceutically acceptable salts
5 thereof, may be administered as pharmaceutical compositions, comprising one or more pharmaceutically acceptable excipients.

Therefore, in one embodiment there is provided a pharmaceutical composition comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

10 The excipient(s) selected for inclusion in a particular composition will depend on factors such as the mode of administration and the form of the composition provided. Suitable pharmaceutically acceptable excipients are well known to persons skilled in the art and are described, for example, in the *Handbook of Pharmaceutical Excipients*, Sixth edition, Pharmaceutical Press, edited by Rowe,
15 Ray C; Sheskey, Paul J; Quinn, Marian. Pharmaceutically acceptable excipients may function as, for example, adjuvants, diluents, carriers, stabilisers, flavourings, colorants, fillers, binders, disintegrants, lubricants, glidants, thickening agents and coating agents. As persons skilled in the art will appreciate, certain pharmaceutically acceptable excipients may serve more than one function and may
20 serve alternative functions depending on how much of the excipient is present in the composition and what other excipients are present in the composition.

The pharmaceutical compositions may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for
25 example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing), or as a
30 suppository for rectal dosing. The compositions may be obtained by conventional procedures well known in the art. Compositions intended for oral use may contain

additional components, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The compound of Formula **(I)** will normally be administered to a warm-blooded animal at a unit dose within the range 2.5-5000 mg/m² body area of the animal, or approximately 0.05-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 0.1-250 mg of active ingredient. The daily dose will necessarily be varied depending upon the host treated, the particular route of administration, any therapies being co-administered, and the severity of the illness being treated. Accordingly the practitioner who is treating any particular patient may determine the optimum dosage.

The pharmaceutical compositions described herein comprise compounds of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and are therefore expected to be useful in therapy.

As such, in one embodiment there is provided a pharmaceutical composition comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, for use in therapy.

In one embodiment there is provided a pharmaceutical composition comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, for use in the treatment of a disease in which inhibition of ATM kinase is beneficial.

In one embodiment there is provided a pharmaceutical composition comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, for use in the treatment of cancer,

In one embodiment there is provided a pharmaceutical composition comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, for use in the treatment of a cancer in which inhibition of ATM kinase is beneficial.

In one embodiment there is provided a pharmaceutical composition comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient for use in the

treatment of colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer or non-small cell lung cancer.

5 In one embodiment there is provided a pharmaceutical composition for use in therapy, comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

 In one embodiment there is provided a pharmaceutical composition for use in the treatment of a disease in which inhibition of ATM kinase is beneficial,
10 comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

 In one embodiment there is provided a pharmaceutical composition for use in the treatment of cancer, comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically
15 acceptable excipient.

 In one embodiment there is provided a pharmaceutical composition for use in the treatment of a cancer in which inhibition of ATM kinase is beneficial, comprising a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

20 In one embodiment there is provided a pharmaceutical composition for use in the treatment of colorectal cancer, glioblastoma, gastric cancer, ovarian cancer, diffuse large B-cell lymphoma, chronic lymphocytic leukaemia, acute myeloid leukaemia, head and neck squamous cell carcinoma, breast cancer, hepatocellular carcinoma, small cell lung cancer or non-small cell lung cancer, comprising a
25 compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

EXAMPLES

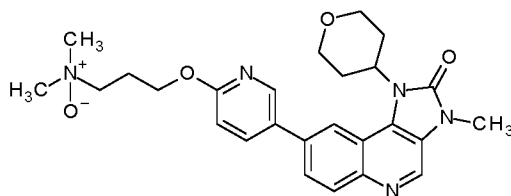
During the following experimental descriptions, and unless otherwise stated, generally:

- 5 i. Evaporations were carried out by rotary evaporation or utilising Genevac equipment *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;
- ii. Flash chromatography purifications were performed on an automated Armen Glider Flash: Spot II Ultimate (Armen Instrument, Saint-Ave,
10 France) or automated Presearch combiflash companions using prepacked Merck normal phase Si60 silica cartridges (granulometry: 15-40 or 40-63µm) obtained from Merck, Darmstad, Germany, silicycle silica cartridges or gracesolv silica cartridges;
- iii. Yields, where present, are not necessarily the maximum attainable;
- 15 iv. Structures of end-products of Formula **(I)** were confirmed by nuclear magnetic resonance (NMR) spectroscopy, with NMR chemical shift values measured on the delta scale. Proton magnetic resonance spectra were determined using a Bruker advance 700 (700MHz), Bruker Avance 500 (500 MHz), Bruker 400 (400 MHz) or Bruker 300 (300 MHz) instrument;
20 ¹⁹F NMR were determined at 282 MHz or 376 MHz; ¹³C NMR were determined at 75 MHz or 100 MHz; measurements were taken at around 20 - 30°C unless otherwise specified; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublet of doublet; dt, doublet of triplets; br s,
25 broad signal;
- v. End-products of Formula **(I)** were also characterised by mass spectroscopy following liquid chromatography (LCMS); LCMS was carried out using an Waters Alliance HT (2790 & 2795) fitted with a Waters ZQ ESCi or ZMD ESCi mass spectrometer and an X Bridge 5µm C-18 column (2.1 x 50 mm)
30 at a flow rate of 2.4 mL/min, using a solvent system of 95% A + 5% C to 95% B + 5% C over 4 minutes, where A = water, B = methanol, C = 1:1 methanol:water (containing 0.2% ammonium carbonate); or by using a

- Shimadzu UFLC or UHPLC coupled with DAD detector, ELSD detector and 2020 EV mass spectrometer (or equivalent) fitted with a Phenomenex Gemini-NX C18 3.0x50 mm, 3.0 μ M column or equivalent (basic conditions) or a Shim pack XR – ODS 3.0 x 50 mm, 2.2 μ M column or Waters BEH C18 2.1 x 50 mm, 1.7 μ M column or equivalent using a solvent system of 95% D + 5% E to 95% E + 5% D over 4 minutes, where D = water (containing 0.05% TFA), E = Acetonitrile (containing 0.05% TFA) (acidic conditions) or a solvent system of 90% F + 10% G to 95% G + 5% F over 4 minutes, where F = water (containing 6.5 mM ammonium hydrogen carbonate and adjusted to pH10 by addition of ammonia), G = Acetonitrile (basic conditions);
- vi. The following abbreviations have been used: KRED = (Ketoreductase)-P1-H10; BVMO = (Baeyer Villiger Monooxygenase)-P1-D08 and
- vii. IUPAC names were generated using either ELN, a proprietary program or “Canvas” or “IBIS”, AstraZeneca proprietary programs.

Example 1

***N,N*-Dimethyl-3-[[5-(3-methyl-2-oxo-1-tetrahydropyran-4-yl)imidazo[4,5-c]quinolin-8-yl)-2-pyridyl]oxy]propan-1-amine oxide**



- A 100 mL jacketed vessel was charged with 8-[6-(3-dimethylaminopropoxy)pyridin-3-yl]-3-methyl-1-(oxan-4-yl)imidazo[5,4-c]quinolin-2-one (1.22 g, 2.64 mmol). A solution of dibasic potassium phosphate (1.74 g, 9.99 mmol,) in water (100 mL) was prepared and the pH adjusted to pH 9.0 by the dropwise addition of 2M hydrochloric acid. The vessel was charged with 28 mL of the phosphate buffer solution prepared above followed by 2-propanol (4.8 mL), beta-nicotinamide adenine dinucleotide phosphate disodium salt (0.016 g, 0.020321 mmol), Codexis KRED (32 mg) and Codexis BVMO (292 mg). The reaction mixture was stirred vigorously (400 rpm) at 32°C (jacket temp) with air

passed into the vessel continually using a needle attached to a compressed air supply. After 17 hours further 2-propanol (4.8 mL) was added as well as water (5.0 mL) to replace solvent that had evaporated due to purging the vessel headspace. The reaction mixture was stirred for a further 24 hours before HPLC analysis

5 revealed no further progress of the reaction (~54% conversion). Acetonitrile (61.0 mL) was added to the jacketed vessel, the suspension stirred for 5 minutes and the reaction mixture filtered through a 7 cm diameter split Buchner funnel. The filtrate was concentrated under reduced pressure to give an aqueous residue of ~ 30 mL volume. The pH of this aqueous solution was checked, adjusted to pH 11 with 5M

10 sodium hydroxide and extracted twice with dichloromethane (2 x 24 mL). The combined organic layers were dried over anhydrous sodium sulphate and evaporated under reduced pressure to give unreacted 8-[6-(3-dimethylaminopropoxy)pyridin-3-yl]-3-methyl-1-(oxan-4-yl)imidazo[5,4-c]quinolin-2-one as an off white solid (0.479g). Sodium chloride (~6.0 g) was

15 added to the aqueous layer until saturation was achieved then the aqueous layer extracted twice with 1-butanol (2 x 37 mL). The 1-butanol extracts were dried over anhydrous sodium sulphate and evaporated under reduced pressure to give a white solid (1.31g). The solid was dissolved in chloroform (5 mL) and filtered to remove inorganics. The filtrate was evaporated under reduced pressure to give a 4:1

20 mixture of the desired material with unreacted 8-[6-(3-dimethylaminopropoxy)pyridin-3-yl]-3-methyl-1-(oxan-4-yl)imidazo[5,4-c]quinolin-2-one as a white solid (0.711 g). The white solid was purified by silica gel chromatography, eluting with 100:10:1 DCM:MeOH:cNH₃, to give the desired material as a white solid (0.487g, 39%). *NMR Spectrum*: ¹H NMR (400MHz, CDCl₃) δ 1.95 (2H, m), 2.51 (2H, m), 2.97 (2H, m), 3.28 (6H, s), 3.53 (2H, m), 3.62 (5H, m), 4.26 (2H, dd), 4.54 (2H, t), 5.11 (1H, br s), 6.90 (1H, d), 7.82 (1H, dd), 7.97 (1H, m), 8.24 (1H, d), 8.42 (1H, br s), 8.52 (1H, d), 8.73 (1H, s). *Mass Spectrum*: m/z (ES+)[M+H]⁺ = 478.

25

30 8-[6-(3-Dimethylaminopropoxy)pyridin-3-yl]-3-methyl-1-(oxan-4-yl)imidazo[5,4-c]quinolin-2-one may be prepared as described in WO2015/170081 (see Example 1, page 53 of the description). The contents of WO2015/170081 are herein

incorporated in their entirety.

BIOLOGICAL ASSAYS

5 The following assays were used to measure the effects of the compounds of the present invention: a) ATM cellular potency assay; b) PI3K cellular potency assay; c) mTOR cellular potency assay; d) ATR cellular potency assay. During the description of the assays, generally:

- 10 i. The following abbreviations have been used: 4NQO = 4-Nitroquinoline *N*-oxide; Ab = Antibody; BSA = Bovine Serum Albumin; CO₂ = Carbon Dioxide; DMEM = Dulbecco's Modified Eagle Medium; DMSO = Dimethyl Sulphoxide; EDTA = Ethylenediaminetetraacetic Acid; EGTA = Ethylene Glycol Tetraacetic Acid; ELISA = Enzyme-linked Immunosorbent Assay; EMEM = Eagle's Minimal Essential Medium; FBS = Foetal Bovine Serum; 15 h = Hour(s); HRP = Horseradish Peroxidase; i.p. = intraperitoneal; PBS = Phosphate buffered saline; PBST = Phosphate buffered saline / Tween; TRIS = Tris(Hydroxymethyl)aminomethane; MTS reagent: [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt, and an electron coupling reagent (phenazine 20 methosulfate) PMS; s.c. sub-cutaneously.
- ii. IC₅₀ values were calculated using a smart fitting model in Genedata. The IC₅₀ value was the concentration of test compound that inhibited 50% of biological activity.

25 Assay a): ATM Cellular Potency

Rationale:

Cellular irradiation induces DNA double strand breaks and rapid intermolecular autophosphorylation of serine 1981 that causes dimer dissociation 30 and initiates cellular ATM kinase activity. Most ATM molecules in the cell are rapidly phosphorylated on this site after doses of radiation as low as 0.5 Gy, and

binding of a phosphospecific antibody is detectable after the introduction of only a few DNA double-strand breaks in the cell.

The rationale of the pATM assay is to identify inhibitors of ATM in cells. HT29 cells are incubated with test compounds for 1hr prior to X-ray-irradiation. 1h
5 later the cells are fixed and stained for pATM (Ser1981). The fluorescence is read on the arrayscan imaging platform.

Method details:

HT29 cells (ECACC #85061109) were seeded into 384 well assay plates
10 (Costar #3712) at a density of 3500 cells / well in 40µl EMEM medium containing 1% L glutamine and 10% FBS and allowed to adhere overnight. The following morning compounds of Formula (I) in 100% DMSO were added to assay plates by acoustic dispensing. After 1h incubation at 37°C and 5% CO₂, plates (up to 6 at a time) were irradiated using the X-RAD 320 instrument (PXi) with equivalent to
15 ~600cGy. Plates were returned to the incubator for a further 1h. Then cells were fixed by adding 20µl of 3.7% formaldehyde in PBS solution and incubating for 20 minutes at r.t. before being washed with 50µl/well PBS, using a Biotek EL405 plate washer. Then 20µl of 0.1% Triton X100 in PBS was added and incubated for 20 minutes at r.t., to permeabilise cells. Then the plates were washed once with 50µl /
20 well PBS, using a Biotek EL405 plate washer.

Phospho-ATM Ser1981 antibody (Millipore #MAB3806) was diluted 10000 fold in PBS containing 0.05% polysorbate/Tween and 3% BSA and 20µl was added to each well and incubated over night at r.t. The next morning plates were washed three times with 50µl / well PBS, using a Biotek EL405 plate washer, and then 20µl
25 of secondary Ab solution, containing 500 fold diluted Alexa Fluor® 488 Goat anti-rabbit IgG (Life Technologies, A11001) and 0.002mg/ml Hoeschst dye (Life technologies #H-3570), in PBS containing 0.05% polysorbate/Tween and 3% BSA, was added. After 1h incubation at r.t., the plates were washed three times with 50µl / well PBS, using a Biotek EL405 plate washer, and plates were sealed and kept in
30 PBS at 4°C until read. Plates were read using an ArrayScan VTI instrument, using an XF53 filter with 10X objective. A two laser set up was used to analyse nuclear

staining with Hoeschst (405nm) and secondary antibody staining of pSer1981 (488nm).

Assay b): ATR Cellular Potency

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Rationale:

ATR is a PI 3-kinase-related kinase which phosphorylates multiple substrates on serine or threonine residues in response to DNA damage during or replication blocks. Chk1, a downstream protein kinase of ATR, plays a key role in DNA damage checkpoint control. Activation of Chk1 involves phosphorylation of Ser317 and Ser345 (the latter regarded as the preferential target for phosphorylation/activation by ATR). This was a cell based assay to measure inhibition of ATR kinase, by measuring a decrease in phosphorylation of Chk1 (Ser 345) in HT29 cells, following treatment with compound of Formula (I) and the UV mimetic 4NQO (Sigma #N8141).

15

Method details:

HT29 cells (ECACC #85061109) were seeded into 384 well assay plates (Costar #3712) at a density of 6000 cells / well in 40µl EMEM medium containing 1% L glutamine and 10% FBS and allowed to adhere overnight. The following morning compound of Formula (I) in 100% DMSO were added to assay plates by acoustic dispensing. After 1h incubation at 37°C and 5% CO₂, 40nl of 3mM 4NQO in 100% DMSO was added to all wells by acoustic dispensing, except minimum control wells which were left untreated with 4NQO to generate a null response control. Plates were returned to the incubator for a further 1h. Then cells were fixed by adding 20µl of 3.7% formaldehyde in PBS solution and incubating for 20 mins at r.t. Then 20µl of 0.1% Triton X100 in PBS was added and incubated for 10 minutes at r.t., to permeabilise cells. Then the plates were washed once with 50µl / well PBS, using a Biotek EL405 plate washer.

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Phospho-Chk1 Ser 345 antibody (Cell Signalling Technology #2348) was diluted 150 fold in PBS containing 0.05% polysorbate/Tween and 15µl was added to each well and incubated over night at r.t. The next morning plates were washed

three times with 50µl / well PBS, using a Biotek EL405 plate washer, and then 20µl of secondary Ab solution, containing 500 fold diluted Alexa Fluor 488 Goat anti-rabbit IgG (Molecular Probes #A-11008) and 0.002mg/ml Hoeschst dye (Molecular Probes #H-3570), in PBST, was added. After 2h incubation at r.t., the plates were washed three times with 50µl / well PBS, using a Biotek EL405 plate washer, and plates were then sealed with black plate seals until read. Plates were read using an ArrayScan VTI instrument, using an XF53 filter with 10X objective. A two laser set up was used to analyse nuclear staining with Hoeschst (405nm) and secondary antibody staining of pChk1 (488nm).

Assay c): PI3K Cellular Potency

Rationale:

This assay was used to measure PI3K- α inhibition in cells. PDK1 was identified as the upstream activation loop kinase of protein kinase B (Akt1), which is essential for the activation of PKB. Activation of the lipid kinase phosphoinositide 3 kinase (PI3K) is critical for the activation of PKB by PDK1.

Following ligand stimulation of receptor tyrosine kinases, PI3K is activated, which converts PIP2 to PIP3, which is bound by the PH domain of PDK1 resulting in recruitment of PDK1 to the plasma membrane where it phosphorylates AKT at Thr308 in the activation loop.

The aim of this cell-based mode of action assay is to identify compounds that inhibit PDK activity or recruitment of PDK1 to membrane by inhibiting PI3K activity. Phosphorylation of phospho-Akt (T308) in BT474c cells following treatment with compounds for 2h is a direct measure of PDK1 and indirect measure of PI3K activity.

Method details:

BT474 cells (human breast ductal carcinoma, ATCC HTB-20) were seeded into black 384 well plates (Costar, #3712) at a density of 5600 cells / well in DMEM containing 10% FBS and 1% glutamine and allowed to adhere overnight.

The following morning compounds in 100% DMSO were added to assay plates by acoustic dispensing. After a 2h incubation at 37°C and 5% CO₂, the medium was aspirated and the cells were lysed with a buffer containing 25mM Tris, 3mM EDTA, 3mM EGTA, 50mM sodium fluoride, 2mM Sodium orthovanadate, 5 0.27M sucrose, 10mM β-glycerophosphate, 5mM sodium pyrophosphate, 0.5% Triton X-100 and complete protease inhibitor cocktail tablets (Roche #04 693 116 001, used 1 tab per 50ml lysis buffer).

After 20 minutes, the cell lysates were transferred into ELISA plates (Greiner # 781077) which had been pre-coated with an anti total-AKT antibody in 10 PBS buffer and non-specific binding was blocked with 1% BSA in PBS containing 0.05% Tween 20. Plates were incubated over night at 4°C. The next day the plates were washed with PBS buffer containing 0.05% Tween 20 and further incubated with a mouse monoclonal anti-phospho AKT T308 for 2h. Plates were washed again as above before addition of a horse anti-mouse-HRP conjugated secondary 15 antibody. Following a 2h incubation at r.t., plates were washed and QuantaBlu substrate working solution (Thermo Scientific #15169, prepared according to provider's instructions) was added to each well. The developed fluorescent product was stopped after 60 minutes by addition of Stop solution to the wells. Plates were read using a Tecan Safire plate reader using 325nm excitation and 420nm emission 20 wavelengths respectively. Except where specified, reagents contained in the Path Scan Phospho AKT (Thr308) sandwich ELISA kit from Cell Signalling (#7144) were used in this ELISA assay.

Assay d): mTOR Cellular Potency

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Rationale:

The phospho-AKTser473 cell assay was performed in the MDA-MB-468 cell line, a PTEN null breast adenocarcinoma human cell line. As a consequence of the lack of PTEN, pAKT is constitutively activated which eliminates the 30 requirement for stimulation to induce phosphorylation.

Method details:

MDA-MB-468 cells were cultured in cell media composed of DMEM (Dulbecco's modified Eagle's medium #D6546), 10% (v/v) Foetal Calf Serum and 1% (v/v) L-Glutamine. After harvesting, cells were dispensed into black, 384-well
5 Costar plates (#3712, Corning) to give 1500 cells per well in a total volume of 40µl cell media, and were incubated overnight at 37°C, 90% relative humidity and 5% CO₂ in a rotating incubator. Compounds were then tested by one of two assay protocols A or B:

10 *Protocol A:*

The cell plates were incubated for 2 hours at 37°C before being fixed by the addition of 20µl 3.7% formaldehyde in PBS/A (1.2% final concentration), followed by a 40 minute room temperature incubation, and then a 2x wash with 150µl PBS/A (phosphate buffered saline) using a BioTek ELx406 platewasher. Cells were
15 permeabilised and blocked with 20µl of assay buffer (0.5% Tween 20 in PBS/A + 1% milk powder) for 1h at room temperature, and then washed 1x with 50µl PBS/A. Primary phospho-AKT (Ser473) 736E11 rabbit monoclonal antibody (#3787, Cell Signaling Technology) was diluted 1:500 in assay buffer, 20µl added per well, and plates were incubated at 4°C overnight. Cell plates were washed 3x
20 with 200µl PBS/T (phosphate buffered saline containing 0.05% Tween-20), then 20µl 1:1000 dilution in assay buffer of Alexa Fluor® 488 goat anti-rabbit IgG secondary antibody (#A11008, Molecular Probes, Life Technologies), with a 1:5000 dilution of Hoechst 33342, was added per well. Following a 2 hour incubation at room temperature, plates were washed 3x with 200µl PBS/T, and
25 40µl PBS/A was added per well.

Stained cell plates were covered with black seals, and then read on the Acumen (TTP Labtech) plate reader. The primary channel (green fluorescence, 488nm) is used to set the intensity settings for the max/min cut off to allow for weekly variation in staining and the 'AKT+: No of objects (No)' data is used for
30 the analysis. Data was analysed and IC₅₀s were calculated using Genedata Screener® software.

Protocol B:

The cell plates were incubated for 2 hours at 37°C before being fixed by the addition of 20µl 3.7% formaldehyde in PBS/A (1.2% final concentration), followed by a 30 minute room temperature incubation, and then a 2 x wash with 150µl

5 PBS/A using a BioTek ELx406 platewasher. Cells were permeabilised and blocked with 20µl of assay buffer (0.1% Triton X-100 in PBS/A + 1% BSA) for 1h at room temperature, and then washed 1x with 50µl PBS/A. Primary phospho-AKT (Ser473) D9E XP® rabbit monoclonal antibody (#4060, Cell Signaling Technology) was diluted 1:200 in assay buffer, 20µl added per well, and plates

10 were incubated at 4°C overnight. Cell plates were washed 3x with 200µl PBS/T, then 20µl 1:750 dilution in assay buffer of Alexa Fluor® 488 goat anti-rabbit IgG secondary antibody (#A11008, Molecular Probes, Life Technologies), with a 1:5000 dilution of Hoechst 33342, was added per well. Following a 1 hour incubation at room temperature, plates were washed 3x with 200µl PBS/T, and

15 40µl PBS w/o Ca, Mg and Na Bicarb (Gibco #14190-094) was added per well.

Stained cell plates were covered with black seals, and then read on the Cell Insight imaging platform (Thermo Scientific), with a 10x objective. The primary channel (Hoechst blue fluorescence 405nm, BGRFR_386_23) is used to Autofocus and to count number of events (this will provide information about cytotoxicity of

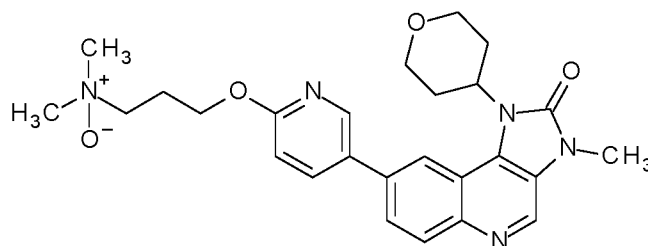
20 the compounds tested). The secondary channel (Green 488nm, BGRFR_485_20) measures pAKT staining. Data was analysed and IC₅₀s were calculated using Genedata Screener® software.

Table 1: Potency Data for Example 1 in Assays a) - d)

Example	Assay a) ATM Cell IC₅₀ (µM)	Assay b) ATR Cell IC₅₀ (µM)	Assay c) PI3Kα Cell IC₅₀ (µM)	Assay d) mTOR Cell IC₅₀ (µM)
1	0.0054	10.3	17.8	>1.25

Claims

1. A compound of Formula **(I)**:

**(I)**

or a pharmaceutically acceptable salt thereof.

2. A compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in claim 1, where the compound is in isolated form.
3. A compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in claim 1, where the compound has been produced *ex-vivo*.
4. A compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in claim 3, where the compound has been produced by organic synthesis.
5. A compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, for use in therapy.
6. A compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, for use in the treatment of cancer.
7. A compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to claim 6, where the compound of Formula **(I)** is administered simultaneously, separately or sequentially with radiotherapy.
8. A compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to claim 6, where the compound of Formula **(I)**

is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance selected from cisplatin, oxaliplatin, carboplatin, valrubicin, idarubicin, doxorubicin, pirarubicin, irinotecan, topotecan, amrubicin, epirubicin, etoposide, mitomycin, bendamustine, chlorambucil, cyclophosphamide, ifosfamide, carmustine, melphalan, bleomycin, olaparib, MEDI4736, AZD1775 and AZD6738.

9. Use of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 3, in the manufacture of a medicament for the treatment of cancer.
10. A method of treating cancer in a warm-blooded animal in need of such treatment, which comprises administering to said warm-blooded animal a therapeutically effective amount of a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 3.
11. A pharmaceutical composition which comprises a compound of Formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, and at least one pharmaceutically acceptable excipient.
12. A pharmaceutical composition as claimed in claim 11, for use in therapy.
13. A pharmaceutical composition as claimed in claim 11, for use in the treatment of cancer.
14. A pharmaceutical composition for use in the treatment of cancer according to claim 13, where the pharmaceutical composition is administered simultaneously, separately or sequentially with radiotherapy.
15. A pharmaceutical composition for use in the treatment of cancer according to claim 13, where the pharmaceutical composition is administered simultaneously, separately or sequentially with at least one additional anti-tumour substance

selected from cisplatin, oxaliplatin, carboplatin, valrubicin, idarubicin, doxorubicin, pirarubicin, irinotecan, topotecan, amrubicin, epirubicin, etoposide, mitomycin, bendamustine, chlorambucil, cyclophosphamide, ifosfamide, carmustine, melphalan, bleomycin, olaparib, MEDI4736, AZD1775 and AZD6738.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/057624

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P35/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/170081 A1 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]) 12 November 2015 (2015-11-12) cited in the application same pharmacology and medical use; difference: N-oxide page 53; example 1 -----	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/057624

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		DO P2016000281 A	15-12-2016
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