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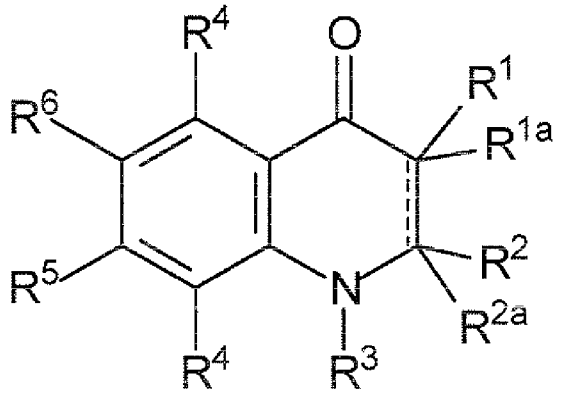
(54) Title: OXOQUINOLINE DERIVATIVES AS MTHl INHIBITORS FOR THE THERAPY OF CANCER



(i)

(57) Abstract: The present invention relates to oxoquinoline derivatives of formula (I) for use as medicaments as well as pharmaceutical compositions comprising these compounds, particularly for use as inhibitors of MTHl and for use in the treatment or prevention of cancer.

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Oxoquinoline derivatives as MTH1 inhibitors for the therapy of cancer

The present invention relates to oxoquinoline derivatives of formula (I) for use as medicaments as well as pharmaceutical compositions comprising these compounds, particularly for use as inhibitors of MTH1 and for use in the treatment or prevention of cancer.

Cancer is a leading cause of death in both economically developed countries as well as in developing countries (Mathers C et al., The global burden of disease; 2004 update, World Health Organization, 2008; Jemal A et al., CA Cancer J Clin, 2011, 61(2):69-90), and there is an ongoing and urgent need for novel therapeutic agents against cancer.

The enzyme human MutT homolog 1 (MTH1) is a 2-hydroxy-dATP diphosphatase (EC 3.6.1.56) which sanitizes oxidized dNTP pools to prevent incorporation of damaged nucleotides during DNA replication and has been described as a target for cancer therapy (Huber KV et al., Nature, 2014, 508(7495):222-7; Gad H et al., Nature, 2014, 508(7495):215-21; Cancer Discovery, 2014, 4:631, doi: 10.1158/2159-8290.CD-RW2014-085). Since MTH1 is generally required for the survival of a variety of different cancers, regardless of their specific genetic changes, the inhibition of MTH1 provides an effective and versatile approach for the therapy of cancer, which does not rely on the targeting of specific genetic defects.

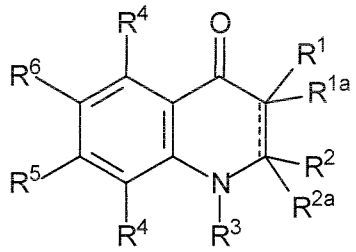
To date, only a limited number of compounds have been proposed as MTH1 inhibitors, including the compound SCH 51344, the (S)-enantiomer of crizotinib and related derivatives (Huber KV et al., Nature, 2014, 508(7495):222-7; WO 2014/033136) as well as the compounds TH287 and TH588 and related pyrimidine-2,4-diamine derivatives (Gad H et al., Nature, 2014, 508(7495):215-21; WO 2014/084778).

Various other therapeutic applications distinct from the inhibition of MTH1 have further been described for certain quinoline compounds, e.g., in Nasr M et al., J Med Chem, 1978, 21(3):295-8, Pedemonte N et al., Mol Pharmacol, 2005, 67(5):1797-807, Rosini M et al., Bioorg Med Chem, 2006, 14(23)7846-53, Borrok MJ et al., J Am Chem Soc, 2007, 129(42):12780-5, Abouzid K et al., Bioorg Med Chem, 2008, 16(16):7543-51, Tobe M et al., Bioorg Med Chem Lett, 2001, 11(4):545-8, Moreno E et al., Eur J Med Chem, 2012, 47(1):283-98, Liu P et al., Eur J Med Chem, 2014, 79:413-21, Lee AY et al., Science, 2014,

344(61 80):208-1 1, WO 01/64645, WO 2005/120497, WO 2006/041900, WO 2008/021250, WO 2008/089307, WO 2009/001060, WO 2009/023558, WO 2010/039538, WO 2010/151737, EP 0268871 A, CN 103224466 A, US 2004/0209902, US 2007/0148185, US 2009/0088420 and US 2009/0163545.

It is an object of the present invention to provide novel and/or improved therapeutic agents for the medical intervention in cancer, particularly inhibitors of MTH1 , which should be effective in the treatment of a wide range of different cancers having different genetic defects. In the context of the invention, it has surprisingly been found that the oxoquinoline derivatives of formula (I) as described and defined in the following are potent inhibitors of MTH1 and can thus advantageously be used for the treatment or prevention of cancer.

Accordingly, the present invention provides a compound of the following formula (I)



(I)

or a pharmaceutically acceptable salt, solvate or prodrug thereof, for use in the treatment or prevention of cancer.

In formula (I), R^1 is -CO-N(R^{11})-R^{12} or -N(R^{11})-CO-R^{12}.

R^{11} is hydrogen or d-5 alkyl.

R^{12} is selected from C_{1-5} alkyl, carbocyclyl, and heterocyclyl, wherein said carbocyclyl and said heterocyclyl are each optionally substituted with one or more groups R^{13}.

Each R^{13} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-0(C_{1-5} alkyl), -(C_{0-3} alkylene)-0(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-0(d-s alkylene)-0(d-s alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(d-5 alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(d-5 alkyl), -(C_{0-3} alkylene)-N(d-5 alkyl)(d-5 alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(d-5 haloalkyl), -(C_{0-3} alkylene)-CF_3, -(d-3 alkylene)-CN,

-(Co-3 alkylene)-N0 2, -(C 0-3 alkylene)-N 3, -(C 0-3 alkylene)-CHO, -(C 0-3 alkylene)-CO-(C 1-5 alkyl), -(C 0_3 alkylene)-COOH, -(C 0-3 aikylene)-CO-0-(C 1-5 alkyl) , -(C 0-3 alkylene)-0-CO-(C 1-5 aikyl), -(Co-3 alkylene)-CO-NH 2, -(C 0-3 alkylene)-CO-NH(C 1-5 alkyl) , -(C 0-3 alkylene)-CO-N(C 1-5 alkyl)(d _5 alkyl), -(C 0-3 alkylene)-NH-CO-(C 1-5 alkyl) , -(C 0-3 alkylene)-N(d_ 5 alkyl)-CO-(Ci -5 alkyl) , -(C 0-3 alkylene)-S0 2-NH 2, -(C 0-3 alkylene)-S0 2-NH(C 1-5 alkyl) , -(C 0-3 alkylene)-S0 2-N(C 1-5 alkyl)(C 1-5 alkyl) , -(C 0-3 alkylene)-NH-S0 2-(C 1-5 aikyl) , and -(C 0-3 alkylene)-N(C 1-5 alkyi)-S0 2-(C 1-5 aikyl).

----- is a double bond or a single bond.

If ----- is a double bond, then R^{1a} and R^{2a} are absent, and R^2 is selected from hydrogen, C 1-5 alkyl, C2-5 alkenyl , C 2-5 alkynyl, -OH , -0(d_ 5 alkyl), -0 (C 1-5 alkylene)-OH , -0(Ci_ 5 alkylene)-0(d. 5 alkyl) , -SH , -S(d. 5 alkyl) , -S(d-s alkylene)-SH, -S(d. 5 alkylene)-S(d_ 5 alkyl) , -NH 2, -NH(d_5 alkyl), -N(d. 5 alkyl)(C,. 5 alkyl), halogen, d _5 haloalkyl, -CF 3, and -CN.

If ----- is a single bond, then: R^{1a} is selected from hydrogen, C 1-5 alkyl, C2-5 a!keny!, C2.5 alkynyl, -OH , -0(d. 5 alkyl) , -0(d .5 alkylene)-OH, -0(Ci. 5 alkylene)-0(d. 5 alkyl), -SH , -S(d. 5 alkyl) , -S(d_ 5 alkylene)-SH, -S(d -5 alkylene)-S(d .5 alkyl) , -NH 2, -NH(d. 5 alkyl) , -N(d. 5 alkyl)(d. 5 alkyl), halogen, d _5 haloalkyl, -CF 3, and -CN ; R^2 is selected from hydrogen, C 1-5 alkyl, C 2-5 alkenyl , C 2-5 alkynyl, -OH , -0(d_ 5 alkyl) , -0 (C 1-5 alkylene)-OH , -0(d. 5 alkylene)-0(d .5 alkyl), -SH, -S(d. 5 alkyl), -S(d. 5 alkylene)-SH , -S(d .5 alkylene)-S(d. 5 alkyl) , -IMH2, -NH(C 1-5 alkyl), -N(d_ 5 alkyl)(C 1-5 alkyl), halogen, d .5 haloalkyl, -CF 3, and -CN; and R^{2a} is selected from hydrogen, d .5 alkyl, C 2-5 alkenyl, C 2-5 alkynyl, -OH , =0(d. 5 a!ky!) , -0 (C 1-5 alkylene)-OH, -0(C 1-5 alkylene)-0(d. 5 alkyl) , -SH, -S(C 1-5 alkyl) , -S(C 1-5 alkylene)-SH, -S(d. 5 alkylene)-S(d. 5 alkyl) , -NH 2, -NH(d_ 5 alkyl), -N(d .5 alkyl)(d. 5 alkyl) , halogen, d .5 haloalkyl , -CF 3, and -CN ; and the groups R^2 and R^{2a} may also together form an oxo group.

R^3 is hydrogen or d .-5 alkyl.

Each R^4 is independently selected from hydrogen, d _5 alkyl, C2-5 alkenyl , C2-5 alkynyl, -(C 0-3 alkylene)-OH, -(C 0-3 alkylene)-0(C 1-5 alkyi), -(C 0-3 alkylene)-0(d .5 alkylene)-OH, -(C 0-3 alkylene)-0(C 1-5 alkylene)-0(C 1-5 alkyl) , -(C 0-3 alkylene)-SH , -(C 0-3 alkylene)-S(d .5 alkyl) , -(C 0-3 alkylene)-S(C-i _5 alkylene)-SH , -(C 0-3 alkylene)-S(C 1-5 a!kylene)-S(Ci_s alkyl) , -(C 0-3 alkylene)-NH 2, -(C 0-3 alkylene)-NH(d. 5 alkyl), -(C 0-3 alkylene)-N(d .5 alkyl)(d. 5 alkyl) , -(C 0-3 alkylene)-halogen, -(C 0-3 alkylene)-(C 1-5 haloalkyl) , -(C 0-3 alkylene)-CF 3, -(C 0-3 alkylene)-CN , -(CQ-3 alkylene)-N0 2, -(C 0-3 alkyiene)-N 3, -(C 0-3 alkyienei-CHO, -(C 0-3 alkylene)-CO-(d_ 5 aikyl), -(C 0-3 alkylene)-COOH , -(C 0-3 alkylene)-CO-0-(C 1-5 alkyl), -(C 0-3 alkylene)-0-CO-(d_ 5 alkyl) ,

-(Co-3 alkylene)-CO-NH $_2$, -(Co-3 alkylene)-CO-NH(C $_{1\text{-}5}$ alkyl), -(C $_{0\text{-}3}$ alkylene)-CO-N(Ci. $_5$ alkyl)(C $_{1\text{-}5}$ alkyl), -(C $_{0\text{-}3}$ alkylene)-NH-CO-(C$_{1\text{-}5}$ alkyl), -(C $_{0\text{-}3}$ alkylene)-N(C $_{1\text{-}5}$ alkyl)-CO-(C $_{1\text{-}5}$ a!kyl), -(C $_{0\text{-}3}$ alkylene)-S0 $_2$-NH $_2$, -(C $_{0\text{-}3}$ alkylene)-S0 $_2$-NH(C $_{1\text{-}5}$ alkyl), -(Co-3 alkyiene)-S0 $_2$-N(C $_{1\text{-}5}$ alkyl)(d. $_5$ alkyl), -(C $_{0\text{-}3}$ alkylene)-NH-S0 $_2$-(C$_{1\text{-}5}$ alkyl), and -(C $_{0\text{-}3}$ alkylene)-N(d $_{1\text{-}5}$ alkyl)-S0 $_2$-(Ci. $_5$ alkyl).

One of R^5 and R^6 is -L-A, and the other one of R^5 and R^6 is a group R^4.

L is $C_{1\text{-}5}$ alkylene, wherein one or two -CH_2- units comprised in said $_{C\ 1\text{-}5}$ alkylene are each optionally replaced by a group independently selected from -S0 $_2$-N(R^{L1})-, -N(R^{L1})-S0 $_2$-, -S0 $_2$-, -SO-, -S-, -0-, -CO-, -C(=0)0-, -0-C(=0)-, -N(R^{L1})-, -N(R^{L1})-CO-, and -CO-N(R^{L1})-

Each R^{L1} is independently selected from hydrogen and $_{C\ 1\text{-}5}$ alkyl.

A is aryl or heteroaryl. wherein said aryl and said heteroaryl are each optionally substituted with one or more groups R^{A1}.

Each R^{A1} is independently selected from d $_{1\text{-}5}$ alkyl, $C_{2\text{-}5}$ alkenyl, $C_{2\text{-}5}$ alkynyl, -(C0-3 alkylene)-OH, -(C $_{0\text{-}3}$ alkylene)-0(C $_{1\text{-}5}$ alkyl), -(C $_{0\text{-}3}$ alkylene)-0(C $_{1\text{-}5}$ alkylene)-OH, -(C $_{0\text{-}3}$ alkylene)-0(Ci. $_5$ alkylene)-0 (d $_{1\text{-}5}$ alkyl), -(C $_{0\text{-}3}$ alkylene)-SH, -(C $_{0\text{-}3}$ alkylene)-S(C,. $_5$ alkyl), -(C $_{0\text{-}3}$ alkylene)-S(d.5 alkylene)-SH, -(C $_{0\text{-}3}$ alkylene)-S(C$_{1\text{-}5}$ alkylene)-S(C $_{1\text{-}5}$ alkyl), -(C $_{0\text{-}3}$ alkylene)-NH $_2$, -(C $_{0\text{-}3}$ alkylene)-NH(C $_{1\text{-}5}$ alkyl), -(C $_{0\text{-}3}$ alkylene)-N(C $_{1\text{-}5}$ alkyl)(d_5 alkyl), -(C0-3 alkylene)-halogen, -(C $_{0\text{-}3}$ a!kylene)-(C $_{1\text{-}5}$ haloalkyl), -(C $_{0\text{-}3}$ alkylene)-CF $_3$, -(C $_{0\text{-}3}$ alkylene)-CN, -(Co-3 alkylene)-N0 $_2$, -(C $_{0\text{-}3}$ alkylene)-N $_3$, -(C $_{0\text{-}3}$ alkylene)-CHO, -(C $_{0\text{-}3}$ alkylene)-CO-(C $_{1\text{-}5}$ alkyl), -(Co- $_3$ alkylene)-COOH, -(C $_{0\text{-}3}$ alkylene)-CO-0-(d_ $_5$ alkyl), -(C $_{0\text{-}3}$ alkylene)-0-CO-(d_ $_5$ alkyl), -(Co- $_3$ alkylene)-CO-NH $_2$, -(C $_{0\text{-}3}$ alkylene)-CO-NH(d_ $_5$ alkyl), -(C $_{0\text{-}3}$ alkylene)-CO-N(d_ $_5$ alkyl)(d. $_5$ alkyl), -(C $_{0\text{-}3}$ alkylene)-NH-CO-(C $_{1\text{-}5}$ alkyl), -(Co-3 a!kylene)-N(d_5 alkyl)-CO-(d. $_5$ alkyl), -(C $_{0\text{-}3}$ alkylene)-S0 $_2$-NH $_2$, -(Cn-4 alkyleneVSOo-NHiC, -5 alkyIV -iC«-3 alkyleneVS0 $_2$-N(d $_{1\text{-}5}$ alkyl)iC$_{1\text{-}5}$ alkyl), -(Co-3 alkylene)-NH-S0 $_2$-(d. $_5$ alkyl), and -(C $_{0\text{-}3}$ alkylene)-N(d_ $_5$ alkyl)-S0 $_2$-(d. $_5$ alkyl), and two groups R^{A1} which are bound to adjacent carbon ring atoms may also be mutually linked to form a group -0-(CH $_2$)$_{1\text{-}3}$-0-.

MTH1 is regarded as the major clearance enzyme for oxidized nucleotides such as 2-OH-dATP and 8-oxo-dGTP (Nakabeppu, Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 2010, 703(1):51-8). Oxidized nucleotides, which are generated by attack of reactive oxygen species (ROS) on DNA or the nucleotide pool, can cause DNA

damage and mutations. Sources of ROS include mitochondrial respiration, chemicals or radiation. The frequently occurring 8-oxo-guanine (8-oxo-G), for example, can lead to transversion mutations during replication. In contrast to unoxidized guanine, 8-oxo-G is able to pair with either cytosine or adenine with almost equal efficiency, thereby generating mutations if 8-oxo-G is inserted opposite A in a nascent DNA strand or vice versa. If the misincorporated oxidized nucleotide is recognized by the DNA repair system, the lesion can be repaired by base excision repair (BER). BER involves induction of a temporary single strand break to remove the falsely inserted base and subsequent replacement. However, high amounts of 8-oxo-G can lead to accumulation of single strand breaks which eventually progress to double strand breaks (DSB), thus inducing cell cycle arrest (quiescence or senescence) and apoptosis. By converting the oxidized nucleoside triphosphates into the corresponding nucleoside monophosphates which can no longer be used as substrates by DNA polymerases, MTH1 prevents the integration of oxidized bases into DNA and thus prevents mutations and oxidative DNA damage induced by ROS. Transformation of cells by oncogenes such as mutant RAS which occurs in about 20% of all tumors can also lead to increased production of ROS (Rai, Oncogene, 201 1, 30(1 2): 1489-96). As for normal cells, oxidative damage caused by ROS can force cancer cells into a state of quiescence or senescence (OIS), and eventually apoptosis. To overcome senescence, RAS-transformed cells upregulate MTH1 which protects the cells from oxidative DNA damage. For instance, it has been shown that human skin fibroblasts transfected with HRAS undergo senescence, but this phenotype can be rescued by concomitant overexpression of MTH1 (Rai, Oncogene, 201 1, 30(12):1489-96). Reports consequently indicate that MTH1 suppression causes proliferative defects in cancer cells expressing mutant RAS (Rai, Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 2010, 703(1):71-81). Moreover, as MTH1-/- knockout mice show a very mild phenotype (Tsuzuki, Proceedings of the National Academy of Sciences, 2001 , 98(20): 1 1456-61), targeting MTH1 with small molecules is considered to provide an effective and well-tolerated therapeutic approach for the treatment or prevention of cancer, including also cancer having an activating RAS mutation (i.e., RAS-dependent cancer).

In the context of the present invention, the compounds of formula (I) have surprisingly been found to be potent inhibitors of MTH1 , as also demonstrated in the appended examples, in which the inhibitory effect of a range of exemplary compounds of formula (I) on MTH1 could be confirmed in an *in vitro* binding assay (differential scanning fluorimetry) and a luminescence-based enzymatic assay. As explained above, MTH1 has recently been identified as a critical factor for cancer cell survival *in vitro* and *in vivo* in a wide range of different cancers (Huber KV et al., Nature, 2014, 508(7495):222-7; Gad H et al., Nature, 2014, 508(7495):215-21 ; Cancer Discovery, 2014, 4:631 , doi:10.1 158/21 59-8290. CD-RW2014-085). Moreover, human MTH1

has also been linked to malignant transformation induced by mutant RAS, which has been shown to enable tumors to overcome the oncogene-induced senescence (OIS) barrier (Rai P et al., Oncogene, 201 1, 30(12):1489-96). The compounds of formula (!) thus constitute highly effective therapeutic agents, particularly in the treatment or prevention of cancer.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof, in combination with a pharmaceutically acceptable excipient, for use in the treatment or prevention of cancer.

The invention furthermore relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof in the preparation of a medicament for the treatment or prevention of cancer.

The invention likewise provides a method of treating or preventing cancer, the method comprising administering a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising any of the aforementioned entities and a pharmaceutically acceptable excipient, to a subject (e.g., a human) in need thereof.

Moreover, the present invention relates to a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising any of the aforementioned entities and a pharmaceutically acceptable excipient. for use in inhibiting MTH1 or for use in treating or preventing cancer by inhibiting MTH1. This invention further refers to the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof in the preparation of a medicament for inhibiting MTH1 or for treating or preventing cancer by inhibiting MTH1 . In addition thereto, the invention provides a method of inhibiting MTH1 in a subject, the method comprising administering a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising any of the aforementioned entities and a pharmaceutically acceptable excipient, to a subject (e.g., a human) in need thereof. The invention also provides a method of treating or preventing cancer by inhibiting MTH1, the method comprising administering a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising any of the aforementioned entities and a pharmaceutically acceptable excipient, to a subject (e.g., a human) in need thereof.

The cancer to be treated or prevented in accordance with the present invention is preferably selected from gastrointestinal cancer, colorectal cancer, liver cancer (e.g., hepatocellular

carcinoma), pancreatic cancer, stomach cancer, genitourinary cancer, bladder cancer, esophageal cancer, prostate cancer (e.g., hormone-refractory prostate cancer), lung cancer (e.g., small cell lung cancer or non-small cell lung cancer), breast cancer (e.g., triple-negative breast cancer, or breast cancer having a BRCA1 and/or BRCA2 gene mutation), hematological cancer, leukemia (e.g., acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, or chronic myeloid leukemia), lymphoma (e.g., Hodgkin lymphoma or non-Hodgkin lymphoma, such as, e.g., follicular lymphoma or diffuse large B-cell lymphoma), ovarian cancer, brain cancer, neuroblastoma, Ewing's sarcoma, kidney cancer, skin cancer, and head and/or neck cancer (e.g., head and neck squamous cell carcinoma).

The cancer to be treated or prevented may also be a cancer having an activating RAS mutation (e.g., an activating KRAS mutation, such as, e.g., G12D, G12V, G12C, or Q61 H) and/or an activating EGFR mutation, including any one of the above-mentioned specific types of cancer further having an activating RAS mutation and/or an activating EGFR mutation. It has been shown that MTH1 specifically assists RAS-induced tumors in preventing tumor-suppressive effects such as senescence whilst enabling maintenance and progression of the tumor. MTH1 inhibition is therefore considered to help impairing tumor growth by abrogating mitogenic signaling, epithelial-mesenchymal transition (EMT), a hallmark of progressing and aggressive tumors, anoikis inhibition and PI3K/Akt-mediated pro-survival signaling (Rai, Proteomics, 2003, 3(8): 1454-63). There is also evidence that MTH1 may be a promising target for adenocarcinomas expressing EGFR as the micro-RNA MiR-145 which suppresses both EGFR and MTH1 is downregulated in these tumors (Cho, RNA Biology, 201 1, 8(1): 125-31) and as the reexpression of MiR-145 led to a downregulation of EGFR and MTH1 on both mRNA and protein level and impaired the growth of EGFR-positive cell lines. The invention thus also relates to the compound of formula (I), as described and defined herein, or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising any of the aforementioned entities and a pharmaceutically acceptable excipient, for use in the treatment or prevention of RAS-dependent and/or EGFR-dependent cancer, wherein the RAS-dependent and/or EGFR-dependent cancer may further be selected from any one of the specific types of cancer described in the preceding paragraph.

Triple negative breast cancer cell lines are also known to be sensitive to oxidative DNA damage which can sensitize these cancers to chemotherapeutics such as PARP inhibitors. MTH1 inhibitors which are considered to induce oxidative DNA lesions can therefore advantageously be used to treat this type of cancer. Accordingly, the present invention particularly relates to a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof, or a pharmaceutical composition comprising any of the aforementioned

entities and a pharmaceutically acceptable excipient, for use in the treatment or prevention of triple negative breast cancer (particularly breast cancer lacking expression of estrogen receptor-a, lacking expression of progesterone receptor, and lacking overexpression or amplification of the HER2/NEU oncogene). Furthermore, the BRCA1 and BRCA2 genes which are mutated in certain types of breast cancer are known to be involved in the repair of oxidative DNA damage including 8-oxo-guanine-based lesions (Le Page, Cancer Res, 2000, 60(19):5548-52), which makes breast cancer cells deficient in BRCA1 and/or BRCA2 particularly sensitive towards oxidative DNA damage (Alii, Cancer Res, 2009, 69(8):3589-96). The compounds of formula (I) are thus also highly advantageous for the treatment or prevention of breast cancer having a BRCA1 and/or BRCA2 gene mutation. The breast cancer to be treated or prevented (e.g., the triple-negative breast cancer or the breast cancer having a BRCA1 and/or BRCA2 gene mutation) may further be EGFR-dependent.

It has further been shown that the mismatch DNA repair pathway (MMR) can affect the loss of MTH1 function (Egashira A et al., *DNA Repair* 2002, 1(11):881-93). Therefore, loss or dysfunction of MMR-related genes and gene products may modulate the response to MTH1 inhibitors. Aberrations in MMR pathways are a frequent phenomenon in malignant disease and therefore the inhibition of MTH1 activity can be used to specifically treat those and related conditions. Moreover, recent studies suggest that hypoxia-related signaling and the cellular redox tumor environment determine the sensitivity of cells to MTH1 inhibition (Brautigam L et al., *Cancer Res.,* 2016, doi: 10.1 158/0008-5472.CAN-1 5-2380). Particularly tumor types with elevated oxidative stress and cancers with dysregulated hypoxia signaling including, e.g., the VHL and/or HIF1-alpha pathways are considered to be sensitive towards MTH1 inhibition and are thus preferred to be treated or prevented using a compound of formula (I) according to the invention.

It is furthermore preferred that the cancer to be treated or prevented is a cancer (including, e.g., any one of the above-mentioned specific types of cancer) wherein MTH1 is involved in the development and/or progression of the cancer. In order to determine whether MTH1 is involved in the development and/or progression of a cancer, the status (e.g., the genetic constitution, expression and/or activity) of MTH1 can be analyzed. The MTH1 status of a cancer represents an appropriate indicator for the involvement of MTH1 in the development and/or progression of that cancer. The present invention thus also relates to stratifying cancer patients with respect to their MTH1 status.

Accordingly, the present invention further relates to an *in vitro* method of determining the effectiveness of a compound of formula (I) in the treatment or prevention of cancer in a subject, the method comprising:

- obtaining a sample (e.g., a cell or tissue sample, particularly a cancer cell sample or a cancer tissue sample) from the subject; and
- determining the subject's MTH1 status in the sample;

wherein a positive MTH1 status is indicative of an effective treatment or prevention of cancer in the subject.

In this *in vitro* method, the MTH1 status may be, e.g., the level of MTH1 biological activity and/or the level of MTH1 expression. The level of MTH1 biological activity may be monitored by purifying MTH1 from the sample obtained from the subject and measuring the production of pyrophosphate (PPi) generated by MTH1-mediated hydrolysis of 8-oxo-dGTP. In particular, purified MTH1 may be contacted with 8-oxo-dGTP and the production of PPi may be measured using, e.g., the PPiLight Inorganic Pyrophosphate Assay (Lonza Rockland Inc.). In order to determine whether a compound of formula (I) will be particularly effective in the treatment or prevention of cancer in a subject, the level of MTH1 biological activity (e.g., the quantity of produced PPi) in the sample obtained from the subject may be compared to the level of MTH1 biological activity (e.g., the quantity of produced PPi) in a sample obtained from of a healthy control subject. The MTH1 status of the subject is positive if the level of MTH1 biological activity (e.g., the quantity of produced PPi) is higher in the sample from the subject as compared to the level of MTH1 biological activity in the sample of the healthy control subject. The level of MTH1 expression may be determined, e.g., by PGR, RT-PCT or Western blot. In this case, the MTH1 status of the subject is positive if the level of expression of MTH1 (e.g., the amount of MTH1 mRNA or of MTH1 protein) is higher in the sample from the subject as compared to the level of expression of MTH1 in a sample obtained from a healthy control subject.

Antibodies, probes and primers that can be used for determining/detecting a subject's MTH1 status are known in the art. Thus, an antibody for determining a subject's MTH1 status is, e.g., Novus Biologicals MTH1 Antibody (NB100-109). Primers for determining a subject's MTH1 status are described, e.g., in Kennedy (1998) FEBS Lett. 429(1);17-20, which is herein incorporated by reference in its entirety. Moreover, the following exemplary primers can also be used for determining a subject's MTH1 status:

Primer sequence for the detection of NUDT1/MTH1 : 5P-AGCCTCAGCGAGTTCTCCTG-3P

Primer sequence for the detection of NUDT1/MTH1 : 5P-GATCTGGCCCACCTTGTGC-3P

Furthermore, the MTH1 status can also be determined, e.g., as described in WO 2014/033136.

Antibodies, probes and primers that can be used for determining/detecting a subject's RAS status are known in the art and are also described, e.g., in WO 2014/033136. For instance, an antibody for detecting a subject's RAS status is, e.g., Cell Signaling Ras Antibody #3965. Primers for detecting a subject's RAS status are described, e.g., in Keohavong (1996) Clin Cancer Res. 2(2):41 1-8 or in Gerry (1999) Mol Biol. 292(2):251-62, which are herein incorporated by reference in their entirety.

The *in vitro* method described herein can be performed prior to the administration of a compound of formula (I) to a subject in order to evaluate whether the subject will particularly benefit from the treatment with this compound. Accordingly, the invention provides a method of treating or preventing cancer in a subject in need thereof, wherein the method comprises:

(i) performing the *in vitro* method described herein; and

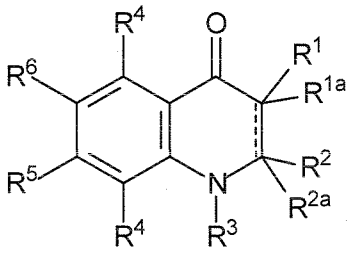
(ii) administering a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof to the subject if the result obtained in step (i) is indicative of an effective treatment or prevention of cancer.

The gene that encodes MTH1 is also known as NUDT1 . At present, four isoforms of NUDT1/MTH1 (p18, p21 , p22 and p26) have been reported, among which p18 is considered to be the dominant isoform. The isoform p18 has been used in the experiments described herein. Mutations have been reported for MTH1, however, their physiological or clinical relevance has not been elucidated. Methods for determining the NUDT/MTH1 -status (e.g., for detecting the level, such as the expression level, of NUDT/MTH1 or for determining whether the nucleotide sequence or amino acid sequence of NUDT/MTH1 contains a specific mutation) are described herein and are also known in the art (see, e.g., WO 2014/033136). Activating and inactivating aberrations include genetic aberrations such as gene mutation, gene copy number increase, aberration of gene expression, and aberration of mRNA expression. For the detection of cytogenetic aberrations, several detection methods are known in the art and are reviewed, e.g., in Speicher (2005) Nat Rev Genet 6(10):782-92. All mutation detection methods should be performed in accordance with best practice. This means that all mutation detection methods should be robust and performed to the highest standards with established Standard Operating Procedures (SOPs). Quality control of each step in the process should be in place. How to perform mutation detection methods in best practice is known in the art and is also described, e.g., in Eberhard (2008) Clin Oncol 26(6):983-93.

The present invention furthermore relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof as an MTH1 inhibitor in research,

particularly as a research tool compound. Accordingly, the invention refers to the *in vitro* use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof as an MTH1 inhibitor and, in particular, to the *in vitro* use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof as a research tool compound acting as an MTH1 inhibitor.

The compounds of formula (I) will be described in more detail in the following:



(I)

R^1 is -CO-N(R^{11})-R^{12} or -N(R^{11})-CO-R^{12}. Preferably, R^1 is -CO-N(R^{11})-R^{12}.

R^{11} is hydrogen or C_{1-5} alkyl. Preferably, R^{11} is hydrogen, methyl or ethyl. More preferably, R^{11} is hydrogen.

R^{12} is selected from C_{1-5} alkyl, carbocyclyl, and heterocyclyl, wherein said carbocyclyl and said heterocyclyl are each optionally substituted with one or more (e.g., one, two, or three) groups R^{13}. Preferably, R^{12} is selected from C_{1-5} alkyl, cycloalkyi, aryl, heterocycloalkyi, and heteroaryl, wherein said cycloalkyi, said aryl, said heterocycloalkyi, and said heteroaryl are each optionally substituted with one or more (e.g., one, two, or three) groups R^{13}. More preferably, R^{12} is selected from C_{1-5} alkyl (e.g., sec-butyl), C_{3-7} cycloalkyi (e.g., cyclopentyl, cyclohexyl, or cycloheptyl), phenyl, heterocycloalkyi having 5 or 6 ring members, and heteroaryl having 5 or 6 ring members, wherein said C_{3-7} cycloalkyi, said phenyl, said heterocycloalkyi having 5 or 6 ring members, and said heteroaryl having 5 or 6 ring members are each optionally substituted with one or more (e.g., one, two, or three) groups R^{13}. Even more preferably, R^{12} is C_{1-5} alkyl (preferably sec-butyl) or C_{3-7} cycloalkyi (preferably cyclopentyl, cyclohexyl, or cycloheptyl), wherein said C_{3-7} cycloalkyi is optionally substituted with one or more (e.g., one, two, or three) groups R^{13}. It is particularly preferred that the aforementioned cyclic groups (e.g., any of the aforementioned carbocyclyl, heterocyclyl, cycloalkyi, aryl, heterocycloalkyi and heteroaryl groups) are unsubstituted, i.e. are not substituted with any group R^{13}.

Each R^{13} is independently selected from d-5 alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-0(C_{1-5} alkyl), -(C_{0-3} alkylene)-0(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-0(d$_{-5}$ alkylene)-0(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(d$_{-5}$ alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(d_5 alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C-,$_{-5}$ alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} aikylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CF_3, -(C_{0-3} aikylene)-CN, -(C_{0-3} alkylene)-N0$_2$, -(C_{0-3} alkylene)-N_3, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(Co-$_3$ alkylene)-COOH, -(C_{0-3} alkylene)-CO-0-(C,.$_5$ alkyl), -(C_{0-3} alkylene)-0-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(d.$_5$ alkyl)(d$_{-5}$ alkyl), -(C_{0-3} alkylene)-NH-CO-(d$_{-5}$ alkyl), -(C_{0-3} alkylene)-N(d$_{-5}$ alkyl)-CO-(d$_{-5}$ alkyl), -(C_{0-3} alkylene)-S0$_2$-NH_2, -(C_{0-3} alkylene)-S0$_2$-NH(Ci-5 alkyl), -(C_{0-3} alkylene)-S0$_2$-N(d$_{-5}$ alkyi)(d-5 alkyl), -(C_{0-3} alkylene)-NH-S0$_2$-(d.$_5$ alkyl), and -(C_{0-3} alkylene)-N(d$_{-5}$ alkyl)-S0$_2$-(d-5 alkyl). Preferably, each R^{13} is independently selected from d$_{-5}$ alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -0(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(d$_{-5}$ alkyl), -N(d.$_5$ alkyl)(d$_{-5}$ alkyl), halogen, C_{1-5} haloalkyl, -CF_3, -CN. -N0$_2$, -N_3, -CHO, -CO-(C_{1-5} alkyl), -COOH, -CO-0-(C_{1-5} alkyl), -0-CO-(d$_{-5}$ alkyl), -CO-NH_2, -CO-NH(d$_{-5}$ alkyl), -CO-N(d.$_5$ alkyl)(d.$_5$ alkyl), -NH-CO-(d$_{-5}$ alkyl), -N(d$_{-5}$ alkyl)-CO-(C_{1-5} alkyl), -S0$_2$-NH_2, -S0$_2$-NH(d-s alkyl), -S0$_2$-N(Ci.$_5$ alkyi)(d.$_5$ alkyl), -NH-S0$_2$-(d$_{-5}$ alkyl), and -N(C_{1-5} alkyl)-S0$_2$-(d$_{-5}$ alkyl). More preferably, each R^{13} is independently selected from d$_{-5}$ alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -0(d.$_5$ alkyl), -Q(d_$_5$ alkylene)-OH, -0(C_{1-5} a!kylene)-0(d,.$_5$ alkyl), -SH, -S(d_$_5$ alkyl), -S(d.$_5$ aikylene)-SH, -S(d-5 alkyiene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(d$_{-5}$ aikyi)(d.5 aikyi), halogen, C_{1-5} haloalkyl, -CF_3, and -CN. Even more preferably, each R^{13} is independently selected from C_{1-4} alkyl (e.g., methyl or ethyl), -OH, -0(d_$_4$ alkyl) (e.g., -OCH_3 or -OCH_2CH_3), -NH_2, -NH(d_4 alkyl) (e.g., -$NHCH_3$), -N(d$_{-4}$ alkyl)(d$_{-4}$ alkyl) (e.g., -$N(CH_3)_2$), halogen (e.g., -F, -Cl, -Br, or -I), -CF_3, and -CN.

----- is a double bond or a single bond. Preferably, ----- is a double bond.

If ----- is a double bond, then R^{1a} and R^{2a} are absent, and R^2 is selected from hydrogen, d$_{-5}$ alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -0(d_$_5$ alkyl), -0(d$_{-5}$ alkylene)-OH, -Q(d-5 aikylene)-0(d_5 alkyl), -SH, -S(d.$_5$ alkyl), -S(C_{T-5} alkylene)-SH, -S(d_$_5$ alkyiene)-S(C_{1-5} alkyl), -NH_2, -NH(d$_{-5}$ alkyl), -N(d$_{-5}$ alkyl)(d_$_5$ alkyl), halogen, d-s haloalkyl, -CF_3, and -CN. In this case, R^2 is preferably selected from hydrogen, d$_{-4}$ alkyl (e.g., methyl or ethyl), -OH, -0(C_{1-4} alkyl) (e.g., -OCH_3 or -$0CH_2CH_3$), -NH_2, -NH(C_{1-4} alkyl) (e.g., -$NHCH_3$), -N(C_{1-4} alkyl)(d$_{-4}$ alky!)

(e.g., **-N(CH$_3$)$_2$**), halogen (e.g., **-F, -Cl,** -Br, or **-I), -CF$_3$,** and **-CN.** More preferably, **R^2** is hydrogen.

If ----- is a single bond, then: **R^{1a}** is selected from hydrogen, **C$_{1-5}$** alkyl, **C$_{2-5}$** alkenyl, **C$_{2-5}$** alkynyl, **-OH, -0** (d$_{-5}$ alkyl), **-0** (**d-s** alkylene)**-OH, -0** (d$_{-5}$ **alkylene)-0(Ci$_{-5}$** alkyl), **-SH,** -S(C$_{1-5}$ alkyl), **-S**(d$_{-5}$ aikylene)**-SH, -S**(d$_{-5}$ alkylene)-S(d$_{-5}$ alkyl), **-NH$_2$, -NH**(**d$_{-5}$** alkyl), -N(C$_{1-5}$ **alkyl)(C$_{1-5}$** alkyl), halogen, d$_{-5}$ haloalkyl, **-CF$_3$,** and **-CN; R^2** is selected from hydrogen, **C$_{1-5}$** alkyl, **C$_{2-5}$** alkenyl, **C$_{2-5}$** alkynyl, **-OH, -0** (d$_{-5}$ alkyl), **-0** (C$_{1-5}$ alkylene)**-OH, -0(C$_{1-5}$** alkyiene)**-0** (d-$_5$ alkyl), **-SH, -S**(d$_{-5}$ alkyl), **-S**(d$_{-5}$ aikylene)-SH, -S(C$_{1-5}$ alkylene)**-S**(d$_{-5}$ alkyl), -NH$_2$, -NH (d.$_5$ alkyl), -N(d$_{-5}$ alkyl)(d$_{-5}$ alkyl), halogen, d$_{-5}$ haloalkyl, **-CF$_3$,** and **-CN;** and **R^{2a}** is selected from hydrogen, **C$_{1-5}$** alkyl, **C$_{2-5}$** alkenyl, **C$_{2-5}$** alkynyl, **-OH, -0(Ci$_{-5}$** alkyl), **-0** (d$_{-5}$ alkylene)-OH, **-0** (d$_{-5}$ alkylene)**-0** (d-5 alkyl), -SH, -S(C$_{1-5}$ aikyl), **-S**(d-5 alkyiene)-SH, **-S**(d.$_5$ **alkylene)-S(Ci.$_5$** alkyl), **-NH$_2$, -NH**(**d$_{-5}$** alkyl), **-N**(d$_{-5}$ alkyl)(d$_{-5}$ alkyl), halogen, d$_{-5}$ haloalkyl, **-CF$_3$,** and **-CN;** and the groups **R^2** and **R^{2a}** may also together form an oxo group (i.e., **=0). R^{1a}** is preferably selected from hydrogen, **C$_{1-4}$** alkyl, -OH, **-0** (d$_{-4}$ alkyl), **-NH$_2$, -NH**(**d$_{-4}$** alkyl), -N(d$_{-4}$ alkyl)(d$_{-4}$ alkyl), halogen, -CF$_3$, and **-CN,** and is more preferably hydrogen. **R^2** is preferably selected from hydrogen, **C$_{1-4}$** alkyl (e.g., methyl or ethyl), **-OH, -0 (C$_{1-4}$** alkyl) (e.g., -OCH$_3$ or -OCH$_2$CH$_3$), -NH$_2$, **-NH**(**d$_{-4}$** alkyl) (e.g., -NHCH$_3$), **-N**(d.$_4$ alkyl)(d-4 alkyl) (e.g., **-N(CH$_3$)$_2$),** halogen (e.g., **-F, -Cl,** -Br, or **-I), -CF$_3$,** and **-CN,** and more preferably **R^2** is hydrogen. **R^{1a}** is preferably selected from hydrogen, d$_{-4}$ alkyl, **-OH, -0** (d.$_4$ alkyl), -NH$_2$, -NH**(C$_{1-4}$** alkyl), **-N(C$_{1-4}$** alkyl)(d$_{-4}$ alkyl), halogen, **-CF$_3$,** and **-CN,** and is more preferably hydrogen. Accordingly, if ----- is a single bond, it is particularly preferred that **R^{1a}** and **R^{2a}** are each hydrogen, and **R^2** is selected from hydrogen, C$_{1-4}$ alkyl (e.g., methyl or ethyl), -OH, **-0** (**C$_{1-4}$** alkyl) (e.g., **-OCH$_3$** or **-OCH$_2$CH$_3$), -NH$_2$,** -NH(C$_{1-4}$ alkyl) (e.g., **-NHCH$_3$), -N**(d.$_4$ alkyl)(d$_{-4}$ alkyl) (e.g., **-N(CH$_3$)$_2$),** halogen (e.g., **-F, -Cl,** -Br, or **-I), -CF$_3$,** and **-CN;** even more preferably, **R^{1a}, R^{2a}** and **R^2** are each hydrogen.

R^3 is hydrogen or C$_{1-5}$ alkyl. Preferably, **R^3** is hydrogen, methyl or ethyl. More preferably, **R^3** is hydrogen.

Each **R^4** is independently selected from hydrogen, C$_{1-5}$ alkyl, **C$_{2-5}$** alkenyl, **C$_{2-5}$** alkynyl, **-(C$_{0-3}$** alkylene)**-OH,** -(C$_{0-3}$ alkylene)**-0** (d$_{-5}$ alkyl), **-(C$_{0-3}$** alkylene)**-0(Ci$_{-5}$** alkylene)**-OH,** -(C$_{0-3}$ alkylene)**-0** (d-$_5$ alkylene)**-0** (C$_{1-5}$ alkyl), **-(C$_{0-3}$** alkylene)**-SH,** -(C$_{0-3}$ alkylene)-S(C$_{1-5}$ alkyl), **-(C$_{0-3}$** alkylene)**-S**(d.$_5$ alkylene)**-SH, -(C$_{0-3}$** alkylene)**-S**(d$_{-5}$ alkylene)**-S**(d$_{-5}$ alkyl), **-(C$_{0-3}$** alkylene)**-NH$_2$, -(C$_{0-3}$** alkylene)**-NH**(d$_{-5}$ alkyl), **-(C$_{0-3}$** alkylene)**-N**(d$_{-5}$ alkyl)(d.$_5$ alkyl), **-(C$_{0-3}$** alkyiene)-halogen, **-(C$_{0-3}$** alkylene)**-(C$_{1-5}$** haloalkyl), **-(C$_{0-3}$** alkylene)**-CF$_3$,** -(C$_{0-3}$ alkylene)**-CN, -(C$_{0-3}$** alkylene)**-N0$_2$, -(C$_{0-3}$** alkylene)-N$_3$, **-(C$_{0-3}$** alkylene)**-CHO,** -(C$_{0-3}$ alkylene)-CO-(C$_{1-5}$ alkyl),

-(Co-3 alkylene)-COOH, -(C_{0-3} alkylene)-CO-0-(C_{1-5} aikyl), -(C_{0-3} alkylene)-0-CO-(d_ 5 alkyl), -(Co-3 aikylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N (**C_{1-5}** alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkyiene)-N(d. 5 alkyl)-CO-(d. 5 alkyl), -(C_{0-3} alkylene)-S0 2-NH_2, -(C_{0-3} alkylene)-S0 2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-S0 2-N(d. 5 alkyl)(d. 5 alkyl), -(C_{0-3} alkylene)-NH-S0 2-(C_{1-5} alkyl), and -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-S0 2-(d. 5 alkyl). Preferably, each R^4 is independently selected from hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -O(**C_{1-5}** alkyl), -0(d -5 alkylene)-OH, -G(d -5 alkylene)-0(C_{1-5} aikyl), -SH, -**S(C_{1-5}** aikyl), -**S(C_{1-5}** alkylene)-SH, -S(d-s alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(d -5 alkyl), -N(C_{1-5} alkyl)(d -5 alkyl), halogen, d-s ha!oalkyl, -CF_3, -CN, -N0 2, -N_3, -CHO, -CO-(d. 5 a!ky!), -COOH, -CO-0-(d_ 5 alkyl), -0 -CO-(d -5 alkyl), -CO-NH_2, -CO-NH(d_ 5 alkyl), -CO-N(d. 5 alkyl)(d -5 alkyl), -NH-CO-(d_ 5 alkyl), -N(d -5 alkyl)-CO-(d. 5 alkyl), -S0 2-NH_2, -S0 2-NH(d -5 alkyl), -S0 2-N(d -5 alkyl)(d. 5 alkyl), -NH-S0 2-(d -5 alkyl), and -N(d -5 alkyl)-S0 2-(d. 5 alkyl). More preferably, each R^4 is independently selected from hydrogen, d -5 alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -0(d-s alkyl), -0 (d -5 alkylene)-OH, -0(d -5 alkylene)-0(d -5 alkyl), -SH, -S(d -5 alkyl), -S(d. 5 alkylene)-SH, -S(d -5 alkylene)-S(d -5 alkyl), -NH_2, -NH(d. 5 alkyl), -N(d -5 alkyl)(C,. 5 alkyl), halogen, d -5 haloalkyl, -CF_3, and -CN. Even more preferably, each R^4 is independently selected from hydrogen, C,_4 alkyl (e.g., methyl or ethyl), -OH, -0(d. 4 alkyl) (e.g., -OCH_3 or -OCH_2CH_3), -NH_2, -NH(d. 4 alkyl) (e.g., -$NHCH_3$), -N(d. 4 alkyl)(C_{1-4} alkyl) (e.g., -$N(CH_3)_2$), halogen (e.g., -F, -Cl, -Br, or -I), -CF_3, and -CN. Yet even more preferably, one group R^4 is independently selected from hydrogen, d _4 alkyl (e.g., methyl or ethyl), -OH, -0(C_{1-4} alkyl) (e.g., -OCH_3 or -OCH_2CH_3), -NH_2, -NH(C_{1-4} alkyl) (e.g., -$NHCH_3$), -N(d. 4 alkyl)(C_{1-4} alkyl) (e.g., -$N(CH_3)_2$), halogen (e.g., -F, -Cl, -Br, or -I), -CF_3, and -CN, and the other group(s) R^4 are each hydrogen. Still more preferably, each R^4 is hydrogen.

One of R^5 and R^6 is -L-A, and the other one of R^5 and R^6 is a group R^4. Preferably, R^6 is -L-A, and R^5 is a group R^4.

L is C_{1-5} alkylene, wherein one or two -CH_2- units comprised in said C_{1-5} alkylene are each optionally replaced by a group independently selected from -S0 2-N(R^{L1})-, -N(R^{L1})-S0 2-, -S0 2-, -SO-, -S-, -0-, -CO-, -C(=0)0-, -0-C(=0)-, -N(R^{L1})-, -N(R^{L1})-CO-, and -CO-N(R^{L1})-. Preferably, L is d -3 alkylene, wherein one -CH_2- unit comprised in said **C_{1-3}** alkylene is replaced by -S0 2-N(R^{L1})- or by -N(R^{L1})-S0 2-. More preferably, L is d -3 alkylene, wherein one -CH_2- unit comprised in said **C_{1-3}** alkylene is replaced by -S0 2-N(R^{L1})-. Even more preferably, L is -S0 2-N(R^{L1})-. It is to be understood that, if L is -S0 2-N(R^{L1})-, then this group will be attached via its sulfur atom to the 4-oxoquinoline moiety comprised in the compound of formula (I) and via its nitrogen atom to the group A.

Each R^{L1} is independently selected from hydrogen and C_{1-5} alkyl. Preferably, each R^{L1} is independently selected from hydrogen, methyl and ethyl. More preferably, each R^{L1} is independently selected from hydrogen and methyl.

A is aryl or heteroaryl, wherein said aryl and said heteroaryl are each optionally substituted with one or more (e.g., one, two, or three) groups R^{A1}. Preferably, A is aryl which is optionally substituted with one or more (e.g., one, two, or three) groups R^{A1}. More preferably, A is phenyl which is optionally substituted with one or more (e.g., one, two, or three; preferably one or two) groups R^{A1}.

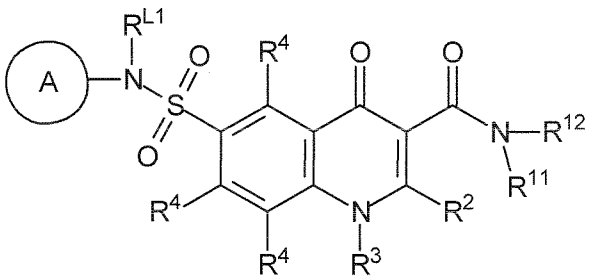
If A is phenyl which is optionally substituted with one group R^{A1}, it is furthermore preferred that said one group R^{A1} (if present) is attached to said phenyl in meta-position or in para-position with respect to the attachment point of the group L. If A is phenyl which is optionally substituted with two groups R^{A1}, it is preferred that said two groups R^{A1} (if present) are attached to said phenyl in meta-position and in para-position, respectively, with regard to the attachment point of the group L.

Each R^{A1} is independently selected from **d-5** alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-0(d-s alkyl), -(C_{0-3} alkyiene)-0(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-0(C_{1-5} alkylene)-0(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(d-5 alkyl), -(C_{0-3} alkylene)-S(C:.5 alkylene)-SH, -(C_{0-3} alkylene)-S(d-5 alkylene)-S(d-5 alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(d.5 alkyi), -(C_{0-3} alkyiene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(d.5 haloalkyl), -(C_{0-3} alkylene)-CF_3, -(C_{0-3} alkylene)-CN, -(**C_{0-3}** alkylene)-N0 2, -(C_{0-3} alkylene)-N 3, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(d-5 alkyl), -(Co-3 alkylene)-COOH, -(C_{0-3} alkylene)-CO-0-(d-5 alkyl), -(C_{0-3} alkylene)-0-CO-(d-5 alkyl), -(Co-3 alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(d-s alkyl), -(C_{0-3} alkylene)-NH-CO-(d.5 alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-S0 2-NH(d.5 alkyl), -(C_{0-3} alkylene)-S0 2-N(d.5 alkyl)(d.5 alkyl), -(Co-3 alkylene)-NH-S0 2-(d.5 alkyl), and -(C_{0-3} alkylene)-N(d.5 alkyl)-S0 2-(d.5 alkyl), and two groups R^{A1} which are bound to adjacent carbon ring atoms may also be mutually linked to form a group -0-(CH_2)$_{1-3}$-0-. Preferably, each R^{A1} is independently selected from **d-5** alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -0(d.5 alkyl), -0(d.5 alkylene)-OH, -0(d.5 alkylene)-0(d.5 alkyl), -SH, -S(d.5 alkyl), -S(d-5 alkylene)-SH, -S(d.5 alkylene)-S(d_5 alkyl), -NH_2, -NH(d.5 alkyl), -N(d-5 alkyl)(d-5 alkyl), halogen, d-5 haloalkyl, -CF_3, -CN, -N0 2, -N_3, -CHO, -CO-(d.5 alkyl), -COOH, -CO-0-(d_5 alkyl), -0-CO-(d.5 alkyl), -CO-NH_2, -CO-NH(d_5 alkyl),

-CO-N(d_ 5 alkyl)(d. 5 alkyl), -NH-CO-(d_ 5 alkyl), -N(d. 5 alky!)-CO-(Ci -5 alkyl), -S0 2-NH 2, -S0 2-NH(Ci. 5 alkyi), -S0 2-N(d -5 alkyl)(d -5 alkyl), -NH-S0 2-(C1-5 alkyl), and -N(d_ 5 alkyl)-S0 2-(C 1-5 alkyl), and two groups R^{A1} which are bound to adjacent carbon ring atoms may also be mutually linked to form a group -0-(CH 2)1-3-0-. More preferably, each R^{A1} is independently selected from d-5 alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -0(d. 5 alkyl), -0(d. 5 alkylene)-OH, -0(C 1-5 alkylene)-0(d. 5 alkyl), -SH, -S(C 1-5 alkyl), -S(d -5 alkylene)-SH, -S(C1-5 alkylene)-S(d_ 5 alkyl), -NH 2, -NH(d. 5 alkyl), -N(d. 5 alkyl)(d -5 alkyl), halogen, C1-5 haloalkyl, -CF 3, and -CN, and two groups R^{A1} which are bound to adjacent carbon ring atoms may also be mutually linked to form a group -0-(CH 2)i.3-0-. Even more preferably, each R^{A1} is independently selected from C1-4 alkyl, -OH, -0(d_ 4 alkyl), -NH 2, -NH(d -4 alkyl), -N(d_ 4 alkyl)(C 1-4 alkyl), halogen, -CF 3, and -CN, and two groups R^{A1} which are bound to adjacent carbon ring atoms may also be mutually linked to form a group -0-(CH 2)1-3-0-. Yet even more preferably, each R^{A1} is independently selected from C 1-4 alkyl (e.g., methyl, ethyl, or propyl), -OH, -0(d-4 alkyl) (e.g., -OCH 3 or -OCH 2CH 3), halogen (e.g., -F or -Cl), and -CF 3, and two groups R^{A1} which are bound to adjacent carbon ring atoms may also be mutually linked to form a group -0-(CH 2)1-3-0- (e.g., -OCH 2CH 20-).

Accordingly, it is particularly preferred that A is phenyl which is optionally substituted with one or two groups independently selected from C 1-4 alkyl (e.g., methyl, ethyl, or propyl), -OH, -0(C 1-4 alkyl) (e.g., -OCH 3 or -OCH 2CH 3), -NH 2, -NH(C1-4 alkyl), -N(d_ 4 alkyl)(d. 4 alkyl), halogen (e.g., -F or -Cl), -CF 3, and -CN, or A is phenyl which is substituted on adjacent ring atoms with two groups that are mutually linked to form a group -0-(CH 2)1-3-0- (e.g., -OCH 2CH 2O-). If A is phenyl which is substituted on adjacent ring atoms with two groups that are mutually linked to form a group -OCH 2CH 20-, it is furthermore preferred that A is 2,3-dihydrobenzo[b][1 ,4]dioxin-6-yl.

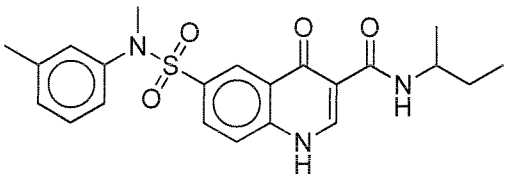
It is particularly preferred that the compound of formula (I) is a compound of the following formula (Ia) or a pharmaceutically acceptable salt, solvate or prodrug thereof:



(Ia)

The groups comprised in the compound of formula (Ia), particularly R^{11}, R^{12}, R^2, R^3, R^4, R^{L1} and A, have the same meanings, including the same preferred meanings, as described and defined herein for the corresponding groups comprised in compound of formula (I).

Preferred examples of the compounds of formula (I) or (Ia) are the following compounds (1) to (17) as well as pharmaceutically acceptable salts, solvates and prodrugs of any of these compounds:



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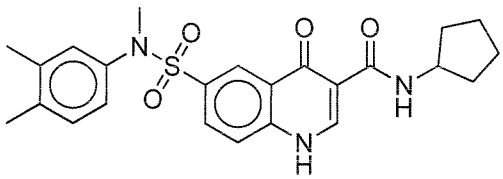

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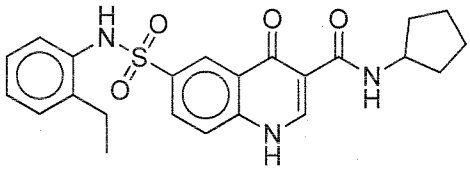

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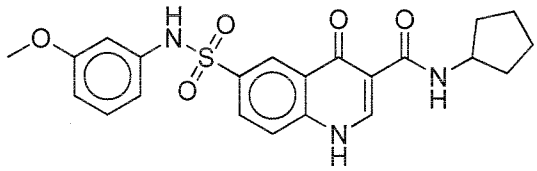

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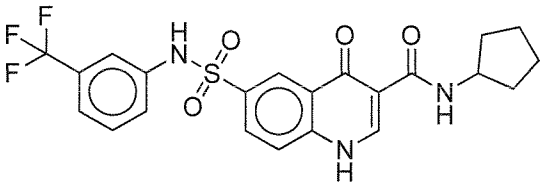

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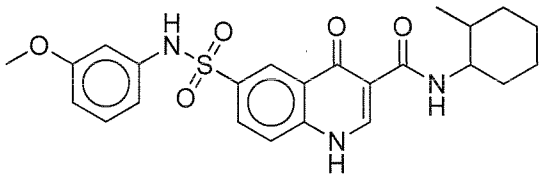

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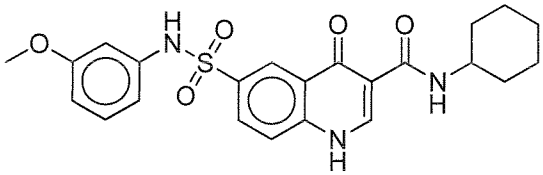

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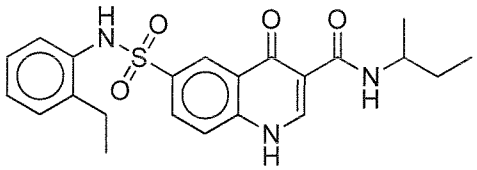

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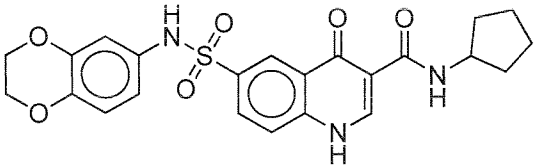

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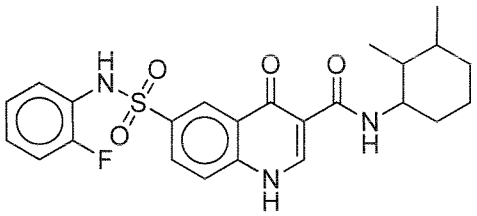

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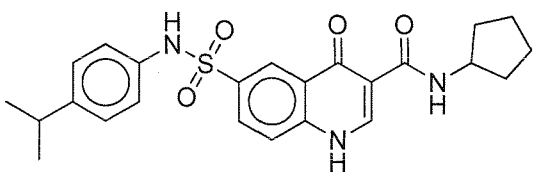

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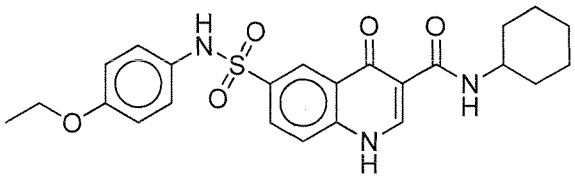

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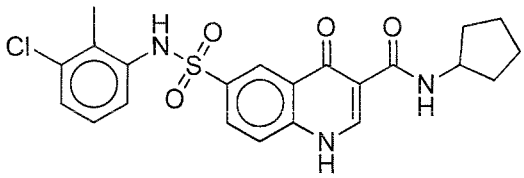

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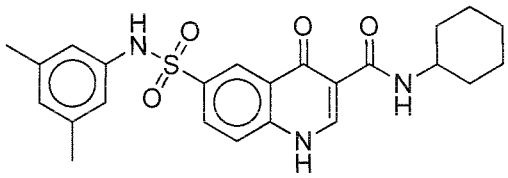

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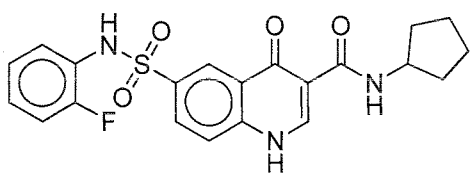

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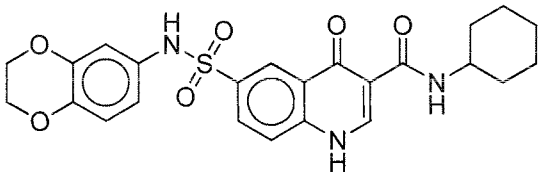

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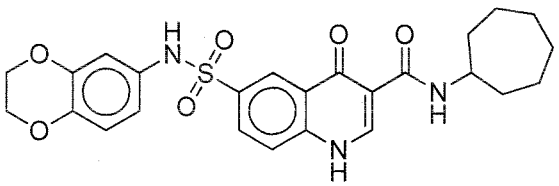
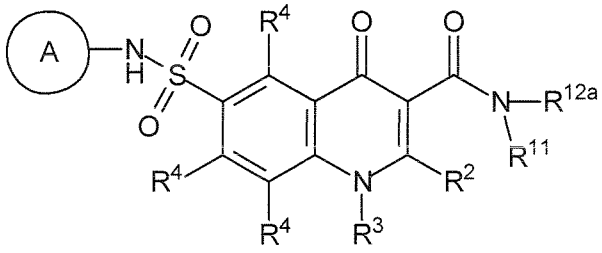


(17)

The present invention furthermore provides compounds that have not previously been known as therapeutic agents. Accordingly, the invention relates to a compound of the following formula (Ib) or a pharmaceutically acceptable salt, solvate or prodrug thereof, for use as a medicament:



(Ib)

In formula (Ib), R^{12a} is selected from sec-butyl, carbocyclyl, and heterocyclyl, wherein said carbocyclyl and said heterocyclyl are each optionally substituted with one or more (e.g., one, two, or three) groups R^{13}. Preferably, R^{12a} is selected from sec-butyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, wherein said cycloalkyl, said aryl, said heterocycloalkyl, and

said heteroaryl are each optionally substituted with one or more (e.g., one, two, or three) groups R^{13}. More preferably, R^{12a} is selected from sec-butyl, C_{3-7} cycloalkyl (e.g., cyclopentyl, cyclohexyl, or cycloheptyl), phenyl, heterocycloalkyl having 5 or 6 ring members, and heteroaryl having 5 or 6 ring members, wherein said C_{3-7} cycloalkyl, said phenyl, said heterocycloalkyl having 5 or 6 ring members, and said heteroaryl having 5 or 6 ring members are each optionally substituted with one or more (e.g., one, two, or three) groups R^{13}. Even more preferably, R^{12a} is sec-butyl or C_{3-7} cycloalkyl (preferably cyclopentyl, cyclohexyl, or cycloheptyl), wherein said C_{3-7} cycloalkyl is optionally substituted with one or more (e.g., one, two, or three) groups R^{13}. It is particularly preferred that the aforementioned cyclic groups (e.g., any of the aforementioned carbocyclyl, heterocyclyl, cycloalkyl, aryl, heterocycloalkyl and heteroaryl groups) are unsubstituted, i.e. are not substituted with any group R^{13}.

The other groups comprised in the compound of formula (Ib), particularly R^{11}, R^{13}, R^2, R^3, R^4 and A, have the same meanings, including the same preferred meanings, as described and defined herein for the corresponding groups comprised in compound of formula (I), with the proviso that if R^{11} is hydrogen and R^{12a} is cyclopropyl or cyclohexyl, then A is not 3-(trifluoromethyl)phenyl.

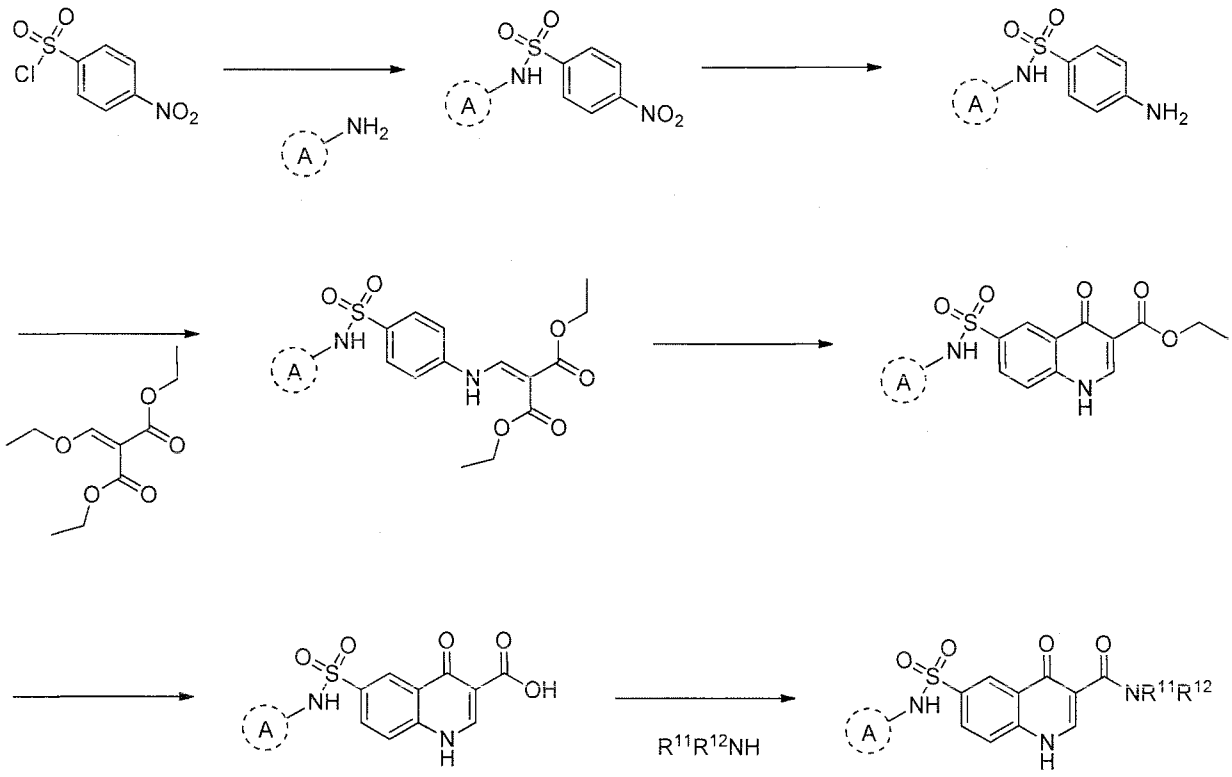
Preferred examples of the compounds of formula (Ib) are the compounds (3) to (17) as shown herein above as well as pharmaceutically acceptable salts, solvates and prodrugs of any of these compounds. The invention thus also refers to each one of the compounds (3) to (17), or a pharmaceutically acceptable salt, solvate or prodrug thereof, for use as a medicament. Moreover, the invention aiso relates to the compound (2) or a pharmaceutically acceptable salt, solvate or prodrug thereof for use as a medicament.

The compounds of formula (Ib) are useful as medicaments, particularly in the treatment or prevention of cancer, as described herein above and as also illustrated in the appended examples.

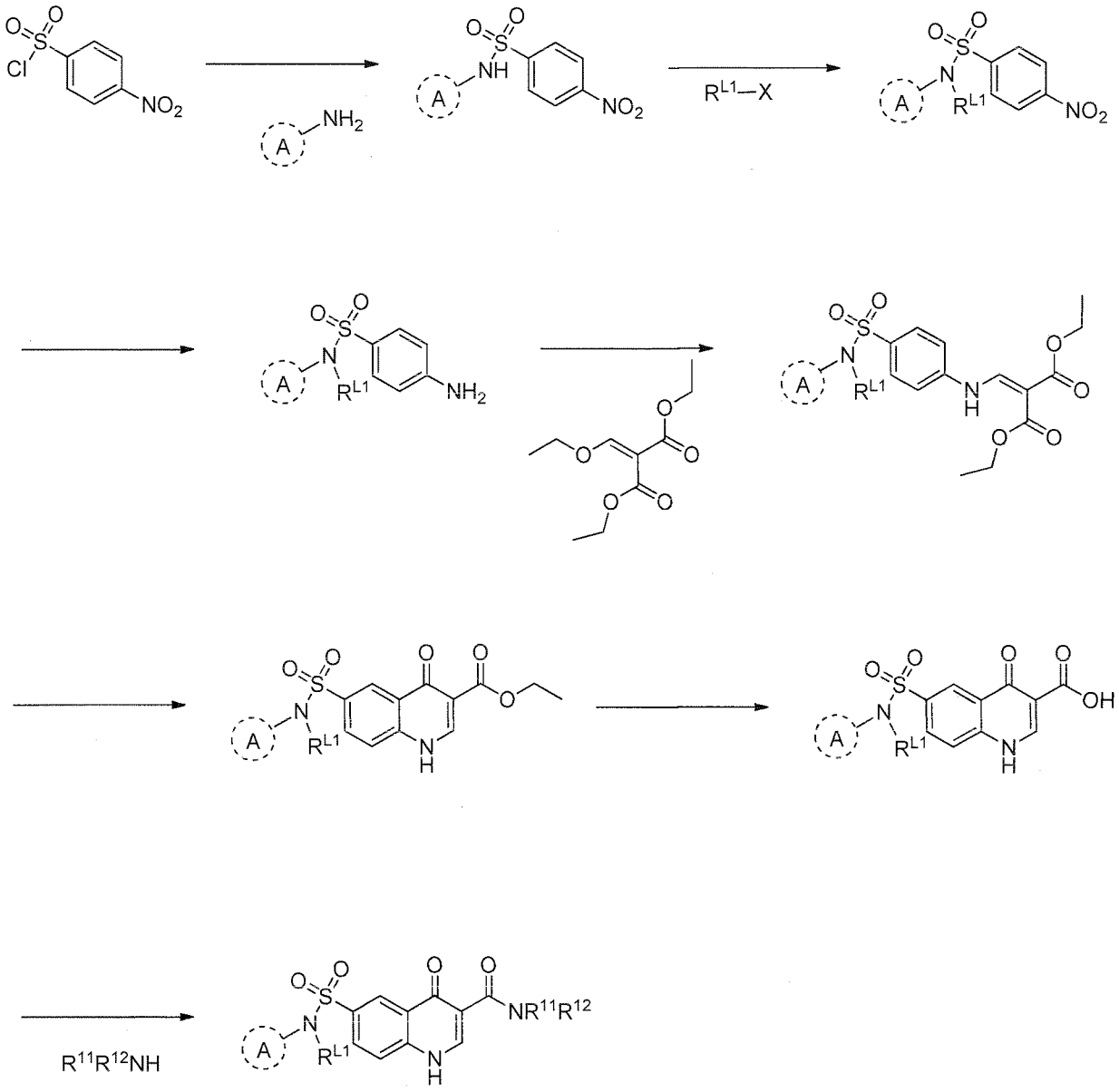
The present invention also relates to a pharmaceutical composition comprising a compound of formula (Ib) or a pharmaceutically acceptable salt, solvate or prodrug thereof, in combination with a pharmaceutically acceptable excipient.

Moreover, the invention relates to the use of a compound of formula (Ib) or a pharmaceutically acceptable salt, solvate or prodrug thereof in the preparation of a medicament, particularly for the treatment or prevention of a disease/disorder such as, e.g., cancer.

The compounds of formula (I), including also the compounds of formula (Ia) and the compounds of formula (Ib), can be prepared by methods known in the field of synthetic chemistry. For example, these compounds can be prepared in accordance with or in analogy to the synthetic routes described in the literature cited in this specification, including in particular Liu P et al., Eur J Med Chem, 2014, 79:413-21 and WO 2005/120497. The synthetic routes outlined in Schemes 1 and 2 below can also be used to prepare compounds of formula (I). Sulfonamides can be synthesized, e.g., by reaction of 4-nitrobenzene-1-sulfonyl chloride with appropriately substituted aromatic amines. Reduction of the aromatic nitro group followed by reaction with diethyl ethoxymethylene malonate and cyclization yields the oxoquinoline. Upon hydrolysis of the carboxylic acid amides may be prepared by reaction with appropriately substituted amines (Scheme 1). Disubstituted sulfonamides as shown in Scheme 2 may be prepared by, e.g., alkylation of the monosubstituted sulfonamide building block. Certain compounds of formula (I) are furthermore commercially available, e.g., from ChemDiv (San Diego, CA, USA).



Scheme 1: Synthetic route to oxoquinoline compounds



Scheme 2: Synthetic **route** to oxoquinoline compounds

The following definitions apply throughout the present specification, unless specifically indicated otherwise.

As used herein, the term "hydrocarbon group" refers to a group consisting of carbon atoms and hydrogen atoms.

The term "alicyclic" is used in connection with cyclic groups and denotes that the corresponding cyclic group is non-aromatic.

As used herein, the term "alkyl" refers to a monovalent saturated acyclic (i.e., non-cyclic) hydrocarbon group which may be linear or branched. Accordingly, an "alkyl" group does not comprise any carbon-to-carbon double bond or any carbon-to-carbon triple bond. A "C_{1-5} alkyl" denotes an alkyl group having 1 to 5 carbon atoms. Preferred exemplary alkyl groups are methyl, ethyl, propyl (e.g., n-propyl or isopropyl), or butyl (e.g., n-butyl, isobutyl, sec-butyl, or tert-butyl). Unless defined otherwise, the term "alkyl" preferably refers to C_{1-4} alkyl, more preferably to methyl or ethyl, and even more preferably to methyl.

As used herein, the term "alkenyl" refers to a monovalent unsaturated acyclic hydrocarbon group which may be linear or branched and comprises one or more (e.g., one or two) carbon-to-carbon double bonds while it does not comprise any carbon-to-carbon triple bond. The term "C_{2-5} alkenyl" denotes an alkenyl group having 2 to 5 carbon atoms. Preferred exemplary alkenyl groups are ethenyl, propenyl (e.g., prop-1-en-1-yl, prop-1-en-2-yl, or prop-2-en-1-yl), butenyl, butadienyl (e.g., buta-1,3-dien-1-yl or buta-1,3-dien-2-yl), pentenyl, or pentadienyl (e.g., isoprenyl). Unless defined otherwise, the term "alkenyl" preferably refers to C_{2-4} alkenyl.

As used herein, the term "alkynyl" refers to a monovalent unsaturated acyclic hydrocarbon group which may be linear or branched and comprises one or more (e.g., one or two) carbon-to-carbon triple bonds and optionally one or more carbon-to-carbon double bonds. The term "C_{2-5} alkynyl" denotes an alkynyl group having 2 to 5 carbon atoms. Preferred exemplary alkynyl groups are ethynyl, propynyl, or butynyl. Unless defined otherwise, the term "alkynyl" preferably refers to C_{2-4} alkynyl.

As used herein, the term "alkylene" refers to an alkanediyl group, i.e. a divalent saturated acyclic hydrocarbon group which may be linear or branched. A "C_{1-5} alkylene" denotes an alkylene group having 1 to 5 carbon atoms, and the term "C_{0-3} alkylene" indicates that a covalent bond (corresponding to the option "C_0 alkylene") or a C_{1-3} alkylene is present. Preferred exemplary alkylene groups are methylene (-CH_2-), ethylene (e.g., -CH_2-CH_2- or -CH(-CH_3)-), propylene (e.g., -CH_2-CH_2-CH_2-, -CH(-CH_2-CH_3)-, -CH_2-CH(-CH_3)-, or -CH(-CH_3)-CH_2-), or butylene (e.g., -CH_2-CH_2-CH_2-CH_2-). Unless defined otherwise, the term "alkylene" preferably refers to C_{1-4} alkylene (including, in particular, linear C_{1-4} alkylene), more preferably to methylene or ethylene, and even more preferably to methylene.

As used herein, the term "carbocyclyl" refers to a hydrocarbon ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings), wherein said ring group may be saturated, partially unsaturated (i.e., unsaturated but not aromatic) or aromatic. Unless defined otherwise, "carbocyclyl"

preferably refers to aryl, cycloalkyl or cycloalkenyl.

As used herein, the term "heterocyclyl" refers to a ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings), wherein said ring group comprises one or more (such as, e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms are carbon atoms, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) may optionally be oxidized, wherein one or more carbon ring atoms may optionally be oxidized (i.e., to form an oxo group), and further wherein said ring group may be saturated, partially unsaturated (i.e., unsaturated but not aromatic) or aromatic. Unless defined otherwise, "heterocyclyl" preferably refers to heteroaryl, heterocycloalkyl or heterocycloalkenyl.

As used herein, the term "aryl" refers to an aromatic hydrocarbon ring group, including monocyclic aromatic rings as well as bridged ring and/or fused ring systems containing at least one aromatic ring (e.g., ring systems composed of two or three fused rings, wherein at least one of these fused rings is aromatic; or bridged ring systems composed of two or three rings, wherein at least one of these bridged rings is aromatic). "Aryl" may, e.g., refer to phenyl, naphthyl, dialinyl (i.e., 1,2-dihydronaphthyl), tetralinyl (i.e., 1,2,3,4-tetrahydronaphthyl), anthracenyl, or phenanthrenyl. Unless defined otherwise, an "aryl" preferably has 6 to 14 ring atoms, more preferably 6 to 10 ring atoms, and most preferably refers to phenyl.

As used herein, the term "heteroaryl" refers to an aromatic ring group, including monocyclic aromatic rings as well as bridged ring and/or fused ring systems containing at least one aromatic ring (e.g., ring systems composed of two or three fused rings, wherein at least one of these fused rings is aromatic; or bridged ring systems composed of two or three rings, wherein at least one of these bridged rings is aromatic), wherein said aromatic ring group comprises one or more (such as, e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms are carbon atoms, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) may optionally be oxidized, and further wherein one or more carbon ring atoms may optionally be oxidized (i.e., to form an oxo group). "Heteroaryl" may, e.g., refer to thienyl (i.e., thiophenyl), benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl (i.e., furanyl), benzofuranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, pyrrolyl (e.g., 2H-pyrrolyl), imidazolyl, pyrazolyl, pyridyl (i.e., pyridinyl; e.g., 2-pyridyl, 3-pyridyl, or 4-pyridyl), pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, indolyl (e.g., 3H-indolyl), indazolyl, purinyl, Isoqulnolyl, quinoly!, phthalazinyl, naphthyridinyl, quinoxalinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl,

perimidinyl, phenanthrolinyl (e.g., [1,10]phenanthrolinyl, [1,7]phenanthrolinyl, or [4,7]phenanthrolinyl), phenazinyl, thiazolyl, isothiazolyl, phenothiazinyl, oxazolyl, isoxazolyl, furazanyl, phenoxazinyl, pyrazolo[1,5-a]pyrimidinyl (e.g., pyrazolo[1,5-a]pyrimidin-3-yl), 1,2-benzoisoxazol-3-yl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, 1H-tetrazolyl, 2H-tetrazolyl, coumarinyl, or chromonyl. Unless defined otherwise, a "heteroaryl" preferably refers to a 5 to 14 membered (more preferably 5 to 10 membered) monocyclic ring or fused ring system comprising one or more (e.g., one, two, three or four) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized; even more preferably, a "heteroaryl" refers to a 5 or 6 membered monocyclic ring comprising one or more (e.g., one, two or three) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized.

As used herein, the term "cycloalkyl" refers to a saturated hydrocarbon ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings: such as, e.g., a fused ring system composed of two or three fused rings). "Cycloalkyl" may, e.g., refer to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or adamantyl. Unless defined otherwise, "cycloalkyl" preferably refers to a C_{3-11} cycloalkyl, and more preferably refers to a C_{3-7} cycloalkyl. A particularly preferred "cycloalkyl" is a monocyclic saturated hydrocarbon ring having 3 to 7 ring members.

As used herein, the term "heterocycloalkyl" refers to a saturated ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings; such as, e.g., a fused ring system composed of two or three fused rings), wherein said ring group contains one or more (such as, e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms are carbon atoms, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) may optionally be oxidized, and further wherein one or more carbon ring atoms may optionally be oxidized (i.e., to form an oxo group). "Heterocycloalkyl" may, e.g., refer to oxetanyl, tetrahydrofuranyl, piperidinyl, piperazinyl, aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, morpholinyl (e.g., morpholin-4-yl), pyrazolidinyl, tetrahydrothienyl, octahydroquinolinyl, octahydroisoquinolinyl, oxazolidinyl, isoxazolidinyl, azepanyl, diazepanyl, oxazepanyl or 2-oxa-5-aza-bicyclo[2.2.1]hept-5-yl. Unless defined otherwise, "heterocycloalkyl" preferably refers to a 3 to 11 membered saturated ring group, which is a monocyclic ring or a fused ring system (e.g., a fused ring system composed of two fused rings), wherein said ring

group contains one or more (e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized; more preferably, "heterocycloalkyl" refers to a 5 to 7 membered saturated monocyclic ring group containing one or more (e.g., one, two, or three) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, and wherein one or more carbon ring atoms are optionally oxidized.

As used herein, the term "cycloalkenyl" refers to an unsaturated alicyclic (non-aromatic) hydrocarbon ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings; such as, e.g., a fused ring system composed of two or three fused rings), wherein said hydrocarbon ring group comprises one or more (e.g., one or two) carbon-to-carbon double bonds and does not comprise any carbon-to-carbon triple bond. "Cycloalkenyl" may, e.g., refer to cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, or cycloheptadieny!. Unless defined otherwise, "cycloalkenyl" preferably refers to a C_{3-11} cycloalkenyl, and more preferably refers to a C_{3-7} cycloalkenyl. A particularly preferred "cycloalkenyl" is a monocyclic unsaturated alicyclic hydrocarbon ring having 3 to 7 ring members and containing one or more (e.g., one or two; preferably one) carbon-to-carbon double bonds.

As used herein, the term "heterocycioaikenyi" refers to an unsaturated alicyclic (non-aromatic) ring group, including monocyclic rings as well as bridged ring, spiro ring and/or fused ring systems (which may be composed, e.g., of two or three rings; such as, e.g., a fused ring system composed of two or three fused rings), wherein said ring group contains one or more (such as, e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, and the remaining ring atoms and carbon atoms, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) may optionally be oxidized, wherein one or more carbon ring atoms may optionally be oxidized (i.e., to form an oxo group), and further wherein said ring group comprises at least one double bond between adjacent ring atoms and does not comprise any triple bond between adjacent ring atoms. "Heterocycloalkenyi" may, e.g., refer to 1,2.3,6-tetrahydropyridinyl. Unless defined otherwise, "heterocycloalkenyi" preferably refers to a 3 to 11 membered unsaturated alicyclic ring group, which is a monocyclic ring or a fused ring system (e.g., a fused ring system composed of two fused rings), wherein said ring group contains one or more (e.g., one, two, three, or four) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or

one or more N ring atoms (if present) are optionally oxidized, wherein one or more carbon ring atoms are optionally oxidized, and wherein said ring group comprises at least one double bond between adjacent ring atoms and does not comprise any triple bond between adjacent ring atoms; more preferably, "heterocycloalkenyl" refers to a 5 to 7 membered monocyclic unsaturated non-aromatic ring group containing one or more (e.g., one, two, or three) ring heteroatoms independently selected from O, S and N, wherein one or more S ring atoms (if present) and/or one or more N ring atoms (if present) are optionally oxidized, wherein one or more carbon ring atoms are optionally oxidized, and wherein said ring group comprises at least one double bond between adjacent ring atoms and does not comprise any triple bond between adjacent ring atoms.

As used herein, the term "halogen" refers to fluoro (-F), chloro (-Cl), bromo (-Br), or iodo (-I).

As used herein, the term "haloalkyl" refers to an alkyl group substituted with one or more (preferably 1 to 6, more preferably 1 to 3) halogen atoms which are selected independently from fluoro, chloro, bromo and iodo, and are preferably all fluoro atoms. It will be understood that the maximum number of halogen atoms is limited by the number of available attachment sites and, thus, depends on the number of carbon atoms comprised in the alkyl moiety of the haloalkyl group. "Haloalkyl" may, e.g., refer to $-CF_3$, $-CHF_2$, $-CH_2F$, $-CF_2-CH_3$, $-CH_2-CF_3$, $-CH_2-CHF_2$, $-CH_2-CF_2-CH_3$, $-CH_2-CF_2-CF_3$, or $-CH(CF_3)_2$.

Various groups are referred to as being "optionally substituted" in this specification. Generally, these groups may carry one or more substituents, such as, e.g., one, two, three or four substituents. It will be understood that the maximum number of substituents is limited by the number of attachment sites available on the substituted moiety. Unless defined otherwise, the "optionally substituted" groups referred to in this specification carry preferably not more than two substituents and may, in particular, carry only one substituent. Moreover, unless defined otherwise, it is preferred that the optional substituents are absent, i.e. that the corresponding groups are unsubstituted.

As used herein, the terms "optional", "optionally" and "may" denote that the indicated feature may be present but can also be absent. Whenever the term "optional", "optionally" or "may" is used, the present invention specifically relates to both possibilities, i.e., that the corresponding feature is present or, alternatively, that the corresponding feature is absent. For example, the expression "X is optionally substituted with Y" (or "X may be substituted with Y") means that X Is either substituted with Y or Is unsubstituted. Likewise, if a component of a composition is indicated to be "optional", the invention specifically relates to both possibilities, i.e., that the

corresponding component is present (contained in the composition) or that the corresponding component is absent from the composition.

A skilled person will appreciate that the substituent groups comprised in the compounds of formula (I) may be attached to the remainder of the respective compound via a number of different positions of the corresponding specific substituent group. Unless defined otherwise, the preferred attachment positions for the various specific substituent groups are as illustrated in the examples.

As used herein, the term "about" preferably refers to ±10% of the indicated numerical value, more preferably to =5% of the indicated numerical value, and in particular to the exact numerical value indicated.

The scope of the invention embraces all pharmaceutically acceptable salt forms of the compounds of formula (I) which may be formed, e.g., by protonation of an atom carrying an electron lone pair which is susceptible to protonation, such as an amino group, with an inorganic or organic acid, or as a salt of an acid group (such as a carboxylic acid group) with a physiologically acceptable cation. Exemplary base addition salts comprise, for example: alkali metal salts such as sodium or potassium salts; alkaline earth metal salts such as calcium or magnesium salts; zinc salts; ammonium salts; aliphatic amine salts such as trimethylamine, triethylamine, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine, procaine salts, meglumine salts, ethylenediamine salts, or choline salts; aralkyl amine salts such as N,N-dibenzylethylenediamine saits, benzathine salts, benethamine salts; heterocyclic aromatic amine salts such as pyridine salts, picoline salts, quinoline salts or isoquinoline salts; quaternary ammonium salts such as tetramethylammonium salts, tetraethylammonium salts, benzyltrimethylammonium salts, benzyltriethylammonium salts, benzyltributylammonium salts, methyltrioctylammonium salts or tetrabutylammonium salts; and basic amino acid salts such as arginine salts, lysine salts, or histidine salts. Exemplary acid addition salts comprise, for example! mineral acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate salts (such as, e.g., sulfate or hydrogensulfate salts), nitrate salts, phosphate salts (such as, e.g., phosphate, hydrogenphosphate, or dihydrogenphosphate salts), carbonate salts, hydrogencarbonate salts, perchlorate salts, borate salts, or thiocyanate salts; organic acid salts such as acetate, propionate, butyrate, pentanoate, hexanoate, heptanoate, octanoate, cyclopentanepropionate, decanoate, undecanoate, oleate, stearate, lactate, maleate, oxalate, fumarate, tartrate, malate, citrate, succinate, adipate, gluconate, glycolate, nicotinate, benzoate, salicylate, ascorbate, pamoate (embonate), camphorate, glucoheptanoate, or pivalate salts; sulfonate salts such as methanesulfonate (mesylate), ethanesulfonate (esylate),

2-hydroxyethanesulfonate (isethionate), benzenesulfonate (besylate), p-toluenesulfonate (tosylate), 2-naphthalenesulfonate (napsylate), 3-phenylsulfonate, or camphorsulfonate salts; glycerophosphate salts; and acidic amino acid salts such as aspartate or glutamate salts. Preferred pharmaceutically acceptable salts of the compounds of formula (I) include a hydrochloride salt, a hydrobromide salt, a mesylate salt, a sulfate salt, a tartrate salt, a fumarate salt, an acetate salt, a citrate salt, and a phosphate salt. A particularly preferred pharmaceutically acceptable salt of the compound of formula (I) is a hydrochloride salt. Accordingly, it is preferred that the compound of formula (I), including any one of the specific compounds of formula (I) described herein, is in the form of a hydrochloride salt, a hydrobromide salt, a mesylate salt, a sulfate salt, a tartrate salt, a fumarate salt, an acetate salt, a citrate salt, or a phosphate salt, and it is particularly preferred that the compound of formula (I) is in the form of a hydrochloride salt.

Moreover, the scope of the invention embraces the compounds of formula (I) in any solvated form, including, e.g., solvates with water, for example hydrates, or with organic solvents such as, e.g., methanol, ethanol or acetonitrile, i.e., as a methanolate, ethanolate or acetonitrilate, respectively, or in the form of any polymorph. It is to be understood that such solvates of the compounds of the formula (I) also include solvates of pharmaceutically acceptable salts of the compounds of the formula (I).

Furthermore, the compounds of formula (I) may exist in the form of different isomers, in particular stereoisomers (including, e.g., geometric isomers (or cis/trans isomers), enantiomers and diastereomers) or tautomers. All such isomers of the compounds of formula (I) are contemplated as being part of the present invention, either in admixture or in pure or substantially pure form. As for stereoisomers, the invention embraces the isolated optical isomers of the compounds according to the invention as well as any mixtures thereof (including, in particular, racemic mixtures/racemates). The racemates can be resolved by physical methods, such as, e.g., fractional crystallization, separation or crystallization of diastereomeric derivatives, or separation by chiral column chromatography. The individual optical isomers can also be obtained from the racemates via salt formation with an optically active acid followed by crystallization. The present invention further encompasses any tautomers of the compounds provided herein.

The scope **of** the invention also embraces compounds of formula (I), in which one or more atoms are replaced by a specific isotope of the corresponding atom. For example, the invention encompasses compounds of formula (I), in which one or more hydrogen atoms (or, e.g., all hydrogen atoms) are replaced by deuterium atoms (i.e., ^{2}H; also referred to as **"D").**

Accordingly, the invention also embraces compounds of formula (I) which are enriched in deuterium. Naturally occurring hydrogen is an isotopic mixture comprising about 99.98 mol-% hydrogen-1 (^{1}H) and about 0.0156 mol-% deuterium (^{2}H or D). The content of deuterium in one or more hydrogen positions in the compounds of formula (I) can be increased using deuteration techniques known in the art. For example, a compound of formula (I) or a reactant or precursor to be used in the synthesis of the compound of formula (I) can be subjected to an H/D exchange reaction using, e.g., heavy water (D_2O). Further suitable deuteration techniques are described in: Atzrodt J et al., *Bioorg Med Chem,* 20(18), 5658-5667, 2012; William JS et al., *Journal of Labelled Compounds and Radiopharmaceuticals,* 53(1 1-12), 635-644, 2010; Modvig A et al., *J Org Chem,* 79, 5861-5868, 2014. The content of deuterium can be determined, e.g., using mass spectrometry or NMR spectroscopy. Unless specifically indicated otherwise, it is preferred that the compound of formula (I) is not enriched in deuterium. Accordingly, the presence of naturally occurring hydrogen atoms or ^{1}H hydrogen atoms in the compounds of formula (I) is preferred.

The present invention also embraces compounds of formula (I), in which one or more atoms are replaced by a positron-emitting isotope of the corresponding atom, such as, e.g., ^{18}F, ^{11}C, ^{13}N, ^{15}0 ,, ^{76}Br, ^{77}Br, ^{120}I and/or ^{124}I. Such compounds can be used as tracers or imaging probes in positron emission tomography (PET). The invention thus includes (i) compounds of formula (I), in which one or more fluorine atoms (or, e.g., all fluorine atoms) are replaced by ^{18}F atoms, (ii) compounds of formula (I), in which one or more carbon atoms (or, e.g., all carbon atoms) are replaced by ^{11}C atoms, (ill) compounds of formula (I), in which one or more nitrogen atoms (or, e.g., all nitrogen atoms) are replaced by ^{13}N atoms, (iv) compounds of formula (I), in which one or more oxygen atoms (or, e.g., all oxygen atoms) are replaced by ^{15}0 atoms, (v) compounds of formula (I), in which one or more bromine atoms (or, e.g., all bromine atoms) are replaced by ^{76}Br atoms, (vi) compounds of formula (I), in which one or more bromine atoms (or, e.g., all bromine atoms) are replaced by ^{77}Br atoms, (vii) compounds of formula (I), in which one or more iodine atoms (or, e.g., all iodine atoms) are replaced by ^{120}I atoms, and (viii) compounds of formula (I), in which one or more iodine atoms (or, e.g., all iodine atoms) are replaced by ^{124}I atoms. In general, it is preferred that none of the atoms in the compounds of formula (I) are replaced by specific isotopes.

Pharmaceutically acceptable prodrugs of the compounds of formula (I) are derivatives which have chemically or metabolically cleavable groups and become, by solvolysis or under physiological conditions, the compounds of formula (I) which are pharmaceutically active *in vivo.* Prodrugs of the compounds according to the the present invention may be formed in a conventional manner with a functional group of the compounds such as, e.g., with an amino,

hydroxy or carboxy group. The prodrug form often offers advantages in terms of solubility, tissue compatibility or delayed release in a mammalian organism (see, Bundgaard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives, such as, e.g., esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. If a compound of the present invention has a carboxyl group, an ester derivative prepared by reacting the carboxyl group with a suitable alcohol or an amide derivative prepared by reacting the carboxyl group with a suitable amine is exemplified as a prodrug. An especially preferred ester derivative as a prodrug is methylester, ethylester, n-propylester, isopropylester, n-butylester, isobutylester, tert-butylester, morpholinoethylester, N,N-diethylglycolamidoester or a-acetoxyethylester. If a compound of the present invention has a hydroxy group, an acyloxy derivative prepared by reacting the hydroxyl group with a suitable acylhalide or a suitable acid anhydride is exemplified as a prodrug. An especially preferred acyloxy derivative as a prodrug is -OC(=0)-CH_3, -OC(=0)-C_2H_5, -OC(=0)-(tert-Bu), **-OC(=0)-$C_{15}H_{31}$**, -OC(=0)-(m-COONa-Ph), -OC(=0)-CH_2CH_2COONa, -0(C=0)-CH(NH_2)CH_3 or -OC(=0)-CH_2-$N(CH_3)_2$. If a compound of the present invention has an amino group, an amide derivative prepared by reacting the amino group with a suitable acid halide or a suitable mixed anhydride is exemplified as a prodrug. An especially preferred amide derivative as a prodrug is -NHC(=0)-$(CH_2)_2OCH_3$ or -NHC(=0)-**CH(NH_2)CH_3**.

The compounds provided herein may be administered as compounds *per se* or may be formulated as medicaments. The medicaments/pharmaceutical compositions may optionally comprise one or more pharmaceutically acceptable excipients, such as carriers, diluents, fillers, disintegrants, lubricating agents, binders, colorants, pigments, stabilizers, preservatives, antioxidants, and/or solubility enhancers.

In particular, the pharmaceutical compositions may comprise one or more solubility enhancers, such as, e.g., poly(ethylene glycol), including poly(ethylene glycol) having a molecular weight in the range of about 200 to about 5,000 Da, ethylene glycol, propylene glycol, non-ionic surfactants, tyloxapol, polysorbate 80, macrogol-15-hydroxystearate, phospholipids, lecithin, dimyristoyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine, cyclodextrins, ct-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-p-cyclodextrin, hydroxyethyl-y-cyclodextrin, hydroxypropyl-v-cyclodextrin, dihydroxypropyl-p-cyclodextrin, sulfobutylether-p-cyclodextrin, sulfobutylether-v-cyclodextrin, glucosyl-a-cyclodextrin, glucosyl-p-cyclodextrin, diglucosyl-p-cyclodextrin, maltosyl-a-cyclodextrin, maltosyl-p-cyclodextrin, maltosyl-y-cyclodextrin, maltotriosyl-β-cyclodextrin, maltotriosyl-y-cyclodextrin, dimaltosyl-p-cyclodextrin, methyl-p-cyclodextrin,

carboxyalkyl thioethers, hydroxypropy! methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, vinyl acetate copolymers, vinyl pyrrolidone, sodium lauryl sulfate, dioctyl sodium sulfosuccinate, or any combination thereof.

The pharmaceutical compositions can be formulated by techniques known to the person skilled in the art, such as the techniques published in "Remington: The Science and Practice of Pharmacy", Pharmaceutical Press, 22nd edition. The pharmaceutical compositions can be formulated as dosage forms for oral, parenteral, such as intramuscular, intravenous, subcutaneous, intradermal, intraarterial, intracardial, rectal, nasal, topical, aerosol or vaginal administration. Dosage forms for oral administration include coated and uncoated tablets, soft gelatin capsules, hard gelatin capsules, lozenges, troches, solutions, emulsions, suspensions, syrups, elixirs, powders and granules for reconstitution, dispersible powders and granules, medicated gums, chewing tablets and effervescent tablets. Dosage forms for parenteral administration include solutions, emulsions, suspensions, dispersions and powders and granules for reconstitution. Emulsions are a preferred dosage form for parenteral administration. Dosage forms for rectal and vaginal administration include suppositories and ovula. Dosage forms for nasal administration can be administered via inhalation and insufflation, for example by a metered inhaler. Dosage forms for topical administration include creams, gels, ointments, salves, patches and transdermal delivery systems.

The compounds of formula (I) or the above described pharmaceutical compositions comprising a compound of formula (I) may be administered to a subject by any convenient route of administration, whether systemically/peripherally or at the site of desired action, including but not limited to one or more of: oral (e.g., as a tablet, capsule, or as an ingestible solution), topical (e.g., transdermal, intranasal, ocular, buccal, and sublingual), parenteral (e.g., using injection techniques or infusion techniques, and including, for example, by injection, e.g., subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, or intrasternal by, e.g., implant of a depot, for example, subcutaneously or intramuscularly), pulmonary (e.g., by inhalation or insufflation therapy using, e.g., an aerosol, e.g., through mouth or nose), gastrointestinal, intrauterine, intraocular, subcutaneous, ophthalmic (including intravitreal or intracameral), rectal, and vaginal.

If said compounds or pharmaceutical compositions are administered parenterally, then examples of such administration include one or more of: intravenously, intraarterially, intraperitoneal^, intrathecally, intraventricularly, intraurethrally. intrasternally, intracardially, intracranially, intramuscularly or subcutaneously administering the compounds or

pharmaceutical compositions, and/or by using infusion techniques. For parenteral administration, the compounds are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

Said compounds or pharmaceutical compositions can also be administered orally in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavoring or coloring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications.

The tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycolate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included. Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the agent may be combined with various sweetening or flavoring agents, coloring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

Alternatively, said compounds or pharmaceutical compositions can be administered in the form of a suppository or pessary, or it may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compounds of the present invention may also be dermally or transdermal^ administered, for example, by the use of a skin patch.

Said compounds or pharmaceutical compositions may also be administered by sustained release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained-release matrices include, e.g., polylactides (see, e.g., US 3,773,919), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22:547-556 (1983)), poly(2-hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15:167-

277 (1981), and R. Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al., Id.) or poly-D-(-)-3-hydroxybutyric acid (EP1 33988). Sustained-release pharmaceutical compositions also include liposomally entrapped compounds. Liposomes containing a compound of the present invention can be prepared by methods known in the art, such as, e.g., the methods described in any one of: DE3218121 ; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. (USA) 77:4030-4034 (1980); EP0052322; EP0036676; EP088046; EP0143949; EP0142641 ; JP 83-1 18008; US 4,485,045; US 4,544,545; and EP0102324.

Said compounds or pharmaceutical compositions may also be administered by the pulmonary route, rectal routes, or the ocular route. For ophthalmic use, they can be formulated as micronized suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

It is also envisaged to prepare dry powder formulations of the compounds of formula (I) for pulmonary administration, particularly inhalation. Such dry powders may be prepared by spray drying under conditions which result in a substantially amorphous glassy or a substantially crystalline bioactive powder. Accordingly, dry powders of the compounds of the present invention can be made according to the emulsification/spray drying process disclosed in WO 99/16419 or WO 01/85136. Spray drying of solution formulations of the compounds of the present invention can be carried out, e.g., as described generally in the "Spray Drying Handbook", 5th ed., K. Masters, John Wiley & Sons, Inc., NY (1991). and in WO 97/41833 or WO 03/05341 1.

For topical application to the skin, said compounds or pharmaceutical compositions can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, 2-octyldodecanol, benzyl alcohol and water.

The present invention thus relates to the compounds or the pharmaceutical compositions provided herein, wherein the corresponding compound or pharmaceutical composition is to be administered by any one of: an oral route; topical route, including by transdermal, intranasal,

ocular, buccal, or sublingual route; parenteral route using injection techniques or infusion techniques, including by subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, intrasternal, intraventricular, intraurethral, or intracranial route; pulmonary route, including by inhalation or insufflation therapy; gastrointestinal route; intrauterine route; intraocular route; subcutaneous route; ophthalmic route, including by intravitreal, or intracameral route; rectal route; or vaginal route. Particularly preferred routes of administration of the compounds or pharmaceutical compositions of the present invention are oral administration or parenteral administration (e.g., subcutaneous or intravenous administration), and most preferably a compound or a pharmaceutical composition of the invention is to be administered orally.

Typically, a physician will determine the actual dosage which will be most suitable for an individual subject. The specific dose level and frequency of dosage for any particular individual subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the individual subject undergoing therapy.

A proposed, yet non-limiting dose of the compounds according to the invention for oral administration to a human (of approximately 70 kg body weight) may be 0.05 to 2000 mg, preferably 0.1 mg to 1000 mg, of the active ingredient per unit dose. The unit dose may be administered, e.g., 1 to 3 times per day. The unit dose may also be administered 1 to 7 times per week, e.g., with not more than one administration per day. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient/subject as well as the severity of the condition to be treated. The precise dose and also the route of administration will ultimately be at the discretion of the attendant physician or veterinarian.

The compounds of formula (I) can be used in combination with other therapeutic agents, including in particular other anticancer agents. When a compound of the invention is used in combination with a second therapeutic agent active against the same disease, the dose of each compound may differ from that when the compound is used alone. The combination of a compound of the present invention with a second therapeutic agent may comprise the administration of the second therapeutic agent simultaneously/concomitantly or sequentially/separately with the compound of the invention.

Preferably, the second therapeutic agent to be administered in combination with a compound of this invention is an anticancer drug. The anticancer drug to be administered in combination with a compound of formula (I) according to the present invention may, e.g., be selected from: a tumor angiogenesis inhibitor (for example, a protease inhibitor, an epidermal growth factor receptor kinase inhibitor, or a vascular endothelial growth factor receptor kinase inhibitor); a cytotoxic drug (for example, an antimetabolite, such as purine and pyrimidine analogue antimetabolites); an antimitotic agent (for example, a microtubule stabilizing drug or an antimitotic alkaloid); a platinum coordination complex; an anti-tumor antibiotic; an alkylating agent (for example, a nitrogen mustard or a nitrosourea); an endocrine agent (for example, an adrenocorticosteroid, an androgen, an anti-androgen, an estrogen, an anti-estrogen, an aromatase inhibitor, a gonadotropin-releasing hormone agonist, or a somatostatin analogue); or a compound that targets an enzyme or receptor that is overexpressed and/or otherwise involved in a specific metabolic pathway that is misregulated in the tumor cell (for example, ATP and GTP phosphodiesterase inhibitors, histone deacetylase inhibitors, protein kinase inhibitors (such as serine, threonine and tyrosine kinase inhibitors (for example, Abelson protein tyrosine kinase)) and the various growth factors, their receptors and corresponding kinase inhibitors (such as epidermal growth factor receptor (EGFR) kinase inhibitors, vascular endothelial growth factor receptor kinase inhibitors, fibroblast growth factor inhibitors, insulin-like growth factor receptor inhibitors and platelet-derived growth factor receptor kinase inhibitors)); methionine, aminopeptidase inhibitors, proteasome inhibitors, cyclooxygenase inhibitors (for example, cyclooxygenase-1 or cyclooxygenase-2 inhibitors), topoisomerase inhibitors (for example, topoisomerase I inhibitors or topoisomerase II inhibitors), and poly ADP ribose polymerase inhibitors (PARP inhibitors).

An alkylating agent which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, a nitrogen mustard (such as cyclophosphamide, mechlorethamine (chlormethine), uramustine, melphalan, chlorambucil, ifosfamide, bendamustine, or trofosfamide), a nitrosourea (such as carmustine, streptozocin, fotemustine, lomustine, nimustine, prednimustine, ranimustine, or semustine), an alkyl sulfonate (such as busulfan, mannosulfan, or treosulfan), an aziridine (such as hexamethylmelamine (altretamine), triethylenemelamine, ThioTEPA (N,N'N'-triethylenethiophosphoramide), carboquone, or triaziquone), a hydrazine (such as procarbazine), a triazene (such as dacarbazine), or an imidazotetrazines (such as temozolomide).

A platinum coordination complex which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, cisplatin, carboplatin, nedaplatin, oxaliplatin, satraplatin, or triplatin tetranitrate.

A cytotoxic drug which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, an antimetabolite, including folic acid analogue antimetabolites (such as aminopterin, methotrexate, pemetrexed, or raltitrexed), purine analogue antimetabolites (such as cladribine, clofarabine, fludarabine, 6-mercaptopurine (including its prodrug form azathioprine), pentostatin, or 6-thioguanine), and pyrimidine analogue antimetabolites (such as cytarabine, decitabine, 5-fluorouracil (including its prodrug forms capecitabine and tegafur), floxuridine, gemcitabine, enocitabine, or sapacitabine).

An antimitotic agent which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, a taxane (such as docetaxel, larotaxel, ortataxel, paclitaxei/taxol, or tesetaxel), a Vinca alkaloid (such as vinblastine, vincristine, vinflunine, vindesine, or vinorelbine), an epothilone (such as epothilone A, epothilone B, epothilone C, epothilone D, epothilone E, or epothilone F) or an epothilone B analogue (such as ixabepilone/azaepothilone B).

An anti-tumor antibiotic which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, an anthracycline (such as aclarubicin, daunorubicin, doxorubicin, epirubicin, idarubicin, amrubicin, pirarubicin, valrubicin, or zorubicin), an anthracenedione (such as mitoxantrone, or pixantrone) or an anti-tumor antibiotic isolated from Streptomyces (such as actinomycin (including actinomycin D), bleomycin, mitomycin (including mitomycin C), or plicamycin).

A tyrosine kinase inhibitor which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, axitinib, bosutinib, cediranib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, nilotinib, semaxanib, sorafenib, sunitinib, or vandetanib.

A topoisomerase-inhibitor which can be **used** as an anticancer drug in combination with a compound of the present invention may be, for example, a topoisomerase I inhibitor (such as irinotecan, topotecan, camptothecin, belotecan, rubitecan, or lamellarin D) or a topoisomerase II inhibitor (such as amsacrine, etoposide, etoposide phosphate, teniposide, or doxorubicin).

A PARP inhibitor which can be used as an anticancer drug in combination with a compound of the present invention may be, for example, BMN-673, olaparib, rucaparib, veliparib, CEP 9722, MK 4827, BGB-290, or 3-aminobenzamide.

Further anticancer drugs may also be used in combination with a compound of the present invention. The anticancer drugs may comprise biological or chemical molecules, like TNF-related apoptosis-inducing ligand (TRAIL), tamoxifen, amsacrine, bexarotene, estramustine, irofulven, trabectedin, cetuximab, panitumumab, tositumomab, alemtuzumab, bevacizumab, edrecolomab, gemtuzumab, alvocidib, seliciclib, aminolevulinic acid, methyl aminolevulinate, efaproxiral, porfimer sodium, talaporfin, temoporfin, verteporfin, alitretinoin, tretinoin, anagrelide, arsenic trioxide, atrasentan, bortezomib, carmofur, celecoxib, demecolcine, elesclomol, elsamitrucin, etoglucid, lonidamine, lucanthone, masoprocol, mitobronitol, mitoguazone, mitotane, oblimersen, omacetaxine, sitimagene, ceradenovec, tegafur, testolactone, tiazofurine, tipifarnib, vorinostat, or iniparib.

Also biological drugs, like antibodies, antibody fragments, antibody constructs (for example, single-chain constructs), and/or modified antibodies (like CDR-grafted antibodies, humanized antibodies, "full humanized" antibodies, etc.) directed against cancer or tumor markers/factors/cytokines involved in proliferative diseases can be employed in co-therapy approaches with the compounds of the invention. Examples of such biological molecules are anti-HER2 antibodies (e.g. trastuzumab, Herceptin®), anti-CD20 antibodies (e.g. Rituximab, Rituxan®, MabThera®, Reditux®), anti-CD19/CD3 constructs (see, e.g., EP-B1 1071752) and anti-TNF antibodies (see, e.g., Taylor PC. Antibody therapy for rheumatoid arthritis. Curr Opin Pharmacol. 2003. 3(3):323-328). Further antibodies, antibody fragments, antibody constructs and/or modified antibodies to be used in co-therapy approaches with the compounds of the invention can be found in Taylor PC. Curr Opin Pharmacol. 2003. 3(3):323-328; Roxana A. Maedica. 2006. 1(1):63-65.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation. The individual components of such combinations may be administered either sequentially or simultaneously/concomitantly in separate or combined pharmaceutical formulations by any convenient route. When administration is sequential, either the compound of the present invention (i.e., the compound of formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof) or the second therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same pharmaceutical composition or in different pharmaceutical compositions. When combined in the same formulation, it will be appreciated that the two compounds must

be stable and compatible with each other and the other components of the formulation. When formulated separately, they may be provided in any convenient formulation.

The compounds of formula (I) can also be administered in combination with physical therapy, such as radiotherapy. Radiotherapy may commence before, after, or simultaneously with administration of the compounds of the invention. For example, radiotherapy may commence 1-10 minutes, 1-10 hours or 24-72 hours after administration of the compounds. Yet, these time frames are not to be construed as limiting. The subject is exposed to radiation, preferably gamma radiation, whereby the radiation may be provided in a single dose or in multiple doses that are administered over several hours, days and/or weeks. Gamma radiation may be delivered according to standard radiotherapeutic protocols using standard dosages and regimens.

Based on the physiological effects of MTH1 suppression, MTH1 inhibitors are considered to synergize with radiotherapy and/or chemotherapeutics/anticancer drugs, particularly with DNA damaging agents, agents that interfere with DNA repair mechanisms, and agents that induce the production or inhibit the clearance of reactive oxygen species (ROS). It is thus particularly preferred that an anticancer drug to be administered in combination with a compound of formula (I) is a PARP inhibitor (e.g., BMN-673, olaparib, rucaparib, veliparib, CEP 9722, MK 4827, BGB-290, or 3-aminobenzamide) or an EGFR inhibitor/antagonist (e.g., gefitinib, erlotinib, lapatinib, afatinib, neratinib, ABT-414, dacomitinib, AV-412, PD 153035, vandetanib, PKI-166, pelitinib, canertinib, icotinib, poziotinib, BMS-690514, CUDC-101 , AP261 13, XL647, cetuximab, panitumumab, zalutumumab, nimotuzumab, or matuzumab).

It is furthermore preferred that an anticancer drug to be administered in combination with a compound of formula (I) is an immunooncology therapeutic (e.g., a monoclonal antibody or a polyclonal antibody) targeting any one of CTLA-4, PD-1/PD-L1 , TIM3, LAG3, OX4, CSF1 R, IDO, or CD40. Such immunooncology therapeutics include, e.g., an anti-CTLA-4 antibody (particularly an antagonistic or pathway-blocking anti-CTLA-4 antibody; e.g., ipllimumab or tremelimumab), an anti-PD-1 antibody (particularly an antagonistic or pathway-blocking anti-PD-1 antibody; e.g., nivolumab (BMS-936558), pembrolizumab (MK-3475), pidilizumab (CT-011), AMP-224, or APE02058), an anti-PD-LI antibody (particularly a pathway-blocking anti-PD-L1 antibody; e.g., BMS-936559, MEDI4736, MPDL3280A (RG7446), MDX-1 105, or MEDI6469), an anti-TIM3 antibody (particularly a pathway-blocking anti-TIM3 antibody), an anti-LAG3 antibody (particularly an antagonistic or pathway-blocking anti-LAG3 antibody; e.g., BMS-986016. IMP701 , or IMP731), an anti-OX4 antibody (particularly an agonistic anti-OX4 antibody; e.g., MEDI0562), an anti-CSF1R antibody (particularly a pathway-blocking

anti-CSF1 R antibody; e.g., IMC-CS4 or RG7155), an anti-IDO antibody (particularly a pathway-blocking anti-IDO antibody), or an anti-CD40 antibody (particularly an agonistic anti-CD40 antibody; e.g., CP-870,893 or Chi Lob 7/4). Further immunooncology therapeutics are known in the art and are described, e.g., in Kyi C et al., FEBS Lett, 2014, 588(2):368-76; Intlekofer AM et al., J Leukoc Biol, 2013, 94(1):25-39; Callahan MK et al., J Leukoc Biol, 2013, 94(1):41-53; Ngiow SF et al., Cancer Res, 201 1, 71(21):6567-71 ; and Blattman JN et al., Science, 2004, 305(5681):200-5.

The present invention thus relates to a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or prodrug thereof, or a pharmaceutical composition comprising any of the aforementioned entities in combination with a pharmaceutically acceptable excipient, for use in the treatment or prevention of cancer, wherein the compound or the pharmaceutical composition is to be administered in combination with an anticancer drug and/or in combination with radiotherapy.

Yet, the compounds of formula (I) can also be used in monotherapy, particularly in the monotherapeutic treatment or prevention of cancer (i.e., without administering any other anticancer agents until the treatment with the compound(s) of formula (I) is terminated). Accordingly, the invention also relates to a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or prodrug thereof, or a pharmaceutical composition comprising any of the aforementioned entities in combination with a pharmaceutically acceptable excipient, for use in the monotherapeutic treatment or prevention of cancer.

The subject or patient, such as the subject in need of treatment or prevention, may be an animal (e.g., a non-human animal), a vertebrate animal, a mammal, a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), a murine (e.g., a mouse), a canine (e.g., a dog), a feline (e.g., a cat), a porcine (e.g., a pig), an equine (e.g., a horse), a primate, a simian (e.g., a monkey or ape), a monkey (e.g., a marmoset, a baboon), an ape (e.g., a gorilla, chimpanzee, orang-utan, gibbon), or a human. In the context of this invention, it is particularly envisaged that animals are to be treated which are economically, agronomically or scientifically important. Scientifically important organisms include, but are not limited to, mice, rats, and rabbits. Lower organisms such as, e.g., fruit flies like *Drosophila melagonaster* and nematodes like *Caenorhabditis elegans* may also be used in scientific approaches. Non-limiting examples of agronomically important animals are sheep, cattle and pigs, while, for example, cats and dogs may be considered as economically important animals. Preferably, the subject/patient is a mammal; more preferably, the subject/patient is a human or a non-human mammal (such as, e.g., a guinea pig, a hamster, a rat, a mouse, a rabbit, a dog, a cat, a horse, a monkey, an ape, a

marmoset, a baboon, a gorilla, a chimpanzee, an orang-utan, a gibbon, a sheep, cattle, or a pig); most preferably, the subject/patient is a human.

The term "treatment" of a disorder or disease as used herein (e.g., "treatment" of cancer) is well known in the art. "Treatment" of a disorder or disease implies that a disorder or disease is suspected or has been diagnosed in a patient/subject. A patient/subject suspected of suffering from a disorder or disease typically shows specific clinical and/or pathological symptoms which a skilled person can easily attribute to a specific pathological condition (i.e., diagnose a disorder or disease).

The "treatment" of a disorder or disease may, for example, lead to a halt in the progression of the disorder or disease (e.g., no deterioration of symptoms) or a delay in the progression of the disorder or disease (in case the halt in progression is of a transient nature only). The "treatment" of a disorder or disease may also lead to a partial response (e.g., amelioration of symptoms) or complete response (e.g., disappearance of symptoms) of the subject/patient suffering from the disorder or disease. Accordingly, the "treatment" of a disorder or disease may also refer to an amelioration of the disorder or disease, which may, e.g., lead to a halt in the progression of the disorder or disease or a delay in the progression of the disorder or disease. Such a partial or complete response may be followed by a relapse. It is to be understood that a subject/patient may experience a broad range of responses to a treatment (such as the exemplary responses as described herein above). The treatment of a disorder or disease may, *inter alia,* comprise curative treatment (preferably leading to a complete response and eventually to healing of the disorder or disease) and palliative treatment (including symptomatic relief).

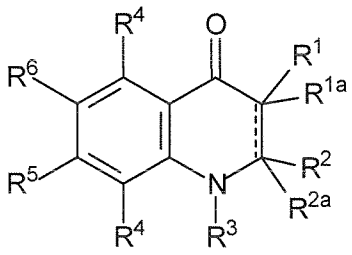
The term "prevention" of a disorder or disease as used herein (e.g., "prevention" of cancer) is also well known in the art. For example, a patient/subject suspected of being prone to suffer from a disorder or disease may particularly benefit from a prevention of the disorder or disease. The subject/patient may have a susceptibility or predisposition for a disorder or disease, including but not limited to hereditary predisposition. Such a predisposition can be determined by standard methods or assays, using, e.g., genetic markers or phenotypic indicators. It is to be understood that a disorder or disease to be prevented in accordance with the present invention has not been diagnosed or cannot be diagnosed in the patient/subject (for example, the patient/subject does not show any clinical or pathological symptoms). Thus, the term "prevention" comprises the use of a compound of the present invention before any clinical and/or pathological symptoms are diagnosed or determined or can be diagnosed or determined by the attending physician.

It is to be understood that the present invention specifically relates to each and every combination of features and embodiments described herein, including any combination of general and/or preferred features/embodiments. In particular, the invention specifically relates to each combination of meanings (including general and/or preferred meanings) for the various groups and variables comprised in formula (I).

In this specification, a number of documents including patent applications and scientific literature are cited. The disclosure of these documents, while not considered relevant for the patentability of this invention, is herewith incorporated by reference in its entirety. More specifically, all referenced documents are incorporated by reference to the same extent as if each individual document was specifically and individually indicated to be incorporated by reference.

The present invention particularly relates to the following items:

1. A compound of the following formula (I)



(I)

wherein:

R^1 is -CO-N(R^{11})-R^{12} or -N(R^{11})-CO-R^{12};

R^{11} is hydrogen or C_{1-5} alkyl;

R^{12} is selected from C_{1-5} alkyl, carbocyclyl, and heterocyclyl, wherein said carbocyclyl and said heterocyclyl are each optionally substituted with one or more groups R^{13};

each R^{13} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(Co-3 alkylene)-OH, -(C_{0-3} alkylene)-0(C_{1-5} alkyl), -(C_{0-3} alkylene)-0(C,.

alkylene)-OH, -(C_{0-3} alkylene)-0(C_{1-5} alkylene)-0(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(Co-3 alkylene)-S(C_{1-5} alkyl), -(C_{0-3} aikylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(d. $_5$ alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CF_3, -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-N0 $_2$, -(C_{0-3} alkylene)-N $_3$, -(C_{0-3} alkylene)-CHO, -(Co-3 alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-0-(C_{1-5} alkyl), -(C_{0-3} alkylene)-0-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(Ci_5 alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} aikylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(d_ $_5$ alkyl), -(C_{0-3} alkylene)-S0 $_2$-NH_2, -(C_{0-3} alkylene)-S0 $_2$-NH(C,. $_5$ alkyl), -(C_{0-3} alkylene)-S0 $_2$-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-S0 $_2$-(C_{1-5} alkyl), and -(C_{0-3} alkylene)-N(Ci- $_5$ alkyl)-S0 $_2$-(C_{1-5} alkyl);

$\overline{\text{-----}}$ is a double bond or a single bond;

if $\overline{\text{-----}}$ is a double bond, then R^{1a} and R^{2a} are absent, and R^2 is selected from hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -0 (C_{1-5} alkyl), -0(d. $_5$ alkylene)-OH, -0(C_{1-5} alkylene)-0(d. $_5$ alkyl), -SH, -S(d_ $_5$ alkyl), -S(C_{1-5} alkylene)-SH, -S(d. $_5$ alkylene)-S(d. $_5$ alkyl), -NH_2, -NH(d. $_5$ alkyl), -N(C_{1-5} alkyi)(Ci. $_5$ alkyl), halogen, d $_{-5}$ haloalkyl, -CF_3, and -CN;

if $\overline{\text{-----}}$ is a single bond, then R^{1a} is selected from hydrogen, d $_{-5}$ alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -0(d. $_5$ alkyl), -0(d. $_5$ alkylene)-OH, -0(d. $_5$ alkylene)-0(d- $_5$ alkyl), -SH, -S(d-s alkyl), -S(d. $_5$ alkylene)-SH, -S(d. $_5$ alkylene)-S(d.5 alkyl), -NH_2, -NH(d. $_5$ alkyl), -N(d_ $_5$ alkyl)(d. $_5$ alkyl), halogen, d $_{-5}$ haloalkyl, -CF_3, and -CN,

R^2 is selected from hydrogen, d $_{-5}$ alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -0(Ci. $_5$ alkyl), -0(C,. $_5$ alkylene)-OH, -0(Ci. $_5$ alkylene)-0(d. $_5$ alkyl), -SH, -S(C-. $_5$ alkyl), -S(d. $_5$ alkylene)-SH, -S(d_ $_5$ alkylene)-S(d. $_5$ alkyl), -NH_2, -NH(C,. $_5$ alkyl), -N(d_ $_5$ alkyl)(C_{1-5} alkyl), halogen, d $_{-5}$ haloalkyl, -CF_3, and -CN,

R^{2a} is selected from hydrogen, **d $_{-5}$** alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -0(C,. $_5$ alkyl), -0(d. $_5$ alkylene)-OH, -0(d. $_5$ alkylene)-0(C_{1-5} alkyl), -SH, -S(d. $_5$ alkyl), -S(**d** $_{-5}$ alkylene)-SH, -S(d. $_5$ alkylene)-S(C,. $_5$ alkyl), -NH_2, -NH(**d** $_{-5}$ alkyl), -N(C,. $_5$ alkyl)(d. $_5$ alkyl), halogen, d $_{-5}$ haloalkyl, -CF_3, and -CN, and

R^2 and R^{2a} may also together form an oxo group;

R^3 is hydrogen or C_{1-5} alkyl;

each R^4 is independently selected from hydrogen, d $_{-5}$ alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(d $_{-3}$ alkylene)-OH, -(C_{0-3} alkylene)-0(C_{1-5} alkyl), -(C_{0-3} alkylene)-0(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-0 (C_{1-5} alkylene)-0(d $_{-5}$ alkyl), -(C_{0-3} alkylene)-SH. -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(d $_{-5}$ alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyi)(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(d $_{-5}$ haloalkyl), -(C_{0-3} alkylene)-CF_3, -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-N0 $_2$, -(C_{0-3} alkylene)-N $_3$, -(C_{0-3} alkylene)-CHO, -(Co-$_3$ alkylene)-CO-(Ci. $_5$ alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-0-(C_{1-5} alkyl), -(C_{0-3} alkylene)-0-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(d-s alkyl), -(C_{0-3} alkylene)-NH-CO-(Ci $_{-5}$ alkyl), -(C_{0-3} alkylene)-N(Ci. $_5$ alkyl)-CO-(d-s alkyl), -(C_{0-3} alkylene)-S0 $_2$-NH_2, -(C_{0-3} alkylene)-S0 $_2$-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-S0 $_2$-N(C_{1-5} alkyl)(d $_{-5}$ alkyl), -(C_{0-3} alkylene)-NH-S0 $_2$-(C_{1-5} alkyl), and -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl);

one of R^5 and R^6 is -L-A, and the other one of R^5 and R^6 is a group R^4;

L is C_{1-5} alkylene, wherein one or two -CH_2- units comprised in said d $_{-5}$ alkylene are each optionally replaced by a group independently selected from -S0 $_2$-N(R^{L1})-, -N(R^{L1})-S0 $_2$-, -S0 $_2$-, -SO-, -S-, -0-, -CO-, -C(=0)0-, -0-C(=0)-, -N(R^{L1})-, -N(R^{L1})-CO-, and -C0-N(R^{L1})-;

each R^{L1} is independently selected from hydrogen and d $_{-5}$ alkyl;

A is aryl or heteroaryl, wherein said aryl and said heteroaryl are each optionally substituted with one or more groups R^{A1}; and

each R^{A1} is independently selected from d $_{-5}$ alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(Co-$_3$ alkylene)-OH, -(C_{0-3} alkylene)-0 (d $_{-5}$ alkyl), -(C_{0-3} alkylene)-0(d $_{-5}$ alkylene)-OH, -(C_{0-3} alkylene)-0(d. $_5$ alkylene)-0(d $_{-5}$ alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(d $_{-5}$ alkyl), -(C_{0-3} alkylene)-S(d. $_5$ alkylene)-SH, -(C_{0-3} alkylene)-S(d_ $_5$ alkylene)-S(d $_{-5}$ alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(d. $_5$ aikyl)(d. $_5$ alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CF_3, -(C_{0-3}

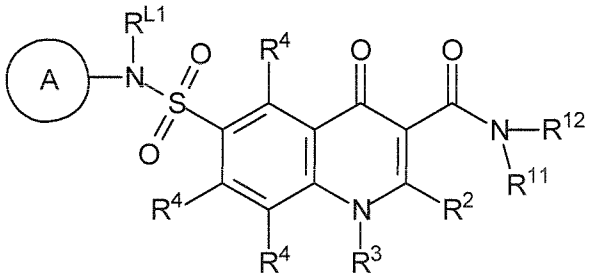
alkylene)-CN , -(C_{0-3} alkylene)-N0 $_2$, -(C_{0-3} alkylene)-N $_3$, -(C_{0-3} alkylene)-CHO, -(C_{0-3} alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-0-(C_{1-5} alkyl) , -(C_{0-3} alkylene)-0-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH $_2$, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyi)(d- $_5$ alkyl) , -(C_{0-3} alkylene)-NH-C0-(C_{1-5} alkyl) , -(C_{0-3} alkylene)-N(d-s alkyl)-C0-(d-5 alkyl) , -(C_{0-3} alkylene)-S0 $_2$-NH $_2$, -(C_{0-3} alkylene)-S0 $_2$-NH(C_{1-5} alkyl) , -(C_{0-3} alkylene)-S0 $_2$-N(d. $_5$ aikyl)(C_{1-5} alkyl) , -(C_{0-3} alkylene)-NH-S0 $_2$-(d-5 alkyl), and -(CQ-3 alkylene)-N(d. $_5$ alkyl)-S0 $_2$-(d. $_5$ alkyl) , and two groups R^{A1} which are bound to adjacent carbon ring atoms may also be mutually linked to form a group -0-(CH_2)$_{1-3}$-0-;

or a pharmaceutically acceptable salt, solvate or prodrug thereof

for use in the treatment or prevention of cancer.

2. The compound for use according to item 1, wherein R^5 is a group R^4, R^6 is -L-A, and L is d $_{-3}$ alkylene, wherein one -CH_2- unit comprised in said d-3 alkylene is replaced by -S0 $_2$-N(R^{L1})- or by -N(R^{L1})-S0 $_2$-.

3. The compound for use according to item 1, wherein said compound is a compound of the following formula (la)



(la)

wherein R^{11}, R^{12}, R^2, R^3, R^4, R^{L1} and A are as defined in item 1,

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

4. The compound for use according to any one of items 1 to 3, wherein R^{12} is selected from C_1-5 alkyl, cycloalkyl, aryl, heterocycloalkyl, and heteroaryl, wherein said

cycloalkyl, said aryl, said heterocycloalkyi, and said heteroaryl are each optionally substituted with one or more groups R^{13}.

5. The compound for use according to any one of items 1 to 4, wherein R^{12} is d $_{-5}$ alkyl or C_{3-7} cycloalkyl, wherein said C_{3-7} cycloalkyl is optionally substituted with one or more groups R^{13}.

6. The compound for use according to any one of items 1 to 5, wherein each R^{13} is independently selected from C_{1-5} alkyl, C2.5 alkenyl, C2-5 alkynyl, -OH , -0(d-5 alkyl), -0(d- $_5$ alkylene)-OH, -0(d. $_5$ alkylene)-0(d. $_5$ alkyl), -SH , -S(d $_{-5}$ alkyl), -S(d. $_5$ alkylene)-SH, -S(C $_{1-5}$ alkylene)-S(d. $_5$ alkyl), -NH $_2$, -NH (d $_{-5}$ alkyl), -N(d_ $_5$ alkyl)(d. $_5$ alkyl), halogen, d $_{-5}$ haloalkyl, -CF $_3$, and -CN .

7. The compound for use according to any one of items 1 to 6, wherein R^3 is hydrogen.

8. The compound for use according to any one of items 1 to 7, wherein each R^4 is independently selected from hydrogen, d $_{-5}$ alkyl, C2-5 alkenyl, C2-5 alkynyl, -OH , -0(d $_{-5}$ alkyl), -0(d_ $_5$ alkylene)-OH, -0(d. $_5$ alkylene)-0(d. $_5$ alkyl), -SH, -S (d-5 alkyl), -S (d-s alkylene)-SH , -S (d $_{-5}$ alkylene)-S(d. $_5$ alkyl), -NH $_2$, -NH (d. $_5$ alkyl), -N(d_ $_5$ alkyl)(d. $_5$ alkyl), halogen, d $_{-5}$ haloalkyl, -CF $_3$, and -CN .

9. The compound for use according to any one of items 1 to 8, wherein A is phenyl which is optionally substituted with one or more groups R^{A1}.

10. The compound for use according to any one of items 1 to 9, wherein each R^{A1} is independently selected from d $_{-5}$ alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -0(d_ $_5$ alkyl), -0 (d $_{-5}$ alkylene)-OH , -0(C $_{1-5}$ alkylene)-0(d. $_5$ alkyl), -SH , -S (d- $_5$ alkyl), -S (d. $_5$ alkylene)-SH , -S (d_ $_5$ alkylene)-S(d_ $_5$ alkyl), -NH_2, -NH (d_ $_5$ alkyl), -N(d-s alkyl)(d. $_5$ alkyl), halogen, C_{1-5} haloalkyl, -CF_3, and -CN, and two groups R^{A1} which are bound to adjacent carbon ring atoms may also be mutually linked to form a group -0-(CH $_2$)1-$_3$-0-.

11. The compound for use according to any one of items 1 to 3, wherein said compound is selected from:

$_N$-(sec-butyl)-6-(N-methyl-N-(m-tolyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

$_N$-cyclopentyl-6-(N-(3,4-dimethylphenyl)-N-methylsulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclopentyl-6-(N-(2-ethylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclopentyl-6-(N-(3-methoxyphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclopenty!-4-oxo-6-(N-(3-(trifluoromethyl)phenyl)sulfamoyl)-1 ,4-dihydroquinoline-3-carboxamide;

6-(N-(3-methoxyphenyl)sulfamoyl)-N-(2-methylcyclohexyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclohexyl-6-(N-(3-methoxyphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-(sec-butyl)-6-(N-(2-ethylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclopentyl-6-(N-(2,3-dihydrobenzo[b][1 ,4]dioxin-6-yl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoiine-3-carboxamide;

N-(2,3-dimethylcyclohexyl)-6-(N-(2-fluorophenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide:

N-cyclopentyl-6-(N-(4-isopropylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclohexyl-6-(N-(4-ethoxyphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

6-(N-(3-chloro-2-methylpheny!)sulfamoyl)-N-cyclopentyi-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclohexyl-6-(N-(3,5-dimethylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclopentyl-6-(N-(2-fluorophenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclohexyl-6-(N-(2,3-dihydrobenzo[b][1 ,4]dioxin-6-y!)sulfamoyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide;

N-cycloheptyl-6-(N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfamoyl)-4-oxo-1,Δ-dihydroquinoiine-3-carboxamide; and

a pharmaceutically acceptable salt, solvate or prodrug of any one of these compounds.

12. A pharmaceutical composition comprising a compound as defined in any one of items 1 to 11 and a pharmaceutically acceptable excipient for use in the treatment or prevention of cancer.

13. Use of a compound as defined in any one of items 1 to 11 in the preparation of a medicament for the treatment or prevention of cancer.

14. A method of treating or preventing cancer, the method comprising administering a compound as defined in any one of items 1 to 11 or a pharmaceutical composition as defined in item 12 to a subject in need thereof.

15. The compound for use according to any one of items 1 to 11 or the pharmaceutical composition for use according to item 12 or the use of item 13 or the method of item 14, wherein said cancer is selected from gastrointestinal cancer, colorectal cancer, liver cancer, pancreatic cancer, stomach cancer, genitourinary cancer, bladder cancer, esophageal cancer, prostate cancer, lung cancer, breast cancer, hematological cancer, leukemia, lymphoma, ovarian cancer, brain cancer, neuroblastoma, Ewing's sarcoma, kidney cancer, skin cancer, and head and/or neck cancer.

16. The compound for use according to item 15 or the pharmaceutical composition for use according to item 15 or the use of item 15 or the method of item 15, wherein said cancer is breast cancer which is selected from triple-negative breast cancer and breast cancer having a BRCA1 and/or BRCA2 gene mutation.

17. The compound for use according to any one of items 1 to 11, 15 or 16 or the pharmaceutical composition for use according to item 12, 15 or 16 or the use of item 13, 15 or 16 or the method of any one of items 14 to 16, wherein said cancer has an activating RAS mutation and/or an activating EGFR mutation.

18. The compound for use according to any one of items 1 to 11 or 15 to 17 or the pharmaceutical composition for use according to item 12 or 15 to 17 or the use of any one of items 13 or 15 to 17 or the method of any one of items 14 to 17, wherein the compound, the pharmaceutical composition or the medicament is to be administered orally or parenterally.

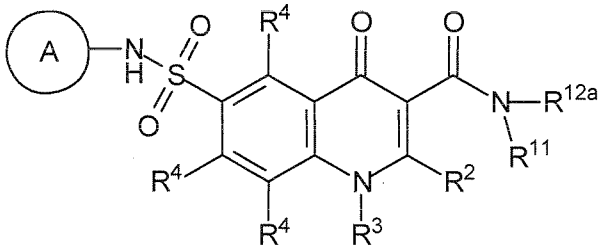
19. The compound for use according to any one of items 1 to 11 or 15 to 18 or the pharmaceutical composition for use according to item 12 or 15 to 18 or the use of any one of items 13 or 15 to 18 or the method of any one of items 14 to 18, wherein the compound, the pharmaceutical composition or the medicament is to be administered in combination with an anticancer drug and/or in combination with radiotherapy.

20. The compound for use according to any one of items 1 to 11 or 15 to 18 or the pharmaceutical composition for use according to item 12 or 15 to 18 or the use of any one of items 13 or 15 to 18 or the method of any one of items 14 to 18, wherein the compound, the pharmaceutical composition or the medicament is to be administered in combination with a PARP inhibitor and/or an EGFR inhibitor/antagonist, wherein the PARP inhibitor may be selected from BMN-673, olaparib, rucaparib, veliparib, CEP 9722, MK 4827, BGB-290 and 3-aminobenzamide, and further wherein the EGFR inhibitor/antagonist may be selected from gefitinib, erlotinib, lapatinib, afatinib, neratinib, ABT-414, dacomitinib, AV-412, PD 153035, vandetanib, PKI-166, pelitinib, canertinib, icotinib, poziotinib, BMS-690514, CUDC-101 , AP261 13, XL647, cetuximab, panitumumab, zalutumumab, nimotuzumab and matuzumab.

21. The compound for use according to any one of items 1 to 11 or 15 to 20 or the pharmaceutical composition for use according to item 12 or 15 to 20 or the use of any one of items 13 or 15 to 20 or the method of any one of items 14 to 20, wherein the subject to be treated is a human.

22. *In vitro* use of a compound as defined in any one of items 1 to 11 as an MTH1 inhibitor.

23. A compound of the following formula (Ib)



(Ib)

wherein:

R^{11} is hydrogen or C_{1-5} alkyl;

R^{12a} is selected from sec-butyl, carbocyclyL and heterocyclyl, wherein said carbocyclyl and said heterocyclyl are each optionally substituted with one or more groups R^{13};

each R^{13} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(Co-3 alkylene)-OH, -(C_{0-3} alkylene)-0 (C_{1-5} alkyl), -(C_{0-3} alkylene)-0(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-0(C_{1-5} alkylene)-0(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(Co-3 alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CF_3, -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-NO_2, -(C_{0-3} alkylene)-N_3, -(C_{0-3} alkylene)-CHO, -(Co-3 alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-0-(C_{1-5} alkyl), -(C_{0-3} alkylene)-0-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-N H-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} aikyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-N(C_{1-5} alkyl)(C_{1-5} alkyl), and -(Co-3 alkylene)-N(C_{1-5} alkyl)-SO_2-(C_{1-5} alkyl);

R^2 is selected from hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -0(C_{1-5} alkyl), -0(C_{1-5} alkylene)-OH, -0(C_{1-5} alkylene)-0(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -CF_3, and -CN;

R^3 is hydrogen or C_{1-5} alkyl;

each R^4 is independently selected from hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-0(C_{1-5} alkyl), -(C_{0-3} alkyleneJ-OiC^s alkylene)-OH, -(C_{0-3} alkylene)-0(C_{1-5} alkylene)-Q(d-5 alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkyiene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkyiene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(Ci.$_5$ alkyl)(Cu$_5$ alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CF_3, -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-NO_2, -(C_{0-3} alkylene)-N_3, -(C_{0-3} alkylene)-CHO, -(Co-3 alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-0-(C_{1-5} alkyl), -(C_{0-3} alkylene)-0-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-N H-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-SO_2-NH_2, -(C_{0-3} alkylene)-SO_2-NH(C_{1-5} alkyl), -(C_{0-3}

alkylene)-S0 $_2$-N(Ci. $_5$ alkyl)(C$_{1.5}$ alkyl), -(C$_{0\text{-}3}$ alkylene)-NH-S0 $_2$-(d-5 alkyl), and -(Co-3 alkylene)-N(C $_{1\text{-}5}$ alkyl)-S0 $_2$-(C $_{1\text{-}5}$ alkyl);

A is aryl or heteroaryl, wherein said aryl and said heteroaryl are each optionally substituted with one or more groups R^{A1}; and

each R^{A1} is independently selected from C$_{1\text{-}5}$ alkyl, d-s alkenyl, C$_{2\text{-}5}$ alkynyl, -(Co-3 alkylene)-OH, -(C$_{0\text{-}3}$ alkylene)-0(C $_{1\text{-}5}$ alkyl), -(C$_{0\text{-}3}$ alky!ene)-0(d-5 alkylene)-OH, -(C$_{0\text{-}3}$ alkylene)-0(d- $_5$ aikylene)-0(d-s alkyl), -(C$_{0\text{-}3}$ alkylene)-SH, -(Co-3 alkylene)-S(d-s alkyl), -(C$_{0\text{-}3}$ alkylene)-S(C $_{1\text{-}5}$ alkylene)-SH, -(C$_{0\text{-}3}$ alkylene)-S(C,. $_5$ alkylene)-S(d-s alkyl), -(C$_{0\text{-}3}$ alkylene)-NH $_2$, -(d-s a!kylene)-NH(C $_{1\text{-}5}$ alkyl), -(C$_{0\text{-}3}$ alkylene)-N(d-s alkyl)(Ci$_$ $_5$ alkyl), -(d-3 alkylene)-halogen, -(C$_{0\text{-}3}$ alkylene)-(C $_{1\text{-}5}$ haloalkyl), -(C$_{0\text{-}3}$ a!kylene)-CF $_3$, -(C$_{0\text{-}3}$ alkylene)-CN, -(d-3 alkylene)-N0 $_2$, -(C$_{0\text{-}3}$ alkylene)-N $_3$, -(C$_{0\text{-}3}$ alkylene)-CHO, -(d-3 alkylene)-CO-(Ci. $_5$ alkyl), -(d-3 alkylene)-COOH, -(d- $_3$ alkylene)-CO-0-(d. $_5$ alkyl), -(d-3 alkylene)-0-CO-(d. $_5$ alkyl), -(C$_{0\text{-}3}$ alkylene)-CO-NH $_2$, -(d. $_3$ alkylene)-CO-NH(d $_{\text{-}5}$ alkyl), -(C$_{0\text{-}3}$ alkylene)-CO-N(d $_{\text{-}5}$ alkyl)(d- $_5$ alkyl), -(C$_{0\text{-}3}$ alkylene)-NH-CO-(C $_{1\text{-}5}$ alkyl), -(d- $_3$ alkylene)-N(C $_{1\text{-}5}$ alkyl)-CO-(d. $_5$ alkyl), -(C$_{0\text{-}3}$ alkylene)-S0 $_2$-NH $_2$, -(C$_{0\text{-}3}$ alkylene)-S0 $_2$-NH(d. $_5$ alkyl), -(C$_{0\text{-}3}$ alkylene)-S0 $_2$-N(d-5 alkyl)(C $_{1\text{-}5}$ alkyl), -(C$_{c\text{-}3}$ alkylene)-NH-S0 $_2$-(d. $_5$ alkyl), and -(d-3 alkylene)-N(d-5 alkyl)-S0 $_2$-(C$_{1\text{-}5}$ alkyl), and two groups R^{A1} which are bound to adjacent carbon ring atoms may also be mutually linked to form a group -0-(CH $_2$)i-$_3$-0-;

with the proviso that if R^{11} is hydrogen and R^{12a} is cyclopropyl or cyclohexyl, then A is not 3-(trifluoromethyl)phenyl;

or a pharmaceutically acceptable salt, solvate or prodrug thereof

for use as a medicament

24. The compound for use according to item 23, wherein R^{12a} is selected from sec-butyl, cycloalkyi, aryl, heterocycloalkyl, and heteroaryl, wherein said cycloalkyi, said aryl, said heterocycloalkyl, and said heteroaryl are each optionally substituted with one or more groups R^{13}.

25. The compound for use according to item 23 or 24, wherein R^{12a} is sec-butyl or C_{3-7} cycloalkyl, wherein said C_{3-7} cycloalkyl is optionally substituted with one or more groups R^{13}.

26. The compound for use according to any one of items 23 to 25, wherein each R^{13} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -CF_3, and -CN.

27. The compound for use according to any one of items 23 to 26, wherein R^3 is hydrogen.

28. The compound for use according to any one of items 23 to 27, wherein each R^4 is independently selected from hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{1-5} alkynyl, -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -CF_3, and -CN.

29. The compound for use according to any one of items 23 to 28, wherein A is phenyl which is optionally substituted with one or more groups R^{A1}.

30. The compound for use according to any one of items 23 to 29, wherein each R^{A1} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -O(C_{1-5} alkyl), -O(C_{1-5} alkylene)-OH, -O(C_{1-5} alkylene)-O(C_{1-5} alkyl), -SH, -S(C_{1-5} alkyl), -S(C_{1-5} alkylene)-SH, -S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -NH_2, -NH(C_{1-5} alkyl), -N(C_{1-5} alkyl)(C_{1-5} alkyl), halogen, C_{1-5} haloalkyl, -CF_3, and -CN, and two groups R^{A1} which are bound to adjacent carbon ring atoms may also be mutually linked to form a group -O-(CH_2)$_{1-3}$-O-.

31. The compound for use according to item 23, wherein said compound is selected from:
N-cyclopentyl-6-(N-(2-ethylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;
N-cyclopentyl-6-(N-(3-methoxyphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;
N-cyclopentyl-4-oxo-6-(N-(3-(trifluoromethyl)phenyl)sulfamoyl)-1,4-dihydroquinoline-3-carboxamide;
6-(N-(3-methoxyphenyl)sulfamoyl)-N-(2-methylcyclohexyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclohexyl-6-(N-(3-methoxyphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-(sec-butyl)-6-(N-(2-ethylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclopenty!-6-(N-(2,3-dlhydrobenzo[b][1 ,4]dioxin-6-yl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-(2,3-dimethylcyclohexyl)-6-(N-(2-fluorophenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclopentyl-6-(N-(4-isopropylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclohexyi-6-(N-(4-ethoxyphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

6-(N-(3-chloro-2-methylphenyl)sulfamoyl)-N-cyclopentyl-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclohexyl-6-(N-(3,5-dimethylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclop8ntyl-6-(N-(2-fluorophenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclohexyl-6-(N-(2,3-dihydrobenzo[b][1 ,4]dioxin-6-yl)suIfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cycloheptyl-6-(N-(2,3-dihydrobenzo[b][1 .4]dioxin-6-yl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamlde; and

a pharmaceutically acceptable salt, solvate or prodrug of any one of these compounds.

32. A pharmaceutical composition comprising a compound as defined in any one of items 23 to 31 and a pharmaceutically acceptable excipient.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

EXAMPLES

The compounds described in this section are defined by their chemical formulae and their corresponding chemical names. In case of conflict between any chemical formula and the corresponding chemical name indicated herein, the present invention relates to both the compound defined by the chemical formula and the compound defined by the chemical name.

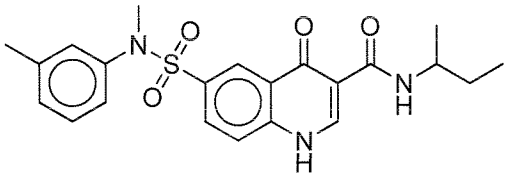
Expression of recombinant MTH1

Recombinant MTH1 was expressed and purified as described in Huber KV et al., Nature, 2014, 508(7495):222-7. In particular, codon-optimized human MTH1 cDNA subcloned into a pETM-11 vector (Gunther Stier, EMBL) featuring a His-tag and TEV site was obtained from GenScript (GenScript, NJ, USA) and expressed in the *E. coli* strain BL21 DE3. After harvesting, bacteria were lysed using buffer (50 mM Tris-HCl pH 7.5, 500 mM NaCl, 5% glycerol, 5 mM β-mercaptoethanol, 1 mM PMSF) containing lysozyme (Sigma-Aldrich) and DNase I (Roche). His-tagged protein was purified with NiNTA agarose (Qiagen), washed with buffer, and eluted with an imidazole gradient. Following removal of the His-tag by incubation with TEV protease, fractions were dialyzed and purified using size-exclusion chromatography (Sephadex, GE Healthcare). Protein concentration of the purified fractions was determined by UV (A_{280}).

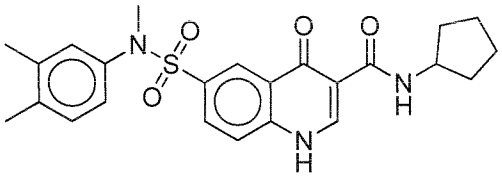
Oxoquinoline compounds

The following compounds (1) to (17) were obtained from ChemDiv (San Diego, CA, USA) and were tested for their activity on MTH1 as described further below:

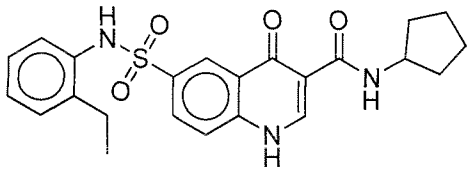
Compound (1): N-(sec-butyl)-6-(N-methyl-N-(m-tolyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide



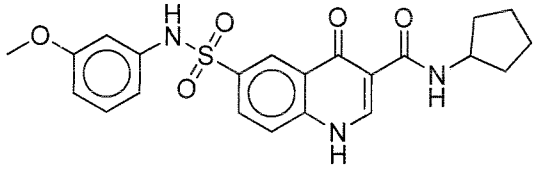
Compound (2): N-cyclopentyl-6-(N-(3,4-dimethylphenyl)-N-methylsulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide



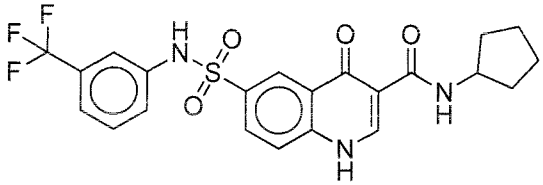
Compound (3): N-cyclopentyl-6-(N-(2-ethylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide



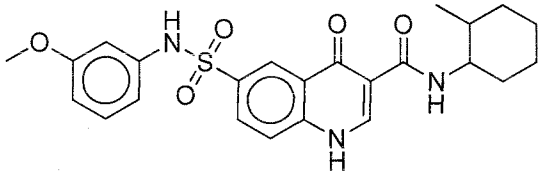
Compound (4): N-cyclopentyl-6-(N-(3-methoxyphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide



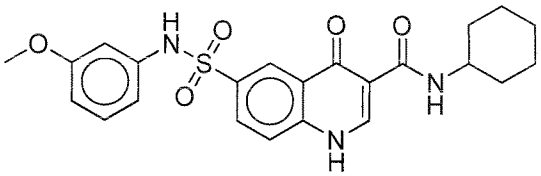
Compound (5): N-cyclopentyl-4-oxo-6-(N-(3-(trifluoromethyl)phenyl)sulfamoyl)-1 ,4-dihydroquinoline-3-carboxamide



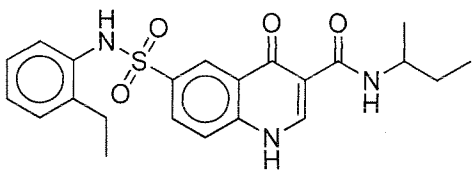
Compound (6): 6-(N-(3-methoxypheny!)sulfamoyl)-N-(2-methylcyclohexyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide



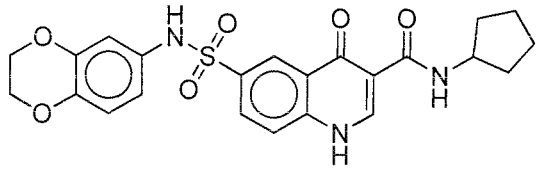
Compound (7): N-cyc!ohexyl-6-(N-(3-methoxyphenyi)suifamoyi)-4-oxo-1 ,4-dihydroquinoiine-3-carboxamide



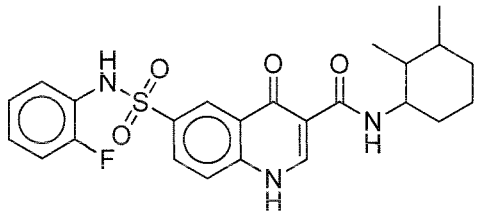
Compound (8): N-(sec-butyl)-6-(N-(2-ethylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxarnide



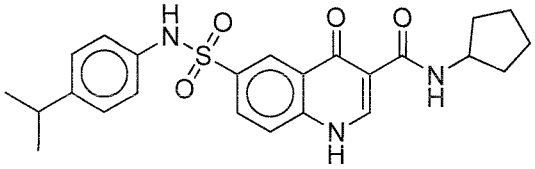
Compound (9): N-cyclopentyl-6-(N-(2,3-dihydrobenzo[b][1 ,4]dioxin-6-yl)suifamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide



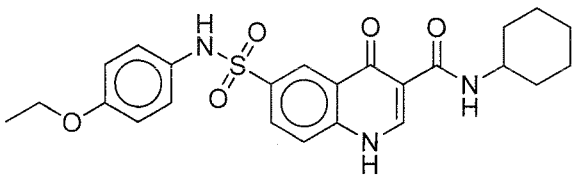
Compound (10): N-(2,3-dimethylcyclohexyl)-6-(N-(2-fluorophenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide



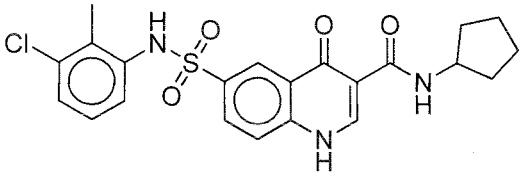
Compound (11): N-cyclopentyl-6-(N-(4-isopropylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide



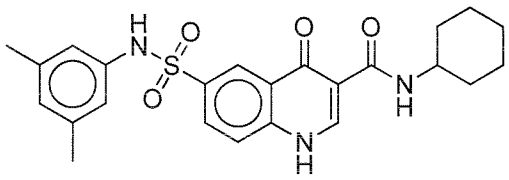
Compound (12): N-cyclohexyl-6-(N-(4-ethoxyphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide



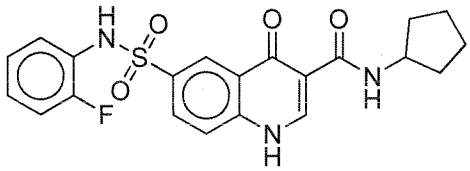
Compound (13): 6-(N-(3-chloro-2-methylphenyl)sulfamoyl)-N-cyclopentyl-4-oxo-1 ,4-dihydroquinoline-3-carboxamide



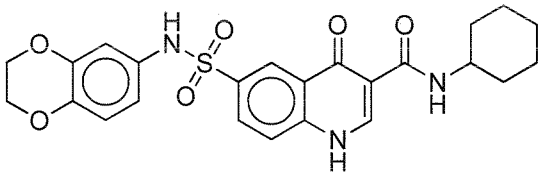
Compound (14): N-cyclohexyl-6-(N-(3,5-dimethylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide



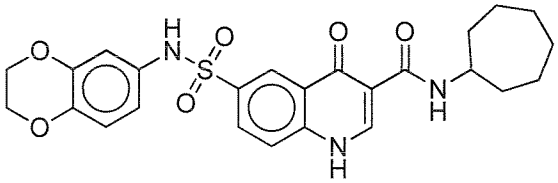
Compound (15): N-cyclopentyl-6-(N-(2-fiuorophenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide



Compound (16): N-cyclohexyl-6-(N-(2,3-dihydrobenzo[b][1 ,4]dioxin-6-yl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide



Compound (17): N-cycloheptyl-6-(N-(2,3-dihydrobenzo[b][1 ,4]dioxin-6-yl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide



Differential scanning fluorimetry (DSF) assay

The DSF assay was performed as follows. Compounds were dissolved in dimethyl sulfoxide (DMSO) and diluted in assay buffer (10 mM HEPES-NaOH, **pH** 7.5, 500 mM NaCl, final concentration 10 μM). Upon addition of MTH1 recombinant protein (final concentration 2 μM**),** SYPRO Orange (Sigma Aldrich) was added and samples were analysed in a qPCR machine as described in literature (Niesen, F.H., Berglund, H. & Vedadi, M., Nat. Protocols *2*, 2212-2221 (2007)). Tm shift values were determined by fitting a curve to the data points using non-linear regression analysis.

A threshold of 4°C with regard to the shift in MTH1 protein melting temperature (Tm) relative to DMSO controls was applied to distinguish strong from weak binders. Compounds exhibiting a Tm shift greater than 4°C were considered strong binders, and compounds exhibiting a Tm shift greater than 8°C were considered highly potent binders. A strong binding affinity to MTH1 as determined in the DSF assay is known to correlate with an inhibition of the catalytic activity of MTH1 (Huber KV et al., Nature, 2014, 5Q8(7495):222-7).

The compounds (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16) and (17) were found to show a Tm shift between 4°C and 8°C, and the compounds (1) and (2) exhibited a Tm shift greater than 8°C.

These results demonstrate that the compounds of formula (I), including in particular the compounds (1) to (17), exhibit strong binding affinity for human MTH1 , which indicates that these compounds are potent inhibitors of MTH1 and can thus advantageously be used for the medical intervention in cancer.

MTH1 catalytic assay

MTH1 hydrolyzes oxidized nucleotides such as 2-OH-dATP and 8-oxo-dGTP, yielding the corresponding nucleoside monophosphate and pyrophosphate (PPi). A luminescence-based assay was performed which monitors the production of PPi generated by MTH1-mediated hydrolysis of oxidized nucleotides, as described in Huber KV et aL, Nature, 2014, 508(7495):222-7 and as further detailed in the following.

The activity of MTH1 was monitored using dGTP (Fermentas) using the PPiLight Inorganic Pyrophosphate Assay (Lonza Rockland Inc.). IC_{50} values were determined using non-linear regression analysis utilizing GraphPad Prism Software.

More specifically, the MTH1 catalytic assay was performed as follows. Half-maximal inhibitory concentrations (IC_{50}) were determined using a luminescence-based assay as described previously (Svensson (2011) FEBS Letters 585, 2617-2621) with some minor modifications. Briefly, serial dilutions of compounds were dissolved in assay buffer (100 mM Tris-acetate pH 7.5, 40 mM NaCI and 10mM $Mg(OAc)_2$ containing 0.005% Tween-20 and 2 mM dithiothreitol (DTT). Upon addition of MTH1 recombinant protein (final concentration 2 nM), plates were incubated on a plate shaker for 15 min at room temperature. After addition of the substrate dGTP (Fermentas, final concentration 100 mM), the generation of pyrophosphate (PPi) as a result of nucleotide triphosphate hydrolysis by MTH1 was monitored over a time course of 15

min using the PPiLight Inorganic Pyrophosphate Assay kit (Lonza Rockland). IC_{50} values were determined by fitting a dose-response curve to the data points using nonlinear regression analysis using the GraphPad Prism software.

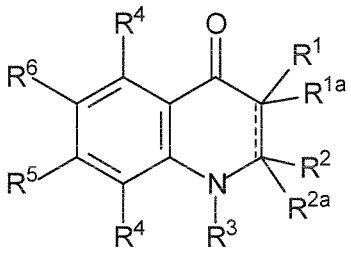
For compound (1), which is a representative example of the compounds of formula (I) according the invention, an IC_{50} of 456 nM was determined.

These results confirm that the compounds of formula (I) are potent inhibitors of MTH1 , which makes them highly valuable as therapeutic agents for the treatment or prevention of cancer.

It is well established that cancer cells are subject to high levels of oxidative stress due to increased proliferation leading to the production of reactive oxygen species (ROS) as a result of mitochondrial respiration. The nucleotide pool represents a major target of ROS and oxidation of DNA bases contributes significantly to mutations and DNA damage. Consequently, tumor cells which bear a considerable amount of genetic aberrations and concomitant defects in DNA repair mechanisms are particularly sensitive to ROS-induced DNA damage. By removing oxidized nucleotides and thus maintaining nucleotide pool homeostasis, MTH1 relieves cancer cells of proliferative stress and is therefore an attractive target for anticancer therapeutics. Indeed, MTH1 levels are increased in Ras-expressing cancers ranging from lung cancer (Speina Journal of the National Cancer Institute, 2005, 97:384-95; Kennedy, FEBS Letters, 1998, 429:17-20) to renal carcinoma (Okamoto, Int J Cancer, 1996, 65:437-41), indicating that there is a connection between oncogenic transformation and oxidative stress. This is also supported by the fact that the MTH1 inhibitor SCH 51344 was shown to prevent the growth of fibroblasts infected with a variety of different oncogenes such as v-abl. Remarkably, MTH1 deficiency in knockout mice confers a mild phenotype, indicating that there is a therapeutic window for MTH1 inhibitors (Tsuzuki, Proceedings of the National Academy of Sciences, 2001 , 98:1 1456-61). The compounds of formula (I) as described and defined herein can thus advantageously be used in the treatment or prevention of cancer.

CLAIMS

1. A compound of the following formula (I)



(I)

wherein:

R^1 is -CO-N(R^{11})-R^{12} or -N(R^{11})-CO-R^{12};

R^{11} is hydrogen or $C_{1.5}$ alkyl;

R^{12} is selected from C_{1-5} alkyl, carbocyciyi, and heterocyclyl, wherein said carbocyciyi and said heterocyclyl are each optionally substituted with one or more groups R^{13};

each R^{13} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(Co-3 alkylene)-OH, -(C_{0-3} alkyleneJ-O(d-s alkyl), -(C_{0-3} aikylene)-0(C-|.$_5$ alkylene)-OH, -(C_{0-3} alkylene)-0(C,.$_5$ alkylene)-0(C_{1-5} alkyl), -(C_{0-3} aikylene)-SH, -(Co-3 alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(Ci.$_5$ alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(Co-3 alkylene)-(Ci.$_5$ haloalkyl), -(C_{0-3} alkylene)-CF_3, -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-$N0_2$, -(C_{0-3} alkylene)-N_3, -(C_{0-3} alkylene)-CHO, -(Co-3 alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-0-(C_1-s alkyl), -(Co-3 alkylene)-0-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{c-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C,.$_5$ alkyO-CO-iC_{1-5} alkyl), -(C_{0-3}

alkylene)-S0 $_2$-NH $_2$, -(C $_{0\text{-}3}$ alkylene)-S0 $_2$-NH(C $_{1\text{-}5}$ alkyl) , -(C $_{0\text{-}3}$ alkylene)-S0 $_2$-N(C $_{1\text{-}5}$ alkyl)(d. $_5$ alkyl) , -(C $_{0\text{-}3}$ alkylene)-NH-S0 $_2$-(d-5 alkyl), and -(Co-3 alkylene)-N(Ci. $_5$ alkyl)-S0 $_2$-(d. $_5$ alkyl) ;

⎯⎯⎯ is a double bond or a single bond;

if ⎯⎯⎯ is a double bond, then R^{1a} and R^{2a} are absent, and R^2 is selected from hydrogen, d $_{\text{-}5}$ alkyl, $C_{2\text{-}5}$ alkenyl, $C_{2\text{-}5}$ alkynyl , -OH, -0(C $_{1\text{-}5}$ alkyl) , -0 (C$_{1\text{-}5}$ alkylene)-OH, -0(C $_{1\_5}$ alkylene)-0(C $_{1\text{-}5}$ alkyl) , -SH, -S(C$_{1\text{-}5}$ alkyl) , -S(d$_{_5}$ alkyiene)-SH, -S(C $_{1\text{-}5}$ alkylene)-S(C $_{1\text{-}5}$ alkyl), -NH$_2$, -NH(d $_{\text{-}5}$ alkyl), -N(d$_{_5}$ alkyl)(C $_{1\_5}$ alkyl) , halogen, C $_{1\text{-}5}$ haloalkyl, -CF$_3$, and -CN;

if ⎯⎯⎯ is a single bond, then R^{1a} is selected from hydrogen , d $_{\text{-}5}$ alkyl , C_2s alkenyl, $C_{2\text{-}5}$ alkynyl, -OH, -0(d-s alkyl), -0(C $_{1\text{-}5}$ alkylene)-OH, -0 (d $_{\text{-}5}$ alkylene)-0(d $_{\text{-}5}$ alkyl) , -SH, -S(d-s alkyl) , -S(d. $_5$ alkylene)-SH, -S(C,$_{\text{-}5}$ alkylene)-S(d. $_5$ **alkyl),** -NH$_2$, -NH(d-s **alkyl),** -N(d. $_5$ alkyl)(C, $_{\text{-}5}$ **alkyl),** halogen, C$_{1\text{-}5}$ haloalkyl , -CF$_3$, and -CN,

R^2 is selected from hydrogen, d $_{\text{-}5}$ alkyl, $C_{2\text{-}5}$ alkenyl, $C_{2\text{-}5}$ alkynyl, -OH, -0 (C$_{1\text{-}5}$ alkyl) , -0(d- $_5$ alkylene)-OH, -0(d. $_5$ alkylene)-0(d. $_5$ alkyl), -SH, -S(d $_{\text{-}5}$ alkyl) , -S(d$_{_5}$ alkylene)-SH, -S(d. $_5$ alkylene)-S(C,. $_5$ alkyl) , -NH$_2$, -NH(d $_{\text{-}5}$ alkyl) , -N(d $_{\text{-}5}$ alkyl)(C $_{1\text{-}5}$ alkyl), halogen, d $_{\text{-}5}$ haloalkyl, -CF$_3$, and -CN,

R^{2a} is selected from hydrogen, d $_{\text{-}5}$ alkyl, $C_{2\text{-}5}$ alkenyl, $C_{2\text{-}5}$ alkynyl, -OH, -0(d$_{_5}$ alkyl) , -0(d $_{\text{-}5}$ alkylene)-OH, -0 (d $_{\text{-}5}$ alkylene)-0(d $_{\text{-}5}$ alkyl) , -SH , -S(d. $_5$ alkyl) , -S(d$_{_5}$ alkylene)-SH, -S(d. $_5$ alkylene)-S(d. $_5$ alkyl) , -NH$_2$, -NH(C $_{1\text{-}5}$ alkyl) , -N(d. $_5$ aikyl)(C $_{1\text{-}5}$ alkyl) , halogen, d $_{\text{-}5}$ haloalkyl, -CF$_3$, and -CN. and

R^2 and R^{2a} may also together form **an** oxo group;

R^3 is hydrogen or d $_{\text{.}5}$ alkyl;

each R^4 is independently selected from hydrogen, $C_{1\text{-}5}$ alkyl, $C_{2\text{-}5}$ alkenyl, $C_{2\text{-}5}$ alkynyl, -(C$_{0\text{-}3}$ alkylene)-OH, -(C$_{0\text{-}3}$ alkylene)-0(C-.s alkyl) , -(C $_{0\text{-}3}$ alkylene)-0(C $_{1\text{-}5}$ alkylene)-OH, -(C$_{0\text{-}3}$ alkylene)-0(C $_{1\text{-}5}$ alkylene)-0(d. $_5$ alkyl), -(C$_{0\text{-}3}$ alkylene)-SH, -(Co-3 alkylene)-S(d. $_5$ alkyl) , -(C$_{0\text{-}3}$ alkylene)-S(C,. $_5$ alkylene)-SH, -(C$_{0\text{-}3}$ alkylene)-S(Cv5 alkylene)-S(d $_{\text{-}5}$ alkyl) , -(C$_{0\text{-}3}$ alkylene)-NH $_2$, -(C$_{0\text{-}3}$ alkylene)-NH(d$_{_5}$ alkyl), -(C$_{0\text{-}3}$ alkylene)-N(d-s alkyl)(d. $_5$ alkyl) , -(C$_{0\text{-}3}$ alkyiene)-halogen, -(C$_{0\text{-}3}$ alkylene)-(d. $_5$ haloalkyl) , -(C $_{0\text{-}3}$ alkylene)-CF $_3$, -(C$_{0\text{-}3}$ alkylene)-CN, -(C$_{0\text{-}3}$ alkylene)-N0 $_2$, -(C$_{0\text{-}3}$ alkylene)-N $_3$, -(C$_{0\text{-}3}$ alkylene)-CHO.

-(Co-3 alkylene)-CO-(C 1-5 alkyl), -(C 0-3 alkylene)-COOH, -(C 0-3 alkylene)-CO-0-(C1.5 alky!), -(C 0-3 alkylene)-0-CO-(C 1-5 alkyl), -(C 0-3 alkylene)-CO-NH 2, -(C 0-3 alkylene)-C0-NH(C 1-5 alkyl), -(C 0-3 alkylene)-CO-N(d. 5 aikyl)(d. 5 alkyl), -(C 0-3 alkylene)-NH-CO-(C 1-5 alkyl), -(C 0-3 alkylene)-N(C 1-5 alkyl)-C0-(d_ 5 alkyl), -(C 0-3 alkylene)-S0 2-NH 2, -(C 0-3 alkylene)-S0 2-NH(C 1-5 alkyl), -(C 0-3 alkylene)-S0 2-N(C 1_5 aikyl)(C 1-5 alkyl), -(C 0-3 alkylene)-NH-S0 2-(C 1-5 alkyl), and -(C 0-3 alkylene)-N(C 1-5 alkyl)-S0 2-(Ci. 5 alkyl);

one of R5 and R6 is -L-A, and the other one of R5 and R6 is a group R4;

L is Ci-5 alkylene, wherein one or two -CH 2- units comprised in said C 1-5 alkylene are each optionally replaced by a group independently selected from -S0 2-N(R L1)-, -N(R L1)-S0 2-, -S0 2-, -SO-, -S-, -0-, -CO-, -C(=0)0-, -0-C(=0)-, -N(R L1)-, -N(R L1)-CO-, and -C0-N(R L1)-;

each R L1 is independently selected from hydrogen and C 1-5 alkyl;

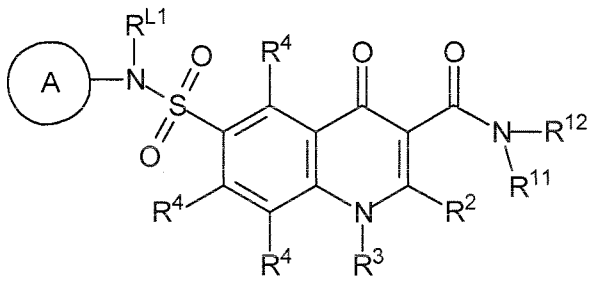
A is ary! or heteroaryl, wherein said ary! and said heteroaryl are each optionally substituted with one or more groups R A1; and

each R A1 is independently selected from d 5 alkyl, C 2-5 alkenyl, C 2.5 alkynyl, -(Co-3 alkylene)-OH, -(C 0-3 alkylene)-0(C 1-5 alkyl), -(C 0-3 alkylene)-0(C 1-5 alkylene)-OH, -(C 0-3 alkylene)-0(C 1-5 alkylene)-0(C,. 5 alkyl), -(C 0-3 alkylene)-SH, -(Co-3 alkylene)-S(C 1_5 alkyl), -(C 0-3 alkylene)-S(C,. 5 aikylene)-SH, -(C 0-3 alkylene)-S(C 1-5 aikylene)-S(C 1-5 alkyl), -(C 0-3 alkylene)-NH 2, -(C 0-3 alkylene)-NH(C 1-5 alkyl), -(C 0-3 alkylene)-N(d. 5 alkyl)(d. 5 alkyl), -(C 0-3 alkylene)-halogen, -(C 0-3 aikylene)-(Ci_ 5 haloalkyl), -(C 0-3 alkylene)-CF 3, -(C 0-3 alkylene)-CN, -(C 0-3 alkylene)-N0 2, -(C 0-3 alkylene)-N 3, -(C 0-3 alkylene)-CH0, -(Co-3 alkylene)-CO-(d_5 alkyl), -(C 0-3 alkylene)-COOH, -(C 0-3 alkylene)-C0-0-(d-5 alkyl), -(C 0-3 alkylene)-0-CO-(d. 5 alkyl), -(C 0-3 alkylene)-CO-NH 2, -(C 0-3 alkylene)-CO-NH(d- 5 alkyl), -(C 0-3 alkylene)-CO-N(d. 5 alkyl)(d- 5 alkyl), -(C 0-3 alkylene)-NH-CO-(d. 5 alkyl), -(C 0-3 alkylene)-N(d. 5 alkyl)-CO-(d. 5 alkyl), -(C 0-3 alkylene)-S0 2-NH 2, -(C 0-3 alkylene)-S0 2-NH(d. 5 alkyl), -(C 0-3 alkylene)-S0 2-N(d- 5 alkyl)(C,. 5 alkyl), -(C 0-3 alkylene)-NH-S0 2-(C 1-5 alkyl), and -(Co-3 alkylene)-N(d- 5 alkyl)-S0 2-(C 1-5 alkyl), and two groups R A1 which are bound to adjacent carbon ring atoms may also be mutually linked to form a group -0-(CH 2)1-3-0-;

or a pharmaceutically acceptable salt, solvate or prodrug thereof

for use in the treatment or prevention of cancer.

2. The compound for use according to claim 1, wherein said compound is a compound of the following formula (Ia)



(Ia)

wherein R^{11}, R^{12}, R^2, R^3, R^4, R^{L1} and A are as defined in claim 1,

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

3. The compound for use according to claim 1 or 2, wherein R^{12} is C_{1-5} alkyl or C_{3-7} cycloalkyl, wherein said C_{3-7} cycloalkyl is optionally substituted with one or more groups R^{13}.

4. The compound for use according to any one of claims 1 to 3, wherein A is phenyl which is optionally substituted with one or more groups R^{A1}.

5. The compound for use according to claim 1 or 2, wherein said compound is selected from:

N-(sec-butyl)-6-(N-methyl-N-(m-tolyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclopentyl-6-(N-(3,4-dimethylphenyl)-N-methylsulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclopentyl-6-(N-(2-ethylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclopentyl-6-(N-(3-methoxyphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclopentyl-4-oxo-6-(N-(3-(trifluoromethyl)phenyl)sulfamoyl)-1 ,4-dihydroquinoline-3-carboxamide;

6-(N-(3-methoxyphenyl)sulfamoyl)-N-(2-methylcyclohexyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclohexyl-6-(N-(3-methoxyphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-(sec-butyl)-6-(N-(2-ethylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclopentyl-6-(N-(2,3-dihydrobenzo[b][1 ,4]dioxin-6-yl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-(2,3-dimethylcyclohexyl)-6-(N-(2-fluorophenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclopentyl-6-(N-(4-isopropylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyc!ohexyl-6-(N-(4-ethoxyphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

6-(N-(3-chloro-2-methylphenyl)sulfamoyl)-N-cyclopentyl-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclohexyl-6-(N-(3,5-dimethylphenyl)suifamoyI)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclopentyl-6-(N-(2-fluorophenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cyclohexyl-6-(N-(2,3-dihydrobenzo[b][1 ,4]dioxin-6-yl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;

N-cycloheptyl-6-(N-(2.3-dihydrobenzo[b][1 ,4]dioxin-6-yl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide; and

a pharmaceuticaiiy acceptable salt, solvate or prodrug of any one of these compounds.

6. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 5 and a pharmaceutically acceptable excipient for use in the treatment or prevention of cancer.

7. Use of a compound as defined in any one of claims 1 to 5 in the preparation of a medicament for the treatment or prevention of cancer.

8. A method of treating cancer, the method comprising administering a compound as defined in claim 1 to a subject in need thereof.

9. The compound for use according to any one of claims 1 to 5 or the pharmaceutical composition for use according to claim 6 or the use of claim 7 or the method of claim 8, wherein said cancer is selected from gastrointestinal cancer, colorectal cancer, liver cancer, pancreatic cancer, stomach cancer, genitourinary cancer, bladder cancer, esophageal cancer, prostate cancer, lung cancer, breast cancer, hematological cancer, leukemia, lymphoma, ovarian cancer, brain cancer, neuroblastoma, Ewing's sarcoma, kidney cancer, skin cancer, and head and/or neck cancer.

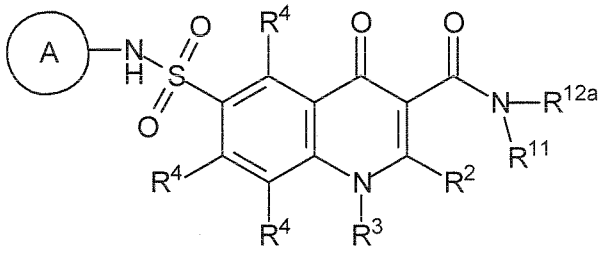
10. The compound for use according to claim 9 or the pharmaceutical composition for use according to claim 9 or the use of claim 9 or the method of claim 9, wherein said cancer is breast cancer which is selected from triple-negative breast cancer and breast cancer having a BRCA1 and/or BRCA2 gene mutation.

11. The compound for use according to any one of claims 1 to 5, 9 or 10 or the pharmaceutical composition for use according to claim 6, 9 or 10 or the use of claim 7, 9 or 10 or the method of claim 8, wherein said cancer has an activating RAS mutation and/or an activating EGFR mutation.

12. The method of claim 8, wherein the subject to be treated is a human.

13. *In vitro* use of a compound as defined in any one of claims 1 to 5 as an MTH1 inhibitor.

14. A compound of the following formula (Ib)



(Ib)

wherein :

R^{11} is hydrogen or C_{1-5} alkyl;

R^{12a} is selected from sec-butyl, carbocyclyl, and heterocyclyl, wherein said carbocyclyl and said heterocyclyl are each optionally substituted with one or more groups R^{13};

each R^{13} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(Co-3 alkylene)-OH, -(C_{0-3} alkylene)-0(C_{1-5} alkyl), -(C_{0-3} alkylene)-0(C_{1-5} alkylene)-OH, -(C_{0-3} alkylene)-0(C_{1-5} alkylene)-0(C_{1-5} alkyl), -(C_{0-3} alkylene)-SH, -(Co-3 alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(C_{1-5} alkylene)-S(C_{1-5} alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} alkyl)(C_{1-5} alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CF_3, -(C_{0-3} alkylene)-CN, -(Co-3 alkylene)-NO_2, -(C_{0-3} alkylene)-N_3, -(C_{0-3} alkylene)-CHO, -(Co-3 alkylene)-CO-(C,.5 alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-0-(C_1-5 alkyl), -(C_{0-3} alkylene)-0-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3} alkylene)-CO-NH(C_{1-5} alkyl), -(C_{0-3} aikylene)-CO-N(C-i-$_5$ alkyl)(Ci.$_5$ alkyl), -(C_{0-3} alkylene)-NH-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-N(C_{1-5} a!kyl)-CO-(d -s alkyl), -(C_{0-3} alkylene)-S0$_2$-NH_2, -(C_{0-3} alky!ene)-S0$_2$-NH(C_{1-5} alkyl), -(C_{0-3} alkylene)-S0$_2$-N(C_{1-5} alkyl)(d.$_5$ alkyl), -(C_{0-3} alkylene)-NH-S0$_2$-(C_{1-5} alkyl), and -(Co-3 alkylene)-N(d-$_5$ alkyl)-S0$_2$-(d.$_5$ alkyl);

R^2 is selected from hydrogen, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -OH, -0(d.$_5$ alkyl), -0(d_$_5$ alkylene)-OH, -0(d.$_5$ alkylene)-0(d.$_5$ alkyl), -SH, -S(d_$_5$ alkyl), -S(d-$_5$ alkylene)-SH, -S(d.$_5$ alkylene)-S(d.$_5$ alkyl), -NH_2, -NH(d_$_5$ alkyl), -N(d_$_5$ alkyl)(d.$_5$ alkyl), halogen, d$_{-5}$ haloalkyl, -CF_3, and -CN;

R^3 is hydrogen or d$_{-5}$ alkyl;

each R^4 is independently selected from hydrogen, C_{1-5} aikyi, C_{2-5} alkenyl, C_{2-5} alkynyl, -(C_{0-3} alkylene)-OH, -(C_{0-3} alkylene)-0(d.$_5$ alkyl), -(C_{0-3} alkylene)-0(d.$_5$ alkylene)-OH, -(C_{0-3} alkylene)-0(d.$_5$ alkylene)-0(d_$_5$ alkyl), -(C_{0-3} alkylene)-SH, -(C_{0-3} alkylene)-S(d-5 alkyl), -(C_{0-3} aikylene)-S(C_{1-5} alkylene)-SH, -(C_{0-3} alkylene)-S(d.$_5$ alkylene)-S(d.$_5$ alkyl), -(C_{0-3} alkylene)-NH_2, -(C_{0-3} alkylene)-NH(d_5 alkyl), -(C_{0-3} alky!ene)-N(C_{1-5} alkyl)(d.$_5$ alkyl), -(C_{0-3} alkylene)-halogen, -(C_{0-3} alkylene)-(C_{1-5} haloalkyl), -(C_{0-3} alkylene)-CF_3, -(C_{0-3} alkylene)-CN, -(C_{0-3} alkylene)-N0$_2$, -(C_{0-3} alkylene)-N$_3$, -(C_{0-3} alkylene)-CHO, -(Co-$_3$ alkylene)-CO-(C_{1-5} alkyl), -(C_{0-3} alkylene)-COOH, -(C_{0-3} alkylene)-CO-0-(d-5 alkyl), -(C_{0-3} alkylene)-0-CO-(Ci.$_5$ alkyl), -(C_{0-3} alkylene)-CO-NH_2, -(C_{0-3}

alkylene)-CO-NH $(C_{1-5}$ alkyl), $-(C_{0-3}$ alkylene)-CO-N (d-5 alkyl)$(C_{1-5}$ alkyl), $-(C_{0-3}$ alkylene)-NH-CO-$(C_{1-5}$ alkyl), $-(C_{0-3}$ alkylene)-N (d-$_5$ alkyl)-CO-(d-$_5$ alkyl), $-(C_{0-3}$ alkylene)-S0$_2$-NH$_2$, $-(C_{0-3}$ alkylene)-S0$_2$-NH$(C_{1-5}$ alkyl), $-(C_{0-3}$ alkylene)-S0$_2$-N(d-$_5$ alkyl)(d-5 alkyl), $-(C_{0-3}$ alkylene)-NH-S0$_2$-(d-5 alkyl), and -(Co-3 alkylene)-N(d-$_5$ alkyl)-S0$_2$-(d-5 alkyl);

A is aryl or heteroaryl, wherein said aryl and said heteroaryl are each optionally substituted with one or more groups R^{A1}; and

each R^{A1} is independently selected from C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -(Co-3 alkylene)-OH, $-(C_{0-3}$ alkylene)-0(C_{1-5} alkyl), $-(C_{0-3}$ alkylene)-0(C_{1-5} alkylene)-OH, $-(C_{0-3}$ alkylene)-0(C_{1-5} aikylene)-G(d-5 alkyl), $-(C_{0-3}$ alkylene)-SH, $-(C_{0-3}$ alkylene)-S$(Ci_5$ alkyl), $-(C_{0-3}$ aikyiene)-S(d-5 alkylene)-SH, $-(C_{0-3}$ alkylene)-S(C_{1-5} alkylene)-S(d,.$_5$ alkyl), $-(C_{0-3}$ alkylene)-NH$_2$, -(C0-3 alkylene)-NH $(Ci_5$ alkyl), $-(C_{0-3}$ alkylene)-N(C_{1-5} alkyi)$(Ci_5$ alkyl), $-(C_{0-3}$ alkylene)-halogen, $-(C_{0-3}$ alkylene)-$(C_{1-5}$ haloalkyl), $-(C_{0-3}$ alkylene)-CF_3, $-(C_{0-3}$ alkylene)-CN, -(C_{0-3} alkylene)-N0$_2$, $-(C_{0-3}$ alkylene)-N_3, $-(C_{0-3}$ alkylene)-CHO, -(C_{0-3} alkylenei-CO-Cd$_5$ alkyl), $-(C_{0-3}$ alkylene)-COOH, $-(C_{0-3}$ alkylene)-CO-0-(d_5 alkyl), $-(C_{0-3}$ alkylene)-0-CO-(C,.$_5$ alkyl), $-(C_{0-3}$ alkylene)-CO-NH$_2$, $-(C_{0-3}$ alkylene)-CO-NH(d.$_5$ alkyl), $-(C_{0-3}$ alkylene)-CO-N(d_$_5$ alkyl)(d_$_5$ alkyl), $-(C_{0-3}$ alkylene)-NH-CO-(d_5 alkyl), $-(C_{0-3}$ alkylene)-N(d.$_5$ alkyl)-CO-(d_$_5$ alkyl), $-(C_{0-3}$ alkylene)-S0$_2$-NH$_2$, $-(C_{0-3}$ alkylene)-S0$_2$-NH(C,.$_5$ alkyl), $-(C_{0-3}$ alkylene)-S0$_2$-N(d_$_5$ alkyl)(d.$_5$ alkyl), $-(C_{0-3}$ alkylene)-NH-S0$_2$-(d.$_5$ alkyl), and -(Co-3 alkyiene)-N(d-5 alkyl)-S0$_2$-$(C_{1-5}$ alkyl), and two groups R^{A1} which are bound to adjacent carbon ring atoms may also be mutually linked to form a group -0 $-(CH_2)_{1-3}$-0-;

with the proviso thai if R^{11} is hydrogen and R^{12a} is cyciopropyl or cyciohexyi, then A is not 3-(trifluoromethyl)phenyl;

or a pharmaceutically acceptable salt, solvate or prodrug thereof

for use as a medicament.

15. The compound for use according to claim 14, wherein R^{12a} is sec-butyl or C_{3-7} cycloalkyl, wherein said C_{3-7} cycloalkyl is optionally substituted with one or more groups R^{13}.

16. The compound for use according to claim 14 or 15, wherein A is phenyl which is optionally substituted with one or more groups R^{A1}.

17. The compound for use according to claim 14, wherein said compound is selected from:
N-cyclopentyl-6-(N-(2-ethylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;
N-cyclopentyl-6-(N-(3-methoxyphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;
N-cyclopentyl-4-oxo-6-(N-(3-(trifluoromethyl)phenyl)sulfamoyl)-1 ,4-dihydroquinoline-3-carboxamide;
6-(N-(3-methoxyphenyl)sulfamoyl)-N-(2-methylcyclohexyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;
N-cyclohexyl-6-(N-(3-methoxyphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;
N-(sec-butyl)-6-(N-(2-ethylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;
N-cyclopentyi-6-(N-(2,3-dihydrobenzo[b][1 ,4]dioxin-6-yl)suifamoyi)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;
N-(2,3-dimethylcyclohexyl)-6-(N-(2-fluorophenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;
N-cyclopentyl-6-(N-(4-isopropylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;
N-cyclohexyl-6-(N-(4-ethoxyphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;
6-(N-(3-chloro-2-methylphenyl)sulfamoyl)-N-cyclopentyl-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;
N-cyclohexyl-6-(N-(3,5-dimethylphenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;
N-cyclopentyl-6-(N-(2-fluorophenyl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;
N-cyclohexyl-6-(N-(2,3-dihydrobenzo[b][1 ,4]dioxin-6-yl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide;
N-cycloheptyl-6-(N-(2,3-dihydrobenzo[b][1 ,4]dioxin-6-yl)sulfamoyl)-4-oxo-1 ,4-dihydroquinoline-3-carboxamide: and
a pharmaceutically acceptable salt, solvate or prodrug of any one of these compounds.

18. A pharmaceutical composition comprising a compound as defined in any one of claims 14 to 17 and a pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/053766

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/473 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)
A61K A61P

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 , BIOSIS, WPI Data, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/023558 A1 (VM DISCOVERY INC [US]; WU JAY JIE-QIANG [US]; WANG LING [US]) 19 February 2009 (2009-02-19) cited in the application page 77, lines 1-16	1-18
A	WO 2008/021250 A2 (HUTCHINSON FRED CANCER RES [US]; VM DISCOVERY INC [US]; WU JAY JIE-QIA) 21 February 2008 (2008-02-21) cited in the application page 2, lines 25-31 page 5 - page 6; compounds 13-14 page 21, lines 12-29	1-18

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[X] Further documents are listed in the continuation of Box C. [X] 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" documentwhich may throw doubts on priority claim(s) orwhich 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	Date of mailing of the international search report
20 April 2016	03/05/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Houyvet-Landri sci na

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/120497 A2 (UNIV CALIFORNIA [US] ; VERKMAN ALAN [US] ; GUY R KIPLIN [US] ; PEDEMONTE) 22 December 2005 (2005-12-22) cited in the application page 5, paragraph 13 - page 6 page 30, paragraph 100 - page 31 pages 53-55 ; table 2	1-18
A	LIU PENG ET AL: "4-0xo-l ,4-dihydro-quinoline-3-carboxamides as BACE-1 inhibitors : Synthesis, biological evaluation and docking studies" , EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol . 79, 12 April 2014 (2014-04-12) , pages 413-421 , XP028652734, ISSN: 0223-5234, DOI: 10. 1016/J . EJMECH .2014.04.025 page 415 ; compound 8g	14-18
A	HELGE GAD ET AL: "MTH1 inhibition eradicates cancer by preventing sanitation of the dNTP pool ", NATURE, vol . 508, no. 7495 , 2 April 2014 (2014-04-02) , pages 215-221 , XP055140550, ISSN: 0028-0836, DOI: 10. 1038/naturel3181 cited in the application abstract	1-18
A	HUBER KILIAN V M ET AL: "Stereospecific targeting of MTH1 by (S) -crizotinib as an anti cancer strategy" , NATURE (LONDON) , vol . 508, no. 7495 , April 2014 (2014-04) , pages 222-227 , XP002739608, cited in the application abstract	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2016/053766

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13fer1 (a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13fer1 (a)).

      [ ] on paper or in the form of an image file (Rule 13fer1 (b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/053766

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009023558 A1	19-02-2009	CN 101778563 A	14-07-2010
		EP 2194783 A1	16-06-2010
		US 2010267671 A1	21-10-2010
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W0 2008021250 A2	21- 02-2008	NONE	
W0 2005120497 A2	22- 12-2005	AU 2005251745 A1	22-12-2005
		CA 2569402 A1	22-12-2005
		EP 1765347 A2	28-03-2007
		US 2008319008 A1	25- 12-2008
		US 2012101143 A1	26- 04-2012
		W0 2005120497 A2	22-12-2005