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A61P 3/10 (2006.01)  A61P 29/00 (2006.01)

Abstract: Compounds of general formula (I) or enantiomers, diastereomers and pharmaceutically acceptable salts thereof, for use as a medicament, in particular as inhibitors of sirtuins, with particular reference to SIRT6; such compounds increase glucose tissue uptake and find employment in the treatment of type I and type II diabetes mellitus and complications thereof; reduce the production of TNF-alpha and other inflammatory, chemotactic, or proangiogenic cytokines, finding use in the treatment of inflammatory diseases; interfere with DNA repair in tumor cells and thus exert an anticancer effect and sensitize such cells to antineoplastic agents and radiotherapy, hence finding employment in the treatment of neoplastic diseases.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): EU, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, HU, IE, IT, LU, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR, HU, IS, IE, IT, US, ZA, ZM.


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(1) Title: QUENAZOLINEDIONE COMPOUNDS WITH A SIRTUIN INHIBITING ACTIVITY

Declaration under Rule 4.17:
— if inventorship (Rule 4.17(iv))
— with international search report (Art. 21(3))
Title: Quinazolinedione compounds with a sirtuin inhibiting activity

DESCRIPTION

The work that has led to this invention was funded by the Seventh Framework Programme of the European Union (FP7 2007-2013) under the grant agreement No 256986.

Field of application

The present invention relates to the technical field of pharmaceutical industry and, in particular, concerns quinazolinedione compounds with sirtuin inhibiting activity, which are useful in the treatment of different diseases, such as for example metabolic, inflammatory and tumor diseases.

Known art

Sirtuins are NAD⁺-dependent enzymes, playing a role in ageing, metabolism, nutritional behavior, cancer and inflammation. Due to their wide implication in the physiopathology of highly prevalent diseases, sirtuins represent an interesting therapeutic target.

Seven sirtuins (SIRT1-7) are known, and activators of SIRT1 were described, with a potentially positive role in regulating metabolism and extending the duration of a healthy life ("healthspan"), although their mode of action is still controversial. Inhibitors of SIRT1, SIRT2 and SIRT5 were reported too.

SIRT6 is involved in genome stability and its deficiency was associated to the development of a progeroid syndrome in mice. SIRT6 promotes DNA repair by different mechanisms comprising deacetylation of histone H3 lysine 9 (H3K9) at telomeric chromatin with consequent association of WRN and telomere maintenance, stabilization of DNA-dependent protein kinase (DNA-PK) at chromatin, as well as poly(ADP-ribose) polymerase 1 (PARP1) mono-ADP-ribosylation and consequent promotion of its activity.

In addition to its role in DNA repair, SIRT6 regulates glucose uptake by virtue of its capacity of co-repressing the transcription factor
Hifla, a critical regulator of nutrient stress responses. SIRT6 deficient cells exhibit increased Hifla activity, increased glucose uptake and glycolysis, and diminished mitochondrial respiration.

In line with these findings, SIRT6-deficient mice develop hypoglycaemia and exhibit a pronounced increase in glucose uptake in muscle and brown adipose tissue.

Finally, SIRT6 plays a role in inflammation, as shown by the immune defects of SIRT6-deficient mice and by the ability to promote the expression of TNFa, IFN-γ and IL8 in response to activating stimuli. The immunogenic activity of SIRT6 reflects, at least in part, its propensity to increase intracellular ADP-ribose levels by virtue of its enzymatic activity. In turn, SIRT6-derived ADP-ribose appears to promote Ca²⁺ responses, cytokine gene transcription (via the transcription factor NFAT) and cell motility.

Thus, SIRT6 inhibition appears as a viable strategy for the treatment of cancer (as a means to sensitize cancer cells to anticancer agents and radiotherapy and to reduce cancer-associated inflammation), metabolic disorders (by virtue of its capacity to increase tissue glucose uptake) and inflammation. However, to date, no specific SIRT6 inhibitors have been described, whereas the availability of selective SIRT6 inhibitors could lead to the achievement of therapeutic agents with wide application possibilities.

Patent application WO 2008/138943 relates to a sirtuin inhibitor other than suramin for use in the reduction of TNF-alpha and/ or reduction of local or systemic inflammation in a subject and/ or treatment of TNF-alpha mediated diseases. The inhibitor in question is selected from sirtinol, m-sirtinol, p-sirtinol, splitomicin, dehydrosplitomicin, cambinol and dihydrocoumarin.

Patent application WO 2011/038110 concerns the use of a SIRT6 inhibitor to reduce or inhibit hyperglycaemia or obesity in a subject. Among SIRT6 inhibitors, antibodies anti-SIRT6, interfering RNA molecules and antisense nucleic acids can be mentioned.

Summary of the invention
The problem underlying the present invention was that of providing compounds having inhibiting activity towards sirtuins, in particular, even if not exclusively, towards SIRT6, for the use in inducing glucose tissue uptake (and thus in obtaining a reduction of glycaemic levels) and/or in reducing the production of TNF-alpha and other proinflammatory, chemotactic, or proangiogenic cytokines (such as IFN-γ and IL8) and/or in interfering with DNA repair in tumor cells, so as to be used as therapeutic agents in the treatment of type I or II diabetes-related diseases and/or inflammatory diseases and/or neoplastic diseases.

Such a problem was solved according to the invention by the provision of compounds of formula (I).

\[
\text{(I)}
\]

in which:

\[R^1 = H, \text{ d-Csalkyl;} \]

\[R^2 = H, \text{ Ci-Csalkyl;} \]

\[R^3 = \text{optionally substituted phenyl; optionally substituted phenoxy; } -\text{CH}_2-(\text{CH}_2)_n-\text{phenyl optionally substituted on the benzene ring, where } n = 0, 1 \text{ or } 2; \text{ or } -Y-R^5, \]

where \( Y = \text{ single bond, } -\text{O, } -\text{CH}_2, \text{ and} \)

\[R^5 = 5- \text{ or 6-membered, saturated or aromatic heterocyclic ring containing one or more heteroatoms selected from } N, S \text{ and } O, \text{ optionally substituted with a } \text{Ci-Csalkyl;} \]

\[R^4 = H, \text{ Ci-ealkyl, Cs-ecycloalkyl, halogen, } -\text{NO}_2, -\text{CN, } -\text{OH, } -\text{SH, } -\text{CF}_3, -\text{CCl}_3, -\text{COOH, } -\text{COOCi-salkyl, } -\text{SO}_2\text{OC}_{1-5}\text{alkyl, } -\text{OC}_{1-5}\text{alkyl,} \]

or enantiomers, diastereomers and pharmaceutically acceptable salts.
thereof, for use as a medicament.

With "alkyl" both straight chain and branched chain alkyls are meant.

Preferably, in the compounds of formula (I) the substituents have the following meanings:

5  \( R^1 = H, \text{CH}_3 \)

\[ R^2 = H, \text{CH}_3 \]

\( R^3 = \text{phenyl, phenoxy, benzyl or phenylethyl optionally substituted with a } \text{Ci-3alkyl on the aromatic ring or Y-R}_5, \)

where \( Y = \) a single bond, -O-, -C¾-, and

10 \( R^5 = \) 5- or 6-membered heteroaromatic ring, containing 1 or 2 N atoms, optionally substituted with a Ci-Csalkyl;

\( R^4 = H. \)

Particularly preferred are compounds of formula (I) in which:

\( R^1 = H, \text{CH}_3 \)

15 \( R^2 = H, \text{CH}_3 \)

\( R^3 = \text{phenyl, benzyl, phenylethyl or Y-R}_5, \)

where \( Y = \) a single bond, -O-, -CH2-, and

\( R^5 = \text{pyridinyl or imidazolyl; } \)

\( R^4 = H. \)

20 Further preferably, compounds of formula (I) comprise the following compounds:

(1) 2,4-dioxo-N-[4-(pyridin-3-yloxy)phenyl]-1,2,3,4-tetrahydroquinazoline-6-sulfonamide;

(2) N-[4-(lH-imidazol-1-ylmethyl)phenyl]-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6- sulfonamide;
The abovementioned compounds of formula (I) can be used as inhibitors of one or more sirtuins and, in particular SIRT6, to increase glucose tissue uptake in a subject.

According to an aspect of the present invention, such compounds can be used in the treatment of:

type I and type II diabetes mellitus and complications thereof, such as ketoacidotic coma, hyperglycaemic hyperosmolar condition, atherosclerosis, ischaemic heart disease (angina and myocardial infarction), stroke, peripheral vasculopathy, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy and diabetic foot.

According to another aspect of the present invention, compounds of formula (I) can be used as inhibitors of one or more sirtuins, and in particular SIRT6, to reduce the production of TNF-alpha and other proinflammatory, chemotactic, or proangiogenic cytokines (such as IFN-γ and IL8) in a subject and/or to reduce local or systemic inflammation in a subject and/or to treat a pathology mediated by TNF-alpha or other proinflammatory, chemotactic, or proangiogenic cytokines (such as IFN-γ and IL8) in a subject having local or systemic excessive or dysregulated cytokine production.

Consequently, such compounds find application in the treatment of inflammatory diseases comprising rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, systemic lupus erythematosus, vasculitis, Goodpasture syndrome, scleroderma, atherosclerosis, graft versus host disease (GVHD), organ transplant rejection, myocardial infarction, stroke,
reperfusion injury after revascularization in heart and other organs.

According to a further aspect of the present invention, compounds of formula (I) are used as inhibitors of one or more sirtuins, and in particular SIRT6, to interfere with DNA repair in tumor cells and thus exert an anticancer effect and sensitize said cells to antineoplastic agents and radiotherapy.

Consequently, such compounds find application in the treatment of neoplastic diseases comprising pancreatic cancer, breast cancer, colorectal cancer, prostatic cancer, ovarian cancer, melanoma, lung cancer, oesophageal cancer, hepatic carcinoma, lymphomas, leukemias, myeloma, sarcomas, neoplastic cachexia.

In a further aspect, the present invention relates to a pharmaceutical composition containing a therapeutically effective amount of at least one compound of formula (I) or an enantiomer, diastereomer or pharmaceutically acceptable salt thereof, as defined above and a pharmaceutically acceptable vehicle.

Examples of pharmaceutically acceptable salts are those formed with organic acids such as oxalic, tartaric, maleic, succinic and citric, and with inorganic acids such as nitric, hydrochloric, sulphuric and phosphoric acid.

Compounds according to the invention having one or more asymmetric carbon atoms can exist as pure enantiomers, pure diastereomers, racemic mixtures of enantiomers, racemates and mixtures of racemates.

Compounds and compositions according to the invention can be administered with any available and efficient delivery system, comprising, but not limited to, oral, buccal, parenteral, inhalatory routes, topical application, injection, transdermal or rectal route (e.g. suppositories), in unit dose formulations containing conventional pharmaceutically acceptable and non-toxic supports, adjuvants and carriers. Administration by parenteral route includes subcutaneous, intravenous, intramuscular, intracisternal injection or infusion techniques.

Solid dosage forms for administration by oral route comprise, for example,
capsule, tablets, powders, granules and gels. In such solid dosage forms the active compound can be mixed with at least one inert diluent, such as for example saccharose, lactose or starch. Normally, these dosage forms also comprise additional substances different from inert diluents, such as for example lubricating agents like magnesium stearate.

Injection preparations, for example sterile, aqueous or oily solutions or suspensions for injection, can be formulated according to known art and optionally using suitable dispersing, wetting agents and/or suspending agents.

Pharmaceutical preparations according to the present invention can be manufactured by using conventional pharmaceutical techniques, as described in various pharmacopoeias or handbooks in the field such as for example "Remington's Pharmaceutical Sciences Handbook", Mack Publishing, New York, 18th Ed., 1990.

The average daily dose of the compounds according to the present invention depends on many factors, such as for example severity of the disease and state of the patient (age, weight, gender): the dose can generally range from 1 mg to 1500 mg/day of compound according to the invention, optionally partitioned in more administrations.

Finally, in a further aspect, the present invention relates to a method for reducing the production of TNF-alpha and other proinflammatory, chemotactic, or proangiogenic cytokines in cells in vitro, comprising the step of exposing the cells to a compound as defined above, a method for increasing glucose uptake in cells in vitro, comprising the step of exposing the cells to said compound, as well as a method for increasing the antiproliferative and cytotoxic effect of antineoplastic drugs and ionizing radiations in vitro, comprising the step of exposing tumor cells to said compound.

Pharmaceutical formulations can be prepared with the compounds according to the present invention for the treatment of different pathologic conditions mediated by sirtuins and, in particular, SIRT6. Some of these diseases, such as type II diabetes mellitus, neoplastic diseases and inflammatory diseases, have a very strong epidemiological impact and hence pharmaceutical formulations containing compounds according to
the present invention are susceptible of wide employment in different fields of medical therapy, with technical, economical and manufacturing advantages related to the fact of being based on low molecular weight and stable organic molecules.

Moreover, the formulations can comprise further active substances, or can be used in combination with other formulations containing other active substances, such as for example antiinflammatory, blood glucose lowering agents, chemotherapies, or with radiotherapy.

Detailed description

Compounds of formula (I) described above can be prepared starting from the corresponding 6-chlorosulfonyl-quinazoline-2,4-diones of formula

![Chemical structure](image)

by reaction with a compound of formula (III)

![Chemical structure](image)

in which R³ and R⁴ are as defined with reference to compounds of formula (II).

The reaction is carried out under the conditions described in Kuryazov R. Sh. et al, Chemistry of Heterocyclic Compounds, Vol. 44, No. 3, 2008 "Quinazolines 1. Synthesis and chemical reactions of 6-chlorosulfonyl-quinazoline-2,4-diones".

Preferred compounds mentioned above are available on the market from the following sources:
(1): from the company Asinex, product identification: SYN17739303;
(2): from the company Asinex, product identification: SYN17738896;
(3): from the company Asinex, product identification: SYN17742030;
(4): from the company Asinex, product identification: SYN17736818;
(5): from the company Asinex, product identification: SYN17735999;

By the term "subject" reference is made, in the present application, to animals, preferably mammals and, in a particularly preferred way, human individuals.

By the term "treating" or "treatment" both a therapeutic treatment and a preventive, prophylactic treatment are meant, as well as a treatment achieving a prolongation of the survival in comparison with what expected in the absence of treatment.

The expression "therapeutically effective amount" refers to an amount able to determine a biological or therapeutic response in an animal or human tissue or system pursued by a researcher, physician or veterinary and, in particular, that can prevent or alleviate at least one local or systemic symptom of the treated disease.

The activity of the compounds according to the present invention was evaluated by a series of biological tests and in particular those summarized hereinafter.

Sirtuin inhibition test

In vitro activity of the compounds according to the present invention in terms of sirtuin inhibition was determined using commercial
kits for SIRT6, SIRT1 and SIRT2 available from the company Cayman, Ann Arbor, USA, following the instructions of the manufacturer.

IC50 values were determined using assays in commercial kits. All the compounds were dissolved at a 50mM concentration in DMSO. The compounds concentrations in the measurements for IC50 determination were in the range from 8µM to 5mM. IC50 values were determined from non-linear logarithmic regression curves by GraphPad Prism (GraphPad Software, the Jolla, CA - USA). Three independent IC50 measurements were performed for each compound.

Western Blot analysis.

Pancreatic adenocarcinoma BxPC3 cells were incubated for 18 hours with various compounds (100µM final concentration). Cells were lysed in lysis buffer (50mM Tris-HCl, pH 7.5, 150mM NaCl, 1% NP40 and cocktail of protease inhibitors) and 30 µg of proteins were loaded onto 15% polyacrylamide gel and separated by SDS-PAGE. Proteins were transferred onto nitrocellulose membranes and incubated with the primary antibody specific against acetylated H3K9 (Sigma, Milan) and with the antibody against actin (Santa Cruz Biotechnology, Santa Cruz, USA). After incubation with suitable secondary antibodies and ECL detection (GE Healthcare, Milan), band intensity was measured with the ChemiDoc imaging system (BioRad) and the H3K9 acetylation level was normalized to actin.

Effects on TNF-alpha

BxPC-3 cells overexpressing SIRT6 (Bauer I. et al., J. Biol. Chem. 2012 Oct 18) (3 x 10^5 cells/well) were seeded in 6-well plates and allowed to adhere for 24 hours before being incubated for 18 hours with the various compounds (100µM final concentration). Subsequently, to induce cytokine expression, cells were stimulated for 48 hours with 25 ng/ml of phorbol myristate acetate (PMA; Sigma Aldrich). Subsequently, supernatants were collected and assayed for IL8 and TNF using DuoSet® ELISA kits available on the market (R&D Systems, Minneapolis, USA). The concentration in supernatants was normalized to the cell density measured with sulforhodamine B.
Glucose uptake experiments

1 x 10^5 BxPC-3 cells engineered to express the pRETROSUPER vector (pRS) or a SIRT6-targeted shRNA (sh2 SIRT6) (Bauer I, et al. J Biol Chem. 2012 Oct 18) were plated in each well of a 12-well plate in 500 µl of standard culture medium. 72 hours later, cells were incubated (or not incubated) in the presence of the compounds at a concentration of 200 µM for 18 h. Cells were then washed once with 1 ml of PBS buffer and glucose transport was measured by addition of D-glucose/0.5mM [14C]-2-deoxy-D-glucose (0.2 µCi/well) in KRH buffer for 5 mins at 37°C. Glucose uptake (absorption) was stopped by immediately removing the labelling mixture and washing the cells 3 times with ice-cold KRH. The cells were then lysed with 0.1% sodium dodecyl sulfate (SDS) and an aliquot of each lysate was used for the scintillation count in a LS 6500 Beta-Counter (Beckman-Coulter, CA). Non-specific uptake in the presence of 20µM citocalasine B and 200µM phloretin was subtracted from each experimental value.

AutoADP-ribosylation of SIRT6 assay

Reactions were performed in a total volume of 10 µl, containing 20 µg of recombinant SIRT6 (produced following published protocols) in 50mM Tris-HCl, pH 8.0, 150mM NaCl, 10mM dithiothreitol, and 0.4 µCi [3H]NAD (40 Ci mmol⁻¹; Perkin Elmer, Boston, MA), in the presence or absence of different compounds (200 µM final concentration) or nicotinamide (100mM final concentration) for 45 minutes at 22°C. At the end of incubation, samples were filtered on a nitrocellulose membrane (Bio-Rad), filters were washed twice with 3 ml of washing buffer (50mM Tris-HCl, pH 8.0, 150mM NaCl) and then dried, and radioactivity was measured in 3.0 ml of Ultima-Gold on a Packard β-counter.

The following table summarizes experimental data obtained subjecting some compounds according to the present invention to the tests described above.
The data reported above demonstrate that the compounds according to the present invention display inhibitory activity against sirtuins SIRT1, SIRT2 and SIRT6, with good selectivity towards SIRT6, as well as inhibitory activity against the production of TNF-alpha by BxPC3 cells; ability to increase glucose uptake in BxPC3 cells; (limited) ability to reduce autoADP-ribosylation of SIRT6; and ability to reduce viability of BxPC3 cells in the presence of a low concentration (inM) of gemcitabine, which would be inactive as such in the absence of SIRT6 inhibitors (% of viability inhibition by inM gemcitabine alone = 4%).

Literature references:


family of cancer drug targets. Current pharmaceutical design 2012.


CLAIMS

1. A compound of general formula (I)

\[
\begin{align*}
R^1 &= H, \text{Ci-Csalkyl;} \\
R^2 &= H, \text{Ci-Csalkyl;} \\
R^3 &= \text{optionally substituted phenyl; optionally substituted phenoxy; } -\text{CH}_2-(\text{CH}_2)_n \text{-phenyl optionally substituted on the benzene ring, where } n = 0, 1 \text{ or } 2; \text{ or } -Y-R^5, \\
Y &= \text{a single bond, } -O, \text{ } -\text{CH}_2, \text{ and} \\
R^5 &= \text{5- or 6-membered, saturated or aromatic heterocyclic ring containing one or more heteroatoms selected from } N, S \text{ and } O, \text{ optionally substituted with a Ci-Csalkyl;}
\end{align*}
\]

where \(Y\) = a single bond, -O, -CH₂, and

\[
R^4 = H, \text{C}_{1-6} \text{alkyl, } \text{C}_{3-6} \text{cycloalkyl, halogen, } -\text{NO}_2, -\text{CN}, -\text{OH}, -\text{SH}, -\text{CF}_3, -\text{CCI}_3, -\text{COOH, } -\text{COOC}_{1-5} \text{alkyl, } -\text{SO}_2 \text{OC}_{1-5} \text{alkyl, } -\text{OC}_{1-5} \text{alkyl,}
\]

or enantiomers, diastereomers and pharmaceutically acceptable salts thereof, for use as a medicament.

2. A compound according to claim 1, in which

\[
R^1 = H, \text{CH}_3 \\
R^2 = H, \text{CH}_3
\]

\[
R^3 = \text{phenyl, phenoxy, benzyl or phenylethyl optionally substituted with a Ci-3alkyl on the aromatic ring or } Y-R^5,
\]
where $Y$ = a single bond, -O-, -CH2-, and

$R^5 = 5$- or 6-membered heteroaromatic ring, containing 1 or 2 N atoms, optionally substituted with a Ci-Csalkyl;

$R^4 = H$

or enantiomers, diastereomers and pharmaceutically acceptable salts thereof, for use as a medicament.

3. A compound according to claim 2, in which

$R^1 = H, CH_3$

$R^2 = H, CH_3$

$R^3 =$ phenyl, benzyl, phenylethyl or $Y$-$R^5$,

where $Y$ = a single bond, -O-, -CH2-, and

$R^5 =$ pyridinyl or imidazolyl;

$R^4 = H$

or enantiomers, diastereomers and pharmaceutically acceptable salts thereof, for use as a medicament.

4. A compound according to claim 3, having formula:

2,4-dioxo-$N$-[4-(pyridin-3-yloxy)phenyl]-1,2,3,4-tetrahydroquinazoline-6-sulfonamide;

$N$-[4-(1H-imidazol-1-ylmethyl)phenyl]-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide;

2,4-dioxo-$N$-[3-[2-(pyridin-4-yl)ethyl]phenyl]-1,2,3,4-tetrahydroquinazoline-6-sulfonamide;

$N$-(2-benzylphenyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide;

2,4-dioxo-$N$-(2-phenylphenyl)-1,2,3,4-tetrahydroquinazoline-6-sulfonamide; or
1,3-dimethyl-2,4-dioxo-N-[4-(pyridin-4-ylmethyl)phenyl]-1,2,3,4-tetrahydroquinazoline-6-sulfonamide,

for use as a medicament.

5. A compound according to any one of claims 1 to 4, for use as an inhibitor of one or more sirtuins to increase glucose uptake in a subject.

6. A compound according to claim 5, wherein said compound inhibits sirtuin SIRT6.

7. A compound according to any one of claims 5 and 6, for use in the treatment of:

   type I and type II diabetes mellitus and complications thereof, such as ketoacidotic coma, hyperglycaemic hyperosmolar condition, atherosclerosis, ischaemic heart disease (angina and myocardial infarction), stroke, peripheral vasculopathy, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, diabetic foot.

8. A compound according to any one of claims 1 to 4 for use as an inhibitor of one or more sirtuins to reduce the production of TNF-alpha or other inflammatory, chemotactic, or proangiogenic cytokines in a subject and/or to reduce local or systemic inflammation in a subject and/or to treat a pathology mediated by TNF-alpha or other inflammatory, chemotactic, or proangiogenic cytokines in a subject having local or systemic excessive or dysregulated production of TNF-alpha or other inflammatory, chemotactic, or proangiogenic cytokines.

9. A compound according to claim 8, wherein said compound inhibits sirtuin SIRT6.

10. A compound according to any one of claims 8 and 9, for use in the treatment of inflammatory diseases comprising rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, systemic lupus erythematosus, vasculitis, Goodpasture syndrome, scleroderma, atherosclerosis, graft versus host disease (GVHD), organ transplant rejection, myocardial infarction, stroke, reperfusion injury after revascularization in heart and other organs.
11. A compound according to any one of claims 1 to 4 for use as an inhibitor of one or more sirtuins to interfere with DNA repair in tumor cells and thus exert an anticancer effect and sensitize said cells to antineoplastic agents and radiotherapy.

12. A compound according to claim 11, wherein said compound inhibits sirtuin SIRT6.

13. A compound according to any one of claims 11 and 12, for use in the treatment of neoplastic diseases comprising pancreatic cancer, breast cancer, colorectal cancer, prostatic cancer, ovarian cancer, melanoma, lung cancer, oesophageal cancer, hepatic carcinoma, lymphomas, leukemias, myeloma, sarcomas, neoplastic cachexia.

14. A pharmaceutical composition containing a therapeutically effective amount of at least one compound according to any one of claims 1 to 4 and a pharmaceutically acceptable vehicle.

15. A method for reducing the production of TNF-alpha or other inflammatory, chemotactic, or proangiogenic cytokines in cells in vitro, comprising the step of exposing said cells to a compound according to any one of claims 1 to 4.

16. A method for increasing glucose uptake in cells in vitro, comprising the step of exposing said cells to a compound according to any one of claims 1 to 4.

17. A method for increasing the antiproliferative and cytotoxic effect of antineoplastic drugs and ionizing radiations in vitro, comprising the step of exposing said tumor cells to a compound according to any one of claims 1 to 4.
INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/060829

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K3/517 A61P3/10 A61P35/00 A61P29/00
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, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"Z" document member of the same patent family

Date of the actual completion of the international search
9 July 2014

Date of mailing of the international search report
17/07/2014

Name and mailing address of the ISA/Authorized officer
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Schei the, Rupert
**DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<td>A</td>
<td>WO 2008/138943 A2 (UNIV BRUXELLES [BE]; LEO OBERDAN [BE]; GALLI MARA [BE]; VAN G00L FREDE) 20 November 2008 (2008-11-20) cited in the application on the whole document</td>
<td>1-4, 8-10, 15</td>
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<td>A</td>
<td>WO 02/064572 A1 (WARNER LAMBERT CO) 22 August 2002 (2002-08-22) Examples 27, 33, 462; claims 15, 31</td>
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<td>T</td>
<td>MARCO DANI ELE PARENTI ET AL: &quot;Discovery of Novel and Selective SRT6 Inhibitors&quot;, JOURNAL OF MEDICINAL CHEMISTRY, vol. 57, no. 11, 12 June 2014 (2014-06-12) pages 4796-4804, XP055124815, ISSN: 0022-2623, DOI: 10.1021/jm500487d the whole document</td>
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