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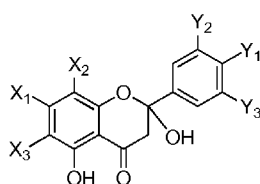
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(54) Title: NATURAL PRODUCT DERIVATIVES FOR INHIBITING CELLULAR NECROPTOSIS, FERROPTOSIS AND OXYTOSIS



(57) Abstract: The present invention relates to a compound of the following general formula (I); or a pharmaceutically acceptable salt and/or solvate thereof, for use as drug, particularly intended for inhibiting a programmed cell death route selected from the group consisting of ferroptosis, oxytosis and cellular necroptosis. The present invention also relates to a compound of general formula (I) for use as a drug for neuroprotection as well as for preventing and/or treating disorders associated with cellular necroptosis or ferroptosis. The present invention also relates to a pharmaceutical composition comprising a compound of general formula (I), or a pharmaceutically acceptable salt and/or solvate thereof. The present invention also encompasses the use of a compound of the general formula (I) for organs preservation.



NATURAL PRODUCT DERIVATIVES FOR INHIBITING CELLULAR NECROPTOSIS, FERROPTOSIS AND OXYTOSIS

The present invention relates to a compound for use as a drug, said drug being particularly intended for inhibiting a programmed cell death route selected from the group consisting of ferroptosis, oxytosis and cellular necroptosis. More particularly, the present invention relates to a compound for use for preventing and/or treating disorders associated with cellular necroptosis.

Programmed cell death is a natural process for removing unwanted cells, such as cancer cells.

Necroptosis, a programmed cell death route, is clearly distinct from apoptosis as it does not involve key apoptosis regulators, such as caspases, Bcl-2 family members or cytochrome c release from mitochondria. "Necroptosis" is a specialized biochemical pathway of programmed necrosis that depends notably on the serine/threonine kinase activity of RIPK1 (Receptor-Interacting Protein Kinase 1). It can be inhibited by necrostatin-1, an inhibitor of RIPK1 (US patent US 8,143,300).

Necroptosis may be activated upon stimulation by TNF- α (Tumor Necrosis Factor α), FasL (Fas ligand) and TRAIL (Tumor-necrosis-factor Related Apoptosis Inducing Ligand), and relies on the activity of two serine-threonine kinases, RIPK1 and RIPK3. TNF via TNFR1 (Tumor Necrosis Factor Receptor 1) leads to the formation of two sequential signaling complexes. The receptor-proximal complex I induces pro-survival signals through activation of NF- κ B (Nuclear Factor – kappa B) and MAPKs (Mitogen Activated Protein Kinases), while the second cytosolic complex II signals two cell death pathways: (a) apoptosis, via formation of complex IIa including FADD (Fas-Associated Death Domain) that recruits caspase-8 and/or caspase-10 to activate a caspase cascade; (b) necroptosis, via activation of RIPK1 and RIPK3 kinases in a complex called the necrosome. TNF- α can induce necroptosis in Jurkat cells when FADD is deleted (Miao and Degterev, *Methods Mol. Biol.* 2009, 559, 79-93).

The ground-breaking finding that necroptosis is a genetically controlled process led to the hypothesis that this programmed cell-death is 'druggable', an emerging breakthrough that carries the potential to revolutionize every day clinical medicine

(Linkermann and Green, *N. Eng. J. Med.* 2014, 370(5), 455-465). Indeed molecular targets, including RIPK1 (Receptor Interacting Protein 1), RIPK3 and MLKL (Mixed Lineage Kinase domain-Like), have convincingly been shown to contribute to multiple disorders where necroptosis is of central pathophysiological relevance, such as: 5 ischemia-reperfusion injury in brain, heart and kidney, inflammatory diseases, sepsis, retinal disorders, neurodegenerative diseases and infectious disorders (Jouan-Lanhouet *et al. Semin. Cell. Dev. Biol.* 2014, 35, 2-13). More recently, it has been shown that human and murine tumour cells induce necroptosis of endothelial cells, which promotes tumour cell extravasation and metastasis (Strilic *et al. Nature* 2016, 536(7615), 215-10 218). Necroptosis can thus also be targeted in the treatment of human metastasis, the leading cause of cancer-related death in humans.

Only few RIPK1 inhibitors have been developed (Degterev *et al. Nat. Chem. Biol.* 2005, 1(2), 112-119, and *Nat Chem Biol.* 2008, 4(5), 313-321). Among them, necrostatin-1 (Nec-1) has been used to specifically inhibit several necrotic processes. 15 However, RIPK1-independent effect of Nec-1 has been pointed out (Cho *et al. PLoS One.* 2011, 6(8):e23209), and Nec-1 is also an inhibitor of indoleamine 2, 3-dioxygenase (Takahashi *et al. Cell Death Dis.* 2012, 3:e437). Moreover, the stability of Nec-1 *in vivo* is very limited. Several structurally distinct necrostatins (Nec-3 (Jagtap *et al. J. Med. Chem.* 2007, 50(8), 1886-1895), Nec-4 (Teng *et al. Bioorg. Med. Chem. Lett.* 2007, 17(24), 6836-6840), Nec-5 (Wang *et al. Bioorg. Med. Chem. Lett.* 2007, 17(5), 1455-1465), Nec-7 (Zheng *et al. Bioorg. Med. Chem. Lett.* 2008, 18(18), 4932-4935)) and corresponding modifications have been reported. Recently, Nec-21, another potent Nec-1 analogue was reported to show an improved off-target profile (Wu *et al. Bioorg. Med. Chem. Lett.* 2013, 23(17), 4903-4906). One of the best stable RIPK1 25 inhibitor is Nec-1s (Nec-1 stable), which was shown to interact with a hydrophobic pocket of the kinase domain, hence stabilizing RIPK1 in an inactive conformation (Xie *et al. Structure* 2013, 21(3), 493-9).

There is therefore a need for new RIPK1 inhibitors with high potential, good 30 stability and low toxicity.

The inventors of the present invention have thus discovered new inhibitors of the necroptotic cell-death. These compounds thus appear to be very attractive in therapy for preventing and/or treating disorders associated with cellular necroptosis. Moreover, such compounds are also for use for the preservation and/or protection of biological materials such as cells, tissues, body fluids and organs, and of microorganisms, advantageously as a medical device.

Surprisingly, these compounds have proved to be potent inhibitors of two others programmed cell death routes, namely ferroptosis and oxytosis.

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Ferroptosis is a non-apoptotic cell death that is catalyzed by iron and is due to a loss of activity of the lipid repair enzyme glutathione peroxidase 4 (GPX4) (Lang and Stockwell, *Trends Cell Biol.* 2016, 26(3), 165-176). The failure of the glutathione-dependent antioxidant defenses leads to an accumulation of lipid-based reactive oxygen species (ROS), resulting notably of lipids peroxidation.

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Ferroptosis can be induced by erastin in diverse cell types. The latter is a small molecular inhibitor of the System X_c⁻, a cystine/glutamate antiporter that typically mediates the exchange of extracellular L-cystine and intracellular L-glutamate across the cellular plasma membrane. Once inside a cell, cystine is rapidly reduced to cysteine, which can then enter glutathione (GSH) and protein biosynthetic pathways. This antiporter is thus a key component essential for protection of cells from oxidative stress.

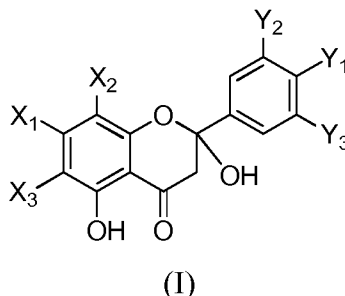
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The L-cystine uptake driven by the System X_c⁻ is potently inhibited by L-glutamate, inducing an oxidative toxicity. When excessive glutamate is present near nerve cells, a non-apoptotic, oxidative form of cell death occurs, which is called oxytosis. L-glutamate-induced toxicity of neuronal cells is also linked to the excitotoxicity related to the Ca²⁺ uptake. High Ca²⁺ concentrations increase risk for mitochondrial damage. This triggers the mitochondrial production of reactive oxygen species (ROS) that can enhance the effect on the X_c⁻ System.

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Thus, the present invention relates to a compound of following general formula (I):



5 or a pharmaceutically acceptable salt and/or solvate thereof, wherein :

- X_1 , X_2 and X_3 each represent, independently of each other, a hydrogen atom; a (C₁-C₆)alkyl; an aryl; an aryl-(C₁-C₆)alkyl group; an OH; or a group selected from OR_X, SR_X, SO₂R_X and NR_XR_Z,
with at least one of X_1 , X_2 and X_3 representing a (C₁-C₆)alkyl; an aryl; an aryl-(C₁-C₆)alkyl group; or a group selected from OR_X, SR_X, SO₂R_X and NR_XR_Z, wherein
10 R_X is selected from a (C₁-C₆)alkyl, an aryl and an aryl-(C₁-C₆)alkyl group,
R_Z is a hydrogen atom or a (C₁-C₆)alkyl group, and
the aryl groups are optionally substituted with one or several groups selected from halo, -OR₁, -NR₂R₃, -SR₄, -S(O)R₅, -SO₂R₆, -OCOR₇, -CO₂R₈, -CONR₉R₁₀, -
15 CO₂R₁₁, nitro (-NO₂) and cyano (-CN);
- Y_1 , Y_2 and Y_3 each represent, independently of each other, a hydrogen atom; a (C₁-C₆)alkyl; an aryl; an aryl-(C₁-C₆)alkyl group; an OH; or a group selected from OR_Y, SR_Y, SO₂R_Y and NR_YR'_Z,
with at least one of Y_1 , Y_2 and Y_3 representing a (C₁-C₆)alkyl; an aryl; an aryl-(C₁-C₆)alkyl group; or a group selected from OR_Y, SR_Y, SO₂R_Y and NR_YR'_Z, wherein
20 R_Y is selected from a (C₁-C₆)alkyl, an aryl and an aryl-(C₁-C₆)alkyl group,
R'_Z is a hydrogen atom or a (C₁-C₆)alkyl group, and
the aryl groups are optionally substituted with one or several groups selected from halo, -OR₁, -NR₂R₃, -SR₄, -S(O)R₅, -SO₂R₆, -OCOR₇, -CO₂R₈, -CONR₉R₁₀, -
25 CO₂R₁₁, nitro (-NO₂) and cyano (-CN);
- R₁ to R₁₁ are, independently of one another, a hydrogen atom or a (C₁-C₆)alkyl group,
for use as a drug.

In a preferred embodiment:

- X_1 represents a (C₁-C₆)alkyl an aryl, an aryl-(C₁-C₆)alkyl group or an OR_X group, wherein
R_X is selected from a (C₁-C₆)alkyl, an aryl and an aryl-(C₁-C₆)alkyl group,
- 5 ▪ X_2 and X_3 each represent, independently of each other, a hydrogen atom or a (C₁-C₆)alkyl group,
- Y_1 , Y_2 and Y_3 each represent, independently of each other, a hydrogen atom, a (C₁-C₆)alkyl, an aryl, an aryl-(C₁-C₆)alkyl group, an OH or an OR_Y group, with at least one of Y_1 , Y_2 and Y_3 representing a (C₁-C₆)alkyl, an aryl, an aryl-(C₁-C₆)alkyl group or an OR_Y group, wherein
10 R_Y is selected from a (C₁-C₆)alkyl, an aryl and an aryl-(C₁-C₆)alkyl group.

For the purpose of the invention, the term “pharmaceutically acceptable” is intended to mean what is useful to the preparation of a pharmaceutical composition, and
15 what is generally safe and non-toxic, for a pharmaceutical use.

The term “pharmaceutically acceptable salt or solvate” is intended to mean, in the framework of the present invention, a salt or solvate of a compound which is pharmaceutically acceptable, as defined above, and which possesses the pharmacological activity of the corresponding compound.

20 The pharmaceutically acceptable salts comprise:

(1) acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric and phosphoric acid and the like; or formed with organic acids such as acetic, benzenesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxynaphthoic, 2-hydroxyethanesulfonic, lactic, maleic, malic, mandelic,
25 methanesulfonic, muconic, 2-naphtalenesulfonic, propionic, succinic, dibenzoyl-L-tartaric, tartaric, p-toluenesulfonic, trimethylacetic, and trifluoroacetic acid and the like, and

(2) base addition salts formed when an acid proton present in the compound is either replaced by a metal ion, such as an alkali metal ion, an alkaline-earth metal ion,
30 or an aluminium ion; or coordinated with an organic or inorganic base. Acceptable organic bases comprise diethanolamine, ethanolamine, N-methylglucamine, triethanolamine, tromethamine and the like. Acceptable inorganic bases comprise

aluminium hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide.

Acceptable solvates for the therapeutic use of the compounds of the present invention include conventional solvates such as those formed during the last step of the preparation of the compounds of the invention due to the presence of solvents. As an
5 example, mention may be made of solvates due to the presence of water (these solvates are also called hydrates) or ethanol.

The term “stereoisomers” used in this invention refers to configurational
10 stereoisomers, such as optical isomers.

The optical isomers result from the different position in space of substituents comprising four different substituents. This atom thus represents a chiral or asymmetric center. Optical isomers which are not mirror images of one another are thus designated as “diastereoisomers,” and optical isomers which are non-superimposable mirror images
15 are designated as “enantiomers”.

An equimolar mixture of two enantiomers of a chiral compound is designated as racemate or racemic mixture.

The terms “(C₁-C₆)alkyl”, as used in the present invention, refers to a straight or
20 branched saturated hydrocarbon chain containing from 1 to 6 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, n-hexyl, and the like.

The term “aryl”, as used in the present invention, refers to an aromatic hydrocarbon group comprising preferably 6 to 10 carbon atoms and comprising one or
25 more, notably 1 or 2, fused rings, such as, for example, a phenyl or naphthyl group, advantageously a phenyl group.

The term “aryl-(C₁-C₆)alkyl”, as used in the present invention, refers to an aryl group as defined above bound to the molecule via a (C₁-C₆)alkyl group as defined above. In particular, the -(C₁-C₆)alkyl-aryl group is a benzyl group.

30 The term “halo”, as used in the present invention, stands for “halogen”, and refers to a fluorine, bromine, chlorine or iodine atom.

According to a particular embodiment of the present invention,
X₁, X₂ and X₃ each represent, independently of each other, a hydrogen atom, or a group
selected from OR_X, SR_X, SO₂R_X and NR_XR_Z,
with at least one of X₁, X₂ and X₃ representing a group selected from OR_X, SR_X, SO₂R_X
5 and NR_XR_Z.

In another particular embodiment of the present invention,
X₁, X₂ and X₃ each represent, independently of each other, a hydrogen atom; a (C₁-
C₆)alkyl; an aryl; an aryl-(C₁-C₆)alkyl group; an OH; or an OR_X group,
with at least one of X₁, X₂ and X₃ representing an OR_X group.

10 In still another particular embodiment of the present invention,
X₁, X₂ and X₃ each represent, independently of each other, a hydrogen atom or an OR_X
group, with at least one of X₁, X₂ and X₃ representing an OR_X group.

In the above embodiments, R_X is preferably a (C₁-C₆)alkyl group, such as
methyl, ethyl, n-propyl, more preferably methyl.

15 In the above embodiments, the aryl groups are optionally substituted with one or
several groups selected from halo, -OR₁, -NR₂R₃, -SR₄, -S(O)R₅, -SO₂R₆, -OCOR₇, -
CO₂R₈, -CONR₉R₁₀, -CO₂R₁₁, nitro (-NO₂) and cyano (-CN).

In another embodiment,
20 X₁ represents a (C₁-C₆)alkyl; an aryl; an aryl-(C₁-C₆)alkyl group; or a group selected
from OR_X, SR_X, SO₂R_X and NR_XR_Z, wherein R_X is selected from a (C₁-C₆)alkyl, an aryl
and an aryl-(C₁-C₆)alkyl group, R_X being preferably a (C₁-C₆)alkyl group, such as
methyl, ethyl, n-propyl, more preferably methyl, and
X₂ and X₃ each represent, independently of each other, a hydrogen atom or a (C₁-
25 C₆)alkyl group, preferably a hydrogen atom.

In still another embodiment,
X₁ represents a group selected from OR_X, SR_X, SO₂R_X and NR_XR_Z, wherein R_X is
selected from a (C₁-C₆)alkyl, an aryl and an aryl-(C₁-C₆)alkyl group, R_X being
preferably a (C₁-C₆)alkyl group, such as methyl, ethyl, n-propyl, more preferably
30 methyl, and
X₂ and X₃ each represent, independently of each other, a hydrogen atom or a (C₁-
C₆)alkyl group, preferably a hydrogen atom.

In a preferred embodiment,

X₁ represents an OR_X group, R_X being advantageously a (C₁-C₆)alkyl group.

In another preferred embodiment,

X₂ and X₃ each represent a hydrogen atom.

5 In a yet another preferred embodiment,

X₁ represents an OR_X group, wherein R_X is selected from a (C₁-C₆)alkyl, an aryl and an aryl-(C₁-C₆)alkyl group, R_X being advantageously a (C₁-C₆)alkyl group, such as methyl, ethyl, n-propyl, more advantageously methyl, and

X₂ and X₃ each represent, independently of each other, a hydrogen atom or a (C₁-
10 C₆)alkyl group, advantageously a hydrogen atom.

According to a particular embodiment of the present invention,

Y₁, Y₂ and Y₃ each represent, independently of each other, a hydrogen atom, or a group selected from OR_Y, SR_Y, SO₂R_Y and NR_YR'_Z,

15 with at least one of Y₁, Y₂ and X₃ representing a group selected from OR_Y, SR_Y, SO₂R_Y and NR_YR'_Z.

In another particular embodiment of the present invention,

Y₁, Y₂ and Y₃ each represent, independently of each other, a hydrogen atom; a (C₁-C₆)alkyl; an aryl; an aryl-(C₁-C₆)alkyl group; an OH; or an OR_Y group,

20 with at least one of Y₁, Y₂ and Y₃ representing an OR_Y group.

In still another particular embodiment of the present invention,

Y₁, Y₂ and Y₃ each represent, independently of each other, a hydrogen atom or an OR_Y group, with at least one of Y₁, Y₂ and Y₃ representing an OR_Y group.

In the above embodiments, R_Y is preferably a -(C₁-C₆)alkyl-aryl group, such as
25 benzyl, or naphthylmethyl, more preferably benzyl.

In the above embodiments, the aryl groups are optionally substituted with one or several groups selected from halo, -OR₁, -NR₂R₃, -SR₄, -S(O)R₅, -SO₂R₆, -OCOR₇, -CO₂R₈, -CONR₉R₁₀, -CO₂R₁₁, nitro (-NO₂) and cyano (-CN).

30 In another embodiment,

Y₁ represents a (C₁-C₆)alkyl; an aryl; an aryl-(C₁-C₆)alkyl group; or a group selected from OR_Y, SR_Y, SO₂R_Y and NR_YR'_Z, wherein R_Y is selected from a (C₁-C₆)alkyl, an

aryl and an aryl-(C₁-C₆)alkyl group, R_Y being preferably a -(C₁-C₆)alkyl-aryl group, such as benzyl, or naphthyl-methyl, more preferably benzyl, and

Y₂ and Y₃ each represent, independently of each other, a hydrogen atom or a (C₁-C₆)alkyl group, preferably a hydrogen atom.

5 In still another embodiment,

Y₁ represents a group selected from OR_Y, SR_Y, SO₂R_Y and NR_YR'_Z, wherein R_Y is selected from a (C₁-C₆)alkyl, an aryl and an aryl-(C₁-C₆)alkyl group, R_Y being preferably -(C₁-C₆)alkyl-aryl group, such as benzyl, or naphthyl-methyl, more preferably benzyl, and

10 Y₂ and Y₃ each represent, independently of each other, a hydrogen atom or a (C₁-C₆)alkyl group, preferably a hydrogen atom.

In a preferred embodiment,

Y₁ represents an OR_Y group, wherein R_Y is selected from a (C₁-C₆)alkyl, an aryl and an aryl-(C₁-C₆)alkyl group, R_Y being advantageously a -(C₁-C₆)alkyl-aryl group, such as
15 benzyl, or naphthyl-methyl, more advantageously benzyl, and

Y₂ and Y₃ each represent, independently of each other, a hydrogen atom or a (C₁-C₆)alkyl group, advantageously a hydrogen atom.

In the above embodiments, the aryl groups are optionally substituted with one or several groups selected from halo, -OR₁, -NR₂R₃, -SR₄, -S(O)R₅, -SO₂R₆, -OCOR₇, -
20 CO₂R₈, -CONR₉R₁₀, -CO₂R₁₁, nitro (-NO₂) and cyano (-CN).

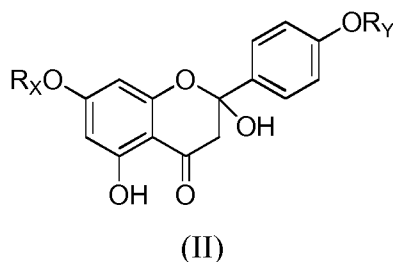
According to a first embodiment of the present invention:

- X₁, X₂ and X₃ each represent, independently of each other, a hydrogen atom, a (C₁-C₆)alkyl an aryl, an aryl-(C₁-C₆)alkyl group or an OR_X group,
25 with at least one of X₁, X₂ and X₃ representing a (C₁-C₆)alkyl, an aryl, an aryl-(C₁-C₆)alkyl group or an OR_X group, wherein
R_X is selected from a (C₁-C₆)alkyl, an aryl and an aryl-(C₁-C₆)alkyl group, and
- Y₁, Y₂ and Y₃ each represent, independently of each other, a hydrogen atom, a (C₁-C₆)alkyl, an aryl, an aryl-(C₁-C₆)alkyl group, an OH or an OR_Y group,
30 with at least one of Y₁, Y₂ and Y₃ representing a (C₁-C₆)alkyl, an aryl, an aryl-(C₁-C₆)alkyl group or an OR_Y group, wherein
R_Y is selected from a (C₁-C₆)alkyl, an aryl and an aryl-(C₁-C₆)alkyl group.

According to a second embodiment:

- X_1 represents an OR_X group, wherein R_X is selected from a (C_1-C_6) alkyl, an aryl and an aryl- (C_1-C_6) alkyl group, R_X being advantageously a (C_1-C_6) alkyl group, such as methyl, ethyl, n-propyl, more advantageously methyl,
- X_2 and X_3 each represent, independently of each other, a hydrogen atom or a (C_1-C_6) alkyl group, advantageously a hydrogen atom,
- Y_1 represents an OR_Y group, wherein R_Y is selected from a (C_1-C_6) alkyl, an aryl and an aryl- (C_1-C_6) alkyl group, R_Y being advantageously a $-(C_1-C_6)$ alkyl-aryl group, such as benzyl, or naphthyl-methyl, more advantageously benzyl, and
- Y_2 and Y_3 each represent, independently of each other, a hydrogen atom or a (C_1-C_6) alkyl group, advantageously a hydrogen atom.

According to a third embodiment, the compound for use according to the present invention is of the following formula (II):

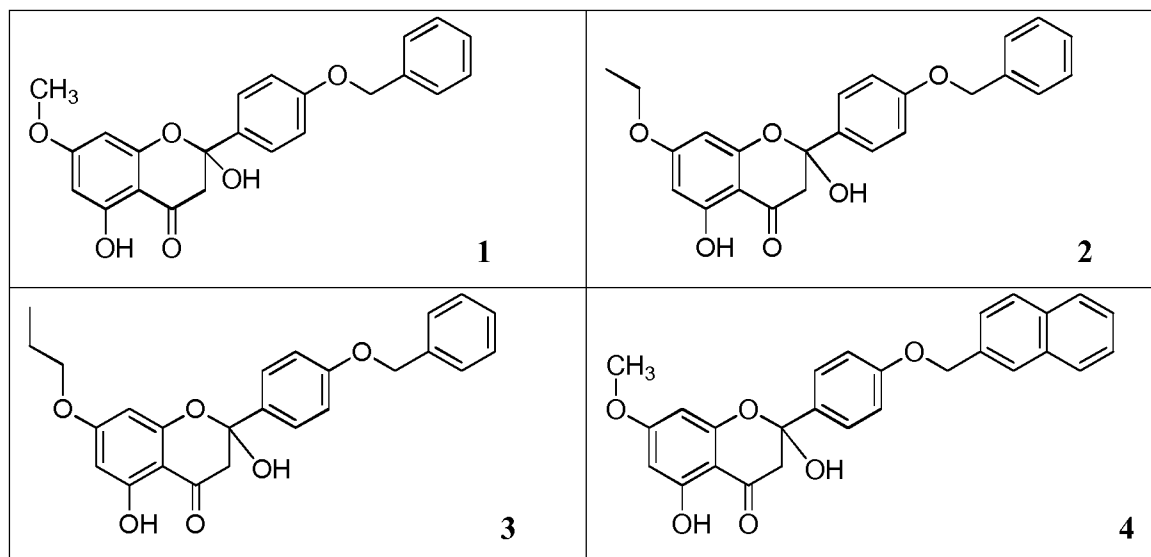


or a pharmaceutically acceptable salt and/or solvate thereof, wherein :

R_X represents a (C_1-C_6) alkyl group, such as methyl, ethyl, n-propyl, more advantageously methyl, and

R_Y represents an aryl- (C_1-C_6) alkyl group, such as benzyl, or naphthyl-methyl, more advantageously benzyl.

The compound of general formula (II) can be selected from compounds 1 to 4, represented below, and the pharmaceutically acceptable salts and solvates thereof.



The compound for use according to the present invention is preferably compound **1**.

Compound **1** is a synthetic derivative of a naturally occurring flavanone, isolated
 5 from *Populus nigra* buds (Chadenson *et al. J. Chem. Soc. Chem. Comm.* 1972, p.107-108; and Chadenson *et al. C. R. Acad. Sc. Paris* 1972, 275 p.1291-1293).

The present invention is also directed to the compound of general formula (I) as defined above, for use as a drug intended for inhibiting a programmed cell death route
 10 selected from the group consisting of ferroptosis, oxytosis and cellular necroptosis, notably for inhibiting cellular necroptosis.

In particular, the present invention is directed to the compound of general formula (I) as defined above, for use as a drug intended for preventing and/or treating
 15 disorders associated with cellular necroptosis.

The cellular necroptosis may be in particular tumour-cell-induced endothelial cell necroptosis.

The disorders associated with cellular necroptosis may be particularly trauma in brain, hepatitis, alcoholic and non-alcoholic steatohepatitis, acute pancreatitis and acute
 20 tubular necrosis, heart or kidney transplantation, atherosclerosis, bone marrow failure, viral infection, Crohn's and ulcerative colitis, terminal ileitis, chronic obstructive pulmonary disease or ischemia reperfusion injury such as myocardial infarction or

stroke. It can also be age-related macular degeneration, psoriasis or toxic epidermal necrolysis.

The disorders associated with tumour-cell-induced endothelial cell necroptosis may be particularly tumour cells extravasation or metastasis.

5

In another particular embodiment, the present invention is directed to the compound of general formula (I) as defined above, for use as a drug intended for preventing and/or treating disorders associated with ferroptosis.

The disorders associated with ferroptosis may be particularly acute kidney
10 failure; a neurodegenerative disease such as Huntington's disease, Alzheimer's disease and Parkinson's disease; hemochromatosis; intracerebral hemorrhage (ICH) stroke or ischemia-reperfusion injuries (brain, kidney, heart).

In still another particular embodiment, the present invention is directed to the
15 compound of general formula (I) as defined above, for use as a drug intended for neuroprotection.

Within the meaning of the present invention, the term "neuroprotection" refers to the relative preservation of neuronal structure and/or function after a deleterious treatment ("a neurodegenerative insult") or in case of pathological conditions. It is thus
20 a treatment option for many central nervous system (CNS) disorders including neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and Amyotrophic Lateral Sclerosis; stroke; traumatic brain injury and spinal cord injury. Despite differences in symptoms or injuries associated with CNS disorders, many of the mechanisms behind neurodegeneration are the same. Common mechanisms
25 include increased levels in oxidative stress and excitotoxicity, which are often targeted by neuroprotective treatments.

The present invention also relates to a method for inhibiting a programmed cell death route selected from the group consisting of ferroptosis, oxytosis and cellular
30 necroptosis, notably for inhibiting cellular necroptosis, comprising the administration to a person in need thereof of an effective dose of a compound of formula (I) as defined above. In particular, the present invention relates to a method for preventing and/or

treating disorders associated with cellular necroptosis, comprising the administration to a person in need thereof of an effective dose of a compound of formula (I) as defined above. It also relates to a method for preventing and/or treating disorders associated with ferroptosis, comprising the administration to a person in need thereof of an effective dose of a compound of formula (I) as defined above. It is also directed to a method of neuroprotection, comprising the administration to a person in need thereof of an effective dose of a compound of formula (I) as defined above.

The present invention also relates to the use of a compound of formula (I) as defined above, for the manufacture of a drug, in particular for inhibiting a programmed cell death route selected from the group consisting of ferroptosis, oxytosis and cellular necroptosis, notably for inhibiting cellular necroptosis. In particular, the present invention also relates to the use of a compound of formula (I) as defined above, for the manufacture of a drug for preventing and/or treating disorders associated with cellular necroptosis. It also relates to the use of a compound of formula (I) as defined above, for the manufacture of a drug for preventing and/or treating disorders associated with cellular ferroptosis.

The cellular necroptosis may be in particular tumour-cell-induced endothelial cell necroptosis.

The disorders associated with cellular necroptosis may be particularly trauma in brain, hepatitis, alcoholic and non-alcoholic steatohepatitis, acute pancreatitis and acute tubular necrosis, heart or kidney transplantation, atherosclerosis, bone marrow failure, viral infection, Crohn's and ulcerative colitis, terminal ileitis, chronic obstructive pulmonary disease or ischemia reperfusion injury such as myocardial infarction or stroke. It can also be age-related macular degeneration, psoriasis or toxic epidermal necrolysis.

The disorders associated with tumour-cell-induced endothelial cell necroptosis may be particularly tumour cells extravasation or metastasis.

The disorders associated with ferroptosis may be particularly acute kidney failure; a neurodegenerative disease such as Huntington's disease, Alzheimer's disease and Parkinson's disease; hemochromatosis; intracerebral hemorrhage (ICH) stroke or ischemia-reperfusion injuries (brain, kidney, hearth).

The present invention also relates to the use of a compound of formula (I) as defined above, for the manufacture of a drug intended for neuroprotection.

5 The present invention also relates to a pharmaceutical composition comprising at least one compound of formula (I) as defined above and at least one pharmaceutically acceptable excipient.

The term “pharmaceutically acceptable excipient” is intended to mean, in the framework of the present invention, a substance which is pharmaceutically acceptable, as defined above, formulated alongside the active ingredient(s) of the pharmaceutical composition, included for the purpose of long-term stabilization, bulking up solid formulations that contain potent active ingredients in small amounts, to confer a therapeutic improvement on the active ingredient in the final dosage form (such as facilitating drug absorption, reducing viscosity, or enhancing solubility), or to enhance the taste or the appearance of the pharmaceutical composition. The appropriate excipients can be easily and wisely selected by the skilled person, taking into account notably the dosage form and the route of administration.

20 According to one particular embodiment, the present invention is directed to the pharmaceutical composition as defined above, for use for inhibiting a programmed cell death route selected from the group consisting of ferroptosis, oxytosis and cellular necroptosis, notably cellular necroptosis.

According to one particular embodiment, the present invention is directed to the pharmaceutical composition as defined above, for use for preventing and/or treating disorders associated with cellular necroptosis.

25 According to another particular embodiment, the present invention is also directed to the pharmaceutical composition as defined above, for use for preventing and/or treating disorders associated with ferroptosis.

30 According to another particular embodiment, the present invention is also directed to the pharmaceutical composition as defined above, for use for neuroprotection.

The present invention also relates to a method for inhibiting a programmed cell death route selected from the group consisting of ferroptosis, oxytosis and cellular necroptosis, notably for inhibiting cellular necroptosis, comprising the administration to a person in need thereof of an effective dose of the pharmaceutical composition as defined above. In particular, the present invention relates to a method for preventing and/or treating disorders associated with cellular necroptosis, comprising the administration to a person in need thereof of an effective dose of the pharmaceutical composition as defined above. It also relates to a method for preventing and/or treating disorders associated with ferroptosis, comprising the administration to a person in need thereof of an effective dose of the pharmaceutical composition as defined above. It is also directed to a method of neuroprotection, comprising the administration to a person in need thereof of an effective dose of the pharmaceutical composition as defined above.

The present invention also relates to the use of the pharmaceutical composition as defined above, for the manufacture of a drug, in particular for inhibiting a programmed cell death route selected from the group consisting of ferroptosis, oxytosis and cellular necroptosis, more particularly for inhibiting cellular necroptosis. In particular, the present invention also relates to the use of the pharmaceutical composition as defined above, for the manufacture of a drug for preventing and/or treating disorders associated with cellular necroptosis. It also relates to the use of the pharmaceutical composition as defined above, for the manufacture of a drug for preventing and/or treating disorders associated with ferroptosis.

The cellular necroptosis may be in particular tumour-cell-induced endothelial cell necroptosis.

The disorders associated with cellular necroptosis may be particularly trauma in brain, hepatitis, alcoholic and non-alcoholic steatohepatitis, acute pancreatitis and acute tubular necrosis, heart or kidney transplantation, atherosclerosis, bone marrow failure, viral infection, Crohn's and ulcerative colitis, terminal ileitis, chronic obstructive pulmonary disease or ischemia reperfusion injury such as myocardial infarction or stroke. It can also be age-related macular degeneration, psoriasis or toxic epidermal necrolysis.

The disorders associated with tumour-cell-induced endothelial cell necroptosis may be particularly tumour cells extravasation or metastasis.

The disorders associated with ferroptosis may be particularly acute kidney failure; a neurodegenerative disease such as Huntington's disease, Alzheimer's disease and Parkinson's disease; hemochromatosis; intracerebral hemorrhage (ICH) stroke or ischemia-reperfusion injuries (brain, kidney, hearth).

5 The present invention also relates to the use of the pharmaceutical composition as defined above, for the manufacture of a drug intended for neuroprotection.

 The pharmaceutical compositions according to the invention may be formulated notably for oral administration or for injection, wherein said compositions are intended
10 for mammals, including humans.

 The pharmaceutical composition can be administered orally by means of tablets and gelatin capsules.

 When a solid composition is prepared in the form of tablets, the main active ingredient is mixed with a pharmaceutical vehicle such as gelatin, starch, lactose,
15 magnesium stearate, talc, gum arabic and the like. The tablets may be coated with sucrose or with other suitable materials, or they may be treated in such a way that they have a prolonged or delayed activity and they continuously release a predetermined amount of active principle.

 A preparation in gelatin capsules is obtained by mixing the active ingredient
20 with a diluent and pouring the mixture obtained into soft or hard gelatin capsules.

 For administration by injection, aqueous suspensions, isotonic saline solutions or sterile and injectable solutions which contain pharmacologically compatible dispersing agents and/or wetting agents are used.

 The active ingredient may be administered in unit dosage forms of
25 administration, in mixture with standard pharmaceutical carriers, to animals or to humans. The compounds of the invention as active ingredients may be used in doses ranging between 0.01 mg and 1000 mg per day, given in a single dose once per day or administered in several doses throughout the day, for example twice a day in equal doses. The dose administered per day advantageously is between 5 mg and 500 mg,
30 even more advantageously between 10 mg and 200 mg. It may be necessary to use doses outside these ranges as determined by the person skilled in the art.

The pharmaceutical compositions according to the invention may further comprise at least one other active ingredient, such as another cellular necroptosis inhibitor, or an apoptosis inhibitor, an autophagy inhibitor, a ferroptosis inhibitor, an inhibitor of MPT (The mitochondrial permeability transition) pore-dependent necrosis, a cyclophilin inhibitor, a Cyclin-dependent kinase 5 (CDK5) inhibitor, a parthanatos inhibitor, a thrombin inhibitor, an antioxidant (such as glutathione or allopurinol) or an inflammatory inhibitor.

The present invention relates also to a pharmaceutical composition comprising:

- (i) at least one compound of formula (I) or of formula (II) as defined above, and
 - (ii) at least one other active ingredient, such as another cellular necroptosis inhibitor, or an apoptosis inhibitor, an autophagy inhibitor, a ferroptosis inhibitor, an inhibitor of MPT (The mitochondrial permeability transition) pore-dependent necrosis, a cyclophilin inhibitor, a Cyclin-dependent kinase 5 (CDK5) inhibitor, a parthanatos inhibitor, a thrombin inhibitor, an antioxidant (such as glutathione or allopurinol) or an inflammatory inhibitor,
- as a combination product for simultaneous, separate or sequential use.

The present invention also relates to the use of a compound of general formula (I) as defined above; for the preservation and/or protection of biological materials such as cells, tissues, body fluids and organs, and of microorganisms, advantageously as a medical device.

In the context of the present invention, a medical device refers to any product which is put in contact with organs, tissues, cells or products from the human or animal body origin during their conservation, their preparation, their transformation, their packaging or their transport prior to their therapeutic use in humans. A medical device according to the present invention can also be any product coming into contact with embryos in the context of an activity of medically assisted procreation. In particular, this category of products includes graft preservation media (tissues, organs), the media used in the context of in vitro fertilization, or media used during the preparation of cell therapy products.

In particular, the present invention is directed to the use of a compound of general formula (I) as defined above, for use in medium for preserving organs,

biological tissue, or living cells, preferably for preserving organs such as for example liver or kidney.

The compound of the invention can thus be used in the case of a graft as a supplementary therapeutic product for preserving cells, tissues or organs between the sampling on a donor and the graft on a receiver.

In another particular embodiment, the present invention also relates to the use of a compound of general formula (I) as defined above as protectant against cold (4°C) and/or oxidative stress injuries, notably H₂O₂-induced necrosis.

In the context of the present invention, “protectant” refers to a substance used to protect biological materials such as cells, tissues, body fluids and organs, and microorganisms from cold damage and/or oxidative stress injuries, notably H₂O₂-induced necrosis.

The present invention is also directed to a culture, storage and/or preservation medium comprising at least one compound general formula (I) as defined above.

The examples which follow illustrate the invention without limiting its scope in any way.

BRIEF SUMMARY OF THE FIGURES

- Figure 1 represents the dose-dependent inhibition by compound 1 of necroptosis induced by TNF- α in human T lymphocyte (Jurkat FADD deficient cell line);
- Figure 2 represents the dose-dependent inhibition by compound 1 of the cell membrane permeabilization induced by TNF- α in human T lymphocyte (Jurkat FADD deficient cell line) (the light grey curve is obtained when cells are treated with compound 1 only);
- Figure 3 represents the dose-dependent inhibition by compound 1 of the ATP depletion induced by TNF- α in human T lymphocyte (Jurkat FADD deficient cell line) (the light grey curve is obtained when cells are treated with compound 1 only);
- Figure 4 represents the viability of human primary blood leukocytes treated with increasing concentrations of compound 1;
- Figure 5 represents the viability of human retinal pigment epithelial cells treated with increasing concentrations of compound 1;

Figure 6 represents the dose-dependent inhibition of RIPK1 autophosphorylation by compound 1;

Figure 7 represents the inhibition of RIPK1 autophosphorylation by compound 1 at high ATP concentrations (up to 1mM);

- 5 Figure 8 represents the analysis of compound 1 selectivity against a large panel of kinases;

Figure 9 represents the determination of binding constant (Kd) of compound 1 for its major cellular target RIPK1 at two different temperatures (4°C and Room Temperature, r.t);

- 10 Figure 10 represents the protection from hypoxic injury of human artery endothelial cells (HAEC) by compound 1 during hypoxic cold storage; and

Figure 11 represents the protection of human artery endothelial cells by compound 1 during both hypoxic cold storage and reoxygenation step.

Figure 12 represents the predictive orientation for compound 1 within the theoretical

- 15 RIPK1-6E11 complex.

Figures 13a et 13b represent the binding sites of compound 1 and Nec1s on RIPK1.

Figure 14 represents the dose-dependent protection from ferroptosis (induced by erastin) and Glutamate-induced oxidative toxicity of murine hippocampal neuronal cell line HT22 by compound 1.

- 20 Figures 15a and 15b represent the dose-dependent protection of compound 1 from the NaIO₃-induced retinal cell death (ARPE-19, a human retinal pigment epithelial cell line).

Figures 16a and 16b represent the dose-dependent protection of compound 1 from the cold-induced cell death (LLC-PK1 cells, porcine kidney proximal tubule cell line).

- 25 Figure 17 represents the protection of rat embryonic myoblastic H9C2 cells by compound 1 from necrosis induced by H₂O₂.

In the above-mentioned figures, “6E11” refers to compound 1.

EXAMPLES

The following abbreviations, commonly used in this field of art, have been used in the following examples:

5

AGC	: Protein kinase A, G, and C families (PKA, PKC, PKG)
BSA	: Bovine Serum Albumin
CAMK	: Ca ²⁺ /calmodulin-dependent protein kinases
CMGC	: CDKs, MAP kinases, GSK and CDK-like kinases
CDK	: Cyclin-dependent kinase
CK1	: Cell Kinases 1 (originally known as Casein Kinase 1)
DMF	: Dimethylformamide
DMSO	: Dimethylsulfoxyde
DTT	: Dithiothreitol
EC ₅₀	: Half maximal effective concentration
EDTA	: Ethylenediaminetetraacetic acid
EGTA	: Ethylene glycol-bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid
Et	: Ethyl (CH ₂ CH ₃)
EtOAc	: Ethyl acetate
FACS	: Fluorescence-activated cell sorting
FADD	: Fas-Associated Death Domain
GSH	: glutathione
GSK	: Glycogen synthase kinases
GST	: Glutathione S-transferase
h	: hour
HAEC	: Human Artery Endothelial Cells
HB	: hydrogen bond
hPBLs	: human Peripheral Blood Lymphocytes
hRPE-1	: human Retinal Pigment Epithelial cell line
IC ₅₀	: Half maximal inhibitory concentration
Kd	: dissociation constant
kg	: kilogram

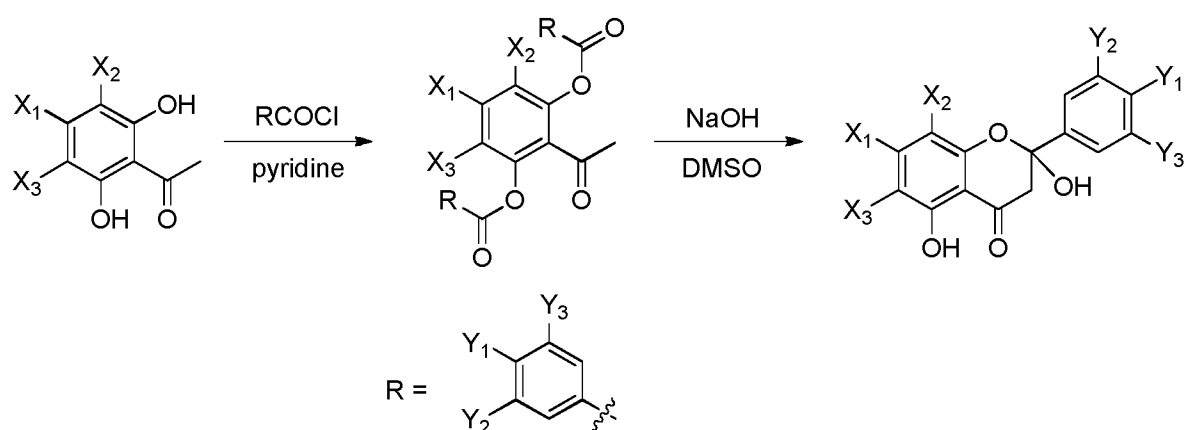
M	: Molar
MAP	: Mitogen-Activated Protein kinases
MD	: Molecular dynamic
Me	: Methyl (CH ₃)
mg	: milligram
MHz	: MegaHertz
min	: minute(s)
ml	: milliliter
mM	: millimolar
mmol	: millimole
MOPS	: 3-(<i>N</i> -morpholino)propanesulfonic acid
MTS	: 3-[4,5- dimethylthiazol-2-yl]-5-[3-carboxymethoxy-phenyl]-2-[4-sulfophenyl]-2H-tetrazolium
n	: number of replicates in an experiment
N	: number of independent experiments
NMR	: Nuclear Magnetic Resonance
PBS	: Phosphate buffered saline
PCR	: Polymerase Chain Reaction
RIPK1	: Receptor-Interacting Protein Kinase 1
ROS	: reactive oxygen species
r.t	: Room temperature
SD	: Standard Deviation
STE	: STE Kinases (Homologs of yeast STERile kinases)
TK	: Tyrosine Kinases
TKL	: Tyrosine Kinases-Like
TNF- α	: Tumor Necrosis Factor α
μ g	: microgram
μ l	: Microliter
μ M	: Micromolar

I. Synthesis of the compounds according to the invention

Example 1: Synthesis of the compounds of general formula (I):

Compound 1 was prepared according to the method disclosed in Hauteville *et al. Tetrahedron* 1980, 37, p.377-381.

- 5 Said method can be generalized to obtain a compound of general formula (I), according the following reaction scheme:



- 10 The starting materials are commercially available, or can be easily prepared according to methods well-known of the one skilled in the art. Optionally, and if necessary, additional protection or deprotection steps well-known of the skilled person might be incorporated within the general procedure represented above.

II. Biological tests of the compounds according to the invention

Example 2: Cell-based screening of chemical libraries for characterization of Necroptosis inhibitors

- 20 TNF- α can induce necroptosis in Jurkat cells (human T lymphocytes) when FADD is deleted. This model was used to screen various libraries of chemical compounds for characterization of new inhibitors of cellular necroptosis. Details on this cell-based assay can be found in Miao and Degterev (*Methods Mol. Biol.* 2009, 559, 79-93). The Jurkat FADD-deficient I 2.1 cell line used was purchased from ATCC and was maintained in RPMI 1640 medium (Gibco) containing Glutamax and 15% fetal calf serum (Life Technology). Necroptosis was induced by addition of 10 ng/ml of human
- 25

recombinant TNF- α (Life Technology). Necrostatin-1 (Nec-1, Enzo Life Sciences) was used as model necroptosis inhibitor. Cells were maintained in 75cm² flask and passed every 2 or 3 days. Chemical collections analysed were formatted in 96-well plates with 80 molecules per plate at 10 mM in 100% DMSO. For each collection plate, two plates were prepared: one corresponding to necroptosis-induced with TNF- α , and the other without TNF- α to evaluate the intrinsic toxicity of the tested compound. Cells were seeded at 20000 cells/well, in 40 μ l of medium, in a 96-well clear, flat bottom plate (CytoOne, Starlab) before treatment. Then, 40 μ l of medium with or without TNF- α at 25 ng/ml were added to all wells in the corresponding plate. Immediately after TNF- α addition, 20 μ l of diluted compound at 50 μ M were added to the plates. Final concentration of each chemical compound was 10 μ M at 0,1 % DMSO. Eight positives (Nec-1 at 10 μ M final) and eight negative (DMSO) controls were used in each plate to validate the assay. Cells were incubated at 37°C, 5% CO₂ for 24 hours before performing MTS viability assay, described hereafter. Compounds were diluted before to treat cells. Liquid handling was performed using the Nimbus Microlab liquid handler (Hamilton Robotics) under microbiological safety workbench. The 10mM compounds were diluted at 50 μ M directly in cell medium.

Compound 1 has emerged from this screening to be a very efficient necroptosis inhibitor, as discussed below.

20

Example 3: Anti-necroptic effect of compound 1

Effect on cell viability: Jurkat FADD-deficient I 2.1 cells were treated by TNF- α (10 ng/ml) and increasing concentrations of compound 1 (0.01 - 0.05 - 0.10 - 0.50 - 1.00 - 2.50 - 5.00 - 10.00 - 25.00 - 50.00 μ M). Cells were incubated at 37°C, 5% CO₂ for 24 hours before performing MTS viability assay. Cell viability was monitored using CellTiter 96® AQueous Non-Radioactive Cell Proliferation Assay (Promega, Fitchburg, WI, USA), based on the water-soluble tetrazolium compound MTS (3-[4,5-dimethylthiazol-2-yl]-5-[3-carboxymethoxy-phenyl]-2-[4-sulfophenyl]-2H-tetrazolium, inner salt) according to the manufacturer's instructions. As it appears from Figure 1, compound 1 protects cells from death induced by TNF- α .

Effect on two hallmarks of necroptosis: Jurkat FADD-deficient I 2.1 cells were treated by TNF- α (10 ng/ml) and increasing concentrations of compound 1 (0, 1, 5, 10, 20 and 50 μ M). Cells untreated by TNF- α are used as control (light grey curves). Cells were incubated at 37°C, 5% CO₂ for 24 hours before performing the measurements of both plasma membrane permeabilization and intracellular ATP levels. Dead cells were detected by FACS analysis of Propidium Iodide-stained nuclei (Figure 2). ATP Quantification is performed using the CellTiter-Glo® Luminescent Cell Viability Assay. The luminescent signal produced by a luciferase reaction is proportional to the amount of ATP present and the amount of ATP is directly proportional to the number of metabolically active cells (n=4) (Figure 3). As reported on Figures 2 and 3, compound 1 inhibits two major hallmarks on necroptosis induced by TNF- α .

Example 4: Compound 1 cytotoxicity assays

- on human peripheral blood lymphocytes (hPBLs) :

hPBLs were treated with increasing concentrations of compound 1 (0, 1, 5, 10, 20, 50 and 100 μ M) for 24 hours. Viability was assessed by cell proliferation assay (MTS). % of cell viability was determined using the CellTiter 96® AQueous Non-Radioactive Cell Proliferation Assay (Promega). Data represent the quantitative analysis of six independent experiments with means $\pm$ SD (n=6 individuals).

As it appears from Figure 4, compound 1 is not cytotoxic towards hPBLs up to a concentration of 20 μ M.

- on the human retinal pigment epithelial cell line (hRPE-1) :

hRPE-1 cells were treated with increasing concentrations of compound 1 (0, 0.01, 0.05, 0.1, 0.5, 1, 2.5, 5, 10, 25 and 50 μ M) for 24 hours. A colorimetric MTS assay was used to calculate the percentage of cell viability.

As it appears from Figure 5, compound 1 is not cytotoxic towards hRPE-1 cells at the tested concentrations.

Example 5: RIPK1 autophosphorylation assay and binding assays- RIPK1 autophosphorylation assay:

Human RIPK1 full length GST-tagged was baculovirally expressed in Sf9 cells according to manufacturer's instructions (Bac-to-Bac expression system, Invitrogen) and purified using glutathion-sepharose beads (GE Healthcare). The elution was made in 50 mM Tris-HCl, pH 8.0 buffer supplemented with 30 mM reduced glutathione (Sigma). The protocol used to detect the enzymatic activity is adapted from Miao and Degterev (*Methods Mol. Biol.* 2009, 559, 79-93). Kinase reaction was initiated mixing 5 μ l of eluted RIPK1, 5 μ l of 3X kinase reaction buffer (5 mM MOPS pH 7.2, 2.5 mM β -glycerophosphate, 4 mM $MgCl_2$, 2.5 mM $MnCl_2$, 1 mM EGTA, 0.4 mM EDTA, 50 μ g/ml BSA, 0.05 mM DTT), 2 μ l H_2O and 3 μ l of the tested molecule. The mixture was kept on ice for 10 minutes. During the incubation, the ATP solution was prepared by mixing 5 μ l of 3X kinase reaction buffer, 4 μ l H_2O , 6 μ l cold ATP at 150 μ M and 2 μ Ci of [γ - ^{32}P] ATP. The ATP solution and the tested inhibitor were added to the kinase and incubated for 30 minutes at 30 °C. To stop the enzymatic reaction, 5 μ l of loading buffer were added and solution was heated for 3 minutes at 95 °C. 25 μ l of each reaction were loaded per well in pre-cast NuPage 12% Bis-Tris gel (Life Technology). Necrostatin-1, a well-described inhibitor of RIPK1, was used as an internal control. Coomassie staining was performed in order to estimate the total amount of protein loaded on polyacrylamide gel. Autophosphorylated RIPK1 band was visualized on radiographic film after 6h exposition at -80°C.

The results of this test obtained with compound 1 are indicated in Figure 6. The decrease of the amount of radioactively labeled RIPK1 indicates that compound 1 inhibits the RIPK1 autophosphorylation in a dose-dependent way.

Besides, as shown in Figure 7, the inhibition of RIPK1 auto-phosphorylation by compound 1 is not affected by high ATP concentrations (e.g. 1mM), which suggests that compound 1 is a non-ATP competitive inhibitor.

- Binding assays:

(i) Characterization of kinase targets of compound 1 ("KINOMEscan Max").

This *in vitro* competition binding assay was used for the profiling of compound 1 against 456 kinases, including eight lipid kinases. This experimental approach quantitatively measures the ability of a compound to compete with an immobilized, active-site directed ligand. The assay is performed by combining three components: DNA-tagged kinase (e.g. RIPK1); immobilized ligand; and a test compound (here compound 1). The ability of compound 1 to compete with the immobilized ligand is measured via quantitative PCR of the DNA tag. The codes reported on the figure 8 indicate the subclasses of protein kinases: CMGC for CDKs, MAP kinases, GSK and CDK-like kinases; AGC for Protein kinase A, G, and C families (PKA, PKC, PKG); CAMK for Ca²⁺/calmodulin-dependent protein kinases; CK1, Cell Kinases 1 (originally known as Casein Kinase 1); STE, STE Kinases (Homologs of yeast STERile kinases); TKL, Tyrosine Kinases-Like; TK, Tyrosine Kinases. Each kinase tested in the assay panel is marked with a circle. The hit kinase reported, RIPK1, is marked with a black circle. The size of the circle is proportional to the binding efficiency of compound 1 to the kinase of interest. Small grey dots represent only poor affinity for the tested kinase (as over 30% of the tested kinase are still on the affinity matrix after competition with the tested compound, here compound 1). For RIPK1, only 0.15% of the initial amount of kinase is still on the affinity matrix after competition with compound 1. The graphic representation of the human kinome phylogenetic tree (TREEspot™ Kinase dendrogram, © DiscoverX, Fremont, USA), reported on figure 8, illustrates the high specificity of compound 1 for RIPK1 among the large panel of tested kinases.

(ii) Determination of dissociation constant (K_d) of compound 1 for RIPK1 kinase.

KdELECT is a service of DiscoverX Corporation, Fremont, USA. This assay is based on a competition binding assay described hereabove. An 11-point 3-fold serial dilution of compound 1 was prepared in 100% DMSO in order to determine the dissociation constant (K_d) at two different temperatures, r.t and 4°C. K_d was then calculated with a standard dose-response curve (reported on Figure 9) using the Hill equation. The calculated K_d of compound 1 for RIPK1 is 128 nM (n=2) at r.t and 136 nM (n=2) at 4°C. It validates compound 1 as a true ligand of RIPK1 kinase. Indeed, since the K_d

value is low (nM range), the interaction between RIPK1 and compound 1 is strong. Moreover, the high affinity of compound 1 for RIPK1 is not affected by low temperature, conditions occurring during cold storage of grafts.

5 Example 6: *In vitro* “hypoxic cold storage” viability assays

Human endothelial cells (HAEC) were grown to confluence, then synchronized using depleted media for 16h. For hypothermia/hypoxia, cells were washed twice with PBS then incubated in University of Wisconsin (UW) solution in 95%N₂ / 5%CO₂ atmosphere at 4°C for 24 hours. Compound 1, Nec1 or Nec1s were added to the
10 preservation solution at the indicated dilution (μM) during hypoxia (Figure 10) or during both hypoxia and reoxygenation steps (Figure 11). Shown are mean +/- SD, n=3. UW are cells treated only with UW preservation solution. Controls are cells not subjected to this protocol (cells are continuously oxygenated) but cultivated for the same amount of time in regular culture conditions. The treatment with compound 1
15 during hypoxia or during hypoxia and reoxygenation brings measurable benefits on cell survival. Compared to the control inhibitors of necroptosis (Nec-1 and Nec-1s), the effect of compound 1 is significantly better. It should be noted that the hypoxic cold storage mimics the process occurring during graft preservation.

20 Example 7: *In silico* analysis of the theoretical RIPK1-6E11 complex

The predictive orientation for compound 1 was studied by *in silico* analysis of the theoretical RIPK1-6E11 complex. Stable contact residues defining a pharmacophore and determined on the most representative structural model included six key amino acids Lys30, Val47, Leu60, Leu78, Tyr88 and Leu90 (Figure 12). Surrounding residues
25 (4.0Å cut-off distance) describing the compound 1 binding pocket observed over the molecular docking simulation trajectory also comprised of Phe28, Val31, Lys45, Thr46, Ala59, Glu63, Val81, Ile83, Ser89 and Asp156. We should note that among these amino acids, three of them (Leu78, Leu90 and Asp156) have been already described to be involved in the interaction with necrostatins (Xie *et al. Structure* 2013, 21, 493–499).
30 Molecular dynamic (MD) simulation of RIPK1-6E11 model allowed us to improve the preferential binding mode identified by docking calculations which is different from Nec-1s (Figures 13a,b). The binding site of Nec-1s is marked as “site #1” on Figure

13a. From analysis of the most frequent contacts of the compound to the kinase, we are able to propose that compound 1 should bind RIPK1 kinase through tight hydrophobic interactions and a non-specific hydrogen bond (HB), as well as other transient HB interactions observed during the simulation (Figures 13a,b). The putative binding site #2 of compound 1 is marked as “site #2” on Figure 13b. Our simulations suggest that compound 1 fits tightly in an alternative and putative cleft surrounded notably by the RIPK1 catalytic triad residues: Lys45, Glu63 and Asp156. This cleft of RIPK1 is mainly hydrophobic but richer in hydrogen bond acceptors than the kinase hinge within the ATP-binding site. Interestingly, this model shows that compound 1 does not make any interaction with the kinase hinge in this conformation of RIPK1 regardless of hydrogen bonds. Moreover, this proposed binding mode for compound 1 occupying a lipophilic pocket in a cleft near the substrate binding site of RIPK1 indicates that this compound is likely a type III kinase inhibitor. This binding mode is in line with the high selectivity of compound 1 detected by the KINOMEScanSM Assay (Figure 8) and also with the non-ATP competitive mode of inhibition (reported on Figure 7).

Example 8: effect of compound 1 on both ferroptosis and oxytosis programmed cell-death routes

Murine hippocampal neuronal cell line HT22 was treated with 10mM of (L)-glutamate (oxytosis initiator) or 1μM erastin (ferroptosis initiator).

In this assay, 5,000 cells were seeded per well and treated with increasing concentrations of compound 1 (2.50 - 5.00 - 10.00 - 25.00 - 50.00 μM) with or without 1μM erastin or 10mM L-glutamate. Cells were then incubated at 37°C, 5% CO₂ for 24 hours before performing MTS viability assay. Cell viability was monitored using CellTiter 96[®] AQueous Non-Radioactive Cell Proliferation Assay (Promega, Fitchburg, WI, USA), based on the water-soluble tetrazolium compound MTS (3-[4,5-dimethylthiazol-2-yl]-5-[3-carboxymethoxy-phenyl]-2-[4-sulfophenyl]-2H-tetrazolium, inner salt) according to the manufacturer's instructions. As it appears from Figure 14, >25 μM of compound 1 protects cells from death induced by both L-glutamate and erastin.

Example 9: effect of compound 1 on a cellular model of age-related macular degeneration (AMD)

At it was previously shown (Hanus *et al. Cell Death Discov.* 2016, 2, 16054), NaIO₃ is an oxidizing agent that induces necroptosis in retinal pigment epithelial cell line that can be inhibited by 200μM of necrostatin-1. The experiment described in the cited literature was reproduced to detect the effect of compound 1. Human retinal pigment epithelial cell line, ARPE-19, was treated with 10mM of NaIO₃ as cellular model of age-related macular degeneration (AMD). In this assay, 10,000 cells were seeded per well and treated with 20 or 200μM of compound 1 or Nec-1s (a specific RIPK-1-dependent necroptosis inhibitor) (Figure 15a) or increasing concentrations of compound 1 (0.01, 0.02, 0.05, 0.10, 0.20, 0.50, 1.00, 2.00, 2.50, 5.00, 10.00, 20.00, 25.00 μM) (Figure 15b) with or without 10mM of NaIO₃. Cells were then incubated at 37°C, 5% CO₂ for 24 hours before performing MTS viability assay. Cell viability was monitored using CellTiter 96® AQueous Non-Radioactive Cell Proliferation Assay (Promega, Fitchburg, WI, USA), based on the water-soluble tetrazolium compound MTS (3-[4,5-dimethylthiazol-2-yl]-5-[3-carboxymethoxy-phenyl]-2-[4-sulfophenyl]-2H-tetrazolium, inner salt) according to the manufacturer's instructions. As it appears from Figures 15a and 15b, subtoxic concentration of compound 1 (+/-20μM) protects significantly cells from death induced by NaIO₃ (N=3, n=2, mean ± SD, *** P<0.001).

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Example 10: effect of compound 1 on cold-induced cell death (cold-stress preservation)

At it was previously shown (Ahlenstiel *et al. Transplantation* 2016, 81(2), 231-239), cold storage induces a cell-death process. Porcine LLC-PK1 cells (kidney proximal tubule cell line) were stored at approximately 4°C during 24 hours with or without the tested molecules. In this assay, 5,000 cells were seeded per well and treated with increasing concentrations of compound 1 or Nec-1s (0.01, 0.05, 0.10, 0.50, 1.00, 2.50, 5.00, 10.00, 25.00 and 50.00 μM) and stored for 24 hours at 4°C. Cells were then incubated at 37°C, 5% CO₂ before performing MTS viability assay. Cell viability was monitored using CellTiter 96® AQueous Non-Radioactive Cell Proliferation Assay (Promega, Fitchburg, WI, USA), based on the water-soluble tetrazolium compound MTS (3-[4,5-dimethylthiazol-2-yl]-5-[3-carboxymethoxy-phenyl]-2-[4-sulfophenyl]-2H-tetrazolium, inner salt) according to the manufacturer's instructions. As it appears

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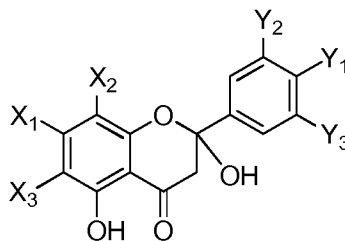
from Figures 16a and 16b, compound 1 protects cells from death induced by cold storage with a maximal activity at 5 μ M. Nec-1s is inactive at the tested doses (Fig. 16a, N=2, n=6, mean $\pm$ SD, *** P<0.05; Fig. 16b, n=2).

5 Example 11: effect of compound 1 on H₂O₂-induced necrosis (anti-oxidant property)

The rat embryonic myoblastic *H9C2* cells were cultured at 10,000 cells/well in 96-well-plates for 24 hours at 37°C/5%CO₂. Then, cells were treated or not (DMSO) with 800 μ M H₂O₂ for 24 hours after a 2 hours pretreatment or not (NT) with 10 μ M compound 1 (comp 1), 10 μ M Necrostatin-1s (Nec-1s), or 10 μ M Ferrostatin-1 (Fer-1). LB
10 corresponds to cells treated with a lysis buffer (100% of cell death). Cell cytotoxicity was determined by a colorimetric assay quantitatively measuring lactate dehydrogenase (LDH) released into the cytosol. As it appears from Figure 17, compound 1 protects from death induced by H₂O₂ in the same extent as Fer-1, Nec-1s being less effective (Fig.17, N=2, n=6, mean $\pm$ SD, ** P<0.005; * P<0.05).

CLAIMS

1. A compound of the following general formula (I):



(I)

or a pharmaceutically acceptable salt and/or solvate thereof, wherein:

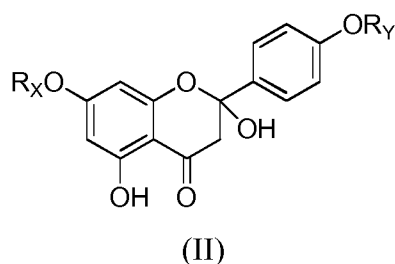
- X_1 represents a (C₁-C₆)alkyl an aryl, an aryl-(C₁-C₆)alkyl group or an OR_X group, wherein
R_X is selected from a (C₁-C₆)alkyl, an aryl and an aryl-(C₁-C₆)alkyl group,
- 10 ▪ X_2 and X_3 each represent, independently of each other, a hydrogen atom or a (C₁-C₆)alkyl group,
- Y_1 , Y_2 and Y_3 each represent, independently of each other, a hydrogen atom, a (C₁-C₆)alkyl, an aryl, an aryl-(C₁-C₆)alkyl group, an OH or an OR_Y group,
with at least one of Y_1 , Y_2 and Y_3 representing a (C₁-C₆)alkyl, an aryl, an aryl-(C₁-C₆)alkyl group or an OR_Y group, wherein
15 R_Y is selected from a (C₁-C₆)alkyl, an aryl and an aryl-(C₁-C₆)alkyl group,
for use as a drug.

2. The compound for use according to claim 1, wherein X_1 represents an OR_X group, R_X being advantageously a (C₁-C₆)alkyl group.

3. The compound for use according to claim 1 or claim 2, wherein Y_1 , Y_2 and Y_3 each represent, independently of each other, a hydrogen atom or an OR_Y group, R_Y being as defined in claim 1, R_Y being advantageously an aryl-(C₁-C₆)alkyl group.

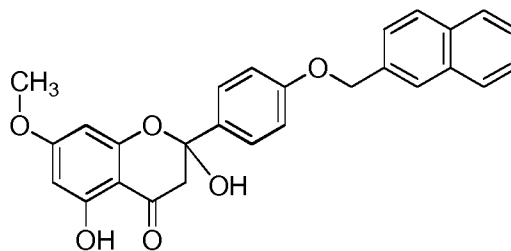
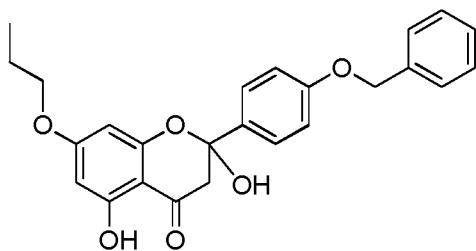
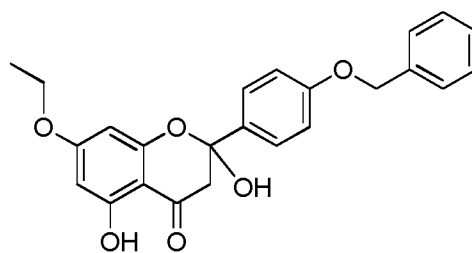
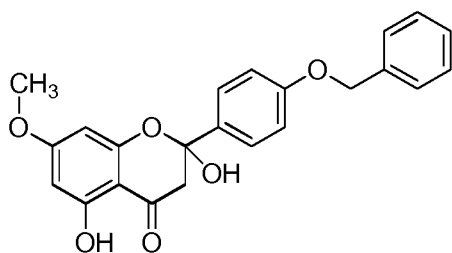
4. The compound for use according to any one of claims 1 to 3, wherein Y_1 represents an OR_Y group, R_Y being advantageously an aryl-(C_1 - C_6)alkyl group, and Y_2 and Y_3 each represent a hydrogen atom.

5. The compound for use according to any one of claims 1 to 4, wherein said compound is of the following general formula (II):



wherein R_X represents a (C_1 - C_6)alkyl group and R_Y represents an aryl-(C_1 - C_6)alkyl group.

6. The compound for use according to claim 5, wherein it is chosen among the following compounds:



and the pharmaceutically acceptable salts and solvates thereof.

7. The compound for use according to any one of claims 1 to 6 wherein the drug is intended for inhibiting a programmed cell death route selected from the group consisting of ferroptosis, oxytosis and cellular necroptosis such as tumour-cell-induced endothelial cell necroptosis.

8. The compound for use according to any one of claims 1 to 7, wherein the drug is intended for preventing and/or treating a disorder associated with cellular necroptosis, wherein said disorder is trauma in brain, hepatitis, alcoholic and non-alcoholic steatohepatitis, acute pancreatitis and acute tubular necrosis, heart or kidney
5 transplantation, atherosclerosis, bone marrow failure, viral infection, Crohn's and ulcerative colitis, terminal ileitis, age-related macular degeneration, chronic obstructive pulmonary disease, psoriasis, toxic epidermal necrolysis or ischemia reperfusion injury such as myocardial infarction or stroke.
- 10 9. The compound for use according to claim 7, wherein the drug is intended for preventing and/or treating a disorder associated with tumour-cell induced endothelial cell necroptosis, wherein said disorder is tumour cell extravasation or metastasis.
- 15 10. The compound for use according to any one of claims 1 to 7, wherein the drug is intended for neuroprotection.
- 20 11. The compound for use according to any one of claims 1 to 7, wherein the drug is intended for preventing and/or treating a disorder associated with ferroptosis, wherein said disorder is acute kidney failure; a neurodegenerative disease such as Huntington's disease, Alzheimer's disease and Parkinson's disease; hemochromatosis; intracerebral hemorrhage stroke or an ischemia-reperfusion injury.
- 25 12. A pharmaceutical composition comprising at least one compound as defined in any one of claims 1 to 6, and at least one pharmaceutically acceptable excipient.
- 30 13. The pharmaceutical composition according to claim 12, for use for preventing and/or treating a disorder associated with cellular necroptosis, wherein said disorder is trauma in brain, hepatitis, alcoholic and non-alcoholic steatohepatitis, acute pancreatitis and acute tubular necrosis, heart or kidney transplantation, atherosclerosis, bone marrow failure, viral infection, Crohn's and ulcerative colitis, terminal ileitis, age-related macular degeneration, chronic obstructive pulmonary disease, psoriasis, toxic epidermal necrolysis or ischemia reperfusion injury such as myocardial infarction or stroke.

14. The pharmaceutical composition according to claim 12, for use for neuroprotection.

- 5 15. The pharmaceutical composition according to claim 12, for use for preventing and/or treating a disorder associated with ferroptosis, wherein said disorder is acute kidney failure; a neurodegenerative disease such as Huntington's disease, Alzheimer's disease and Parkinson's disease; hemochromatosis; intracerebral hemorrhage stroke or an ischemia-reperfusion injury.

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16. The pharmaceutical composition according to any one of claims 12 to 15, characterized in that it further comprises at least one other active ingredient, such as another cellular necroptosis inhibitor, or an apoptosis inhibitor, an autophagy inhibitor, a ferroptosis inhibitor, an inhibitor of MPT (The mitochondrial permeability transition)
15 pore-dependent necrosis, a cyclophilin inhibitor, a Cyclin-dependent kinase 5 (CDK5) inhibitor, a parthanatos inhibitor, a thrombin inhibitor, an antioxidant (such as glutathione or allopurinol) or an inflammatory inhibitor.

17. Use of a compound as defined in any one of claims 1 to 6 for the preservation
20 and/or protection of biological materials such as cells, tissues, body fluids and organs, and of microorganisms, advantageously as a medical device.

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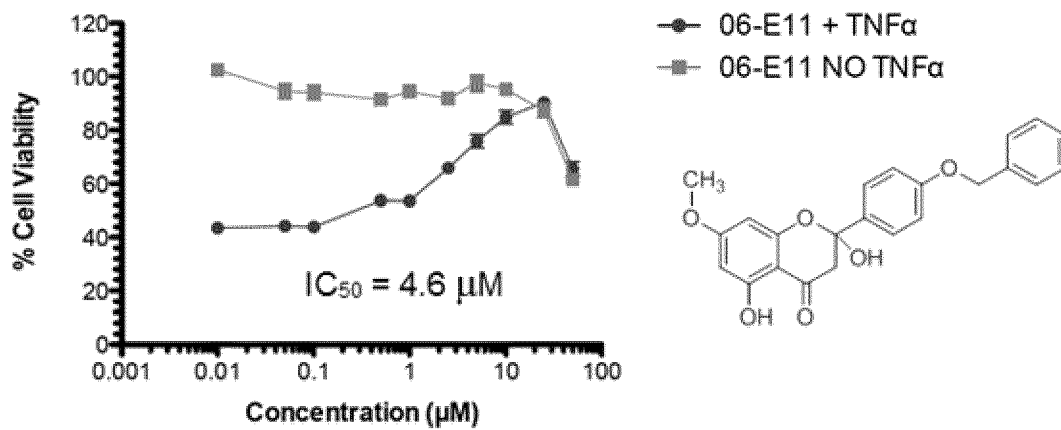


Fig. 1

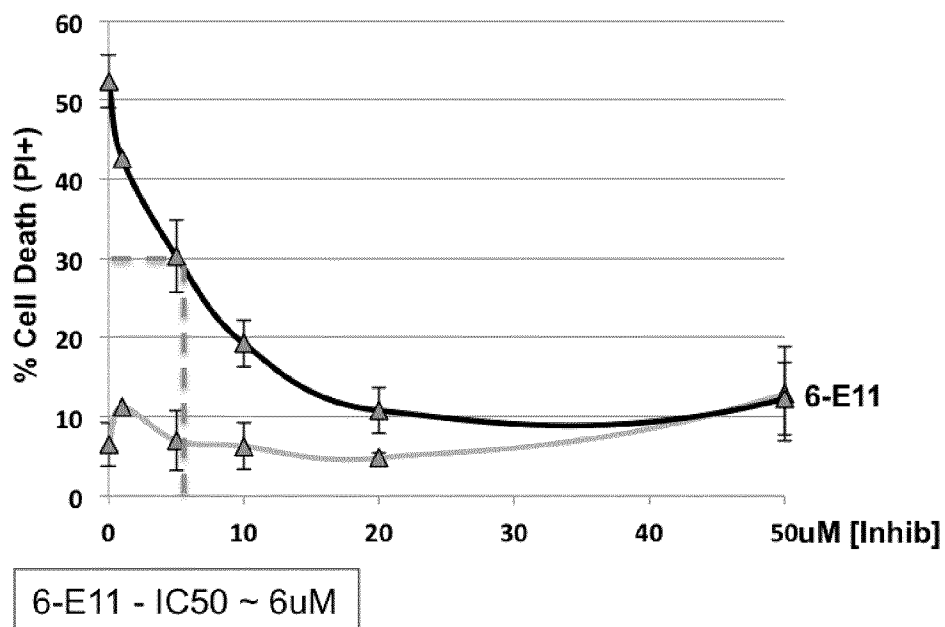


Fig. 2

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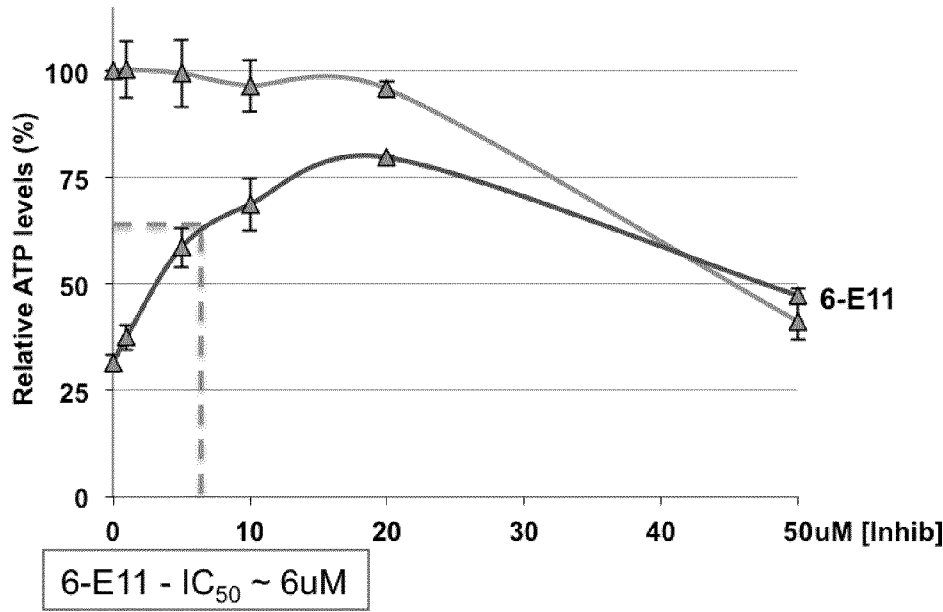


Fig. 3

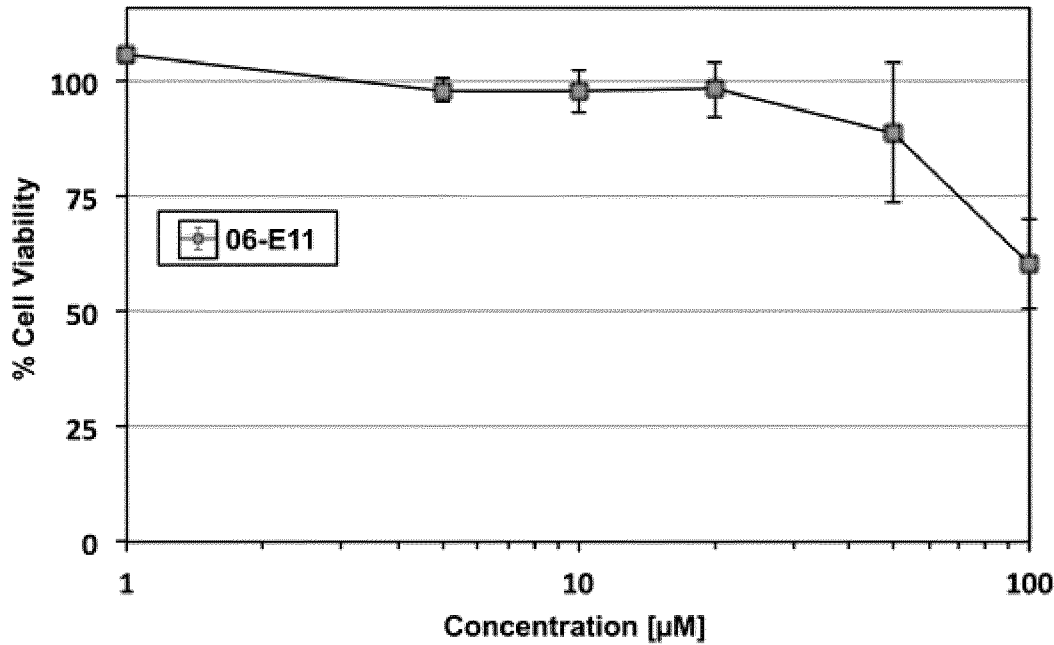


Fig. 4

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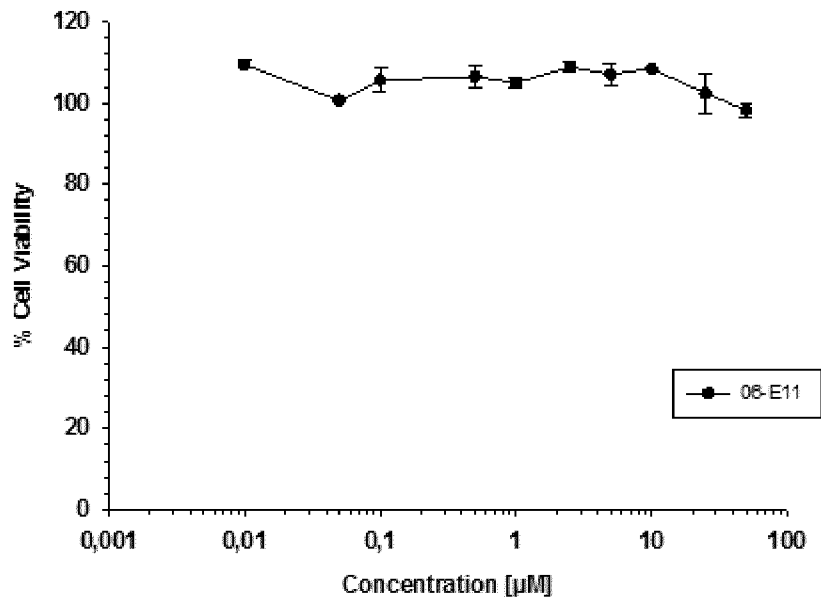


Fig. 5

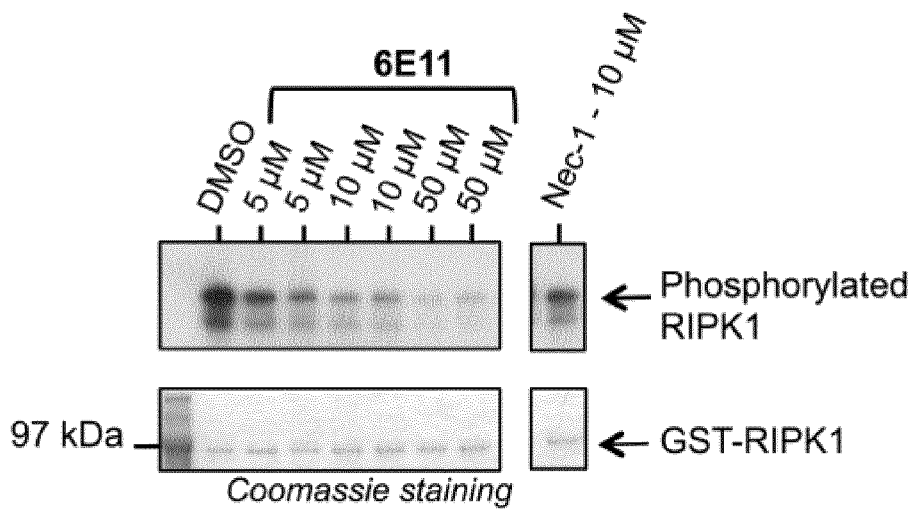


Fig. 6

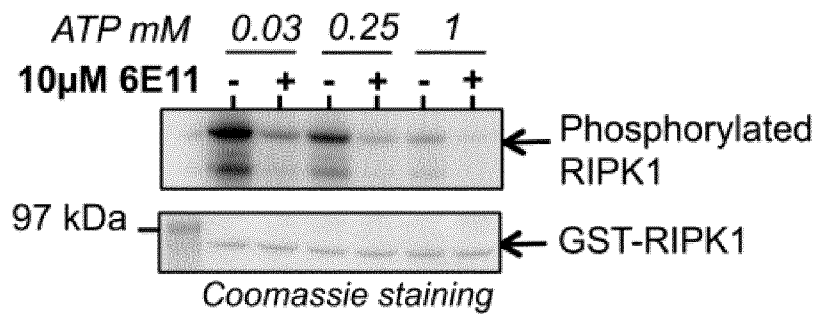


Fig. 7

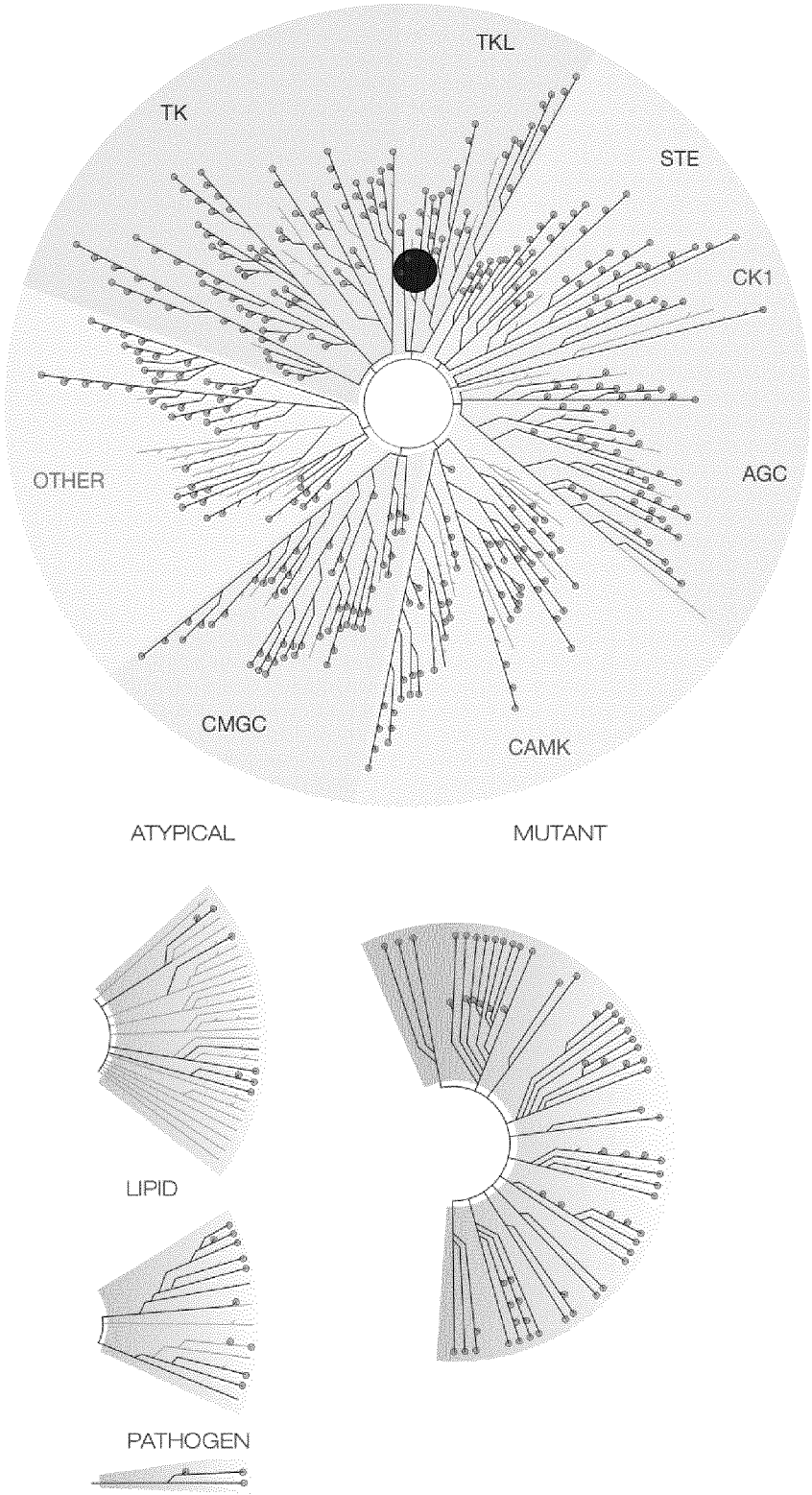


Fig. 8

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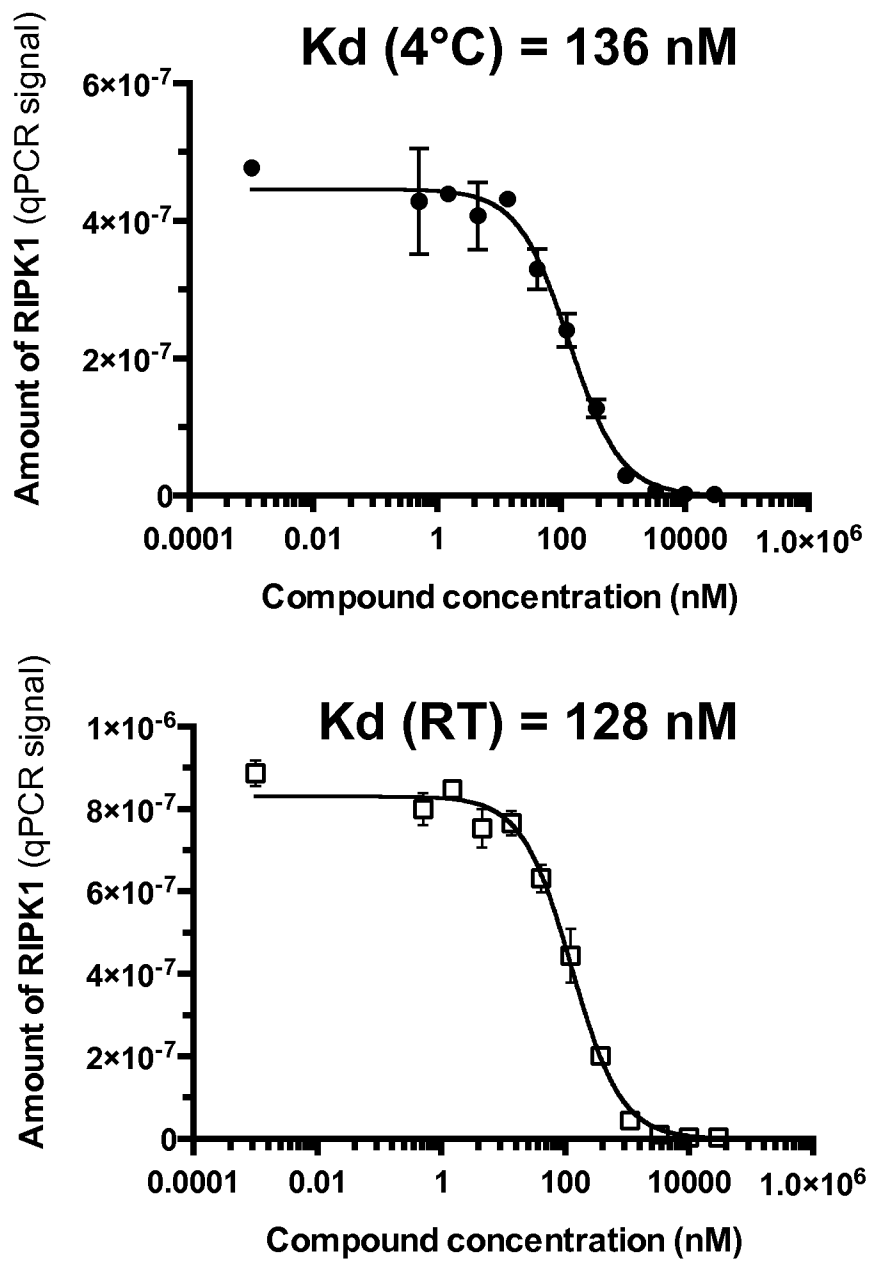


Fig. 9

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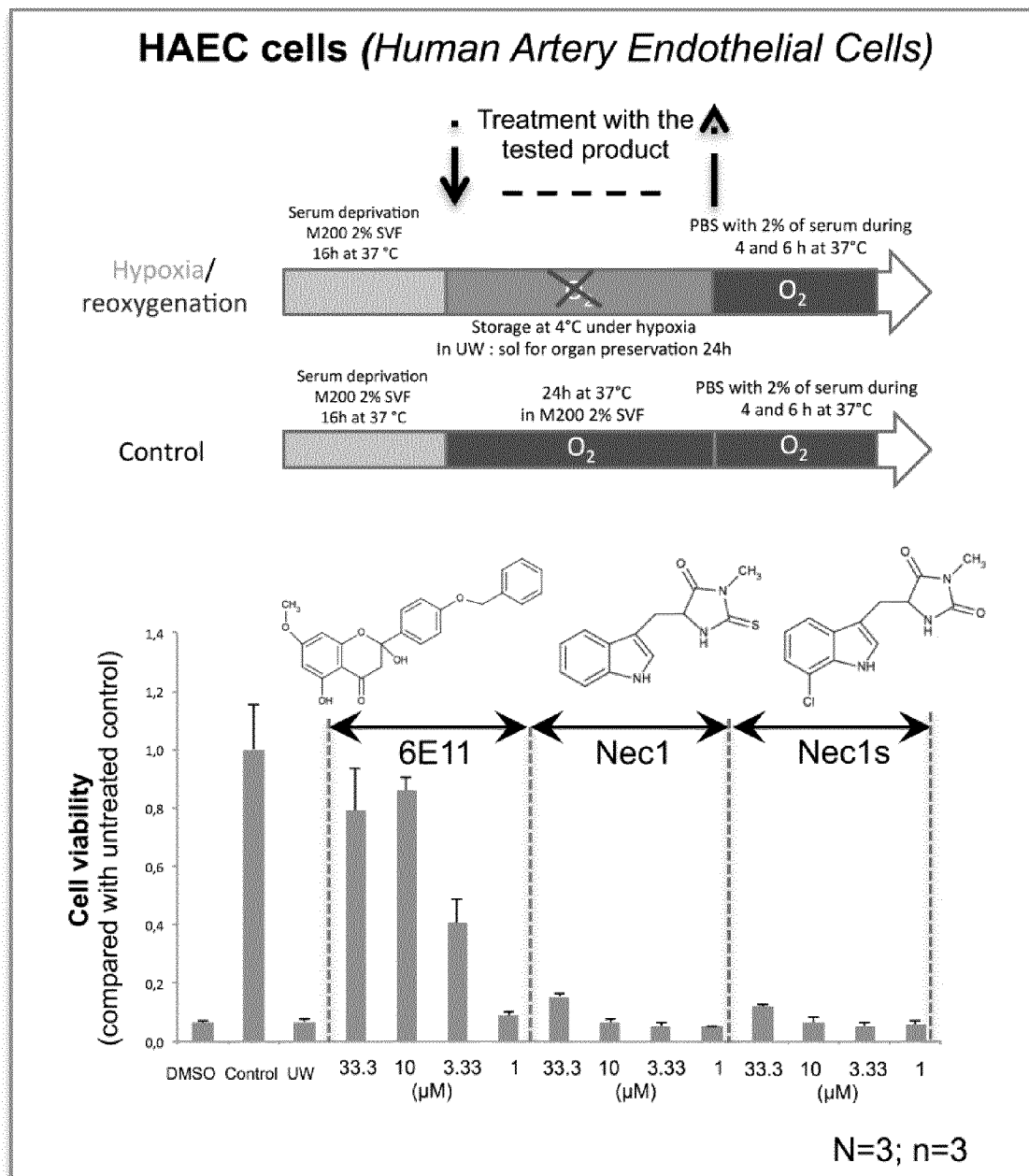


Fig. 10

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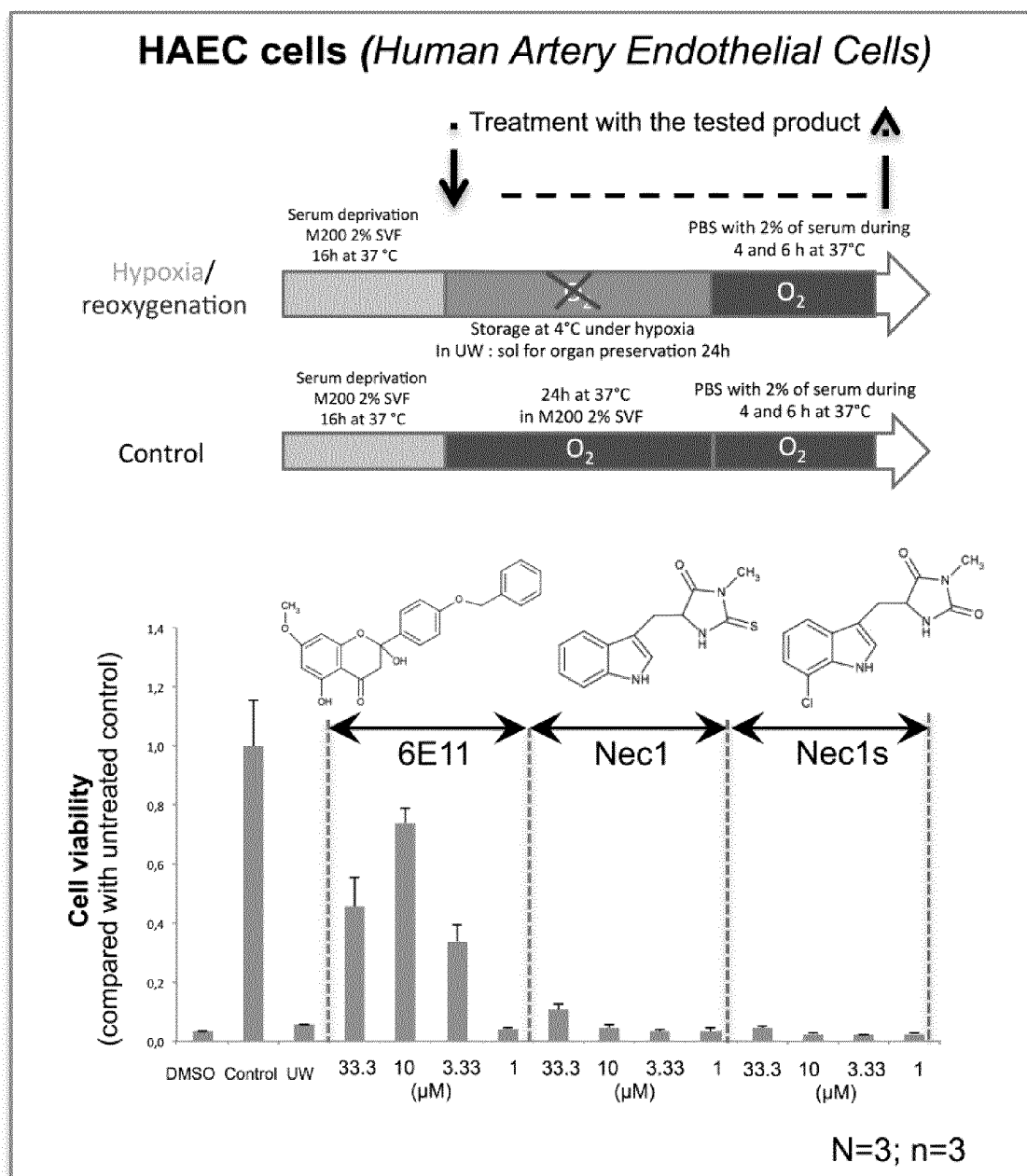


Fig. 11

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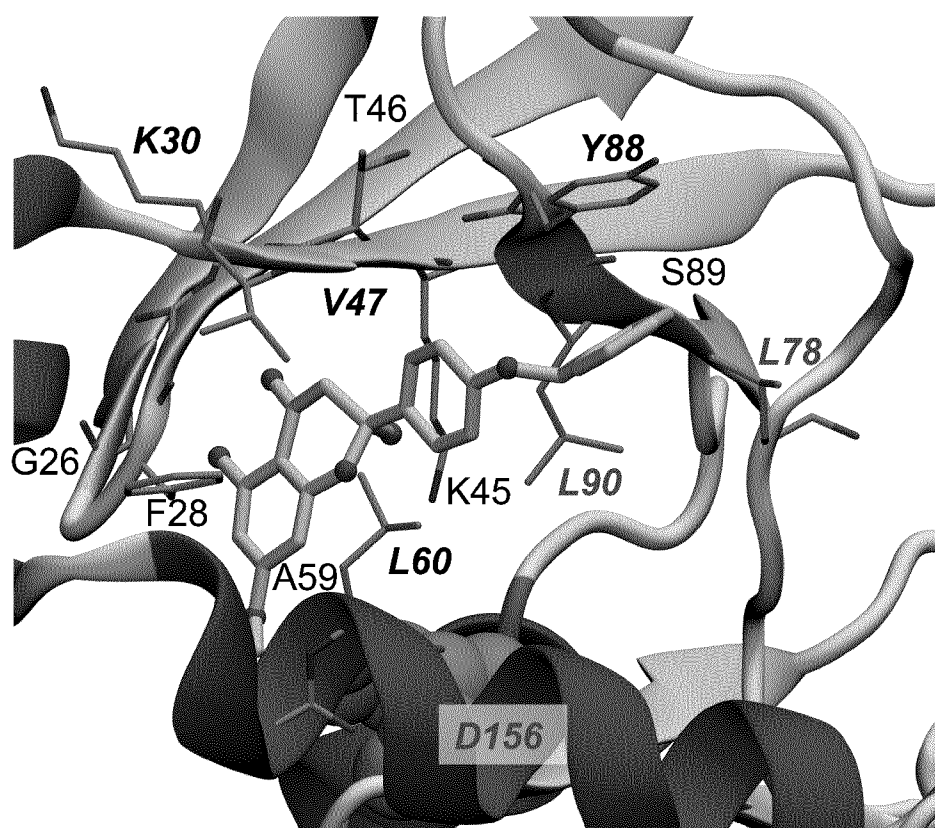


Fig. 12

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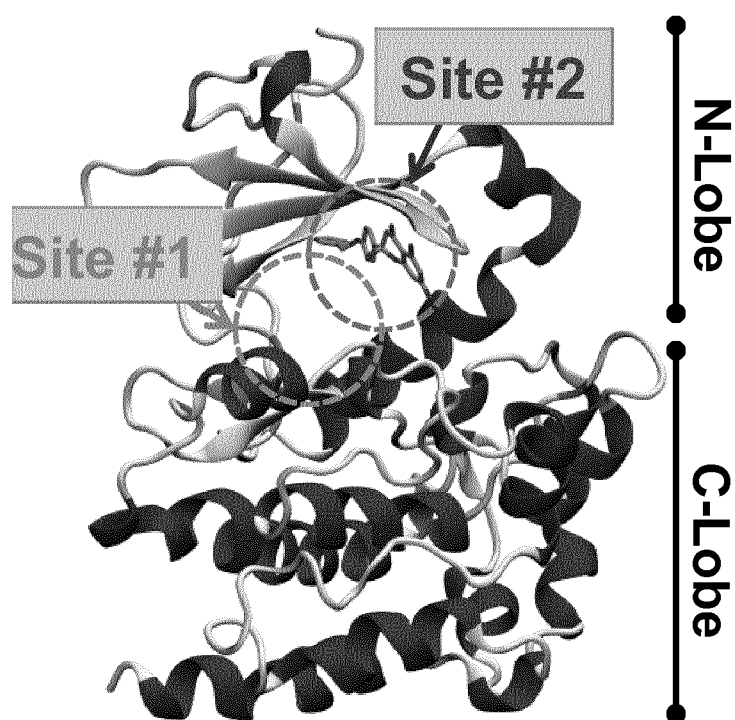


Fig. 13a

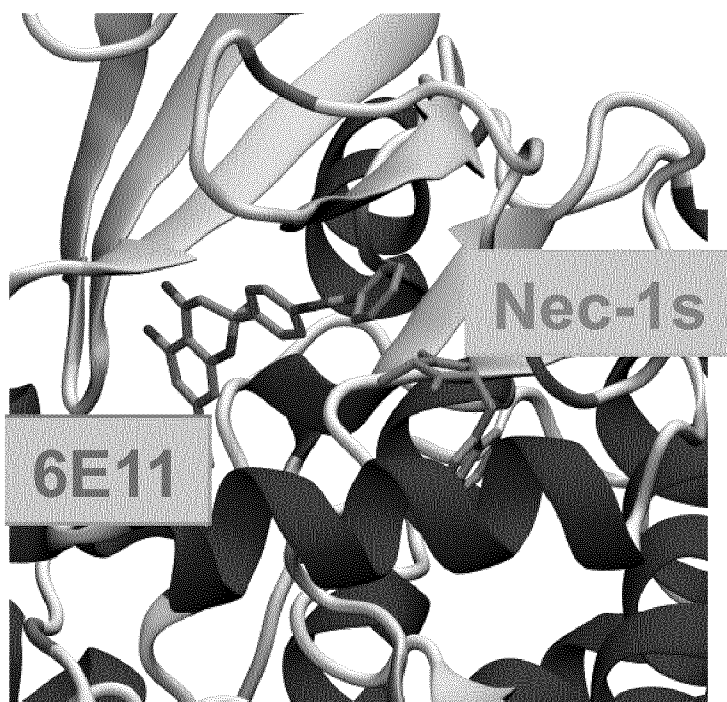


Fig. 13b

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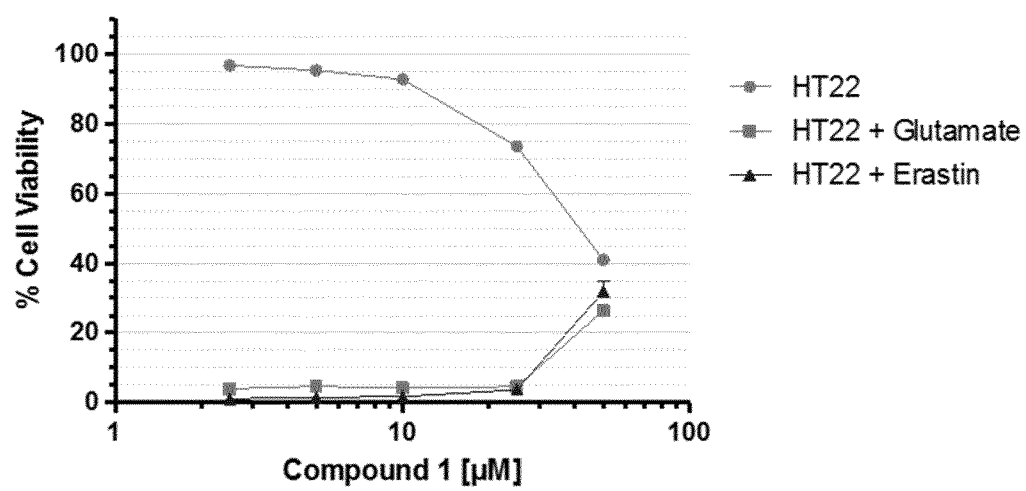


Fig. 14

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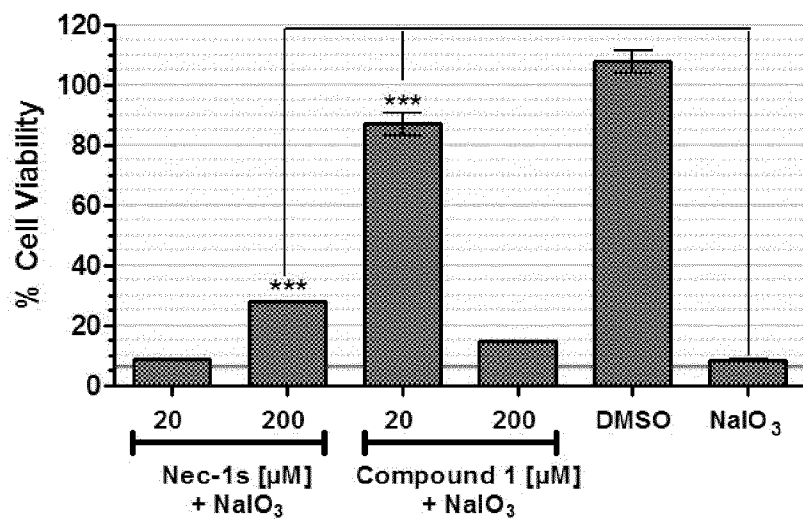


Fig. 15a

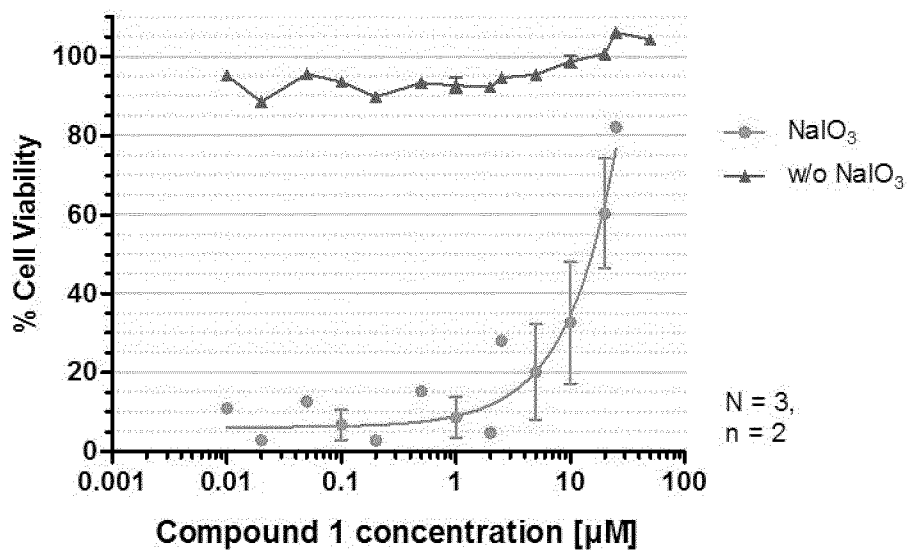


Fig. 15b

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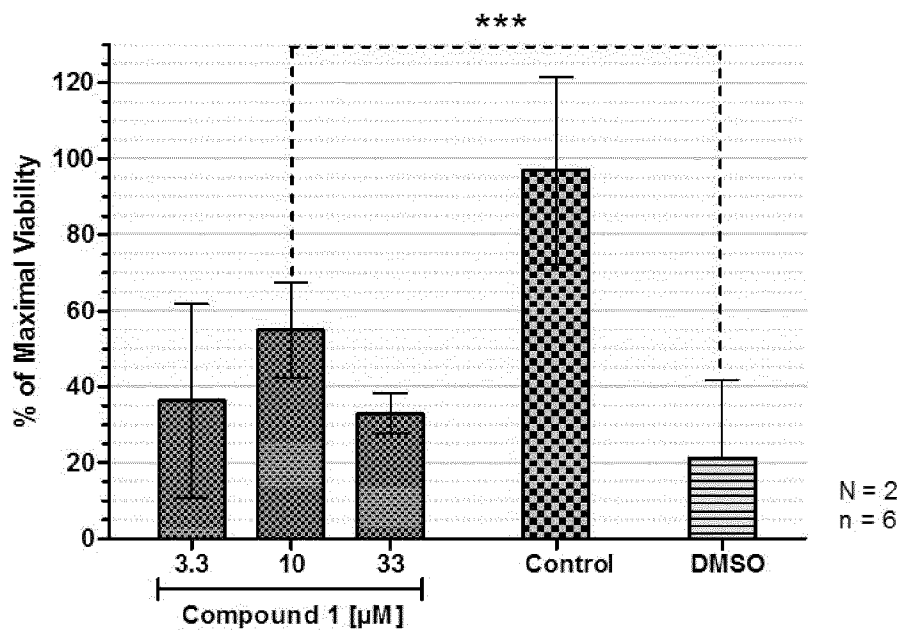


Fig. 16a

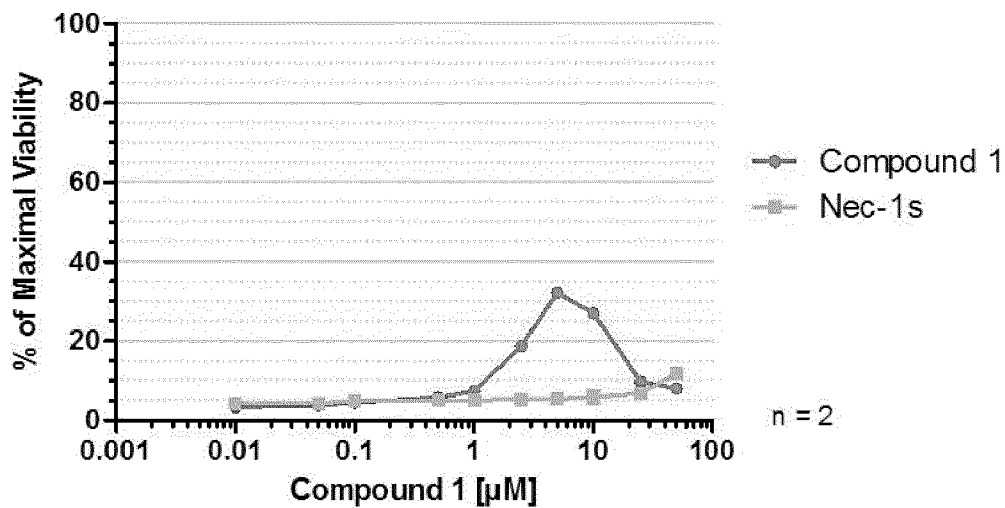


Fig. 16b

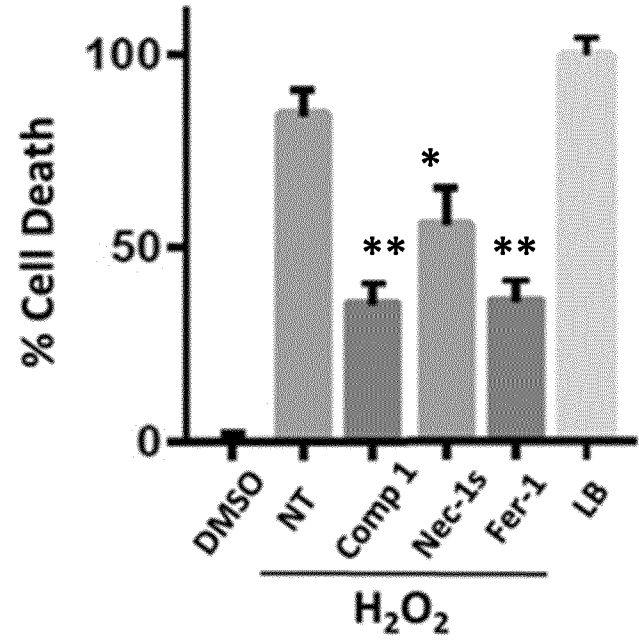


Fig. 17

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/076638

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D311/20 C07D311/54 A61K31/353
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARCELLE HAUTEVILLE ET AL: "PROTOGENKWANIN, A NEW FLAVONOID FROM EQUISETUM ARVENSE L.", TETRAHEDRON, vol. 37, no. 2, 1 January 1981 (1981-01-01), pages 377-381, XP055330788, DOI: 10.1016/S0040-4020(01)92024-1	12,16
A	2-(4-benzoyloxyphenyl)-2,5-dihydroxy-7-meth oxy-4-chromanone; page 381 ----- -/--	1-11, 13-15,17



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search

1 December 2017

Date of mailing of the international search report

11/12/2017

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer

Jeanjean, Fabien

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2017/076638

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HAUTEVILLE MARCELLE ET AL: "New type of natural flavonoid. 2,5-Dihydroxyflavanones. II. Synthesis of some 2,6-dihydroxydibenzolymethanes and evidence for their cyclic structure", BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE, SOCIETE FRANCAISE DE CHIMIE. PARIS, FRANCE, vol. 5, 1 January 1973 (1973-01-01), pages 1784-1788, XP009192890, ISSN: 0037-8968	12,16
A	page 1784; compound 1d	1-11, 13-15,17
X	----- HUIHUI TI ET AL: "Stilbenes and flavonoids from subsp", FITOTERAPIA, vol. 82, no. 4, 2011, pages 662-665, XP028197897, ISSN: 0367-326X, DOI: 10.1016/J.FITOTE.2011.02.001 [retrieved on 2011-02-11] page 663; compound 2	1-17
X	----- WO 2013/142370 A1 (JOHN VARGHESE [US]; BREDESEN DALE E [US]) 26 September 2013 (2013-09-26) page 93; claim 1 -----	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/076638

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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