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(71) Applicant: **SANOFI** [FR/FR]; 46 avenue de la Grande Armée, 75017 PARIS (FR).

(72) Inventors: **GENEVOIS-BORELLA, Arielle**; c/o Sanofi, Patent Department, 46 avenue de la Grande Armée, 75017 PARIS (FR). **OBINU-REIBAUD, Maria-Carmen**; c/o Sanofi, Patent Department, 46 avenue de la Grande Armée, 75017 PARIS (FR).

(74) Agent: **CABINET NONY**; 11 rue Saint-Georges, 75009 PARIS (FR).

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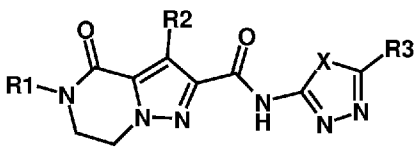
(54) Title: PYRAZOLOPYRAZINONE COMPOUNDS, PROCESS FOR THEIR PREPARATION AND THERAPEUTIC USES THEREOF



(I)

(57) Abstract: The present disclosure relates to a compound of formula (I) wherein R1 represents a hydrogen atom, a -(C_1-C_6)alkyl group optionally substituted; R2 represents a hydrogen atom, a halogen atom, a -(C_1-C_6)alkyl group, a -(C_3-C_7)cycloalkyl group or a -(C_2-C_6)alkenyl group; R3 represents a hydrogen atom, a halogen atom, a -(C_1-C_6)alkyl group, a -(C3-C7)cycloalkyl group, or a -(C5-C10)heteroaryl group; X represents a sulfur or oxygen atom; and Ra and Rb represent a hydrogen atom or a -(C_1-C_6)alkyl group. The present disclosure also relates to a process for their preparation, to novel intermediate compounds, a medicament and a pharmaceutical composition comprising the compounds of formula (I), as well as their therapeutic uses.

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Pyrazolopyrazinone compounds, process for their preparation and therapeutic uses thereof

FIELD OF THE DISCLOSURE

The present disclosure relates to the field of pharmaceutical industry and concerns pyrazolopyrazinone compounds, a process for their preparation, intermediate compounds, a medicament and a pharmaceutical composition comprising said pyrazolopyrazinone compounds, their use as a medicament and more particularly their use for inhibiting the xCT exchanger (subunit of the cystine/glutamate antiporter system xc-) and more particularly their use in the treatment and / or prevention of neurodegenerative diseases and/or cancers.

BACKGROUND OF THE DISCLOSURE

The antiporter system x_c^- imports the amino acid cystine, the oxidized form of cysteine, into cells with a 1:1 counter-transport of glutamate. It is composed of a light chain, xCT, and a heavy chain, 4F2 heavy chain (4F2hc), and, thus, belongs to the family of heterodimeric amino acid transporters. Cysteine is the rate-limiting substrate for the important antioxidant glutathione (GSH) and, along with cystine, it also forms a key redox couple on its own. Glutamate is a major neurotransmitter in the central nervous system (CNS).

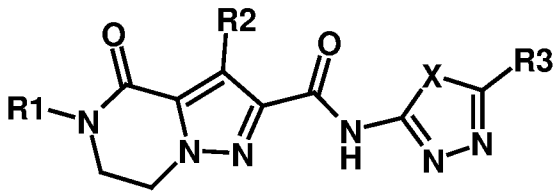
It is well known from the skilled in the art that the system x_c^- plays diverse roles in the regulation of the immune response, in various aspects of cancer and the CNS.

It is also well known that the system Xc- can be inhibited by many small molecules such as synthetic small molecules for instance erastin, sulfasalazine, and sorafenib. However, erastin and sulafasalazine are not selective/specific inhibitors as they can inhibit many other enzymes.

Hence, there is a need to provide novel compounds for specifically inhibiting the xCT exchanger.

SUMMARY OF THE DISCLOSURE

Provided herein is a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R1 represents a hydrogen atom, a -(C_1-C_6)alkyl group optionally substituted with one to five groups, for instance one to two groups, independently selected from a halogen atom, a -(C_1-C_6)alkoxy group, a -halo(C_1-C_6)alkoxy group, a -(C_3-C_7)cycloalkyl group, a hydroxyl group, a -(C_6-C_{10})aryl group, a -(C_5-C_{10})heteroaryl group comprising 4 to 9 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur, and a -(C_3-C_7)heterocycloalkyl group comprising 2 to 6 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur,

said -(C_3-C_7)cycloalkyl group, -(C_6-C_{10})aryl group, -(C_5-C_{10})heteroaryl group and -(C_3-C_7)heterocycloalkyl group being optionally substituted with one to five groups independently selected from a halogen atom, a -(C_1-C_6)alkyl group, a halo(C_1-C_6)alkyl-group, a -(C_1-C_6)alkoxy group, a halo(C_1-C_6)alkoxy- group or a hydroxyl group;

R2 represents a hydrogen atom, a halogen atom, a -(C_1-C_6)alkyl group, a -(C_3-C_7)cycloalkyl group or a -(C_2-C_6)alkenyl group,

said -(C_1-C_6)alkyl group and said -(C_2-C_6)alkenyl group being optionally substituted with one to five substituents independently selected from a halogen atom, a hydroxyl group, or a NRaRb group;

R3 represents a hydrogen atom, a halogen atom, a -(C_1-C_6)alkyl group, a -(C_3-C_7)cycloalkyl group, or a -(C_5-C_{10})heteroaryl group comprising 4 to 9 carbon atoms and 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur,

said -(C_1-C_6)alkyl group being optionally substituted with one to five substituents independently selected from a halogen atom, a (C_1-C_6)alkoxy group, a halo(C_1-C_6)alkoxy group, a hydroxyl group and a nitro group, and said -(C_5-C_{10})heteroaryl group being optionally substituted with one to five substituents independently selected from a halogen atom, a halo(C_1-C_6)alkyl- group, a -(C_1-C_6)alkoxy group, a halo(C_1-C_6)alkoxy- group, a hydroxyl group and a nitro group;

X represents a sulfur or oxygen atom; and

Ra and Rb represent, independently of each other, a hydrogen atom or a -(C_1-C_6)alkyl group.

Herein provided are also:

- a process for preparing a compound of formula (I) according to the present disclosure, or a pharmaceutically acceptable salt thereof,
- intermediates compounds,
- a medicament and a pharmaceutical composition comprising said compound of formula (I) as defined in the present disclosure,
- said compound of formula (I) according to the present disclosure or a pharmaceutically acceptable salt thereof, for use as a medicine,
- said compound of formula (I) according to the present disclosure or a pharmaceutically acceptable salt thereof, for use for preventing and/or treating pathologies involving the xCT exchanger,
- said compound of formula (I) according to the present disclosure or a pharmaceutically acceptable salt thereof, for use for preventing and/or treating neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, HIV-related dementia, strokes, cerebral ischaemia, cerebral and spinal column trauma, epilepsy and pain disorders, and cancers.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1a represents a photograph showing colony formation of ARID1A-Deficient cells A2780 after 6 days treatment with 10µM, 3µM, 1µM, 0.3µM and 0.1µM of Compound 32 (Clonogenic assay).

Figure 1b represents a photograph showing colony formation of ARID1A-Deficient cells TOV21G after 6 days treatment with 10µM, 3µM, 1µM, 0.3µM and 0.1µM of Compound 32 (Clonogenic assay).

Figure 1c represents a photograph showing colony formation of ARID1A-Deficient cells JMSU1 after 6 days treatment with 10µM, 3µM, 1µM, 0.3µM and 0.1µM of Compound 32 (Clonogenic assay).

Figure 1d represents a photograph showing colony formation of ARID1A-Deficient cells LoVo after 6 days treatment with 10µM, 3µM, 1µM, 0.3µM and 0.1µM of Compound 32 (Clonogenic assay).

Figure 1e represents a photograph showing colony formation of ARID1A-Deficient cells MSTO211H after 6 days treatment with 10µM, 3µM, 1µM, 0.3µM and 0.1µM of Compound 32 (Clonogenic assay).

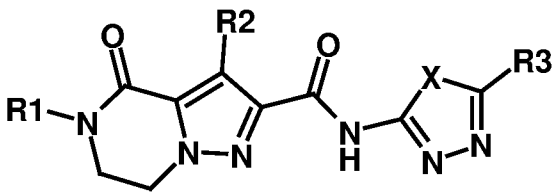
Figure 1f represents a photograph showing colony formation of ARID1A-Deficient cells MIA PaCa2 after 6 days treatment with 10µM, 3µM, 1µM, 0.3µM and 0.1µM of Compound 32 (Clonogenic assay).

Figure 2a represents a graph showing cells growth of A2780 after 7 days treatment with 10µM ( ), 3.33µM ( ), 1.1µM ( ), 370nM ( ), 120nM ( ), 40nM ( ), 10nM ( ), 4.5nM ( ), 1.5nM ( ) and 0.5nM ( ) of Compound 2 without N-AcetylCystein (Incucyte proliferation Assay).

Figure 2b represents a graph showing cells growth of A2780 after 7 days treatment with 10µM ( ), 3.33µM ( ), 1.1µM ( ), 370nM ( ), 120nM ( ), 40nM ( ), 10nM ( ), 4.5nM ( ), 1.5nM ( ) and 0.5nM ( ) of Compound 2 with 5 mM N-AcetylCystein (Incucyte proliferation Assay).

DETAILED DESCRIPTION OF THE DISCLOSURE

As mentioned above, herein is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof :



(I)

wherein:

R1 represents a hydrogen atom, a -(C_1-C_6)alkyl group optionally substituted with one to five groups, for instance one to two groups, independently selected from a halogen atom, a -(C_1-C_6)alkoxy group, a -halo(C_1-C_6)alkoxy group, a -(C_3-C_7)cycloalkyl group, a hydroxyl group, a -(C_6-C_{10})aryl group, a -(C_5-C_{10})heteroaryl group comprising 4

to 9 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur, and a -(C_3-C_7)heterocycloalkyl group comprising 2 to 6 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur,

said -(C_3-C_7)cycloalkyl group, -(C_6-C_{10})aryl group, -(C_5-C_{10})heteroaryl group and -(C_3-C_7)heterocycloalkyl group being optionally substituted with one to five groups independently selected from a halogen atom, a -(C_1-C_6)alkyl group, a halo(C_1-C_6)alkyl-group, a -(C_1-C_6)alkoxy group, a halo(C_1-C_6)alkoxy- group or a hydroxyl group;

R2 represents a hydrogen atom, a halogen atom, a -(C_1-C_6)alkyl group, a -(C_3-C_7)cycloalkyl group or a -(C_2-C_6)alkenyl group,

said -(C_1-C_6)alkyl group and said -(C_2-C_6)alkenyl group being optionally substituted with one to five substituents independently selected from a halogen atom, a hydroxyl group, or a NRaRb group;

R3 represents a hydrogen atom, a halogen atom, a -(C_1-C_6)alkyl group, a -(C_3-C_7)cycloalkyl group, or a -(C_5-C_{10})heteroaryl group comprising 4 to 9 carbon atoms and 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur,

said -(C_1-C_6)alkyl group being optionally substituted with one to five substituents independently selected from a halogen atom, a (C_1-C_6)alkoxy group, a halo(C_1-C_6)alkoxy group, a hydroxyl group and a nitro group, and said -(C_5-C_{10})heteroaryl group being optionally substituted with one to five substituents independently selected from a halogen atom, a halo(C_1-C_6)alkyl- group, a -(C_1-C_6)alkoxy group, a halo(C_1-C_6)alkoxy- group, a hydroxyl group and a nitro group;

X represents a sulfur or oxygen atom; and

Ra and Rb represent, independently of each other, a hydrogen atom or a -(C_1-C_6)alkyl group.

The compounds of formula (I) may comprise one or more asymmetric carbons. They may exist in the form of enantiomers or diastereoisomers. The compounds of formula (I) may also exist in the form of *cis* or *trans* stereoisomers. These stereoisomers, enantiomers and diastereoisomers, and also mixtures thereof, including racemic mixtures, form part of the disclosure.

The compounds of formula (I) may be present as well under tautomer forms.

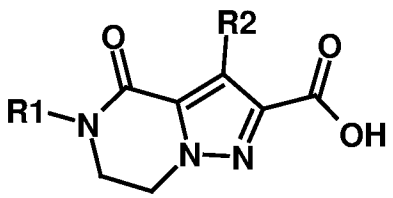
The compounds of formula (I) may exist in the form of bases, acids, zwitterion or of addition salts with acids or bases. Hence, herein are provided compounds of formula (I) or pharmaceutically acceptable salts thereof.

These salts may be prepared with pharmaceutically acceptable acids or bases, although the salts of other acids or bases useful, for example, for purifying or isolating the compounds of formula (I) are also provided.

Among suitable salts of the compounds of formula (I), hydrochloride may be cited.

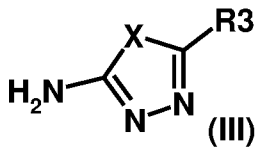
The present disclosure also relates to a process for preparing a compound of formula (I) as defined in the present disclosure or a pharmaceutically acceptable salt thereof, comprising at least the step of :

- reacting a compound of formula (II):



(II)

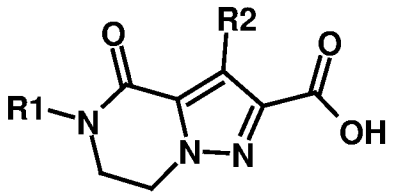
wherein R1 and R2 are as defined in the present disclosure, with a compound of formula (III)



(III)

wherein X and R3 are as defined in the present disclosure.

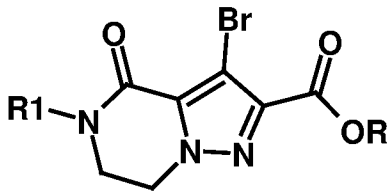
Another subject-matter of the instant disclosure is a compound of formula (II) or a pharmaceutically acceptable salt thereof



(II)

wherein R1 and R2 are as defined in the present disclosure, with the exception of the compounds of formula (II) in which R2 represents a hydrogen atom.

Another subject-matter of the instant disclosure is a compound of formula (X) or a pharmaceutically acceptable salt thereof



(X)

wherein R1 is as defined in the present disclosure, and R represents a methyl or ethyl group.

Another subject-matter of the instant disclosure is a compound of formula (I) in accordance with the disclosure selected from the above and below definitions/lists, or a pharmaceutically acceptable salt thereof, for use as a medicine.

Another subject-matter of the instant disclosure is a compound of formula (I) in accordance with the disclosure selected from the above and below definitions/lists, or a pharmaceutically acceptable salt thereof, for use in the prevention and/or treatment of pathologies involving the xCT exchanger.

Another subject-matter of the instant disclosure is a compound of formula (I) in accordance with the disclosure selected from the above and below definitions/lists, or a pharmaceutically acceptable salt thereof, for use in the prevention and/or treatment of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, HIV-related dementia, strokes, cerebral ischaemia, cerebral and spinal column trauma, epilepsy and pain disorders, and cancers.

In one embodiment, a cancer may be a cancer selected among acute myeloid leukemia (LAML or AML), acute lymphoblastic leukemia (ALL), adrenocortical carcinoma (ACC), bladder urothelial cancer (BLCA), brain stem glioma, brain lower grade glioma (LGG), brain tumor, breast cancer (BRCA), bronchial tumors, Burkitt lymphoma, cancer of unknown primary site, carcinoid tumor, carcinoma of unknown primary site, central nervous system atypical teratoid/rhabdoid tumor, central nervous system embryonal tumors, cervical squamous cell carcinoma, endocervical adenocarcinoma (CESC) cancer, childhood cancers, cholangiocarcinoma (CHOL), chordoma, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorders, colon (adenocarcinoma) cancer (COAD), colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, endocrine pancreas islet cell tumors, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer (ESCA), esthesioneuroblastoma, Ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal cell tumor, gastrointestinal stromal tumor (GIST), gestational trophoblastic tumor, glioblastoma multiforme glioma GBM), hairy cell leukemia, head and neck cancer (HNSD), heart cancer, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, lip cancer, liver cancer, lung adenocarcinoma, lung cancer, Lymphoid Neoplasm Diffuse Large B-cell Lymphoma (DLBCL), malignant fibrous histiocytoma bone cancer, medulloblastoma, medullo epithelioma, melanoma, Merkel cell carcinoma, Merkel cell skin carcinoma, mesothelioma (MESO), malignant mesothelioma, metastatic squamous neck cancer with occult primary, microsatellite instability (MSI) mutated tumors, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes, myeloproliferative neoplasms, nasal cavity cancer, nasopharyngeal cancer, neuroblastoma, Non-Hodgkin lymphoma, nonmelanoma skin cancer, non-small cell lung cancer, oral cancer, oral cavity cancer, oropharyngeal cancer, osteosarcoma, other brain and spinal cord tumors, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, paranasal sinus cancer, parathyroid cancer, pelvic cancer, penile cancer, pharyngeal cancer, pheochromocytoma and paraganglioma (PCPG), pineal parenchymal tumors of intermediate differentiation, pineoblastoma, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleural mesothelioma, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, primary hepatocellular liver cancer, prostate cancer such as prostate adenocarcinoma (PRAD), rectal cancer, renal cancer, renal cell (kidney)

cancer, renal cell cancer, respiratory tract cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma (SARC), Sezary syndrome, skin cutaneous melanoma (SKCM), small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous cell carcinoma (SCC) of head and neck, squamous neck cancer, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, T-cell lymphoma, testicular cancer testicular germ cell tumors (TGCT), throat cancer, thymic carcinoma, thymoma (THYM), thyroid cancer (THCA), transitional cell cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, ureter cancer, urethral cancer, uterine cancer, uterine cancer, uveal melanoma (UVM), vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, classic Hodgkin lymphoma (cHL), hepatocellular carcinoma (HCC), liver hepatocellular carcinoma, urothelial carcinoma, cervical cancer, uterine corpus endometrial carcinoma, skin cancer, primary mediastinal large B-cell lymphoma (PMBCL), glioblastoma, bladder cancer, bladder carcinoma, bladder urothelial carcinoma, mature b-cell neoplasms, esophagogastric cancer, stomach adenocarcinoma, diffuse large B-cell (DLBC) lymphoma (DLBCL), low grade glioma (LGG), kidney renal papillary cell carcinoma, kidney renal clear cell carcinoma, renal cell carcinoma (RCC), or Wilm's tumor.

In a particular embodiment, a cancer may be a cancer selected among lung cancer including small cell lung cancer (SCLC) and non - small cell lung cancer (NSCLC), lung adenocarcinoma, pleural mesothelioma, squamous cell carcinoma (SCC), squamous cell carcinoma of the lung, cervical squamous cell carcinoma, squamous cell carcinoma (SCC) of head and neck, head and neck cancer, pancreatic cancer, microsatellite instability (MSI) mutated tumors, classic Hodgkin lymphoma (cHL), hepatocellular carcinoma (HCC), liver hepatocellular carcinoma, liver cancer, cholangiocarcinoma (CHOL), urothelial carcinoma, breast cancer, cervical cancer, uterine corpus endometrial carcinoma, ovarian cancer, endometrial cancer, skin cancer, melanoma, uveal melanoma, Merkel cell carcinoma (MCC), sarcoma, mesothelioma, malignant mesothelioma, primary mediastinal large B-cell lymphoma (PMBCL), thyroid cancer, glioblastoma, prostate cancer, bladder cancer, bladder carcinoma, bladder urothelial carcinoma, mature b-cell neoplasms, colorectal cancer (CRC), colon cancer, esophagogastric cancer, stomach cancer, stomach adenocarcinoma, esophageal cancer, diffuse large B-cell (DLBC) lymphoma (DLBCL), low grade glioma (LGG), kidney renal papillary cell carcinoma, kidney renal clear cell carcinoma, renal cell carcinoma (RCC), and kidney cancer.

It is well known that the inhibition of the xCT exchanger is involved in the prevention and/or treatment of cancers such as lung cancer including small cell lung cancer (SCLC) and non - small cell lung cancer (NSCLC), lung adenocarcinoma, pleural mesothelioma, squamous cell carcinoma (SCC), squamous cell carcinoma of the lung, cervical squamous cell carcinoma, squamous cell carcinoma (SCC) of head and neck, head and neck cancer, pancreatic cancer, microsatellite instability (MSI) mutated tumors, classic Hodgkin lymphoma (cHL), hepatocellular carcinoma (HCC), liver hepatocellular carcinoma, liver cancer, cholangiocarcinoma, urothelial carcinoma, cervical cancer, uterine corpus endometrial carcinoma, ovarian cancer, endometrial cancer, skin cancer, melanoma, uveal melanoma, Merkel cell carcinoma (MCC), sarcoma, mesothelioma, primary mediastinal large B-cell lymphoma (PMBCL), breast cancer, thyroid cancer, glioblastoma, prostate cancer, bladder cancer, bladder carcinoma, bladder urothelial carcinoma, mature b-cell neoplasms, colorectal cancer (CRC), esophagogastric cancer, stomach cancer, stomach adenocarcinoma, esophageal cancer, diffuse large B-cell (DLBC) lymphoma (DLBCL), low grade glioma (LGG), kidney renal papillary cell carcinoma, kidney renal clear cell carcinoma, renal cell carcinoma (RCC), and kidney cancer. This relationship between inhibition of the xCT exchanger and prevention/treament of cancers has been described for example in the following publications:

- Suman Mukhopadhyay *et al.*, Undermining Glutaminolysis Bolsters Chemotherapy While NRF2 Promotes Chemoresistance in KRAS-Driven Pancreatic Cancers, Metabolism and Chemical Biology, Vol.80, Issue 8, 2020, pp.1630-1643,

- Jonathan K. M. Lim *et al.*, Cystine/glutamate antiporter xCT (SLC7A11) facilitates oncogenic RAS transformation by preserving intracellular redox balance, PNAS, Vol. 116, n°19, 2019, pp. 9433-9442,

- Marc O. Johnson *et al.,* Distinct Regulation of Th17 and Th1 Cell Differentiation by Glutaminase-Dependent Metabolism, CELL, vol. 175, Issue 7, 2018, pp.1780-1795,

Michael D Arensman *et al.,* Cystine–glutamate antiporter xCT deficiency suppresses tumor growth while preserving antitumor immunity. , PNAS, Vol. 116, n°19, 2019, pp. 9533-9542,

- Lang *et al.,* Radiotherapy and immunotherapy promote tumoral lipid oxidation and ferroptosis via synergistic repression of SLC7A11, Cancer Discov., 9(12), 2019, pp.1673–1685,

- Lei *et al.,* The role of ferroptosis in ionizing radiation-induced cell death and tumor suppression, Cell Research, 30, 2020, pp.146–162,

- Ling F. Ye *et al.*, Radiation-Induced Lipid Peroxidation Triggers Ferroptosis and Synergizes with Ferroptosis Inducers, *ACS Chem. Biol.* 15, 2, 2020, pp. 469–484,

- Hideaki Ogiwara *et al*, Targeting the Vulnerability of Glutathione Metabolism in ARID1A-Deficient Cancers, Cancer cell, vol.35, Issue 2, 2019, pp.177-190,

- Tong Zhang *et al.,* Polyamine pathway activity promotes cysteine essentiality in cancer cells, Nature Metabolism ,volume 2, 2020, pp. 1062–1076, and

- Pranavi Koppula *et al.*, Cystine transporter SLC7A11/xCT in cancer: ferroptosis, nutrient dependency, and cancer therapy, protein & cell, vol. 12, n°8, 2021, pp.599-620.

Another subject-matter of the instant disclosure is a method of preventing and/or treating neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, HIV-related dementia, strokes, cerebral ischaemia, cerebral and spinal column trauma, epilepsy and pain disorders, and cancers.

The present disclosure further relates to the use of a compound of formula (I) in accordance with the disclosure selected from the above and below definitions/lists, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for preventing and/or treating neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, HIV-related dementia, strokes, cerebral ischaemia, cerebral and spinal column trauma, epilepsy and pain disorders, and cancers.

Another subject-matter of the instant disclosure is a medicament comprising a compound of formula (I) in accordance with the disclosure selected from the above and below definitions/lists, or a pharmaceutically acceptable salt thereof.

Another subject-matter of the instant disclosure is a pharmaceutical composition comprising a compound of formula (I) in accordance with the disclosure selected from the above and below definitions/lists, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

Definitions

As used herein, the terms below have the following definitions unless otherwise mentioned throughout the instant specification :

- a **hydroxyl** group: a "-OH" group;
- a -**(C_x-C_y)alkyl** group: a linear or branched saturated hydrocarbon-based aliphatic group comprising from x to y carbon atoms, for example from 1 to 6 carbon atoms, By way of examples, mention may be made of, but not limited to: methyl, ethyl, propyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, isopentyl, hexyl, isohexyl groups, and the like;
- a -**(C_x-C_y)alkenyl** group: a linear or branched hydrocarbon-based aliphatic group comprising at least one unsaturation (double bond) and comprising, from x to y carbon atoms (x being an integer of at least 2), for example from 2 to 6 carbon atoms. By way of examples, mention may be made of, but not limited to: ethenyl (also named vinyl group or (-CH=CH_2)), propenyl, butenyl, isobutenyl (=$CH(CH_3)_2$), pentenyl, hexenyl groups, and the like;
- a -**(C_x-C_y)alkoxy** group: an -O-alkyl group where the alkyl group is as previously defined. For example, a -(C_1-C_6)alkoxy group. By way of examples, mention may be made of, but not limited to: methoxy, ethoxy, propoxy, isopropoxy, linear, secondary or tertiary butoxy, isobutoxy, pentoxy, hexyloxy, groups, and the like;
- a **-(C_3-C_7)cycloalkyl** group: a cyclic alkyl group comprising, unless otherwise mentioned, from 3 to 7 carbon atoms, saturated or partially unsaturated and unsubstituted or substituted. By way of examples, mention may be made of, but not limited to: cyclopropyl, cyclobutyl, cyclopentyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexyl, cycloheptyl groups, and the like. The cycloalkyl is advantageously cyclopropyl and cyclohexyl;
- a **-(C_3-C_7)heterocycloalkyl** group: a monocyclic alkyl group comprising, unless otherwise mentioned, from 2 to 6 carbon atoms (also noted "a -(C_3-C_7) membered heterocycloalkyl group") and comprising 1 to 4 heteroatoms selected from oxygen, nitrogen, and sulfur (in other terms, one heteroatom replaces one carbon atom). Such heterocycloalkyl group may be saturated or partially saturated and unsubstituted or substituted. By way of examples of heterocycloalkyl groups, mention may be made of, but not limited to: piperazine, morpholino, pyrrolidine, tetrahydropyrane, piperidine, dihydrofurane, tetrahydrofurane, azetidine, oxetane, thietane, 2H-pyrrole, 1H-, 2H- or 3H-pyrroline, tetrahydrothiophene, oxadiazole and for example 1,3,4-oxadiazole or 1,3,5-oxadioazole, thiadiazole and for

example 1,3,4-thiadiazole, isoxazoline, 2- or 3-pyrazoline, pyrroline, pyrazolidine, imidazoline, imidazolidine, thiazolidine, isooxazoline, isoxazolidine, dioxalane, oxathiazole, oxathiadiazole, dioxazole groups, and the like. The heterocycloalkyl is advantageously oxetane and tetrahydropyrane.

- a -(**C_5-C_{10})heteroaryl** group means: a cyclic aromatic group comprising from 4 to 9 carbon atoms and comprising from 1 and 4 heteroatoms selected from nitrogen, oxygen and sulfur (also noted "a (C_5-C_{10}) membered heteroaryl group") (in other terms, one heteroatom replaces one carbon atom). Such heteroaryl group may be unsubstituted or substituted. By way of examples of 5 to 10-membered heteroaryl groups, mention may be made of, but not limited to: pyridine, furan, pyrrole, thiophene, pyrazole, oxazole, isoxazole, triazole, tetrazole, oxadiazole, furazan, thiazole, isothiazole, thiadiazole, imidazole, pyrimidine, pyridazine, triazine, pyrazine, benzotriazole, benzoxazole, benzimidazole, benzoxadiazole, benzothiazole, benzothiadiazole, benzofuran, indole, isoquinoline, indazole, benzisoxazole, benzisothiazole groups and the like. The heteroaryl is advantageously pyridine and furan;
- a -**(C_6-C_{10})aryl** group: a cyclic aromatic group comprising from 6 to 10 carbon atoms (noted "a (C_6-C_{10}) membered aryl group"). Such aryl group may be unsubstituted or substituted. By way of examples of 6 to 10-membered aryl groups, mention may be made of, but not limited to: phenyl, naphthyl groups, and the like. The aryl is advantageously phenyl;
- a **halo(C_1-C_6)alkyl** group, an alkyl group as defined previously, in which one or more hydrogen atoms have been replaced with one or more identical or different halogen atoms. Examples that may be mentioned include the groups CF_3, CH_2CF_3, CH_2F, CHF_2 and CCl_3;
- a **halo(C_1-C_6)alkoxy** group: a radical -O-alkyl in which the alkyl group is as previously defined and where the alkyl group is substituted with one or more identical or different halogen atoms. Examples that may be mentioned include the groups -OCF_3, -$OCHF_2$ and $OCCl_3$;- a **halogen** atom: a fluorine, a chlorine, a bromine or an iodine atom, and in particular a fluorine atome, a bromine atom and a chlorine atom.
- "**optionally substituted**" means "unsubstituted" or "substituted with";
- r and s indicate the stereochemistry of the pseudo-asymmetric carbon atoms, according to the IUPAC rules.

In the various groups as defined below, the groups R1, R2, R3, X, Ra or Rb, when they are not defined, have the same definitions as those mentioned above.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which R1 represents a -(C_1-C_6)alkyl group optionally substituted with one to two groups independently selected from :

- a -(C_3-C_7)cycloalkyl group,
- a hydroxyl group,
- a -(C_6-C_{10}) aryl group,
- a -(C_5-C_{10})heteroaryl group comprising 4 to 9 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur, and
- a -(C_3-C_7)heterocycloalkyl group comprising 2 to 6 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur,

said -(C_3-C_7)cycloalkyl group, -(C_6-C_{10})aryl group, -(C_5-C_{10})heteroaryl group and -(C_3-C_7)heterocycloalkyl group being optionally substituted with one to five groups independently selected from a halogen atom, a (C_1-C_6)alkyl group, a (C_1-C_6)alkoxy group, and a hydroxyl group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which R1 represents a -(C_1-C_6)alkyl group optionally substituted with one to two groups independently selected from :

- a -(C_3-C_7)cycloalkyl group, said -(C_3-C_7)cycloalkyl group being optionally substituted with one to two halogen atoms,
- a hydroxyl group,
- a -(C_6-C_{10})aryl group, said -(C_6-C_{10})aryl group being optionally substituted with one to two groups independently selected from a halogen atom, a (C_1-C_6)alkoxy group, and a hydroxyl group,
- a -(C_5-C_{10})heteroaryl group comprising 4 to 9 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur, said -(C_5-C_{10})heteroaryl group being optionally substituted with one to two groups independently selected from a halogen atom, and a -(C_1-C_6)alkyl group, and

- a -(C_3-C_7)heterocycloalkyl group comprising 2 to 6 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur, said -(C_3-C_7)heterocycloalkyl group being optionally substituted with one (C_1-C_6)alkyl group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which R_1 represents a methyl group, an ethyl group, a propyl group, or an isopentyl group, said methyl group, ethyl group, propyl group, and isopentyl group being optionally substituted with one to two groups independently selected from :

- a phenyl group, said phenyl group being optionally substituted with one to two groups independently selected from a chlorine atom, a fluorine atom, a methoxy group, and a hydroxy group,
- an oxetane, said oxetane being optionally substituted with a methyl group,
- a pyridine, said pyridine being optionally substituted with one to two groups independently selected from a methyl group, a fluorine atom and a bromine atom,
- a cyclopropyl group,
- a cyclohexyl group, said cyclohexyl group being optionally substituted by one to two fluorine atoms,
- a hydroxyl group, and
- a tetrahydropyrane.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which R1 represents a -(C_5-C_{10})heteroaryl group optionally substituted with a (C_1-C_6)alkyl group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which R1 represents a pyridine substituted by a methyl group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which R2 represents a halogen atom, a -(C_1-C_6)alkyl group, a -(C_3-C_7)cycloalkyl group or a -(C_2-C_6)alkenyl group, said -(C_1-C_6)alkyl group being optionally substituted with a halogen atom, a hydroxyl group, or a NRaRb group; Ra and Rb being independenly a -(C_1-C_6)alkyl group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which R2 represents a bromine atom, a methyl group optionally substituted with a fluorine atom, a hydroxyl group or a -N(CH_3)$_2$ group, an ethyl group optionally substituted by a hydroxyl group, a vinyl group (-CH=CH_2), an isobutenyl group (=CH(CH_3)$_2$), and a cyclopropyl group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which R2 represents a -(C_3-C_7)cycloalkyl group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which R2 represents a cyclopropyl group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which R3 represents a hydrogen atom, a halogen atom, a -(C_1-C_6)alkyl group, a -(C_3-C_7)cycloalkyl group, or a -(C_5-C_{10})heteroaryl group comprising 4 to 9 carbon atoms and 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, said (C_1-C_6)alkyl group being optionally substituted with one to three substituents independently selected from a halogen atom, and a hydroxyl group, and said heteroaryl group being optionally substituted with one nitro group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which R3 represents a hydrogen atom, a methyl group, an ethyl group, an isopropyl group, a CF_3 group, a -CHF_2 group, a -CH_2F group, a -CH_2-CF_3 group, a chlorine atom, a -CH_2OH group, a cyclopropyl group, or a furan group substituted by a nitro group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which R3 represents a -(C_1-C_6)alkyl group substituted with two halogen atoms.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which R3 represents a CHF_2 group.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which X represents a sulfur or oxygen atom.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which X represents a sulfur atom.

Among the compounds of formula (I) that are subject-matter of the disclosure, a group of compounds is composed of the compounds for which X represents an oxygen atom.

All these sub-groups taken alone or in combination are part of the present disclosure.

According to a particular embodiment, the disclosure relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof wherein:

R1 represents a -(C_1-C_6)alkyl group optionally substituted with one to two groups independently selected from :

- a -(C_3-C_7)cycloalkyl group, said -(C_3-C_7)cycloalkyl group being optionally substituted with one to two halogen atoms,
- a hydroxyl group,
- a -(C_6-C_{10})aryl group, said -(C_6-C_{10})aryl group being optionally substituted with one to two groups independently selected from a halogen atom, a (C_1-C_6)alkoxy group, and a hydroxyl group,
- a -(C_5-C_{10})heteroaryl group comprising 4 to 9 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur, said -(C_5-C_{10})heteroaryl group being optionally substituted with one to two groups independently selected from a halogen atom, and a -(C_1-C_6)alkyl group, and
- a -(C_3-C_7)heterocycloalkyl group comprising 2 to 6 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur, said -(C_3-C_7)heterocycloalkyl group being optionally substituted with one (C_1-C_6)alkyl group;

R2 represents a halogen atom, a -(C_1-C_6)alkyl group, a -(C_3-C_7)cycloalkyl group or a -(C_2-C_6)alkenyl group, said -(C_1-C_6)alkyl group being optionally substituted with a halogen atom, a hydroxyl group, or a NRaRb group; Ra and Rb being independenly a -(C_1-C_6)alkyl group ;

R3 represents a hydrogen atom, a halogen atom, a -(C_1-C_6)alkyl group, a -(C_3-C_7)cycloalkyl group, or a -(C_5-C_{10})heteroaryl group comprising 4 to 9 carbon atoms and 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, said (C_1-C_6)alkyl group being optionally substituted with one to three substituents independently selected from a halogen atom, and a hydroxyl group, and said heteroaryl group being optionally substituted with one nitro group ; and

X represents a sulfur or oxygen atom.

According to a particular embodiment, the disclosure relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof wherein:

R1 represents a -(C_1-C_6)alkyl group optionally substituted with one to two groups independently selected from :

- a -(C_3-C_7)cycloalkyl group, said -(C_3-C_7)cycloalkyl group being optionally substituted with one to two halogen atoms,
- a hydroxyl group,
- a -(C_6-C_{10})aryl group, said -(C_6-C_{10})aryl group being optionally substituted with one to two groups independently selected from a halogen atom, a (C_1-C_6)alkoxy group, and a hydroxyl group,
- a -(C_5-C_{10})heteroaryl group comprising 4 to 9 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur, said -(C_5-C_{10})heteroaryl group being optionally substituted with one to two groups independently selected from a halogen atom, and a -(C_1-C_6)alkyl group, and
- a -(C_3-C_7)heterocycloalkyl group comprising 2 to 6 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur, said -(C_3-C_7)heterocycloalkyl group being optionally substituted with one (C_1-C_6)alkyl group ;

R2 represents a halogen atom, a -(C_1-C_6)alkyl group, a -(C_3-C_7)cycloalkyl group or a -(C_2-C_6)alkenyl group, said -(C_1-C_6)alkyl group being optionally substituted with a halogen atom, a hydroxyl group, or a NRaRb group; Ra and Rb being independenly a -(C_1-C_6)alkyl group ;

R3 represents a hydrogen atom, a halogen atom, a -(C_1-C_6)alkyl group, a -(C_3-C_7)cycloalkyl group, or a -(C_5-C_{10})heteroaryl group comprising 4 to 9 carbon atoms and 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, said (C_1-C_6)alkyl

group being optionally substituted with one to three substituents independently selected from a halogen atom, and a hydroxyl group, and said heteroaryl group being optionally substituted with one nitro group ; and

X represents a sulfur atom.

According to a particular embodiment, the disclosure relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof wherein:

R1 represents a methyl group, an ethyl group, a propyl group, or an isopentyl group, said methyl group, ethyl group, propyl group, and isopentyl group being optionally substituted with one to two groups independently selected from :

- a phenyl group, said phenyl group being optionally substituted with one to two groups independently selected from a chlorine atom, a fluorine atom, a methoxy group, and a hydroxy group,
- an oxetane, said oxetane being optionally substituted with a methyl group,
- a pyridine, said pyridine being optionally substituted with one to two groups independently selected from a methyl group, a fluorine atom and a bromine atom,
- a cyclopropyl group,
- a cyclohexyl group, said cyclohexyl group being optionally substituted by one to two fluorine atoms,
- a hydroxyl group, and
- a tetrahydropyrane ;

R2 represents a bromine atom, a methyl group optionally substituted with a fluorine atome, a hydroxyl group or a $-N(CH_3)_2$ group, an ethyl group optionally substituted by a hydroxyl group, a vinyl group ($-CH=CH_2$), an isobutenyl group ($=CH(CH_3)_2$), and a cyclopropyl group ;

R3 represents a hydrogen atom, a methyl group, an ethyl group, an isopropyl group, a CF_3 group, a CHF_2 group, a CH_2F group,a CH_2-CF_3 group, a chlorine atom, a CH_2OH group, a cyclopropyl group, or a furan group substituted by a nitro group ; and

X represents a sulfur or oxygen atom.

According to a particular embodiment, the disclosure relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof wherein:

R1 represents a methyl group, an ethyl group, a propyl group, or an isopentyl group, said methyl group, ethyl group, propyl group, and isopentyl group being optionally substituted with one to two groups independently selected from :

- a phenyl group, said phenyl group being optionally substituted with one to two groups independently selected from a chlorine atom, a fluorine atom, a methoxy group, and a hydroxy group,
- an oxetane, said oxetane being optionally substituted with a methyl group,
- a pyridine, said pyridine being optionally substituted with one to two groups independently selected from a methyl group, a fluorine atom and a bromine atom,
- a cyclopropyl group,
- a cyclohexyl group, said cyclohexyl group being optionally substituted by one to two fluorine atoms,
- a hydroxyl group, and
- a tetrahydropyrane ;

R2 represents a bromine atom, a methyl group optionally substituted with a fluorine atome, a hydroxyl group or a $-N(CH_3)_2$ group, an ethyl group optionally substituted by a hydroxyl group, a vinyl group ($-CH=CH_2$), an isobutenyl group ($=CH(CH_3)_2$), and a cyclopropyl group ;

R3 represents a hydrogen atom, a methyl group, an ethyl group, an isopropyl group, a CF_3 group, a CHF_2 group, a CH_2F group, a CH_2-CF_3 group, a chlorine atom, a CH_2OH group, a cyclopropyl group, or a furan group substituted by a nitro group ; and

X represents a sulfur atom.

Combinations of the subgroups as defined above also form part of the disclosure.

Among the compounds of formula (I), mention may be made especially of the following compounds:

- 5-(2-chlorobenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-fluorobenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide

- 5-(2-fluorobenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-fluorobenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-cyclopropyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(2-fluorobenzyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-methyl-5-(3-methyloxetan-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-methyl-4-oxo-5-pyridin-3-ylmethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-methyl-4-oxo-5-pyridin-3-ylmethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-methyl-5-(2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-methyl-4-oxo-5-pyridin-2-ylmethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-bromo-4-oxo-5-phenethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-bromo-5-(3-fluoropyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-methyl-4-oxo-5-phenethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-[2-(2-chlorophenyl)ethyl]-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-ethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-ethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-cyclopropyl[1,3,4]thiadiazol-2-yl)amide
- 5-[2-(2-fluorophenyl)ethyl]-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide

- 3-methyl-5-(3-methylbutyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-methyl-5-(3-methylbutyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-cyclopropyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-isopropyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-methyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-ethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-cyclopropylmethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-methyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-isopropyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-ethyl[1,3,4]thiadiazol-2-yl)amide (HCl)
- 3-cyclopropyl-5-(3-methylbutyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-ethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-methyl[1,3,4]thiadiazol-2-yl)amide (HCl)
- 3-cyclopropyl-5-(3-methylbutyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-methyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(3-methylpyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-methyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(3-methylpyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-ethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(3-methylpyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide

- 3-cyclopropyl-5-(4,4-difluorocyclohexylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(4,4-difluorocyclohexylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-ethyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(3-methylpyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-cyclopropyl[1,3,4]thiadiazol-2-yl)amide
- 5-[2-(2-chlorophenyl)ethyl]-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-methyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(4-hydroxybenzyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-[2-(2-chlorophenyl)ethyl]-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-[2-(2-chlorophenyl)-2-hydroxyethyl]-3-ethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(3-hydroxybenzyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(2-hydroxybenzyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(3-hydroxypropyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chloro-3-hydroxybenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(3-hydroxy-3-methylbutyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid [1,3,4]thiadiazol-2-ylamide
- 5-(2-chlorobenzyl)-3-(2-methylpropenyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-4-oxo-5-(tetrahydropyran-4-ylmethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-methyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-4-oxo-5-(tetrahydropyran-4-ylmethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide

- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid [5-(5-nitrofuran-2-yl)-[1,3,4]thiadiazol-2-yl]amide
- 3-cyclopropyl-4-oxo-5-(tetrahydropyran-4-ylmethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-cyclopropyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-chloro[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid [5-(2,2,2-trifluoroethyl)[1,3,4]thiadiazol-2-yl]amide
- 3-cyclopropyl-5-(6-fluoro-2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(6-fluoro-2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-4-oxo-3-vinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]oxadiazol-2-yl)amide
- 5-(2-chloro-4-methoxybenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-hydroxymethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(6-fluoro-2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(6-fluoro-2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-dimethylaminomethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide (HCl)
- 5-(2-chlorobenzyl)-3-fluoromethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-fluoromethyl[1,3,4]thiadiazol-2-yl)amide

- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-hydroxymethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(6-bromo-2-methylpyridin-3-ylmethyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-fluoromethyl[1,3,4]thiadiazol-2-yl)amide.

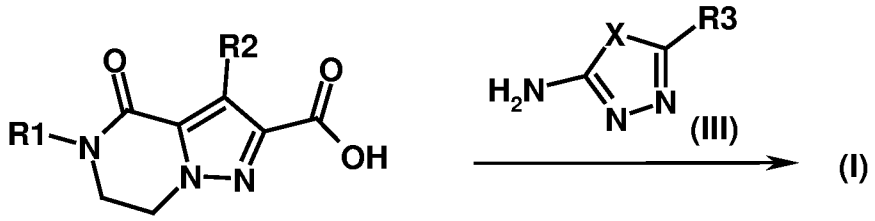
It should be noted that the compounds above were named according to the IUPAC (International Union of Pure and Applied Chemistry) nomenclature using the AutoNom software.

In the text hereinbelow, the term "protecting group (Pg)" means a group that can, firstly, protect a reactive function such as a hydroxyl or an amine during a synthesis and, secondly, regenerate the intact reactive function at the end of the synthesis. Examples of protecting groups and also of protection and deprotection methods are given in *Protective Groups in Organic Synthesis*, Greene et al., 4th Edition (John Wiley & Sons, Inc., New York).

In the text hereinbelow, the term "leaving group (Lg)" means a group that can be readily cleaved from a molecule by breaking a heterolytic bond, with loss of an electron pair. This group can thus be easily replaced with another group in a substitution reaction, for example. Such leaving groups are, for example, halogens or an activated hydroxyl group, such as a mesyl, tosyl, triflate, acetyl, etc. Examples of leaving groups and also the references for preparing them are given in *Advanced Organic Chemistry*, J. March, 5th Edition, Wiley Interscience, pp. 310-316.

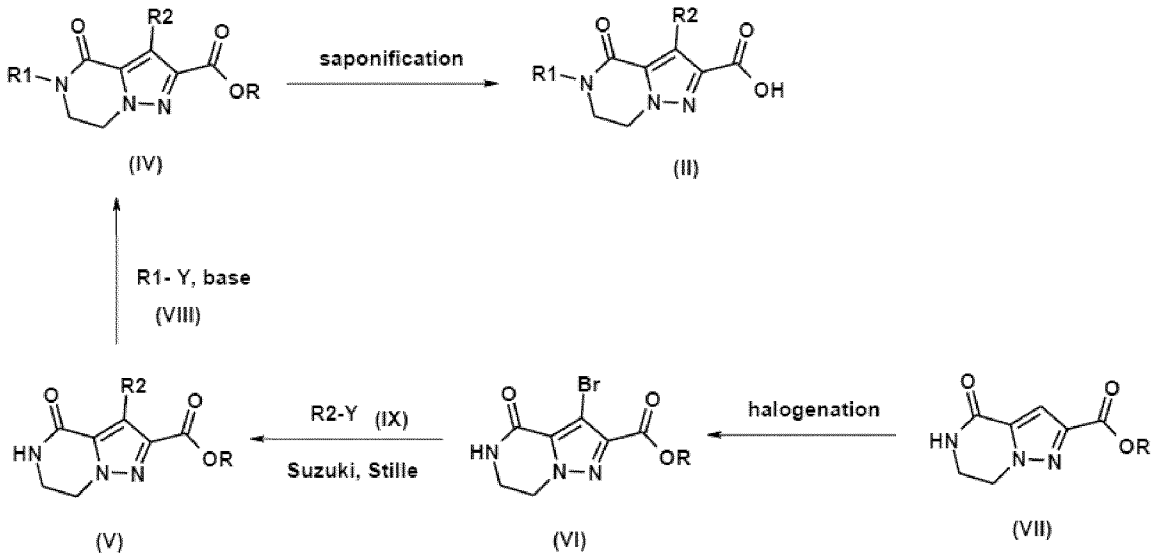
The compounds of the present disclosure of formula (I) may be prepared according to various methods, illustrated by the schemes which follow. These methods, and the intermediate compounds used, are a subject of the present disclosure.

Scheme 1



Thus, one preparation method (scheme 1) consists in reacting an amine of formula (III), in which X and R3 are as defined in the present disclosure, with an acid of formula (II) in which R1 and R2 are as defined in the present disclosure, in the presence of a coupling agent such as 1,3-dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDCI) and of a base such as triethylamine, pyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or *N*,*N*-diisopropylethylamine, in a solvent such as dimethylformamide, toluene, acetonitrile or dichloroethane, at a temperature between room temperature and the reflux temperature of the solvent.

Scheme 2

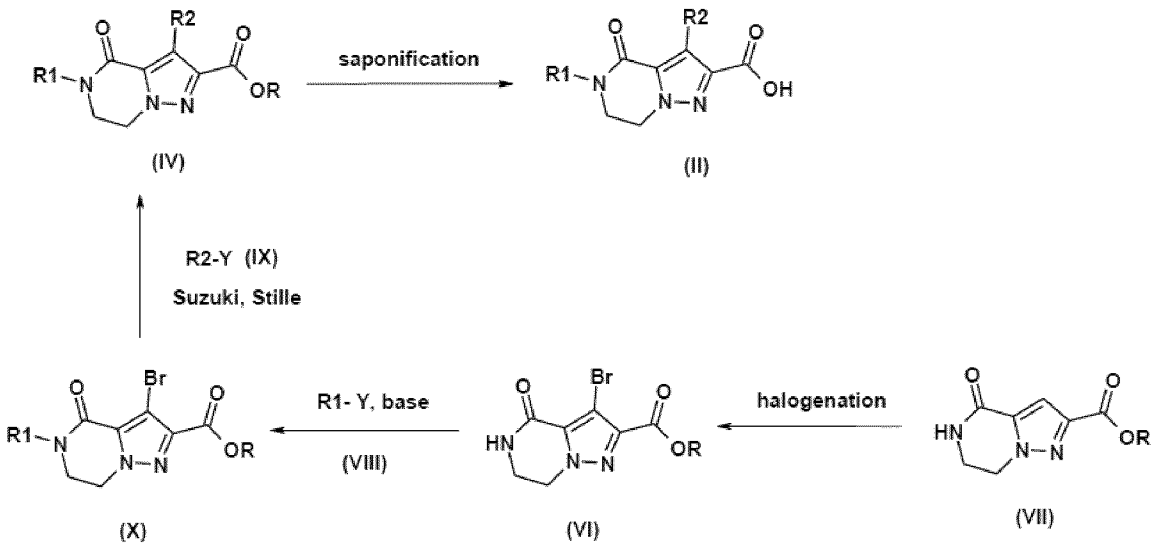


A preparation method (scheme 2) for obtaining the compounds of formula (II), in which R1 and R2 are as defined in the present disclosure, consists in performing, in a first stage, a halogenation step using compounds of formula (VII), in which R represents a methyl or ethyl group, to obtain the compounds of formula (VI), in which R is as defined above. The next step consists in performing a coupling reaction catalysed with a transition metal such as palladium(0) on the intermediate of formula (VI) as defined above with a halogenated compound of formula R2Y (IX), in which R2 is as defined in the present disclosure and Y represents a chlorine, bromine or iodine atom:

- either via a reaction of Suzuki type, for example using a boronic acid, a boronic acid ester or an alkyl, cycloalkyl or alkenyl trifluoroborate;
- or according to a reaction of Stille type, for example using an alkyl or alkenyl trialkyltin compound;
- or via a reaction of Negishi type, for example using an alkyl or cycloalkyl zincate halide compound.

The compound of formula (V) thus obtained is then converted into a compound of formula (IV) according to an alkylation reaction with a halogenated compound of formula R1Y (VIII), in which R1 is as defined in the present disclosure and Y represents a chlorine, bromine or iodine atom, in the presence of a base such as sodium hydride or potassium *tert*-butoxide, and of a solvent such as dimethylformamide or tetrahydrofuran. The compound (IV) thus obtained is then converted into a compound of formula (II), via a saponification reaction in the presence of a base such as sodium hydroxide or potassium hydroxide.

Scheme 3

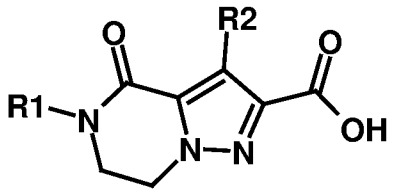


A variant for obtaining the compounds of formula (II) (scheme 3) consists in performing, in a first stage, a halogenation step starting with compounds of formula (VII), in which R represents a methyl or ethyl group, to obtain the compounds of formula (VI), in which R represents a methyl or ethyl group. The compound of formula (VI) thus obtained is then converted into a compound of formula (X) according to an alkylation reaction with a halogenated compound of formula R1Y (VIII), in which R1 is as defined in the present disclosure and Y represents a chlorine, bromine or iodine atom, in the presence of a base such as sodium hydride and of a solvent such as dimethylformamide. The next step consists in performing a coupling reaction catalysed with a transition metal such as palladium(0) on the intermediate of formula (X) as defined above with a halogenated compound of formula R2Y (IX), in which R1 is as defined in the present disclosure and Y represents a chlorine, bromine or iodine atom:

- either via a reaction of Suzuki type, for example using a boronic acid, a boronic acid ester or an alkyl, cycloalkyl or alkenyl trifluoroborate;
- or according to a reaction of Stille type, for example using an alkyl or alkenyl trialkyltin compound;
- or via a reaction of Negishi type, for example using an alkyl or cycloalkyl zincate halide compound.

The compound (IV) thus obtained is then converted into a compound of formula (II), via a saponification reaction in the presence of a base such as sodium hydroxide or potassium hydroxide.

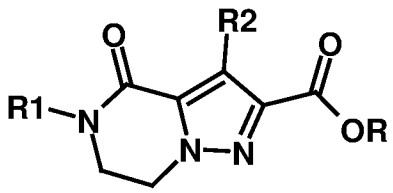
Another subject of the present disclosure relates to the compounds of formula (II):



(II)

in which R1 and R2 are as defined in the present disclosure, with the exception of the compounds of formula (II) in which R2 represents a hydrogen atom.

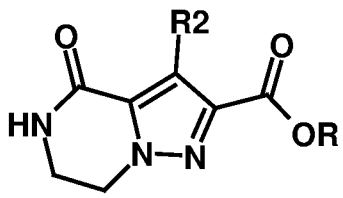
Another subject of the present disclosure relates to the compounds of formula (IV):



(IV)

in which R1 and R2 are as defined in the present disclosure, and R represents a methyl or ethyl group, with the exception of the compounds of formula (IV) in which R2 represents a hydrogen, chlorine or iodine atom or a methyl group.

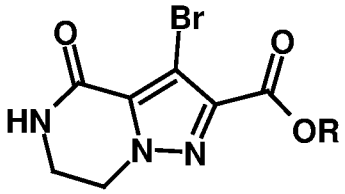
Another subject of the present disclosure relates to the compounds of formula (V):



(V)

in which R2 is as defined in the present disclosure, and R represents a methyl or ethyl group, with the exception of the compounds of formula (V) in which R2 represents a hydrogen, chlorine or iodine atom or a methyl group.

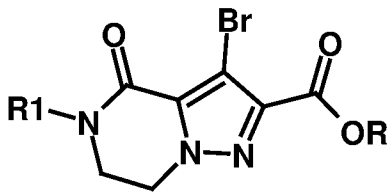
Another subject of the present disclosure relates to the compounds of formula (VI):



(VI)

in which R represents a methyl or ethyl group.

Another subject of the present disclosure relates to the compounds of formula (X):



(X)

in which R1 is as defined in the present disclosure, and R represents a methyl or ethyl group.

The other compounds of formula (III) in which R3 is as defined in the present disclosure, of formula (VII) with R representing a methyl or ethyl group, compounds (VIII) and (IX) and the other reagents are commercially available or described in the literature, or else may be prepared according to methods that are described therein or that are known to those skilled in the art.

The examples that follow illustrate the preparation of a number of compounds of the disclosure. These examples are not limiting and merely illustrate the disclosure. The NMR spectrum and/or the LC-MS analyses confirm the structures and purities of the compounds obtained. The numbers of the compounds exemplified refer to those given in the table hereinafter, which shows the chemical structures and the physical properties of some compounds according to the disclosure.

EXAMPLES

The following abbreviations and molecular formulae are used:

CDI	1,1'-carbonyldiimidazole
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMSO	dimethyl sulfoxide
MHz	MegaHertz
°C	degrees Celsius
DMF	dimethylformamide
h	hour(s)
HCl	hydrochloric acid
LC/MS	liquid chromatography/mass spectrometry
M	molar
MHz	MegaHertz
min	minute(s)
mL	millilitre(s)
Na_2CO_3	sodium hydrogen carbonate
mmol	millimole(s)
N	normal
Pd/C	palladium on charcoal
m.p. (°C)	melting point in degrees Celsius
tBu	*tert*-butyl
THF	tetrahydrofuran

Example 1 (Compound 1, Table 1)

5-(2-Chlorobenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide

1.1 3-Bromo-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester.

0.60 g (2.87 mmol) of 4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester (commercial) were dissolved in 25 mL of acetic acid. 1.3 mL of nitric acid and

0.61 g (3.43 mmol) of N-bromosuccinimide were added. The mixture was placed in a sealed tube and then irradiated at 150°C for 10 minutes. The medium was concentrated to dryness, and water and dichloromethane were then added. After extraction, the residue was purified by chromatography on silica gel, eluting with a 100/0 to 50/50 heptane/ethyl acetate mixture. 0.39 g (48%) of the expected product was obtained in the form of a white powder.

LC-MS: M+ = 288; Tr (min) = 0.51 (method 3)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 1.30 (t, J=7.1 Hz, 3 H); 3.62 (m, 2 H); 4.31 (q, J=7.1 Hz, 2 H); 4.41 (m, 2 H); 8.42 (broad s, 1 H)

1.2 3-Methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester

0.39 g (1.35 mmol) of 3-bromo-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester and 0.56 g of potassium carbonate (4.06 mmol) were dissolved in 8 mL of dioxane. 0.17 g (1.35 mmol) of trimethyl-1,3,5,2,4,6-trioxatriborinane and 0.31 g (0.27 mmol) of tetrakis(triphenylphosphine)palladium were then added. The reactor was then sealed and irradiated at 160°C for 25 minutes with stirring. The reaction mixture was then filtered, and washed with dioxane and then with water. 0.15 g (52%) of the expected product was obtained in the form of a white powder.

LC-MS: M+H = 224; Tr (min) = 0.53 (method 3)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 1.29 (t, J=7.1 Hz, 3 H); 2.44 (s, 3 H); 3.59 (m, 2 H); 4.28 (q, J=7.1 Hz, 2 H); 4.33 (m, 2 H); 8.23 (broad s, 1 H)

1.3 5-(2-Chlorobenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester

0.15 g (0.70 mmol) of 3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester were dissolved in 3 mL of tetrahydrofuran in a reactor with 0.15 g (1.40 mmol) of potassium *tert*-butoxide and 0.43 g (2.10 mmol) of 2-chlorobenzyl bromide. The reactor was then sealed and irradiated at 130°C in a microwave oven for 5 minutes. Saturated aqueous sodium phosphate solution was then added and the product was extracted with dichloromethane. The organic phases were then washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated under

reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 100/0 to 50/50 heptane/ethyl acetate mixture. 0.14 g (60%) of the expected product was obtained in the form of a white solid.

LC-MS: M+H = 348; Tr (min) = 0.96 (method 3)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 1.30 (t, J=7.1 Hz, 3 H); 2.48 (s, 3 H); 3.79 (m, 2 H); 4.29 (q, J=7.1 Hz, 2 H); 4.45 (m, 2 H); 4.75 (s, 2 H); 7.31-7.37 (m, 2 H); 7.40 (m, 1 H); 7.49 (m, 1 H)

1.4 5-(2-Chlorobenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid

0.14 g (0.40 mmol) of 5-(2-chlorobenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester were dissolved in 4 mL of ethanol, and 0.40 mL (2.01 mmol) of 5N sodium hydroxide solution was then added. The medium was stirred at reflux for 30 minutes and then concentrated to dryness. 2N hydrochloric acid solution was added and the product was then extracted with ethyl acetate. The organic phases were then washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure. 0.12 g (99%) of the expected product was obtained in the form of a white powder.

LC-MS: M+H = 320; Tr (min) = 0.74 (method 3)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 2.47 (s, 3 H); 3.78 (m, 2 H); 4.43 (m, 2 H); 4.75 (s, 2 H); 7.31-7.37 (m, 2 H); 7.40 (m, 1 H); 7.49 (m, 1 H); 12.80 (broad s, 1 H)

1.5 5-(2-Chlorobenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide

0.13 g (0.40 mmol) of 5-(2-chlorobenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid was dissolved in 3 mL of dimethylformamide. 0.07 g (0.43 mmol) of 1,1'-carbonyldiimidazole (CDI) was added and the medium was then heated under argon at 60°C for 1 hour. 0.06 g (0.36 mmol) of 2-amino-5-trifluoromethyl-1,3,4-thiadiazole and 0.06 g (0.40 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were then added. The medium was heated at 60°C for 7 hours. The reaction mixture was then concentrated under

vacuum and taken up in a mixture of ethyl acetate and water. After extraction of the aqueous phase with ethyl acetate, the organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 100/0 to 40/60 heptane/ethyl acetate mixture. 0.10 g (63%) of the expected product was obtained in the form of a white powder.

m.p. (°C) = 216-217

LC-MS: M+H = 471; Tr (min) = 1.31 (method 1)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 2.56 (s, 3 H) 3.81 - 3.89 (m, 2 H) 4.50 - 4.58 (m, 2 H) 4.78 (s, 2 H) 7.31 - 7.39 (m, 2 H) 7.41 - 7.54 (m, 2 H) 13.50 (broad s, 1 H)

Example 2 (Compound 32, Table 1)

3-Cyclopropyl-5-(3-methylpyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide

2.1 3-Cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester

1.50 g (5.21 mmol) of 3-bromo-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester (step 1.1, example 1) and 1.54 g (10.42 mmol) of potassium cyclopropyl tetrafluoroboronate were dissolved in 30 mL of a toluene/water mixture (5/1). 2.16 g (15.63 mmol) of potassium carbonate, 0.03 g (0.16 mmol) of palladium acetate and 0.09 g (0.26 mmol) of butylbis(1-adamantyl)phosphine were then added. The medium was refluxed for 2 hours under argon. The mixture was diluted with ethyl acetate and then filtered through Celite. After extraction of the aqueous phase with ethyl acetate, the organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure. 0.81 g (62%) of the expected product was obtained.

LC-MS: M+H = 250; Tr (min) = 0.74 (method 2)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 8.20 (broad s, 1H); 4.30 (m, 4H); 3.60 (m, 2H); 2.50 (m, 1H); 1.30 (m, 3H); 1.10 (m, 2H); 0.80 (m, 2H)

2.2 3-Cyclopropyl-5-(3-methylpyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester

0.80 g (3.21 mmol) of 3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester were dissolved in 32 mL of dimethylformamide, the solution was cooled to -10°C and 0.33 g (8.34 mmol) of sodium hydride were then added slowly. After returning to room temperature and at the end of the evolution of gas, the mixture was cooled to -10°C, and 0.78 g (4.17 mmol) of 3-(chloromethyl)-2-methylpyridine hydrochloride was then added. The mixture was stirred for 15 hours and allowed to return to room temperature. The medium was cooled to 0°C and 4 mL of hydrochloric acid (4N in dioxane) were then added slowly. After stirring for 10 minutes, the medium was concentrated under vacuum and the residue diluted in saturated aqueous sodium carbonate solution, and the product was then extracted with ethyl acetate. The organic phases were then washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 100/0/0 to 98/2/0.2 dichloromethane/methanol/aqueous ammonia mixture. 1.08 g (95%) of the expected product was obtained in the form of a pale pink powder.

LC-MS: M+H = 355; Tr (min) = 3.38 (method 5)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 8.40 (m, 1H); 7.60 (m, 1H); 7.20 (m, 1H); 4.70 (s, 2H); 4.40 (m, 2H); 4.30 (q, 2H); 3.70 (m, 2H); 2.50 (m, 4H); 1.30 (t, 3H); 1.10 (m, 2H); 0.80 (m, 2H)

2.3 3-Cyclopropyl-5-(3-methylpyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid

0.85 g (2.40 mmol) of 3-cyclopropyl-5-(3-methylpyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester were dissolved in 12 mL of an ethanol/water mixture (4/1), and 0.33 g (5.04 mmol) of potassium hydroxide was then added. The medium was stirred at 50°C for 1 hour and then concentrated to dryness. Dioxane was added, followed by slow addition of 3 mL of a 4N solution of hydrogen chloride in dioxane, and the resulting mixture was then evaporated to dryness. 1.16 g (99%) of the

expected product were obtained in the form of a beige-coloured powder, which was used in the following steps without further purification.

2.4 3-Cyclopropyl-5-(3-methylpyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide

0.25 g (0.70 mmol) of 3-cyclopropyl-5-(3-methylpyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid was dissolved in 15 mL of dimethylformamide. 0.13 g (0.84 mmol) of 1,1'-carbonyldiimidazole (CDI) was added and the medium was then heated under argon at 60°C for 1 hour. 0.10 g (0.70 mmol) of 5-(difluoromethyl)-1,3,4-thiadiazol-2-amine and 0.12 mL (0.84 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene were then added. The medium was heated at 60°C for 15 hours. The reaction mixture was then concentrated under vacuum and diluted in ethyl acetate and water. After extraction with ethyl acetate, the organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 97/3/0.3 dichloromethane/methanol/aqueous ammonia mixture. 0.18 g (56%) of the expected product was obtained in the form of a white powder after recrystallization from isopropanol and ethyl acetate.

m.p. (°C) = 230-232

LC-MS: M+H = 460; Tr (min) = 0.92 (method 2)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 0.80 - 0.88 (m, 2H) 1.08 - 1.15 (m, 2H) 2.33 (s, 3H) 2.61 (tt, J=8.82, 5.62 Hz, 1H) 3.84 - 3.92 (m, 2H) 4.44 - 4.52 (m, 2H) 4.83 (s, 2H) 7.19 - 7.26 (m, 1H) 7.34 - 7.65 (m, 2H) 8.34 (dd, J=4.89, 1.13 Hz, 1H) 13.07 (broad s, 1H)

Example 3 (Compound 41, Table 1)

5-[2-(2-Chlorophenyl)-2-hydroxyethyl]-3-ethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide

3.1 4-Oxo-3-vinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester

4.50 g (15.62 mmol) of 3-bromo-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester (example 1, step 1.1) were dissolved in 50 mL of dimethylformamide. 9.91 g (31.24 mmol) of tributyl(vinyl)stannane and 0.91 g (0.78 mmol) of tetrakis(triphenylphosphine)palladium were then added. The mixture was stirred at 110°C for 15 hours under argon. After evaporating to dryness, the medium was diluted with ethyl acetate and saturated aqueous sodium carbonate solution. After extraction of the aqueous phase with ethyl acetate, the organic phases were washed with saturated ammonium chloride solution and then with saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 99/1/0.1 and then 98/2/0.2 isocratic dichloromethane/methanol/aqueous ammonia mixture. 3.20 g (87%) of the expected product were obtained in the form of a white powder.

LC-MS: M+H = 236; Tr (min) = 0.73 (method 1)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 8.40 (bs, 1H), 7.20 (dd, 1H), 6.40 (d, 1H), 5.40 (d, 1H), 4.40 (m, 2H), 4.30 (m, 2H), 3.70 (m, 2H), 1.30 (m, 3H)

3.2 3-Ethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester

1.90 g (8.08 mmol) of 4-oxo-3-vinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester were dissolved in a hydrogenation reactor in 200 mL of ethanol and 20 mL of water. 0.86 g (8.08 mmol) of Pd/C was added and the mixture was subjected to a hydrogen pressure of 5 bar for 3 hours. The medium was then filtered through Celite and then rinsed with ethyl acetate, and the filtrate was concentrated under vacuum. 1.78 g (93%) of a white solid were obtained.

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 8.30 (bs, 1H), 4.30 (m, 4H), 3.60 (m, 2H), 2.95 (m, 2H), 1.25 (t, 3H), 1.05 (t, 3H)

3.3 5-[2-(2-Chlorophenyl)-2-hydroxyethyl]-3-ethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide

0.40 g (1.69 mmol) of 3-ethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester was dissolved in 20 mL of dimethylformamide, and, after cooling

the medium to 0°C, 0.08 g (2.02 mmol) of sodium hydride at 60% in oil was added. The medium was allowed to return to room temperature with stirring, and, after the evolution of gas had ceased, the medium was cooled to -5°C and 0.31 g (2.02 mmol) of 2-(2-chlorophenyl)oxirane was added. The medium was allowed to return slowly to room temperature and was then stirred for 15 hours. The medium was cooled to 0°C, and 2 mL of a hydrogen chloride solution (4N in dioxane) was added slowly. After stirring for 10 minutes, the medium was concentrated under vacuum and the residue was taken up in saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The combined organic phases were washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 99/1/0.1 isocratic dichloromethane/methanol/aqueous ammonia mixture. 0.14 g (21%) of 5-[2-(2-chlorophenyl)-2-hydroxyethyl]-3-ethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester was obtained in the form of a beige-coloured solid, which was used directly in the following step.

0.14 g (0.35 mmol) of 5-[2-(2-chlorophenyl)-2-hydroxyethyl]-3-ethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester was dissolved in 12 mL of an ethanol/water mixture (4/1), and 0.07 g (1.06 mmol) of potassium hydroxide was then added. The medium was stirred at 50°C for 3 hours and then concentrated to dryness. 3 mL of cold aqueous 1N hydrochloric acid solution were added slowly and, after stirring and filtration, 2-(2-chlorophenyl)-2-hydroxyethyl]-3-ethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid was obtained in the form of a white solid, which was used directly in the following step.

0.12 g (0.33 mmol) of 5-[2-(2-chlorophenyl)-2-hydroxyethyl]-3-ethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid was dissolved in 20 mL of dimethylformamide. 0.06 g (0.39 mmol) of 1,1'-carbonyldiimidazole (CDI) was added and the medium was then heated under argon at 60°C for 4 hours. 0.05 g (0.33 mmol) of 5-trifluoromethyl-[1,3,4]thiadiazol-2-ylamine and 0.05 g (0.33 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were then added. The medium was heated at 50°C for 15 hours. The reaction mixture was then concentrated under vacuum and 1N hydrochloric

acid solution was then added. After extraction of the aqueous phase with ethyl acetate, the organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from a minimum amount of ethyl acetate. 0.06 g (38%) of the expected product was obtained in the form of a white solid.

m.p. (°C) = 254-256

LC-MS: M+H = 515; Tr (min) = 1.28 (method 1)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 1.11 (t, J=7.40 Hz, 3H) 3.02 (q, J=7.53 Hz, 2H) 3.61 - 3.72 (m, 2H) 3.78 - 3.99 (m, 2H) 4.39 - 4.52 (m, 2H) 5.26 (dt, J=7.28, 4.64 Hz, 1H) 5.78 (d, J=4.52 Hz, 1H) 7.28 - 7.33 (m, 1H) 7.36 - 7.43 (m, 2H) 7.67 (dd, J=7.78, 1.76 Hz, 1H) 13.43 (br. s., 1H)

Example 4 (Compound 57, Table 1)

5-(2-Chlorobenzyl)-4-oxo-3-vinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide

4.1 5-(2-Chlorobenzyl)-4-oxo-3-vinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester

3.20 g (13.60 mmol) of 4-oxo-3-vinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester (example 3, step 3.1) were dissolved in 80 mL of dimethylformamide, and, after cooling the medium to 0°C, 0.81 g (20.40 mmol) of sodium hydride at 60% in oil was then added. The medium was allowed to return to room temperature with stirring, and, after the evolution of gas had ceased, the medium was cooled to -5°C and 3.35 g (16.32 mmol) of 1-(bromomethyl)-2-chlorobenzene were then added. The medium was allowed to return slowly to room temperature and was then stirred for 3 hours. The medium was cooled to 0°C, and 2 mL of a hydrogen chloride solution (4N in dioxane) were added slowly. The medium was concentrated under vacuum and the residue was taken up in saturated aqueous sodium hydrogen carbonate solution and extracted with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 100/0/0 to 99/1/0.1 isocratic dichloromethane/methanol/aqueous

ammonia mixture. 2.95 g (60%) of the expected product were obtained in the form of a white solid.

LC-MS: M+H = 360; Tr (min) = 1.23 (method 1)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 7.50 (m, 1H); 7.40 (m, 1H); 7.35 (m, 2H); 7.20 (dd, 1H); 6.40 (d, 1H); 5.50 (d, 1H); 4.80 (s, 2H); 4.50 (m, 2H); 4.30 (m, 2H); 3.80 (m, 2H); 1.30 (t, 3H)

4.2 5-(2-Chlorobenzyl)-4-oxo-3-vinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid

2.95 g (8.20 mmol) of 5-(2-chlorobenzyl)-4-oxo-3-vinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester were dissolved in 120 mL of an ethanol/water mixture (4/1), and 1.19 g (18.04 mmol) of potassium hydroxide were then added. The medium was stirred at 50°C for 2 hours and then concentrated to dryness. 3 mL of cold aqueous 1N hydrochloric acid solution were added slowly and, after stirring and filtration, 2.70 g (99%) of the expected product were then obtained in the form of a white solid.

LC-MS: M+H = 332; Tr (min) = 1.0 (method 1)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 7.50 (m, 1H); 7.40 (m, 1H); 7.35 (m, 2H); 7.25 (dd, 1H); 6.40 (d, 1H); 5.40 (d, 1H); 4.75 (s, 2H); 4.45 (m, 2H); 3.80 (m, 2H)

4.3 5-(2-Chlorobenzyl)-4-oxo-3-vinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide

2.70 g (8.14 mmol) of 5-(2-chlorobenzyl)-4-oxo-3-vinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid were dissolved in 50 mL of dimethylformamide. 1.58 g (9.77 mmol) of 1,1'-carbonyldiimidazole (CDI) were added and the mixture was then heated under argon at 60°C until the acid disappeared. 1.23 g (8.14 mmol) of 5-difluoromethyl-[1,3,4]thiadiazol-2-ylamine and 1.36 g (8.95 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were then added. The medium was heated at 50°C for 15 hours. The reaction mixture was then concentrated under vacuum and 1N hydrochloric acid solution was then added. After extraction of the aqueous phase with ethyl acetate, the organic phases were washed with saturated sodium hydrogen carbonate solution and then with sodium chloride solution,

dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from a minimum amount of acetonitrile. 2.85 g (75%) of the expected product were obtained in the form of a white powder.

m.p. (°C) = 200-202

LC-MS: M+H = 465; Tr (min) = 1.29 (method 1)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 3.82 - 3.90 (m, 2H) 4.57 (dd, J=6.78, 5.52 Hz, 2H) 4.81 (s, 2H) 5.51 (dd, J=11.80, 2.26 Hz, 1H) 6.41 (dd, J=17.94, 2.13 Hz, 1H) 7.27 (dd, J=17.94, 11.92 Hz, 1H) 7.33 - 7.67 (m, 5H) 13.26 (br. s., 1H)

Example 5 (Compound 60, Table 1)

5-(2-Chlorobenzyl)-3-hydroxymethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide

5.1 5-(2-Chlorobenzyl)-3-formyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide

0.50 g (1.08 mmol) of 5-(2-chlorobenzyl)-4-oxo-3-vinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide (example 4, step 4.3) was dissolved in a tetrahydrofuran/methanol mixture (1/1). 0.07 g (0.12 mmol) of sodium hydrogen carbonate was added and the medium was then cooled to -78°C and sparged with ozone. After 3 hours at -78°C, the medium was degassed with argon for 2 hours, and 0.39 mL of dimethyl sulfane (5.38 mmol) was then added. The medium was stirred under a stream of argon for 15 hours. The medium was then concentrated under reduced pressure and the residue was taken up in saturated sodium chloride solution and then extracted with ethyl acetate. The organic phases were dried over magnesium sulfate, filtered and concentrated under vacuum. The residue was taken up in ethyl ether and, after filtration, 0.50 g (100%) of product was then isolated in the form of a white solid.

LC-MS: M+H = 467; Tr (min) = 1.07 (method 2)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 13.8 (bs, 1H); 10.4 (s, 1H); 7.50 (m, 3H); 7.40 (m, 2H); 4.80 (s, 2H); 4.60 (m, 2H); 3.90 (m, 2H)

5.2 5-(2-Chlorobenzyl)-3-hydroxymethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide

0.50 g (1.07 mmol) of 5-(2-chlorobenzyl)-3-formyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide was dissolved in methanol, and 0.08 g (2.14 mmol) of sodium tetrahydroborate was then added at 0°C. The medium was allowed to return to room temperature. After 3 hours, the medium was diluted with saturated sodium chloride solution and then extracted with ethyl acetate. The organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate and then filtered and concentrated to dryness. The residue was taken up in a minimum amount of ethyl acetate, and 0.18 g (36%) of a white powder was obtained.

m.p. (°C) = 278-280

LC-MS: M+H = 469; Tr (min) = 1.02-1.06 (method 2)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 3.87 (t, J=6.02 Hz, 2H) 4.57 (t, J=6.02 Hz, 2H) 4.81 (s, 2H) 4.99 (s, 2H) 5.36 - 6.31 (m, 1H) 7.05 - 7.88 (m, 5H) 13.41 (br. s., 1H)

Example 6 (Compound 64, Table 1)

5-(2-Chlorobenzyl)-3-fluoromethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide

0.20 g (0.42 mmol) of 5-(2-chlorobenzyl)-3-hydroxymethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide (example 5, step 5.2) was dissolved in 40 mL of dichloromethane, and 68.76 µL (0.50 mmol) of diethylaminosulfur trifluoride (DAST) were then added at -50°C. The medium was then allowed to return to room temperature. After 2 hours of reaction, the medium was concentrated under reduced pressure and the residue was purified by chromatography on silica gel, eluting with a 99/1/0.1 isocratic dichloromethane/methanol/aqueous ammonia mixture. 0.06 g (32%) of the expected product was obtained in the form of a white powder after recrystallization from acetonitrile.

m.p. (°C) = 240-242

LC-MS: M+H = 471; Tr (min) = 1.21 (method 1)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 3.83 - 3.99 (m, 2H) 4.60 (t, J=6.15 Hz, 2H) 4.81 (s, 2H) 5.72 - 5.96 (m, 2H) 7.23 - 7.78 (m, 5H) 13.44 (br. s., 1H)

Example 7 (Compound 63, Table 1)

5-(2-Chlorobenzyl)-3-dimethylaminomethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide (HCl)

0.20 g (0.43 mmol) of 5-(2-chlorobenzyl)-3-formyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide (example 5, step 5.1) was dissolved in a mixture of 10 mL of methanol and 5 mL of tetrahydrofuran. 428 µL (0.85 mmol) of dimethylamine were added. The medium was allowed to return to room temperature over 10 minutes, 2 drops of glacial acetic acid were then added and, after a further 20 minutes of stirring, 0.10 g (1.71 mmol) of sodium cyanoborohydride was added. After 3 hours at room temperature, the medium was diluted with 20 mL of saturated aqueous sodium hydrogen carbonate solution and then extracted with ethyl acetate. The organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate and then filtered and concentrated to dryness. The residue was purified on preparative silica gel plates, eluting with a 95/5/0.5 dichloromethane/methanol/aqueous ammonia mixture. The residue obtained was dissolved in 20 mL of dioxane, and 0.40 mL of a 4N solution of hydrogen chloride in dioxane was added. After stirring for 1 hour, the medium was concentrated under reduced pressure and the residue was crystallized from ethyl ether. 0.12 g of product was obtained in the form of a white solid.

m.p. (°C) = 248-250

LC-MS: M+H = 496; Tr (min) = 0.76 (method 2)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 2.85 (s, 6H) 3.92 (t, J=6.02 Hz, 2H) 4.63 (t, J=6.15 Hz, 2H) 4.70 (s, 2H) 4.83 (s, 2H) 7.17 - 7.89 (m, 5H) 9.45 (br. s., 1H) 13.63 (br. s., 1H)

Example 8 (Compound 65, Table 1)

5-(2-Chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-fluoromethyl[1,3,4]thiadiazol-2-yl)amide

8.1 5-(2-Chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid

3.50 g (14.04 mmol) of 3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester (example 2, step 2.1) were dissolved in 80 mL of N,N-dimethylformamide (DMF), and, after cooling the medium to 0°C, 1.12 g (28.08 mmol) of sodium hydride were added slowly. After stirring for 2 hours at 0°C, 2.73 mL (21.06 mmol) of 1-(bromomethyl)-2-chlorobenzene were added slowly and the solution was then stirred for 1 hour at 0°C. At the end of the reaction, ethyl acetate and water were added and the organic phases were then washed successively with water and with saturated sodium chloride solution, dried over magnesium sulfate and then filtered and concentrated to dryness. The residue was recrystallized from diisopropyl ether. 4.45 g (85%) of the expected product were obtained in the form of white crystals, which product was used directly in the following step.

3.82 g (10.22 mmol) of 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester were dissolved in 20 mL of methanol and 10 mL of sodium hydroxide (5N). The mixture was refluxed for 1 hour. The mixture was concentrated to dryness, and 5N hydrochloric acid solution and ethyl acetate were then added. The solution was stirred for 1 hour at room temperature. After extraction, the organic phases were washed with water and with saturated sodium chloride solution, dried over magnesium sulfate and then filtered and concentrated to dryness. 3.56 g (99%) of a white powder were obtained.

LC-MS: M+H = 346; Tr (min) = 0.98 (method 2)

8.2 5-(2-Chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-fluoromethyl[1,3,4]thiadiazol-2-yl)amide

0.10 g (0.27 mmol) of 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid and 0.04 g (0.32 mmol) of 5-(fluoromethyl)-1,3,4-thiadiazol-2-amine were dissolved in 5 mL of ethyl acetate. 0.55 mL (0.95 mmol) of 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide was added

slowly. After stirring for 15 hours at room temperature, the medium was heated at 70°C for 1 hour, 13 equivalents of triethylamine were then added and the medium was allowed to return to room temperature. Ethyl acetate and water were added and the organic phases were then washed with 1N hydrochloric acid solution, water and saturated sodium chloride solution, dried over magnesium sulfate and then filtered and concentrated to dryness. The residue was purified by chromatography on silica gel, eluting with a 50/50 to 0/100 isocratic heptane/ethyl acetate mixture. 0.03 g (29%) of the expected product was obtained in the form of a white powder.

m.p. (°C) = 213

LC-MS: M+H = 461; Tr (min) = 1.14 (method 2)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 0.80 - 0.91 (m, 2H) 1.07 - 1.19 (m, 2H) 2.62 (tt, J=8.78, 5.52 Hz, 1H) 3.76 - 3.86 (m, 2H) 4.44 - 4.55 (m, 2H) 4.78 (s, 2H) 5.67 - 5.89 (m, 2H) 7.28 - 7.56 (m, 4H) 12.73 (br. s., 1H)

Example 9 (Compound 68, Table 1)

5-(2-Chlorobenzyl)-3-(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide

9.1 5-(2-Chlorobenzyl)-3-(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester

0.60 g (1.67 mmol) of 5-(2-chlorobenzyl)-4-oxo-3-vinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester (example 4, step 4.1) was dissolved in 50 mL of tetrahydrofuran (THF). 5 mL (2.50 mmol) of 9-borabicyclo[3.3.1]nonane were added slowly with stirring at 0°C and the medium was then stirred at room temperature for 15 hours. At 0°C, 2 mL (2.00 mmol) of 1N sodium hydroxide solution and 340 µL (3.34 mmol) of hydrogen peroxide were added slowly. The medium was stirred for 3 hours at room temperature. The medium was then concentrated under vacuum, and aqueous 1N hydrochloric acid solution was then added. After extraction with ethyl acetate, the organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate and then filtered and concentrated to dryness. The residue was purified by chromatography

on silica gel, eluting with a 98/2/0.2 isocratic dichloromethane/methanol/aqueous ammonia mixture. 0.40 g (64%) of the expected product was obtained in the form of an oil.

LC-MS: M+H = 378; Tr (min) = 0.95 (method 2)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 1.30 (t, 3H); 3.20 (m, 2H); 3.50 (m, 2H); 3.80 (m, 2H); 4.30 (q, 2H); 4.45 (m, 2H); 4.55 (m, 1H); 4.80 (s, 2H); 7.30-7.40 (m, 3H); 7.50 (m, 1H)

9.2 5-(2-Chlorobenzyl)-4-oxo-3-(2-triisopropylsilanyloxyethyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester

0.36 g (0.95 mmol) of 5-(2-chlorobenzyl)-3-(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester and 0.08 g (1.14 mmol) of imidazole were dissolved in 50 mL of dichloromethane. A solution of 0.25 mL (1.14 mmol) of triisopropylsilyl chloride in 2 mL of dichloromethane was added slowly at 0°C. The medium was then stirred at room temperature for 15 hours. The medium was concentrated under vacuum and the residue was taken up in dichloromethane and saturated ammonium chloride solution. After extraction, the organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate and then filtered and concentrated to dryness. The residue was purified by chromatography on silica gel, eluting with a 99/1/0.1 isocratic dichloromethane/methanol/aqueous ammonia mixture. 0.30 g (59%) of the expected product was obtained in the form of a wax, and was used in the following step without further purification.

9.3 5-(2-Chlorobenzyl)-4-oxo-3-(2-triisopropylsilanyloxyethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid

0.30 g (0.56 mmol) of 5-(2-chlorobenzyl)-4-oxo-3-(2-triisopropylsilanyloxyethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid ethyl ester was dissolved in 20 mL of an ethanol/water mixture (5/1), and 0.20 g (3.03 mmol) of potassium hydroxide was then added. The medium was brought to 60°C with stirring. After stirring for 30 minutes, 0.11 g of potassium hydroxide was added and the mixture was stirred for 1 hour at 60°C. The medium was concentrated under reduced pressure and 4 mL of aqueous 1N hydrochloric acid solution were then added. The aqueous phase was extracted with ethyl acetate and the

combined organic phases were then dried over magnesium sulfate, filtered and concentrated to dryness. 0.16 g (56%) of the expected product was isolated in the form of a wax.

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 0.90 (m, 21H); 3.40 (m, 2H); 3.70 (m, 2H); 4.00 (m, 2H); 4.40 (m, 2H); 4.90 (m, 2H); 7.25 (m, 2H); 7.40 (m, 2H)

9.4 5-(2-Chlorobenzyl)-3-(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide

0.16 g (0.31 mmol) of 5-(2-chlorobenzyl)-4-oxo-3-(2-triisopropylsilanyloxyethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid was dissolved in 10 mL of dimethylformamide, and 0.06 g (0.38 mmol) of 1,1'-carbonyldiimidazole (CDI) was then added. The medium was heated to 50°C until conversion of the acid was complete. 0.06 g (0.38 mmol) of 5-(difluoromethyl)-1,3,4-thiadiazol-2-amine and 0.05 g (0.38 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) dissolved in 5 mL of dimethylformamide were then added, and the medium was heated to 50°C. The medium was concentrated under vacuum and ethyl acetate was then added. The organic phase was washed successively with ammonium chloride solution and then with sodium chloride solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure.

10 mL of tetrahydrofuran and 347 µL (0.35 mmol) of tetrabutylammonium fluoride were added and the mixture was then stirred at room temperature for 15 hours. 347 µL (0.35 mmol) of tetrabutylammonium fluoride were then added and the mixture was stirred at 50°C for 2 hours. The medium was concentrated to dryness and 1N hydrochloric acid solution and ethyl acetate were added. After extraction, the organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 98/2/0.2 isocratic dichloromethane/methanol/aqueous ammonia mixture. 0.08 g (52%) of the expected product was obtained in the form of a white solid.

m.p. (°C) = 175-177

LC-MS: M+H = 483; Tr (min) = 1.00 (method 2)

^{1}H-NMR (400 MHz, DMSO) δ (ppm): 0.83 - 0.91 (m, 2 H) 1.11 - 1.16 (m, 2 H) 2.48 (s, 3 H) 2.62 (tt, J=8.85, 5.71 Hz, 1 H) 3.70 - 3.81 (m, 2 H) 4.47 (dd, J=6.78, 5.27 Hz, 2 H) 4.69 (s, 2 H) 7.32 - 7.69 (m, 3 H) 13.07 (br. s., 1 H)

Example 10 (Compound 58, Table 1)

5-(2-Chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]oxadiazol-2-yl)amide

0.10 g (0.29 mmol) of 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (example 8, step 8.1) was dissolved in 2 mL of dimethylformamide. 0.05 g (0.32 mmol) of 1,1'-carbonyldiimidazole (CDI) was added and the mixture was then heated under argon at 60°C until the acid disappeared. 0.05 g (0.32 mmol) of 5-(trifluoromethyl)-1,3,4-oxadiazol-2-amine and 0.05 g (0.32 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were then added. The medium was heated at 50°C for 20 hours. The reaction mixture was then concentrated under vacuum and 1N hydrochloric acid solution was then added. After extraction of the aqueous phase with ethyl acetate, the organic phases were washed with water and then with 2N sodium hydroxide solution and with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 50/50 isocratic heptane/ethyl acetate mixture. 0.05 g (39%) of the expected product was obtained in the form of a white powder.

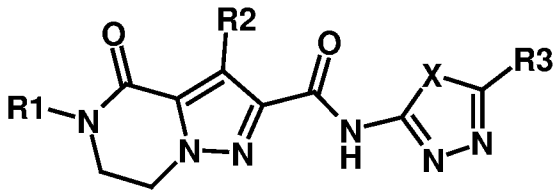
LC-MS: M+H = 481; Tr (min) = 1.17 (method 2)

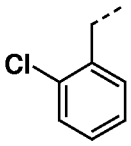
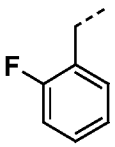
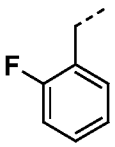
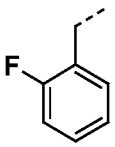
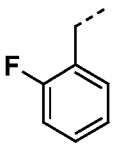
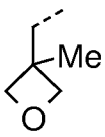
^{1}H-NMR (400 MHz, DMSO) δ (ppm): 0.79 - 0.88 (m, 2 H) 1.11 - 1.20 (m, 2 H) 2.58 - 2.66 (m, 1 H) 3.75 - 3.86 (m, 2 H) 4.42 - 4.53 (m, 2 H) 4.78 (s, 2 H) 7.29 - 7.54 (m, 4 H) 12.40 (br. s., 1 H)

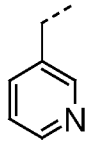
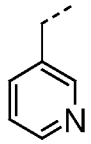
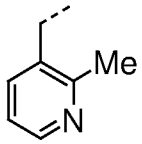
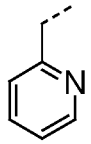
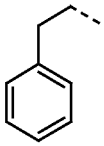
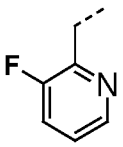
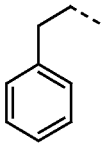
Table 1 which follows illustrates the chemical structures and the physical properties of a number of compounds according to the disclosure. The compounds are in the form of the free base or in the form of a salt (the salt/base ratio is then indicated).

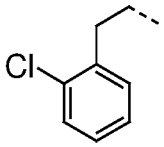
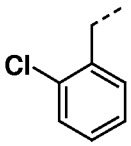
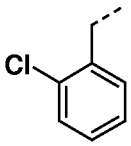
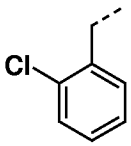
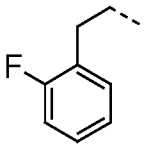
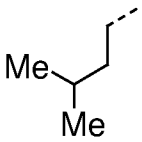
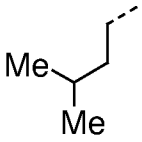
- Me, Et, n-Pr, i-Pr, n-Bu and i-Bu represent, respectively, methyl, ethyl, n-propyl, isopropyl, n-butyl and isobutyl groups,
- the m.p. column indicates the melting point, in °C, of the compound,
- n.d.: not determined

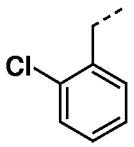
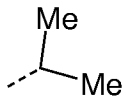
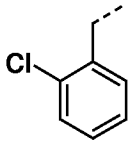
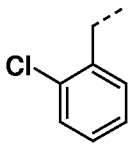
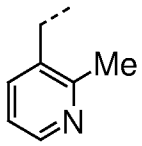
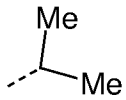
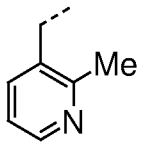
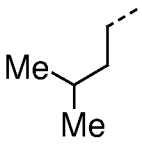
Table 1

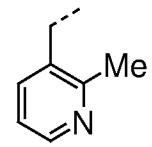
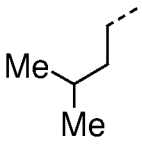
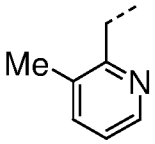
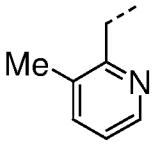
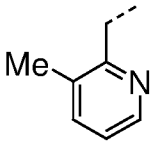
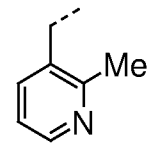
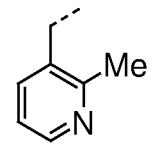


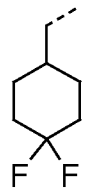
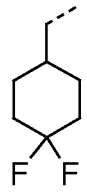
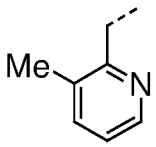
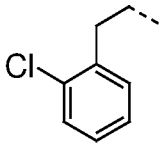
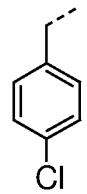
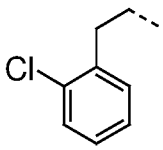
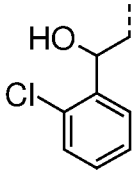
No.	R1	R2	R3	X	m.p. (°C)	salt/base ratio
1.		Me	CF_3	S	216-217	-
2.		Me	CF_3	S	222	-
3.		Me	CHF_2	S	252	-
4.		Me		S	218-220	-
5.		Et	CF_3	S	214	-
6.		Me	CF_3	S	nd	-

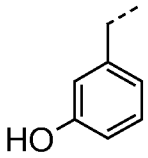
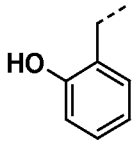
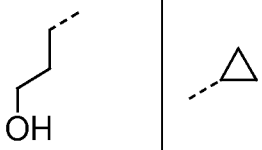
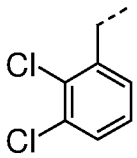
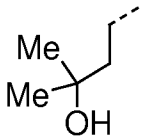
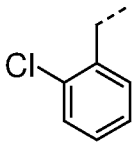
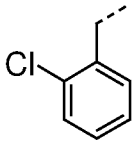
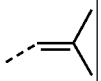
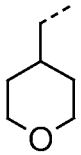
No.	R1	R2	R3	X	m.p. (°C)	salt/base ratio
7.		Me	CF_3	S	nd	-
8.		Me	CHF_2	S	nd	-
9.		Me	CF_3	S	nd	-
10.		Me	CF_3	S nd		-
11.		Br	CF_3	S	nd	-
12.		Br	CF_3	S	nd	-
13.		Me	CF_3	S nd		-

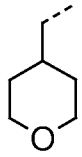
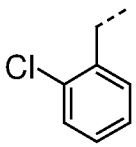
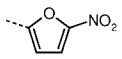
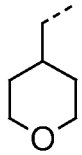
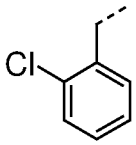
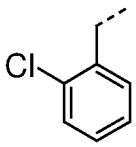
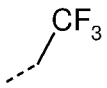
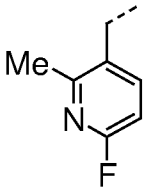
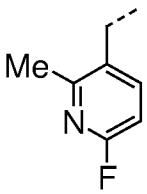
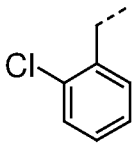
No.	R1	R2	R3	X	m.p. (°C)	salt/base ratio
14.		Me	CF_3	S	nd	-
15.		Et	CHF_2	S	208	-
16.			CHF_2	S	197-199	-
17.		Et		S	amorphous	-
18.		Me	CF_3	S	nd	-
19.		Me	CF_3	S	nd	-
20.		Me		S	nd	-

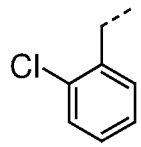
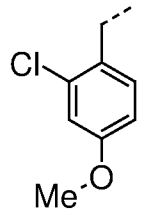
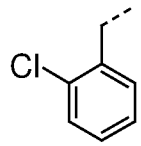
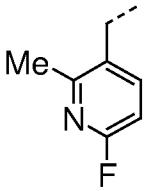
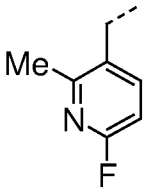
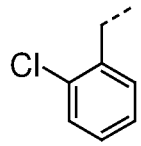
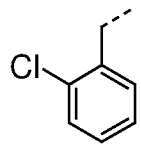
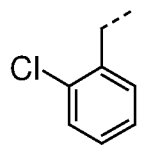
No.	R1	R2	R3	X	m.p. (°C)	salt/base ratio
21.				S	215	-
22.			Me	S	198-200	-
23.			Et	S	206	-
24.			Me	S	228	-
25.				S	222-223	-
26.			Et	S	262-264	1.08[1]
27.			Et	S	174-176	-

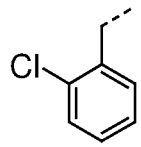
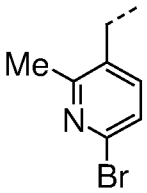
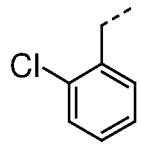
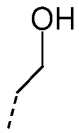
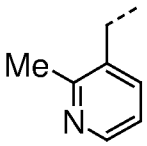
No.	R1	R2	R3	X	m.p. (°C)	salt/base ratio
28.			Me	S	293-295	1.09(1)
29.			Me	S	195-197	-
30.			Me	S	200-202	-
31.			Et	S	202-204	-
32.			CHF_2	S	230-232	-
33.			CHF_2	S	216-217	-
34.		Et	CHF_2	S	230-232	-

No.	R1	R2	R3	X	m.p. (°C)	salt/base ratio
35.			CHF_2	S	201-203	-
36.			Et	S	212-214	-
37.		Et		S	208-210	-
38.			Me	S	246-248	-
39.		Et	CF_3	S	279-281	-
40.			CHF_2	S	194	-
41.		Et	CF_3	S	254-256	-

No.	R1	R2	R3	X	m.p. (°C)	salt/base ratio
42.		Et	CF_3	S	256-258	-
43.		Et	CF_3	S	234-236	-
44.			CF_3	S	178-180	-
45.		Me	CF_3	S	nd	-
46.		Me	CF_3	S	nd	-
47.			H	S	nd	-
48.			CHF_2	S	190-193	-
49.			Me	S	nd	-

No.	R1	R2	R3	X	m.p. (°C)	salt/base ratio
50.			CHF_2	S	nd	-
51.				S	nd	-
52.				S	nd	-
53.			Cl	S	nd	-
54.				S	nd	-
55.			CHF_2	S	220	-
56.			CF_3	S	246	-
57.			CHF_2	S	200-202	-

No.	R1	R2	R3	X	m.p. (°C)	salt/base ratio
58.			CF_3	O	nd	-
59.			CHF_2	S	195	-
60.			CHF_2	S	278-280	-
61.		Et	CHF_2	S	255	-
62.		Et	CF_3	S	264	-
63.			CHF_2	S	248-250	1.07[1]
64.			CHF_2	S	240-242	-
65.			CH_2F	S	213	-

No.	R1	R2	R3	X	m.p. (°C)	salt/base ratio
66.			CH_2OH	S	186	-
67.			CHF_2	S	226	-
68.			CHF_2	S	175-177	-
69.			CH_2F	S	225	-

(1) hydrochloride salt

Table 2 which follows gives the results of the ^1H NMR analyses and the measured masses M+H (and also the method used) for the compounds of Table 1.

The proton nuclear magnetic resonance (^1H NMR) spectra were acquired at 400 MHz (chemical shifts δ in ppm), in dimethyl sulfoxide – d_6 (DMSO). The abbreviations used to characterize the signals are as follows: s = singlet, m = multiplet, d = doublet, t = triplet, q = quartet, sept. : septet, bs = broad singlet.

Examples of LC-MS analysis methods are detailed below. The retention times (Tr) are expressed in minutes.

LC-MS conditions:

Method 1

UPLC/TOF Acquity BEH C18, 2.1X50 mm, 1.7 µm, 1.0 mL/mn, 2 to 100% B (CH_3CN) with 0.035% TFA in 3 mm

Method 2

UPLC/SQD Acquity BEH C18, 2.1X50 mm, 1.7 µm, 1.0 mL/mn, 2 to 100% B (CH_3CN) with 0.1% AF in 3 mn

Method 3

SQD ACQUITY UPLC BEH C18, 1.7 µm, 2.1 X 30 mm, 1 mL/mn, 5 to 100% B (CH_3CN) with 0.1% HCO_2H in 2 mn

Method 4

ZQ XBridge C18, 2.5 µm, 3x50 mm, 900 µL/mn, 5 to 100% B (CH_3CN) with 0.1% HCO_2H in 5 mn

Method 5

HPLC/ZQ Acetate Kromasil C18, 3.5 µm, 2.1x50 mm, 0.8 mL/mn, 0 to 100% B (CH_3CN) in 10 mn

Method 6

Kromasil C18, 3.5 µm, 3x150 mm, 0.6 mL/mn, A: ammonium acetate 20 mM, pH 4.6 + 5% CH_3CN, 10 to 80% B (CH_3CN) in 20 mn

Table 2

No.	^{1}H-NMR 400 MHz (DMSO, δ ppm)	Tr (min)	M+H	Method
1.	2.56 (s, 3 H) 3.81 - 3.89 (m, 2 H) 4.50 - 4.58 (m, 2 H) 4.78 (s, 2 H) 7.31 - 7.39 (m, 2 H) 7.41 - 7.54 (m, 2 H) 13.50 (br. s., 1 H)	1.31	471	1
2.	2.55 (s, 3 H) 3.78 - 3.87 (m, 2 H) 4.50 (dd, J=6.78, 5.27 Hz, 2 H) 4.75 (s, 2 H) 7.15 - 7.29 (m, 2 H) 7.32 - 7.51 (m, 2 H) 13.31 - 13.69 (m, 1 H)	1.27	455	1
3.	2.55 (s, 3 H) 3.79 - 3.86 (m, 2 H) 4.49 (dd, J=6.78, 5.27 Hz, 2 H) 4.76 (s, 2 H) 7.15 - 7.28 (m, 2 H) 7.33 - 7.66 (m, 3 H) 13.12 (br. s., 1 H)	1.15	437	1

No.	^{1}H-NMR 400 MHz (DMSO, δ ppm)	Tr (min)	M+H	Method
4.	0.96 - 1.06 (m, 2 H) 1.11 - 1.22 (m, 2 H) 2.42 (tt, J=8.31, 4.86 Hz, 1 H) 2.54 (s, 3 H) 3.78 - 3.86 (m, 2 H) 4.44 - 4.53 (m, 2 H) 4.76 (s, 2 H) 7.18 - 7.29 (m, 2 H) 7.34 - 7.50 (m, 2 H) 12.32 (br. s., 1 H)	1.10	427	1
5.	0.97 - 1.09 (m, 3 H) 2.96 (q, J=7.28 Hz, 2 H) 3.71 (dd, J=6.90, 5.40 Hz, 2 H) 4.35 - 4.48 (m, 2 H) 4.65 (s, 2 H) 7.06 - 7.16 (m, 2 H) 7.19 - 7.38 (m, 2 H) 13.35 (s, 1 H)	1.35	469	1
6.	1.42 (s, 3 H) 2.69 (s, 3 H) 3.76 (s, 2 H) 3.82 - 3.88 (m, 2 H) 4.40 (d, J=6.02 Hz, 2 H) 4.45 - 4.51 (m, 2 H) 4.66 (d, J=6.27 Hz, 2 H) 10.50 (br. s., 1 H)	1.04	431	1
7.	2.54 - 2.59 (m, 3 H) 3.79 - 3.89 (m, 2 H) 4.46 - 4.54 (m, 2 H) 4.70 - 4.78 (m, 2 H) 7.39 (ddd, J=7.91, 4.77, 0.88 Hz, 1 H) 7.75 - 7.82 (m, 1 H) 8.51 (dd, J=4.77, 1.51 Hz, 1 H) 8.61 (dd, J=2.26, 0.75 Hz, 1 H) 13.48 (br. s., 1 H)	0.85	438	1
8.	2.56 (s, 3 H) 3.79 - 3.87 (m, 2 H) 4.46 - 4.53 (m, 2 H) 4.74 (s, 2 H) 7.33 - 7.64 (m, 2 H) 7.75 - 7.81 (m, 1 H) 8.51 (dd, J=4.77, 1.76 Hz, 1 H) 8.59 - 8.62 (m, 1 H) 13.11 (br. s., 1 H)	0.74	420	1
9.	2.49 - 2.51 (m, 3 H) 2.57 (s, 3 H) 3.74 - 3.83 (m, 2 H) 4.48 - 4.55 (m, 2 H) 4.68 - 4.76 (m, 2 H) 7.22 (dd, J=7.78, 4.77 Hz, 1 H) 7.64 (dd, J=7.53, 1.51 Hz, 1 H) 8.37 (dd, J=4.77, 1.76 Hz, 1 H) 13.50 (br. s., 1 H)	0.86	452	1
10.	2.55 (s, 3 H) 3.87 - 3.96 (m, 2 H) 4.52 (t, J=6.02 Hz, 2 H) 4.81 (s, 2 H) 7.31 (dd, J=7.03, 5.27 Hz, 1 H) 7.41 (d, J=8.03 Hz, 1 H) 7.79 (td, J=7.65, 1.76 Hz, 1 H) 8.50 - 8.57 (m, 1 H) 13.48 (s, 1 H)	0.88	438	1

No.	^{1}H-NMR 400 MHz (DMSO, δ ppm)	Tr (min)	M+H	Method
11.	2.84 - 2.93 (m, 2 H) 3.67 - 3.74 (m, 2 H) 3.76 - 3.85 (m, 2 H) 4.40 - 4.49 (m, 2 H) 7.19 - 7.27 (m, 1 H) 7.27 - 7.37 (m, 4 H) 13.69 (s, 1 H)	1.22	515	1
12.	3.97 (br. s., 2 H) 4.51 (br. s., 2 H) 4.92 (br. s., 2 H) 7.44 (br. s., 1 H) 7.73 (d, J=9.54 Hz, 1 H) 8.40 (br. s., 1 H), NH non visible	3.38	520	5
13.	2.53 (s, 3 H) 2.89 (t, J=7.53 Hz, 2 H) 3.64 - 3.84 (m, 4 H) 4.34 - 4.45 (m, 2 H) 7.17 - 7.41 (m, 5 H) 13.46 (br. s., 1 H)	1.29	451	1
14.	2.54 (s, 3 H) 3.02 (t, J=7.40 Hz, 2 H) 3.67 - 3.87 (m, 4 H) 4.37 - 4.46 (m, 2 H) 7.23 - 7.35 (m, 2 H) 7.38 - 7.50 (m, 2 H) 13.42 - 13.59 (m, 1 H)	1.35	485	1
15.	1.16 (t, J=7.28 Hz, 3 H) 3.07 (q, J=7.28 Hz, 2 H) 3.84 (dd, J=6.90, 5.40 Hz, 2 H) 4.48 - 4.59 (m, 2 H) 4.79 (s, 2 H) 7.30 - 7.66 (m, 5 H) 13.13 (br. s., 1 H)	4.52	467	5
16.	0.82 - 0.91 (m, 2 H) 1.10 - 1.18 (m, 2 H) 2.58 - 2.71 (m, 1 H) 3.74 - 3.85 (m, 2 H) 4.46 - 4.55 (m, 2 H) 4.78 (s, 2 H) 7.32 - 7.65 (m, 5 H) 13.08 (br. s., 1 H)	1.29	479	2
17.	0.96 - 1.02 (m, 2 H) 1.10 - 1.19 (m, 5 H) 2.40 (tt, J=8.28, 4.89 Hz, 1 H) 3.05 (q, J=7.19 Hz, 2 H) 3.79 - 3.85 (m, 2 H) 4.51 (dd, J=6.78, 5.27 Hz, 2 H) 4.78 (s, 2 H) 7.32 - 7.38 (m, 2 H) 7.40 - 7.45 (m, 1 H) 7.47 - 7.53 (m, 1 H) 12.32 (br. s., 1 H)	4.42	457	5
18.	2.50 (br. s., 3 H) 2.94 (t, J=6.65 Hz, 2 H) 3.65 - 3.88 (m, 4 H) 4.42 (t, J=5.65 Hz, 2 H) 7.10 - 7.22 (m, 2 H) 7.38 (t, J=7.78 Hz, 2 H) 13.44 (br. s., 1 H)	4.35	469	5
19.	0.93 (d, J=6.53 Hz, 6 H) 1.42 - 1.50 (m, 2 H) 1.53 - 1.64 (m, 1 H) 2.53 (s, 3 H) 3.44 - 3.54 (m, 2 H) 3.76 - 3.86 (m, 2 H) 4.42 - 4.51 (m, 2 H) 13.45 (br. s., 1 H)	1.31	417	2

No.	^{1}H-NMR 400 MHz (DMSO, δ ppm)	Tr (min)	M+H	Method
20.	0.92 (d, J=6.53 Hz, 6 H) 0.96 - 1.03 (m, 2 H) 1.10 - 1.19 (m, 2 H) 1.39 - 1.50 (m, 2 H) 1.51 - 1.65 (m, 1 H) 2.40 (tt, J=8.31, 4.99 Hz, 1 H) 2.50 (d, J=1.76 Hz, 3 H) 3.43 - 3.54 (m, 2 H) 3.75 - 3.83 (m, 2 H) 4.38 - 4.47 (m, 2 H) 12.26 (br. s., 1 H)	4.05	389	5
21.	0.80 - 0.87 (m, 2 H) 1.08 - 1.14 (m, 2 H) 1.34 - 1.40 (m, 6 H) 2.57 - 2.67 (m, 1 H) 3.31 - 3.41 (m, 1 H) 3.77 - 3.83 (m, 2 H) 4.45 - 4.51 (m, 2 H) 4.78 (s, 2 H) 7.32 - 7.38 (m, 2 H) 7.39 - 7.44 (m, 1 H) 7.47 - 7.52 (m, 1 H) 12.33 (br. s., 1 H)	1.30	471	2
22.	0.81 - 0.88 (m, 2 H) 1.08 - 1.14 (m, 2 H) 2.57 - 2.65 (m, 4 H) 3.77 - 3.82 (m, 2 H) 4.48 (dd, J=6.90, 5.40 Hz, 2 H) 4.78 (s, 2 H) 7.32 - 7.38 (m, 2 H) 7.39 - 7.44 (m, 1 H) 7.47 - 7.52 (m, 1 H) 12.33 (br. s., 1 H)	1.12	443	2
23.	0.81 - 0.87 (m, 2 H) 1.08 - 1.14 (m, 2 H) 1.32 (t, J=7.53 Hz, 3 H) 2.61 (tt, J=8.78, 5.65 Hz, 1 H) 3.01 (q, J=7.53 Hz, 2 H) 3.77 - 3.82 (m, 2 H) 4.45 - 4.51 (m, 2 H) 4.78 (s, 2 H) 7.32 - 7.38 (m, 2 H) 7.39 - 7.44 (m, 1 H) 7.47 - 7.52 (m, 1 H) 12.34 (br. s., 1 H)	1.22	457	2
24.	0.24 - 0.33 (m, 2 H) 0.43 - 0.53 (m, 2 H) 0.78 - 0.87 (m, 2 H) 1.00 - 1.15 (m, 3 H) 2.57 - 2.70 (m, 4 H) 3.34 - 3.42 (m, 2 H) 3.82 - 3.90 (m, 2 H) 4.38 - 4.46 (m, 2 H) 12.28 (br. s., 1 H)	0.99	373	1
25.	0.83 - 0.90 (m, 2 H) 1.08 - 1.18 (m, 2 H) 1.34 - 1.44 (m, 6 H) 2.51 - 2.54 (m, 3 H) 2.58 - 2.72 (m, 1 H) 3.36 - 3.45 (m, 1 H) 3.70 - 3.81 (m, 2 H) 4.43 - 4.51 (m, 2 H) 4.71 - 4.78 (m, 2 H) 7.23 (dd, J=7.65, 4.89 Hz, 1 H) 7.63 (dd, J=7.53, 1.51 Hz, 1 H) 8.39 (dd, J=4.77, 1.76 Hz, 1 H) 12.34 (br. s., 1 H)	0.85	452	1

No.	^{1}H-NMR 400 MHz (DMSO, δ ppm)	Tr (min)	M+H	Method
26.	0.81 - 0.92 (m, 2 H) 1.08 - 1.18 (m, 2 H) 1.28 - 1.41 (m, 3 H) 2.61 (tt, J=8.78, 5.65 Hz, 1 H) 2.76 - 2.83 (m, 3 H) 2.99 - 3.10 (m, 2 H) 3.82 - 3.92 (m, 2 H) 4.53 (dd, J=7.03, 5.27 Hz, 2 H) 4.86 (s, 2 H) 7.86 (dd, J=7.78, 5.77 Hz, 1 H) 8.43 (d, J=7.53 Hz, 1 H) 8.71 (dd, J=5.77, 1.25 Hz, 1 H) 12.36 (br. s., 1 H)	0.78	438	1
27.	0.79 - 0.86 (m, 2 H) 0.92 (d, J=6.78 Hz, 6 H) 1.06 - 1.13 (m, 2 H) 1.27 - 1.37 (m, 3 H) 1.40 - 1.50 (m, 2 H) 1.51 - 1.64 (m, 1 H) 2.60 (tt, J=8.88, 5.55 Hz, 1 H) 3.01 (q, J=7.70 Hz, 2 H) 3.44 - 3.54 (m, 2 H) 3.73 - 3.81 (m, 2 H) 4.37 - 4.45 (m, 2 H) 12.27 (br. s., 1 H)	1.23	403	1
28.	0.78 - 0.93 (m, 2 H) 1.11 (d, J=3.26 Hz, 2 H) 2.56 - 2.69 (m, 4 H) 2.76 (s, 3 H) 3.84 (t, J=5.65 Hz, 2 H) 4.51 (t, J=5.77 Hz, 2 H) 4.84 (s, 2 H) 7.79 (t, J=6.65 Hz, 1 H) 8.36 (d, J=7.53 Hz, 1 H) 8.66 (d, J=5.52 Hz, 1 H) 12.33 (br. s., 1 H)	1.81	424	1
29.	0.79 - 0.85 (m, 1 H) 0.92 (d, J=6.53 Hz, 6 H) 1.07 - 1.12 (m, 2 H) 1.41 - 1.49 (m, 2 H) 1.50 - 1.65 (m, 1 H) 2.55 - 2.66 (m, 4 H) 3.49 (d, J=15.06 Hz, 2 H) 3.71 - 3.81 (m, 2 H) 4.34 - 4.46 (m, 2 H) 12.27 (br. s., 1 H)	1.11	389	2
30.	0.79 - 0.85 (m, 2 H) 1.05 - 1.12 (m, 2 H) 2.33 (s, 3 H) 2.54 - 2.69 (m, 4 H) 3.83 - 3.90 (m, 2 H) 4.42 - 4.50 (m, 2 H) 4.83 (s, 2 H) 7.22 (dd, J=7.53, 4.77 Hz, 1 H) 7.60 (dd, J=7.65, 0.88 Hz, 1 H) 8.34 (dd, J=4.89, 1.13 Hz, 1 H) 12.30 (br. s., 1 H)	0.75	424	2
31.	0.76 - 0.86 (m, 2 H) 1.04 - 1.14 (m, 2 H) 1.26 - 1.38 (m, 3 H) 2.33 (s, 3 H) 2.53 - 2.65 (m, 1 H) 3.01 (q, J=7.45 Hz, 2 H) 3.86 (dd, J=6.78, 5.27 Hz, 2 H) 4.40 - 4.52 (m, 2 H) 4.83 (s, 2 H) 7.22 (dd, J=7.53, 4.77 Hz, 1 H) 7.57 - 7.64 (m, 1 H) 8.34 (dd, J=4.77, 1.00 Hz, 1 H) 12.29 (br. s., 1 H)	0.84	438	2

No.	^{1}H-NMR 400 MHz (DMSO, δ ppm)	Tr (min)	M+H	Method
32.	0.80 - 0.88 (m, 2 H) 1.08 - 1.15 (m, 2 H) 2.33 (s, 3 H) 2.61 (tt, J=8.82, 5.62 Hz, 1 H) 3.84 - 3.92 (m, 2 H) 4.44 - 4.52 (m, 2 H) 4.83 (s, 2 H) 7.19 - 7.26 (m, 1 H) 7.34 - 7.65 (m, 2 H) 8.34 (dd, J=4.89, 1.13 Hz, 1 H) 13.07 (br. s., 1 H)	0.92	460	2
33.	0.83 - 0.92 (m, 2 H) 1.11 - 1.19 (m, 2 H) 2.50 (s, 3 H) 2.59 - 2.68 (m, 1 H) 3.72 - 3.80 (m, 2 H) 4.43 - 4.53 (m, 2 H) 4.73 (s, 2 H) 7.22 (dd, J=7.65, 4.89 Hz, 1 H) 7.35 - 7.67 (m, 2 H) 8.37 (dd, J=4.89, 1.63 Hz, 1 H) 13.08 (br. s., 1 H)	0.79	460	2
34.	1.16 (t, J=7.40 Hz, 3 H) 2.50 (s, 3 H) 3.08 (q, J=7.36 Hz, 2 H) 3.78 (dd, J=6.90, 5.40 Hz, 2 H) 4.52 (dd, J=6.78, 5.27 Hz, 2 H) 4.74 (s, 2 H) 7.22 (dd, J=7.65, 4.89 Hz, 1 H) 7.35 - 7.66 (m, 2 H) 8.37 (dd, J=4.89, 1.63 Hz, 1 H) 13.13 (br. s., 1 H)	0.79	448	1
35.	0.79 - 0.89 (m, 2 H) 1.08 - 1.17 (m, 2 H) 1.18 - 1.32 (m, 2 H) 1.68 - 1.90 (m, 5 H) 1.95 - 2.11 (m, 2 H) 2.62 (tt, J=8.85, 5.58 Hz, 1 H) 3.39 (d, J=7.28 Hz, 2 H) 3.80 (dd, J=6.78, 5.27 Hz, 2 H) 4.45 (dd, J=7.15, 4.64 Hz, 2 H) 7.32 - 7.66 (m, 1 H) 13.04 (br. s., 1 H)	1.24	487	2
36.	0.78 - 0.86 (m, 2 H) 1.06 - 1.14 (m, 2 H) 1.16 - 1.36 (m, 5 H) 1.67 - 1.92 (m, 5 H) 1.95 - 2.09 (m, 2 H) 2.60 (tt, J=8.82, 5.62 Hz, 1 H) 3.01 (q, J=7.53 Hz, 2 H) 3.39 (d, J=7.28 Hz, 2 H) 3.75 - 3.84 (m, 2 H) 4.37 - 4.47 (m, 2 H) 12.29 (br. s., 1 H)	1.17	465	2
37.	ppm 0.96 - 1.02 (m, 2 H) 1.09 - 1.18 (m, 5 H) 2.33 (s, 3 H) 2.40 (tt, J=8.34, 4.83 Hz, 1 H) 3.02 (q, J=7.28 Hz, 2 H) 3.86 - 3.93 (m, 2 H) 4.45 - 4.53 (m, 2 H) 4.81 - 4.86 (m, 2 H) 7.22 (dd, J=7.53, 4.77 Hz, 1 H) 7.58 - 7.63 (m, 1 H) 8.30 - 8.35 (m, 1 H) 12.30 (br. s., 1 H)	0.81	438	1

No.	^{1}H-NMR 400 MHz (DMSO, δ ppm)	Tr (min)	M+H	Method
38.	0.76 - 0.84 (m, 2 H) 1.01 - 1.09 (m, 2 H) 2.53 - 2.65 (m, 4 H) 3.01 (t, J=7.15 Hz, 2 H) 3.68 - 3.78 (m, 4 H) 4.31 - 4.39 (m, 2 H) 7.23 - 7.34 (m, 2 H) 7.37 - 7.47 (m, 2 H) 12.23 (s, 1 H)	1.15	457	2
39.	1.12 - 1.21 (m, 3 H) 3.09 (q, J=7.53 Hz, 2 H) 3.71 (dd, J=6.78, 5.52 Hz, 2 H) 4.41 - 4.48 (m, 2 H) 4.59 (s, 2 H) 6.71 - 6.79 (m, 2 H) 7.12 - 7.22 (m, 2 H) 9.36 (s, 1 H) 13.46 (br. s., 1 H)	1.14	467	2
40.	0.79 - 0.87 (m, 2 H) 1.05 - 1.11 (m, 2 H) 2.53 - 2.62 (m, 1 H) 3.02 (t, J=7.15 Hz, 2 H) 3.74 (dt, J=7.34, 3.73 Hz, 4 H) 4.36 - 4.41 (m, 2 H) 7.24 - 7.33 (m, 2 H) 7.35 - 7.65 (m, 3 H) 13.02 (br. s., 1 H)	1.32	493	1
41.	1.11 (t, J=7.40 Hz, 3 H) 3.02 (q, J=7.53 Hz, 2 H) 3.61 - 3.72 (m, 2 H) 3.78 - 3.99 (m, 2 H) 4.39 - 4.52 (m, 2 H) 5.26 (dt, J=7.28, 4.64 Hz, 1 H) 5.78 (d, J=4.52 Hz, 1 H) 7.28 - 7.33 (m, 1 H) 7.36 - 7.43 (m, 2 H) 7.67 (dd, J=7.78, 1.76 Hz, 1 H) 13.43 (br. s., 1 H)	1.28	515	1
42.	1.17 (t, J=7.28 Hz, 3 H) 3.09 (q, J=7.53 Hz, 2 H) 3.75 (dd, J=6.65, 5.40 Hz, 2 H) 4.47 (dd, J=6.90, 5.40 Hz, 2 H) 4.63 (s, 2 H) 6.68 (dt, J=8.03, 1.25 Hz, 1 H) 6.72 - 6.81 (m, 2 H) 7.15 (t, J=7.78 Hz, 1 H) 9.39 (s, 1 H) 13.47 (br. s., 1 H)	1.16	467	2
43.	1.13 - 1.19 (m, 3 H) 3.08 (q, J=7.28 Hz, 2 H) 3.77 - 3.83 (m, 2 H) 4.45 - 4.53 (m, 2 H) 4.62 - 4.68 (m, 2 H) 6.79 (td, J=7.47, 1.13 Hz, 1 H) 6.86 (dd, J=8.03, 1.00 Hz, 1 H) 7.12 (td, J=7.72, 1.63 Hz, 1 H) 7.19 (dd, J=7.53, 1.51 Hz, 1 H) 9.63 (s, 1 H) 13.47 (br. s., 1 H)	1.22	467	2
44.	0.81 - 0.89 (m, 2 H) 1.09 - 1.18 (m, 2 H) 1.65 - 1.78 (m, 2 H) 2.62 (tt, J=8.82, 5.62 Hz, 1 H) 3.42 - 3.59 (m,	0.97	431	2

No.	^{1}H-NMR 400 MHz (DMSO, δ ppm)	Tr (min)	M+H	Method
	4 H) 3.75 - 3.85 (m, 2 H) 4.39 - 4.52 (m, 3 H) 13.37 (br. s., 1 H)			
45.	2.70 (s, 3H) 3.76 (m, 2H) 4.41 (m, 2H) 4.88 (s, 2H) 6.92 (d, 1H) 6.97 (d, 1H) 7.18 (t, 1H)	17.03	487	6
46.	1.33 (s, 6H) 1.83 (t, 2H) 2.70 (s, 3H) 3.74 (t, 2H) 3.86 (t, 2H) 4.45 (t, 2H) 10.40 (sl, 1H)	13.83	433	6
47.	0.81 - 0.89 (m, 2 H) 1.10 - 1.15 (m, 2 H) 2.63 (tt, J=8.82, 5.62 Hz, 1 H) 3.78 - 3.84 (m, 2 H) 4.46 - 4.52 (m, 2 H) 4.78 (s, 2 H) 7.32 - 7.39 (m, 2 H) 7.39 - 7.44 (m, 1 H) 7.47 - 7.53 (m, 1 H) 9.21 (s, 1 H) 12.53 (br. s., 1 H)	1.07	429	2
48.	1.48 (s, 3 H) 1.84 (s, 3 H) 3.87 (t, J=6.02 Hz, 2 H) 4.56 (t, J=6.02 Hz, 2 H) 4.78 (s, 2 H) 6.33 (s, 1 H) 7.29 - 7.67 (m, 5 H) 13.17 (br. s., 1 H)	1.23	493	2
49.	0.78 - 0.87 (m, 2 H) 1.06 - 1.14 (m, 2 H) 1.22 (qd, J=12.17, 4.39 Hz, 2 H) 1.49 - 1.66 (m, 2 H) 1.92 (ddt, J=11.17, 7.53, 3.70, 3.70 Hz, 1 H) 2.54 - 2.66 (m, 4 H) 3.19 - 3.29 (m, 2 H) 3.37 (d, J=7.28 Hz, 2 H) 3.72 - 3.92 (m, 4 H) 4.36 - 4.47 (m, 2 H) 12.27 (br. s., 1 H)	0.97	417	2
50.	0.81 - 0.88 (m, 2 H) 1.10 - 1.15 (m, 2 H) 1.16 - 1.30 (m, 2 H) 1.53 - 1.62 (m, 2 H) 1.86 - 1.99 (m, 1 H) 2.57 - 2.65 (m, 1 H) 3.23 - 3.29 (m, 2 H) 3.37 (d, J=7.28 Hz, 2 H) 3.72 - 3.95 (m, 4 H) 4.37 - 4.52 (m, 2 H) 7.26 - 7.75 (m, 1 H) 13.03 (br. s., 1 H)	0.81	453	2
51.	0.84 - 0.91 (m, 2 H) 1.13 - 1.18 (m, 2 H) 2.59 - 2.67 (m, 1 H) 3.78 - 3.85 (m, 2 H) 4.48 - 4.54 (m, 2 H) 4.79 (s, 2 H) 7.32 - 7.39 (m, 2 H) 7.40 - 7.46 (m, 1 H) 7.47 - 7.54 (m, 1 H) 7.61 (d, J=3.76 Hz, 1 H) 7.90 (d, J=4.02 Hz, 1 H) 13.14 (br. s., 1 H)	4.67	540	5

No.	^{1}H-NMR 400 MHz (DMSO, δ ppm)	Tr (min)	M+H	Method
52.	0.77 - 0.86 (m, 2 H) 0.95 - 1.02 (m, 2 H) 1.06 - 1.29 (m, 6 H) 1.57 (d, J=11.29 Hz, 2 H) 1.92 (ddd, J=11.23, 7.47, 3.89 Hz, 1 H) 2.36 - 2.45 (m, 1 H) 2.60 (tt, J=8.82, 5.62 Hz, 1 H) 3.26 (t, J=10.92 Hz, 2 H) 3.36 (d, J=7.28 Hz, 2 H) 3.74 - 3.91 (m, 4 H) 4.34 - 4.47 (m, 2 H) 12.35 (br. s., 1 H)	0.96	443	2
53.	0.82 - 0.89 (m, 2 H) 1.10 - 1.17 (m, 2 H) 2.61 (tt, J=8.82, 5.62 Hz, 1 H) 3.77 - 3.84 (m, 2 H) 4.45 - 4.54 (m, 2 H) 4.78 (s, 2 H) 7.31 - 7.39 (m, 2 H) 7.39 - 7.45 (m, 1 H) 7.47 - 7.54 (m, 1 H) 13.02 (br. s., 1 H)	1.27	463	2
54.	0.80 - 0.89 (m, 2 H) 1.09 - 1.16 (m, 2 H) 2.58 - 2.67 (m, 1 H) 3.76 - 3.84 (m, 2 H) 4.29 (q, J=11.04 Hz, 2 H) 4.48 (t, J=6.02 Hz, 2 H) 4.78 (s, 2 H) 7.31 - 7.45 (m, 3 H) 7.47 - 7.53 (m, 1 H) 12.68 (br. s., 1 H)	1.27	511	2
55.	0.80 - 0.90 (m, 2 H) 1.10 - 1.20 (m, 2 H) 2.45 (s, 3 H) 2.59 - 2.66 (m, 1 H) 3.64 - 3.79 (m, 2 H) 4.41 - 4.52 (m, 2 H) 4.72 (s, 2 H) 6.97 (dd, J=8.28, 3.01 Hz, 1 H) 7.32 - 7.66 (m, 1 H) 7.84 (t, J=8.28 Hz, 1 H) 13.07 (br. s., 1 H)	1.1	478	2
56.	0.82 - 0.94 (m, 2 H) 1.10 - 1.22 (m, 2 H) 2.42 - 2.47 (m, 3 H) 2.58 - 2.66 (m, 1 H) 3.68 - 3.83 (m, 2 H) 4.40 - 4.55 (m, 2 H) 4.65 - 4.78 (m, 2 H) 6.97 (dd, J=8.28, 3.01 Hz, 1 H) 7.84 (t, J=8.28 Hz, 1 H) 13.42 (br. s., 1 H)	1.22	496	2
57.	3.82 - 3.90 (m, 2 H) 4.57 (dd, J=6.78, 5.52 Hz, 2 H) 4.81 (s, 2 H) 5.51 (dd, J=11.80, 2.26 Hz, 1 H) 6.41 (dd, J=17.94, 2.13 Hz, 1 H) 7.27 (dd, J=17.94, 11.92 Hz, 1 H) 7.33 - 7.67 (m, 5 H) 13.26 (br. s., 1 H)	1.29	465	1

No.	^{1}H-NMR 400 MHz (DMSO, δ ppm)	Tr (min)	M+H	Method
58.	0.79 - 0.88 (m, 2 H) 1.11 - 1.20 (m, 2 H) 2.58 - 2.66 (m, 1 H) 3.75 - 3.86 (m, 2 H) 4.42 - 4.53 (m, 2 H) 4.78 (s, 2 H) 7.29 - 7.54 (m, 4 H) 12.40 (br. s., 1 H)	1.17	481	2
59.	0.83 - 0.93 (m, 2 H) 1.10 - 1.19 (m, 2 H) 2.63 (tt, J=8.85, 5.58 Hz, 1 H) 3.69 - 3.82 (m, 5 H) 4.41 - 4.49 (m, 2 H) 4.72 (s, 2 H) 6.93 (dd, J=8.53, 2.76 Hz, 1 H) 7.09 (d, J=2.51 Hz, 1 H) 7.27 - 7.69 (m, 2 H) 13.06 (br. s., 1 H)	1.34	509	1
60.	3.87 (t, J=6.02 Hz, 2 H) 4.57 (t, J=6.02 Hz, 2 H) 4.81 (s, 2 H) 4.99 (s, 2 H) 5.36 - 6.31 (m, 1 H) 7.05 - 7.88 (m, 5 H) 13.41 (br. s., 1 H)	1.02-1.06	469	2
61.	1.16 (t, J=7.40 Hz, 3 H) 2.46 (s, 3 H) 3.08 (q, J=7.28 Hz, 2 H) 3.72 - 3.83 (m, 2 H) 4.44 - 4.56 (m, 2 H) 4.73 (s, 2 H) 6.97 (dd, J=8.28, 2.76 Hz, 1 H) 7.30 - 7.69 (m, 1 H) 7.86 (t, J=8.16 Hz, 1 H) 13.12 (br. s., 1 H)	1.11	466	2
62.	1.10 - 1.20 (m, 3 H) 2.46 (s, 3 H) 3.08 (q, J=7.28 Hz, 2 H) 3.73 - 3.84 (m, 2 H) 4.45 - 4.56 (m, 2 H) 4.69 - 4.77 (m, 2 H) 6.97 (dd, J=8.41, 2.89 Hz, 1 H) 7.86 (t, J=8.16 Hz, 1 H) 13.48 (br. s., 1 H)	1.23	484	2
63.	2.85 (s, 6 H) 3.92 (t, J=6.02 Hz, 2 H) 4.63 (t, J=6.15 Hz, 2 H) 4.70 (s, 2 H) 4.83 (s, 2 H) 7.17 - 7.89 (m, 5 H) 9.45 (br. s., 1 H) 13.63 (br. s., 1 H)	0.76	496	2
64.	3.83 - 3.99 (m, 2 H) 4.60 (t, J=6.15 Hz, 2 H) 4.81 (s, 2 H) 5.72 - 5.96 (m, 2 H) 7.23 - 7.78 (m, 5 H) 13.44 (br. s., 1 H)	1.21	471	1
65.	0.80 - 0.91 (m, 2 H) 1.07 - 1.19 (m, 2 H) 2.62 (tt, J=8.78, 5.52 Hz, 1 H) 3.76 - 3.86 (m, 2 H) 4.44 - 4.55 (m, 2 H) 4.78 (s, 2 H) 5.67 - 5.89 (m, 2 H) 7.28 - 7.56 (m, 4 H) 12.73 (br. s., 1 H)	1.14	461	2

No.	^{1}H-NMR 400 MHz (DMSO, δ ppm)	Tr (min)	M+H	Method
66.	0.80 - 0.90 (m, 2 H) 1.08 - 1.16 (m, 2 H) 2.61 (tt, J=8.85, 5.58 Hz, 1 H) 3.75 - 3.85 (m, 2 H) 4.44 - 4.53 (m, 2 H) 4.76 - 4.83 (m, 4 H) 6.01 (t, J=5.90 Hz, 1 H) 7.31 - 7.55 (m, 4 H) 8.55 - 10.02 (m, 1 H)	1.03	459	2
67.	0.82 - 0.90 (m, 1 H) 1.08 - 1.18 (m, 2 H) 2.49 - 2.51 (m, 3 H) 2.57 - 2.66 (m, 1 H) 3.68 - 3.81 (m, 2 H) 4.41 - 4.55 (m, 2 H) 4.73 (s, 2 H) 5.71 - 5.88 (m, 2 H) 7.02 (s, 1 H) 7.22 (dd, J=7.65, 4.89 Hz, 1 H) 7.62 (d, J=6.53 Hz, 1 H) 8.37 (dd, J=4.64, 1.38 Hz, 1 H) 12.68 (br. s., 1 H)	1.18	538	2
68.	0.83 - 0.91 (m, 2 H) 1.11 - 1.16 (m, 2 H) 2.48 (s, 3 H) 2.62 (tt, J=8.85, 5.71 Hz, 1 H) 3.70 - 3.81 (m, 2 H) 4.47 (dd, J=6.78, 5.27 Hz, 2 H) 4.69 (s, 2 H) 7.32 - 7.69 (m, 3 H) 13.07 (br. s., 1 H)	1.00	483	2
69.	3.20 - 3.28 (m, 2 H) 3.60 (t, J=7.03 Hz, 2 H) 3.77 - 3.90 (m, 2 H) 4.48 - 4.61 (m, 2 H) 4.69 - 5.10 (m, 3 H) 7.29 - 7.69 (m, 5 H) 12.98 - 13.57 (m, 1 H)	0.68	442	2

Example 11 : pharmacological data

The compounds of the disclosure underwent pharmacological trials to determine their inhibitory effect on the xCT exchanger (cystine/glutamate antiporter).

These trials consisted in measuring the *in vitro* activity of compounds according to the disclosure.

Study of the inhibition of incorporation of [^{3}H] L-glutamate by CHO cells stably expressing the human (Hu) xCT transporter

About 20 hours before the start of incorporation of [^{3}H]-L-glutamate, CHO cells are seeded at a density of 30 000 cells per well in 96-well culture plates (Costar). The incorporation tests are performed at room temperature in a volume of 100 µL of Na^+-free incubation buffer

containing: 2.7 mM KCl, 1.5 mM KH_2PO_4, 8 mM K_2HPO_4, 0.9 mM $CaCl_2$, 6.5 mM $MgCl_2$ and 137 mM choline chloride, pH 7.2.

The culture medium is washed twice beforehand with sodium-free buffer. The incorporation of amino acid (L-glutamate) is performed for 10 minutes in the presence of the test compounds, 0.1 µCi of [^{3}H]-L-glutamate and 1 µM of cold L-glutamate per well. The incorporation of non-specific [^{3}H]-L-glutamate is determined in the presence of an excess of 10 mM of cold L-glutamate. The incorporation of [^{3}H]-L-glutamate is stopped by washing the CHO cells three times with PBS buffer at 0°C containing 10% FCS. For the radioactivity measurement, the cells are lysed by addition of 200 µL of scintillant (Optiphase supermix, Wallac) to each well. After stirring for 15 minutes, the radioactivity is quantified using a liquid scintillation counter (Wallac MicroBeta counter, Perkin Elmer).

Results:

The dose-effect experiments are performed in triplicate over 8 concentrations. The effects of the compounds on the activity of the human xCT transporter are expressed as a percentage of inhibition of the incorporation of [^{3}H]-L-glutamate.

I % = 100 x (max – cmpd) / (max – min)

max = mean of the raw data for the maximum incorporation of [^{3}H]-L-glutamate

min = mean of the raw data for the minimum incorporation of [^{3}H]-L-glutamate (in the presence of 1 mM of cold L-glutamate)

cmpd = mean for the incorporation of [^{3}H]-L-glutamate in the presence of the compounds at a given concentration (0.3% DMSO).

The data are smoothed out using 4-parameter non-linear logistic regression analysis. The values of the concentrations of compounds producing 50% inhibition of the specific incorporation (IC_{50}) of [^{3}H]-L-glutamate are determined from the dose-response curves using the Speed software, version 2.0-LTSD.

Study of the inhibition of incorporation of [^{3}H] L-glutamate by EOC 13:31 cells natively expressing the murine (m) xCT transporter after treatment with LPS

About 24 hours before the start of incorporation of [^{3}H]-L-glutamate, EOC 13:31 cells are seeded at a density of 60 000 cells per well in 96-well culture plates (Becton Dickinson

356651 white wall transparent base, coated with Poly-D-Lysine). 4 hours after seeding, the cells are treated with 10 µg/mL of LPS (lipopolysaccharide, Sigma, L-8247). After 20 hours of induction of the murine xCT with LPS, the culture medium is replaced by two washes with sodium-free buffer containing: 2.7 mM KCl, 1.5 mM KH_2PO_4, 8 mM K_2HPO_4, 0.9 mM $CaCl_2$, 6.5 mM $MgCl_2$ and 137 mM choline chloride, pH 7.2. The incorporation tests are performed at room temperature in a volume of 100 µL of Na^+-free incubation buffer.

The incorporation of amino acid (L-glutamate) is performed for 10 minutes in the presence of the test compounds, 0.1 µCi of [^{3}H]-L-glutamate and 1 µM of cold L-glutamate per well. The incorporation of non-specific [^{3}H]-L-glutamate is determined in the presence of an excess of 10 mM of cold L-glutamate. The incorporation of [^{3}H]-L-glutamate is stopped by washing the CHO cells three times with PBS buffer at 0°C containing 10% FCS. For the radioactivity measurement, the cells are lysed by addition of 200 µL of scintillant (Optiphase supermix, Wallac) to each well. After stirring for 15 minutes, the radioactivity is quantified using a liquid scintillation counter (Wallac MicroBeta counter, Perkin Elmer).

Results:

The dose-effect experiments are performed in triplicate over 8 concentrations. The effects of the compounds on the activity of the human xCT transporter are expressed as a percentage of inhibition of the incorporation of [^{3}H]-L-glutamate.

$$I\ \% = 100 \times (max - cmpd) / (max - min)$$

max = mean of the raw data for the maximum incorporation of [^{3}H]-L-glutamate

min = mean of the raw data for the minimum incorporation of [^{3}H]-L-glutamate (in the presence of 1 mM of cold L-glutamate)

cmpd = mean for the incorporation of [^{3}H]-L-glutamate in the presence of the compounds at a given concentration (0.3% DMSO).

The data are smoothed out using 4-parameter non-linear logistic regression analysis. The values of the concentrations of compounds producing 50% inhibition of the specific incorporation (IC_{50}) of [^{3}H]-L-glutamate are determined from the dose-response curves using the Speed software, version 2.0-LTSD.

Effect of the reference products:

(S)-CPG (carboxy-phenyl-glycine) shows an IC_{50} of 2 µM

(R)-CPG (carboxy-phenyl-glycine) has no inhibitory effect

Literature references:

S. Hideyo et al., J. Biol. Chem. (1999) 274: 11455-11458

Y. Huang et al., Cancer Res. (2005) 65: 7446-7454

M.T. Bassi et al., Eur. J. Physiol. (2001) 442: 286-296

A.P. Sarjubhai et al., J. Neuropharm. (2004) 46: 273-284

Under the conditions of these two protocols, the preferred compounds according to the disclosure have IC_{50} values (concentration that inhibits 50% of the xCT activity) generally of less than 4 µM, more specifically between 0.001 and 1 µM, more specifically between 0.001 and 0.1 µM. Different synthetic batches (A, B, C) were tested for certain compounds. The IC_{50} values obtained for certain compounds of the disclosure are represented in Table 3 (nd: not determined).

Table 3

No.	Batch	Hu xCT IC_{50} (M)	m xCT IC_{50} (M)
1		1.04E-08	1.22E-08
2		3.20E-08	1.36E-08
3		1.94E-07	5.94E-08
4		2.21E-06	1.47E-06
5		2.50E-08	2.55E-08
6		2.37E-07	6.68E-08
7		5.99E-08	1.22E-07
8		2.23E-07	3.78E-07
9		3.98E-08	2.29E-08
10		7.02E-08	3.42E-08
11		1.28E-08	1.16E-08
12		1.09E-07	1.15E-07
13		1.39E-08	8.76E-09

No.	Batch	Hu xCT IC_{50} (M)	m xCT IC_{50} (M)
14		8.62E-09	6.87E-09
15		1.27E-08	1.94E-08
16		7.70E-09	1.46E-08
17		8.02E-08	1.42E-07
18		7.56E-09	8.28E-09
19		1.44E-08	3.15E-08
20		2.36E-07	3.11E-07
21		1.24E-06	nd
22		2.18E-08	2.77E-08
23		3.94E-08	5.52E-08
24		7.28E-07	4.78E-07
25		2.14E-06	8.33E-07
26		3.27E-07	9.09E-08
27		1.16E-07	1.89E-07
28		1.30E-07	1.93E-07
29		1.73E-07	3.58E-07
30	A	1.38E-07	1.18E-07
30	B	6.78E-08	3.59E-08
31		1.49E-07	2.36E-07
32	A	4.05E-08	2.51E-08
32	B	2.88E-08	3.19E-08
32	C	2.49E-08	3.70E-08
33	A	2.39E-08	2.15E-08
33	B	1.77E-08	1.97E-08
34		3.23E-08	2.56E-08
35		2.41E-08	2.27E-08
36		1.37E-07	1.81E-07
37		1.86E-07	2.66E-07
38		4.90E-08	nd
39		2.35E-08	2.39E-08

No.	Batch	Hu xCT IC_{50} (M)	m xCT IC_{50} (M)
40		1.94E-08	2.05E-08
41		2.19E-08	2.46E-08
42		2.79E-08	1.77E-08
43		2.28E-08	2.00E-08
44		1.12E-07	1.85E-07
45		7.60E-09	6.54E-09
46		1.05E-07	2.58E-08
47		9.49E-08	3.63E-08
48		3.52E-08	1.04E-07
49		9.37E-07	1.27E-07
50		9.10E-08	2.76E-08
52		1.62E-06	2.03E-07
53		9.50E-09	3.72E-09
54		3.40E-06	nd
55		1.52E-08	1.16E-08
56		2.21E-08	1.58E-08
57		2.14E-08	1.00E-08
58		6.93E-08	3.27E-08
59		1.26E-08	8.84E-09
60		8.54E-08	3.83E-08
61		1.92E-08	1.21E-08
62		1.53E-08	5.17E-09
63		nd	2.83E-06
64		2.26E-08	nd
65		9.75E-09	1.96E-08
66		4.51E-08	2.34E-08
67		1.09E-08	1.20E-08
68		1.63E-08	1.07E-08
69		5.54E-08	8.18E-08

It thus appears that the compounds according to the disclosure have inhibitory activity on

xCT.

Study of the inhibition/reducing of colony formation of ARID1A-Deficient cells (clonogenic assay) and study of the inhibition/reducing of the cells growth of A2780 cells (Incucyte proliferation Assay)

Materials and methods

Cell lines. All the cell lines were selected for their ARID1A deficiency. The A2780 cells; the JMSU1 and the MSTO211H cells were grown in RPMI160 media (Life Technologies) with 2mM L-Glutamine and 10% FBS (Fetal Bovine Serum). The TOV21G cells were grown in 1:1 mixture of MCDB 105 media and media 199 with 2mM L-Glutamine and 15 % FBS. The LoVo cells were grown in HAM'S F-12 media (Life Technologies) with 2mM L-Glutamine and 10% FBS. The MIA PaCa2 cells were grown in DMEM (Dulbecco's Modified Eagle Medium) media (Life Technologies) with 2mM L-Glutamine and 10% FBS. All the cell lines were maintained at 37°C in humidified chamber with a 5% CO_2 atmosphere.

Clonogenic assay. Cells were harvested from cell culture amplification, trypsinized, counted and reseeded in 6-well plates at a density of 1000 cells/well. After 24 hours cells were treated in a dose response of Compound 32 that ranges from 10μM, 3μM, 1μM, 0.3μM and 0.1μM. The 10mM compound solution stock was in 100% DMSO (dimethyl sulfoxide). The compound was diluted with DMSO to get a 1000x version of the targeted concentration range. Medium with 0.1% DMSO was used as a control. After 6 days of incubation, cell supernatant was removed and 1ml of crystal violet was added in each well. Culture plates were kept 30 minutes at room temperature. After crystal violet staining, the reagent was removed, and the cell layer was washed with sterile water until complete disappearance of the violet stain in the washing solution. Final wash was removed, and plates are kept open for couple of hours to dry the cell layer.

Incucyte proliferation assay. Cells were harvested from cell culture amplification, trypsinized, counted and reseeded in 96-well plates at a density of 10000 cells/well. After 24 hours cells were treated in a dose response of Compound 32 that ranges from 10μM, 3.33μM, 1.1μM, 370nM, 120nM, 40nM, 10nM, 4.5nM, 1.5nM and 0.5nM with or without 5 mM N-

AcetylCystein. The 10mM compound solution stock was in 100% DMSO. The compound was diluted with DMSO to get a 1000x version of the targeted concentration range. Medium with 0.1% DMSO was used as a control. Once the medium was added, the plate was placed into a IncuCyte S3 and images of the cell growth were recorded every 6 hours for a total duration of 7 Days. Phase analysis and graphs of the cell growth were made on Incucyte S3 software.

Results

The sensitivity of ARID1A-deficient cancer cells to Compound 32 was validated by measuring cell survival in colony formation assay (Figures 1a, 1b, 1c, 1d, 1e and 1f). The Compound 32 was able to inhibit or reduce colony formation for the ovarian cell lines A2780 and TOV21G at 10µm, 3µM, 1µM and 0.3µM, for the bladder cell line JMSU1 at 10µm, 3µM and 1µM, for colon cell line LoVo at 10µm, 3µM and 1µM, for the mesothelioma cell line MSTO211H at 10µm, 3µM, 1µM and 0.3µM, and for the pancreatic cell line MIA PaCa2 at 10µm, 3µM, 1µM, 0.3µM and 0.1µM.

The sensitivity of A2780 to Compound 32 was also confirmed by quantifying cell growth by Incucyte (Figure 2a). The A2780 cells growth was strongly inhibited at 10µM ( ), 3.33µM ( ) and 1.11µM ( ), and reduced at 370nM ( ) and 120nM ( ) by Compound 32. Furthermore, providing with 5mM of anti-oxidant N-AcetylCystein to the cells (Figure 2b) completely abolish the Compound 32's effect on cell growth.

These results suggest that the compounds according to the disclosure may especially be used for the preparation of a medicament for preventing and/or treating pathologies involving the xCT exchanger, in particular the following pathologies: neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, HIV-related dementia; strokes; cerebral ischaemia; cerebral and spinal column trauma; epilepsy; pain disorders, and cancers.

Among the cancers may be particularly cited : ovarian cancer, bladder cancer, colon cancer, malignant mesothelioma and pancreatic cancer. As we provided evidence that xCT inhibition impairs tumour growth through induction of oxidative stress, any genetic context that could increase the basal level reactive oxygen species in the tumor may be associated to increased sensitivity to xCT inhibition (such as the ARID1A deficiency or Keap1/NRF2

mutated tumours). Similarly, xCT inhibition may be seen as synergistic to any treatment that increase the oxidative stress such as DNA alkylating agents or radiation therapy.

Study of the inhibition of the antiporter system xc-

In vivo imaging of system xc- with positron emission tomography (PET) technique is crucial to evaluate the impact of specific inhibitors. The fluorine-18-labeled L-glutamate compound, (4S)-4-(3-[^{18}F]fluoropropyl)-L-glutamate ([^{18}F]FSPG), is taken up by system xc- due to the lack of discrimination between its natural substrate cystine and glutamate for the inward transport. Inhibition of the antiporter system xc- results in a decrease of the [^{18}F]FSPG-PET signal within the tumor.

A2780 Tumor bearing SCID (Severe Combined Immunodeficiency) mice were imaged at the baseline (D10 (the 10th day) post tumor engraftment) with [^{18}F]FSPG-PET to measure signal uptake prior treatment. The day after, a cohort of mice was treated with the compound 32 (b.i.d (bis in die :twice a day); 60mg/kg; p.o (per os (oral route); n=6) or with the vehicle (Captisol 40%; b.i.d.; p.o.; n=6). On D12 (the 12th day), mice were imaged post 3 administrations with [^{18}F]FSPG-PET.

Post treatment, the standardized uptake value (SUV) was calculated for each animal from PET images as a ratio of tissue radioactivity concentration and administered dose divided by body weight of the animal. The mean SUV (+/- SD (standard deviation)) was 0.74 (+/-0.31) and 0.16 (+/- 0.08) for the vehicle and treated group, respectively

Results

It comes out from these results that the compound 32 in accordance with the present disclosure specifically inhibits the antiporter system xc- as the mean SUV is lower for the treated group of animals.

Study of the tolerability of xCT inhibitor in SCID mice

Experimental procedure

The tolerability of compound 32 was evaluated in non-tumor bearing SCID mice at 30 and 100mg/kg twice a day (b.i.d).

Compound 32 was formulated in 40% Captisol pH 8.5. Mice (3 animals per group) were administered p.o. (per os) twice a day xCT inhibitor (compound 32) at 30 and 100mg/kg for 5 consecutive days. The control group received the vehicle only.

Mice were checked and adverse clinical reactions noted. Individual mice were weighed daily until the end of the experiment (day 32). Mice were euthanized when body weight loss ≥ 15% for 3 consecutive days or ≥ 20%. Mice were monitored daily for 30 days after treatment ends.

Results

The results are gathered in the following table 4 (individual body weight change).

Table 4

Days	% body weight change for control with vehicle only			% body weight change for SCID mice at xCT inhibitor (compound 32) 100mg/kg twice a day			% body weight change for SCID mice at xCT inhibitor (compound 32) 30 mg/kg twice a day		
0	0	0	0	0	0	0	0	0	0
1	-0.5	-1.5	-1.8	1.5	1.9	-9.5	-0.5	1.5	-0.5
2	0	-0.5	-1.4	0.5	0.5	-11	0	0.5	-3.8
3	-1.4	-2.5	-2.3	0	-1	-13.3	-0.5	-2.5	-6.2
4	-1.4	-3	-2.8	-0.5	-3.9	-14.8	-1	-0.5	-6.7
5	-2.4	-6.1	-3.2	-0.5	-6.3	-13.8	-0.5	2	-6.7
6	-1.4	-5.1	-5	4.6	-3.9	-10	-1.5	2.5	-6.7
7	-2.4	-1	-3.7	4.6	0.5	-10	-1	1	-5.2
8	-1.4	-1.5	-3.2	6.2	-0.5	-8.6	-3.5	0,5	-4.3
9	1.4	-1.5	-1.4	4.1	0	-11	-3	-1	-6.7
10	-0.9	-5.1	-3.7	1.5	-4.8	-11.9	-5.5	0	-7.1
11	0	-2	-2.8	3.6	-1	-8.1	-2	3.5	-5.2
14	0.5	-3	-0.9	6.2	-2.9	-10	-3.5	0.5	-4.8
16	2.4	-1.5	2.3	6.2	0	-8.6	2.5	3	-2.4

Days	% body weight change for control with vehicle only			% body weight change for SCID mice at xCT inhibitor (compound 32) 100mg/kg twice a day			% body weight change for SCID mice at xCT inhibitor (compound 32) 30 mg/kg twice a day		
17	3.8	-1.5	0	4.6	-1.4	-9.5	-1.5	1	-2.4
18	1.9	-1	-1.4	4.1	-1	-8.1	0	0	-2.9
21	1.4	-4.1	-3.2	2.1	-1.9	-10.5	1	0.5	-3.8
22	6.1	-0.5	2.3	4.1	3.4	-7.6	3	3.5	0.5
23	4.2	1	1.8	3.6	1.4	-7.1	4	5	-1
24	5.2	-1	0.9	4.1	2.9	-7.6	4.5	4.5	-1
25	6.6	1	3.2	2.1	2.4	-9	4	3.5	-0.5
28	5.2	2	3.2	4.6	6.3	-6.2	7	8	-1
30	5.2	0.5	3.7	5.7	5.3	-8.6	2	5.5	-2.4
32	5.2	2.5	2.3	8.8	4.3	-7.6	6.5	4.5	-1

It comes out from these results that treatment with compound 32 induced moderate body weight loss at both the high and low dose, with a maximum of 15% body weight loss in 1 animal in the 100mg/kg group. Mice recovered after treatment stopped.

According to one of its aspects, the disclosure relates to a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a medicine.

According to one of its aspects, the disclosure relates to a medicament comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The use of the compounds of formula (I) or a pharmaceutically acceptable salt thereof according to the disclosure for preventing and/or treating the diseases mentioned above, and also for preparing medicaments intended for treating these diseases, forms an integral part of the disclosure.

The use of the compounds of formula (I) or a pharmaceutically acceptable salt thereof according to the disclosure, or hydrate or solvate thereof, for the preparation of a medicament for preventing and/or treating the pathologies mentioned above forms an integral part of the disclosure.

A subject of the disclosure is also medicaments which comprise a compound of formula (I) or a pharmaceutically acceptable salt thereof, hydrate or solvate of the compound of formula (I). These medicaments find their use in therapeutics, especially in the prevention and/or treatment of the pathologies mentioned above.

According to another of its aspects, the present disclosure relates to pharmaceutical compositions containing, as active principle, at least one compound of formula (I) or a pharmaceutically acceptable salt thereof according to the disclosure. These pharmaceutical compositions contain an effective dose of a compound according to the disclosure, or a pharmaceutically acceptable salt thereof, hydrate or solvate of the said compound, and optionally one or more pharmaceutically acceptable excipients.

The said excipients are chosen, according to the pharmaceutical form and the desired mode of administration, from the usual excipients which are known to those skilled in the art.

In the pharmaceutical compositions of the present disclosure for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, local, intrathecal, intranasal, transdermal, pulmonary, ocular or rectal administration, the active principle of formula (I) above, or the possible salt, solvate or hydrate thereof, may be administered in unit administration form, as a mixture with standard pharmaceutical excipients, to man and animals for the prophylaxis or treatment of the above disorders or diseases.

The appropriate unit administration forms include oral forms, such as tablets, soft or hard gel capsules, powders, granules, chewing gums and oral solutions or suspensions, sublingual, buccal, intratracheal, intraocular and intranasal administration forms, forms of administration by inhalation, subcutaneous, intramuscular or intravenous administration forms, and rectal or vaginal administration forms. For topical application, the compounds according to the disclosure may be used in creams, ointments or lotions.

By way of example, a unit administration form of a compound according to the disclosure in tablet form may comprise the following constituents:

Compound (I) according to the disclosure	50.0 mg
Mannitol	223.75 mg
Croscaramellose sodium	6.0 mg
Corn starch	15.0 mg

Hydroxypropylmethylcellulose	2.25 mg
Magnesium stearate	3.0 mg

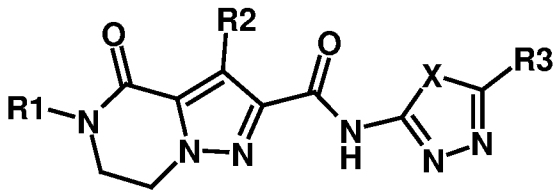
The said unit forms are dosed to allow a daily administration of from 0.01 to 20 mg of active principle per kg of body weight, according to the galenical form.

There may be particular cases where higher or lower dosages are appropriate; such dosages also form part of the disclosure. According to the usual practice, the dosage that is appropriate for each patient is determined by the doctor according to the mode of administration, the weight and the response of the said patient.

According to another of its aspects, the disclosure also relates to a method for preventing and/or treating the pathologies indicated above, which comprises the administration of an effective dose of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to the disclosure, or hydrate or solvate of the said compound.

CLAIMS

1. Compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R1 represents a hydrogen atom, a -(C_1-C_6)alkyl group optionally substituted with one to five groups, for instance one to two groups, independently selected from a halogen atom, a -(C_1-C_6)alkoxy group, a -halo(C_1-C_6)alkoxy group, a -(C_3-C_7)cycloalkyl group, a hydroxyl group, a -(C_6-C_{10})aryl group, a -(C_5-C_{10})heteroaryl group comprising 4 to 9 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur, and a -(C_3-C_7)heterocycloalkyl group comprising 2 to 6 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur,

said -(C_3-C_7)cycloalkyl group, -(C_6-C_{10})aryl group, -(C_5-C_{10})heteroaryl group and -(C_3-C_7)heterocycloalkyl group being optionally substituted with one to five groups independently selected from a halogen atom, a -(C_1-C_6)alkyl group, a halo(C_1-C_6)alkyl-group, a -(C_1-C_6)alkoxy group, a halo(C_1-C_6)alkoxy- group or a hydroxyl group;

R2 represents a hydrogen atom, a halogen atom, a -(C_1-C_6)alkyl group, a -(C_3-C_7)cycloalkyl group or a -(C_2-C_6)alkenyl group,

said -(C_1-C_6)alkyl group and said -(C_2-C_6)alkenyl group being optionally substituted with one to five substituents independently selected from a halogen atom, a hydroxyl group, or a NRaRb group;

R3 represents a hydrogen atom, a halogen atom, a -(C_1-C_6)alkyl group, a -(C_3-C_7)cycloalkyl group, or a -(C_5-C_{10})heteroaryl group comprising 4 to 9 carbon atoms and 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur,

said -(C_1-C_6)alkyl group being optionally substituted with one to five substituents independently selected from a halogen atom, a (C_1-C_6)alkoxy group, a halo(C_1-C_6)alkoxy group, a hydroxyl group and a nitro group, and said -(C_5-C_{10})heteroaryl group being optionally substituted with one to five substituents independently selected from a halogen

atom, a halo(C_1-C_6)alkyl- group, a -(C_1-C_6)alkoxy group, a halo(C_1-C_6)alkoxy- group, a hydroxyl group and a nitro group;

X represents a sulfur or oxygen atom; and

Ra and Rb represent, independently of each other, a hydrogen atom or a -(C_1-C_6)alkyl group.

2. The compound of formula (I) according to Claim 1 or a pharmaceutically acceptable salt thereof, wherein X represents a sulfur atom.

3. The compound of formula (I) according to Claim 1 or a pharmaceutically acceptable salt thereof, wherein X represents an oxygen atom.

4. The compound of formula (I) according to any one of Claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R1 represents a -(C_1-C_6)alkyl group optionally substituted with one to two groups independently selected from :

- a -(C_3-C_7)cycloalkyl group,
- a hydroxyl group,
- a -(C_6-C_{10}) aryl group,
- a -(C_5-C_{10})heteroaryl group comprising 4 to 9 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur, and
- a -(C_3-C_7)heterocycloalkyl group comprising 2 to 6 carbon atoms and 1 to 4 heteroatom(s) selected from oxygen, nitrogen, and sulfur,

said -(C_3-C_7)cycloalkyl group, -(C_6-C_{10})aryl group, -(C_5-C_{10})heteroaryl group and -(C_3-C_7)heterocycloalkyl group being optionally substituted with one to five groups independently selected from a halogen atom, a (C_1-C_6)alkyl group, a (C_1-C_6)alkoxy group, and a hydroxyl group.

5. The compound of formula (I) according to any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R_1 represents a methyl group, an ethyl group, a propyl group, or an isopentyl group, said methyl group, ethyl group, propyl group, and isopentyl group being optionally substituted with one to two groups independently selected from :

- a phenyl group, said phenyl group being optionally substituted with one to two groups independently selected from a chlorine atom, a fluorine atom, a methoxy group, and a hydroxy group,
- an oxetane, said oxetane being optionally substituted with a methyl group,
- a pyridine, said pyridine being optionally substituted with one to two groups independently selected from a methyl group, a fluorine atom and a bromine atom,
- a cyclopropyl group,
- a cyclohexyl group, said cyclohexyl group being optionally substituted by one to two fluorine atoms,
- a hydroxyl group, and
- a tetrahydropyrane.

6. The compound of formula (I) according to any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R2 represents a halogen atom, a -(C_1-C_6)alkyl group, a -(C_3-C_7)cycloalkyl group or a -(C_2-C_6)alkenyl group, said -(C_1-C_6)alkyl group being optionally substituted with a halogen atom, a hydroxyl group, or a NRaRb group; Ra and Rb being independenly a -(C_1-C_6)alkyl group.

7. The compound of formula (I) according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R2 represents a bromine atom, a methyl group optionally substituted with a fluorine atom, a hydroxyl group or a -$N(CH_3)_2$ group, an ethyl group optionally substituted by a hydroxyl group, a vinyl group (-$CH=CH_2$), an isobutenyl group (=$CH(CH_3)_2$), and a cyclopropyl group.

8. The compound of formula (I) according to any one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein R3 represents a hydrogen atom, a halogen atom, a -(C_1-C_6)alkyl group, a -(C_3-C_7)cycloalkyl group, or a -(C_5-C_{10})heteroaryl group comprising 4 to 9 carbon atoms and 1 to 4 heteroatoms independently selected from oxygen, nitrogen and sulfur, said (C_1-C_6)alkyl group being optionally substituted with one to three substituents independently selected from a halogen atom, and a hydroxyl group, and said heteroaryl group being optionally substituted with one nitro group.

9. The compound of formula (I) according to any one of Claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein R3 represents a hydrogen atom, a methyl group, an ethyl group, an isopropyl group, a $-CF_3$ group, a $-CHF_2$ group, a $-CH_2F$ group, a $-CH_2-CF_3$ group, a chlorine atom, a $-CH_2OH$ group, a cyclopropyl group, or a furan group which is substituted by a nitro group.

10. The compound of formula (I) or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 9, wherein the compound is selected from the group consisting of:

- 5-(2-chlorobenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-fluorobenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-fluorobenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-fluorobenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-cyclopropyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(2-fluorobenzyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-methyl-5-(3-methyloxetan-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-methyl-4-oxo-5-pyridin-3-ylmethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-methyl-4-oxo-5-pyridin-3-ylmethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-methyl-5-(2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-methyl-4-oxo-5-pyridin-2-ylmethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-bromo-4-oxo-5-phenethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-bromo-5-(3-fluoropyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide

- 3-methyl-4-oxo-5-phenethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-[2-(2-chlorophenyl)ethyl]-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-ethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-ethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-cyclopropyl[1,3,4]thiadiazol-2-yl)amide
- 5-[2-(2-fluorophenyl)ethyl]-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-methyl-5-(3-methylbutyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-methyl-5-(3-methylbutyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-cyclopropyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-isopropyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-methyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-ethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-cyclopropylmethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-methyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-isopropyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-ethyl[1,3,4]thiadiazol-2-yl)amide (HCl)
- 3-cyclopropyl-5-(3-methylbutyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-ethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-methyl[1,3,4]thiadiazol-2-yl)amide (HCl)

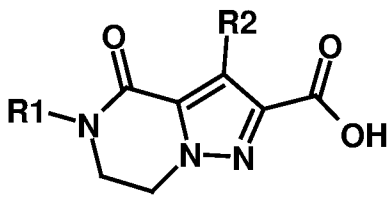
- 3-cyclopropyl-5-(3-methylbutyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-methyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(3-methylpyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-methyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(3-methylpyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-ethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(3-methylpyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(4,4-difluorocyclohexylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(4,4-difluorocyclohexylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-ethyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(3-methylpyridin-2-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-cyclopropyl[1,3,4]thiadiazol-2-yl)amide
- 5-[2-(2-chlorophenyl)ethyl]-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-methyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(4-hydroxybenzyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-[2-(2-chlorophenyl)ethyl]-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-[2-(2-chlorophenyl)-2-hydroxyethyl]-3-ethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(3-hydroxybenzyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(2-hydroxybenzyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(3-hydroxypropyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide

- 5-(2-chloro-3-hydroxybenzyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(3-hydroxy-3-methylbutyl)-3-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid [1,3,4]thiadiazol-2-ylamide
- 5-(2-chlorobenzyl)-3-(2-methylpropenyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-4-oxo-5-(tetrahydropyran-4-ylmethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-methyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-4-oxo-5-(tetrahydropyran-4-ylmethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid [5-(5-nitrofuran-2-yl)-[1,3,4]thiadiazol-2-yl]amide
- 3-cyclopropyl-4-oxo-5-(tetrahydropyran-4-ylmethyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-cyclopropyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-chloro[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid [5-(2,2,2-trifluoroethyl)[1,3,4]thiadiazol-2-yl]amide
- 3-cyclopropyl-5-(6-fluoro-2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-cyclopropyl-5-(6-fluoro-2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-4-oxo-3-vinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]oxadiazol-2-yl)amide
- 5-(2-chloro-4-methoxybenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide

- 5-(2-chlorobenzyl)-3-hydroxymethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(6-fluoro-2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 3-ethyl-5-(6-fluoro-2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-trifluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-dimethylaminomethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide (HCl)
- 5-(2-chlorobenzyl)-3-fluoromethyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-fluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-hydroxymethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(6-bromo-2-methylpyridin-3-ylmethyl)-3-cyclopropyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide
- 5-(2-chlorobenzyl)-3-(2-hydroxyethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-difluoromethyl[1,3,4]thiadiazol-2-yl)amide, and
- 3-cyclopropyl-5-(2-methylpyridin-3-ylmethyl)-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-2-carboxylic acid (5-fluoromethyl[1,3,4]thiadiazol-2-yl)amide.

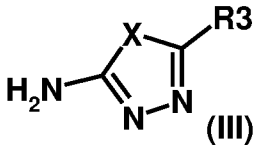
11. Process for preparing a compound of formula (I) according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, comprising at least the step of :

reacting a compound of formula (II):



(II)

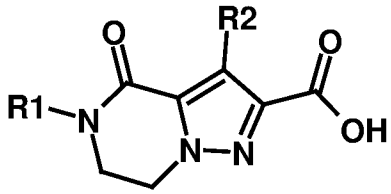
wherein R1 and R2 are as defined in any one of claims 1 and 4 to 7, with a compound of formula (III)



(III)

wherein X and R3 are as defined in any one of claims 1, 2, 3, 8 and 9.

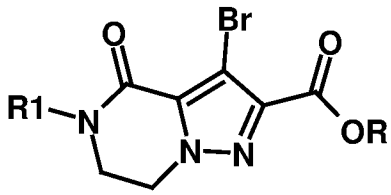
12. Compound of formula (II) or a pharmaceutically acceptable salt thereof



(II)

wherein R1 and R2 are as defined in any one of claims 1 and 4 to 7, with the exception of the compounds of formula (II) in which R2 represents a hydrogen atom.

13. Compound of formula (X) or a pharmaceutically acceptable salt thereof



(X)

wherein R1 is as defined in any one of claims 1, 4 and 5, and R represents a methyl or ethyl group.

14. Medicament comprising a compound of formula (I) according to any one of Claims 1 to 10 or a pharmaceutically acceptable salt thereof.

15. Pharmaceutical composition comprising a compound of formula (I) according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

16. Compound of formula (I) according to any one of Claims 1 to 10 or a pharmaceutically acceptable salt thereof, for use as a medicine.

17. Compound of formula (I) according to any one of Claims 1 to 10 or a pharmaceutically acceptable salt thereof, for use for preventing and/or treating pathologies involving the xCT exchanger.

18. Compound of formula (I) according to any one of Claims 1 to 10 or a pharmaceutically acceptable salt thereof, for use for preventing and/or treating neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, HIV-related dementia, strokes, cerebral ischaemia, cerebral and spinal column trauma, epilepsy and pain disorders, and cancers.

19. Compound of formula (I) or a pharmaceutically acceptable salt thereof, for use according to claim 18, wherein the cancers are selected among lung cancer including small cell lung cancer (SCLC) and non - small cell lung cancer (NSCLC), lung adenocarcinoma, pleural mesothelioma, squamous cell carcinoma (SCC), squamous cell carcinoma of the lung, cervical squamous cell carcinoma, squamous cell carcinoma (SCC) of head and neck, head and neck cancer, pancreatic cancer, microsatellite instability (MSI) mutated tumors, classic Hodgkin lymphoma (cHL), hepatocellular carcinoma (HCC), liver hepatocellular carcinoma, liver cancer, cholangiocarcinoma (CHOL), urothelial carcinoma, breast cancer, cervical cancer, uterine corpus endometrial carcinoma, ovarian cancer, endometrial cancer, skin cancer, melanoma, uveal melanoma, Merkel cell carcinoma (MCC), sarcoma, mesothelioma, malignant mesothelioma, primary mediastinal large B-cell lymphoma (PMBCL), thyroid cancer, glioblastoma, prostate cancer, bladder cancer, bladder carcinoma, bladder urothelial carcinoma, mature b-cell neoplasms, colorectal cancer (CRC), colon cancer, esophagogastric cancer, stomach cancer, stomach adenocarcinoma, esophageal cancer, diffuse large B-cell (DLBC) lymphoma (DLBCL), low grade glioma (LGG), kidney

renal papillary cell carcinoma, kidney renal clear cell carcinoma, renal cell carcinoma (RCC), and kidney cancer.

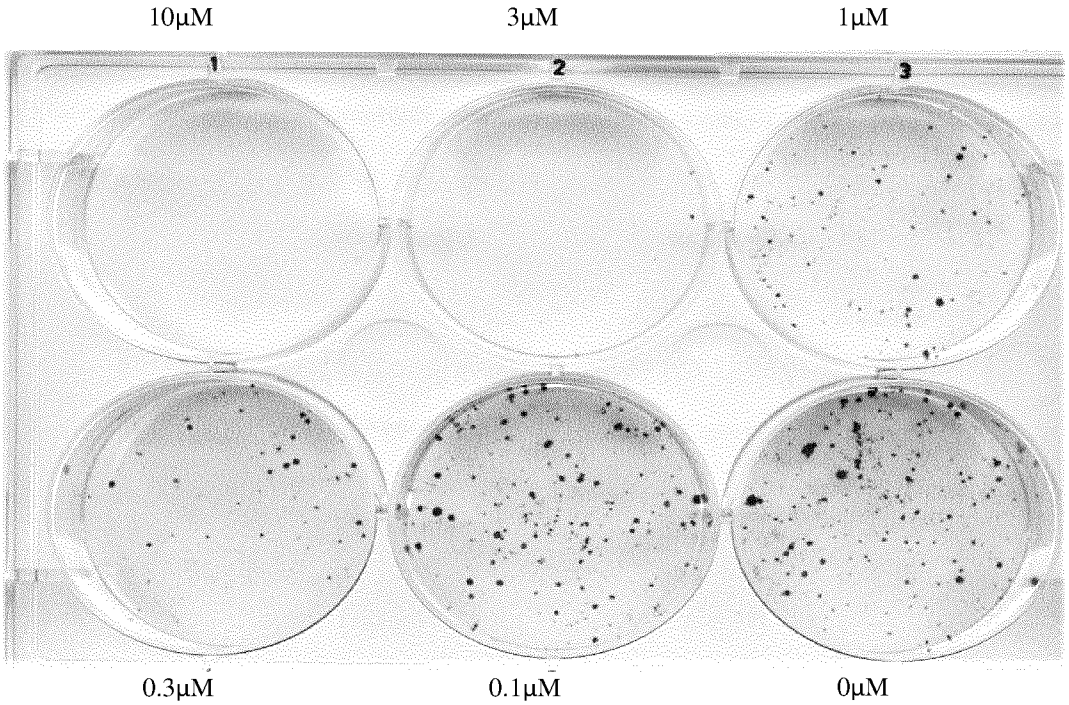


Figure 1a

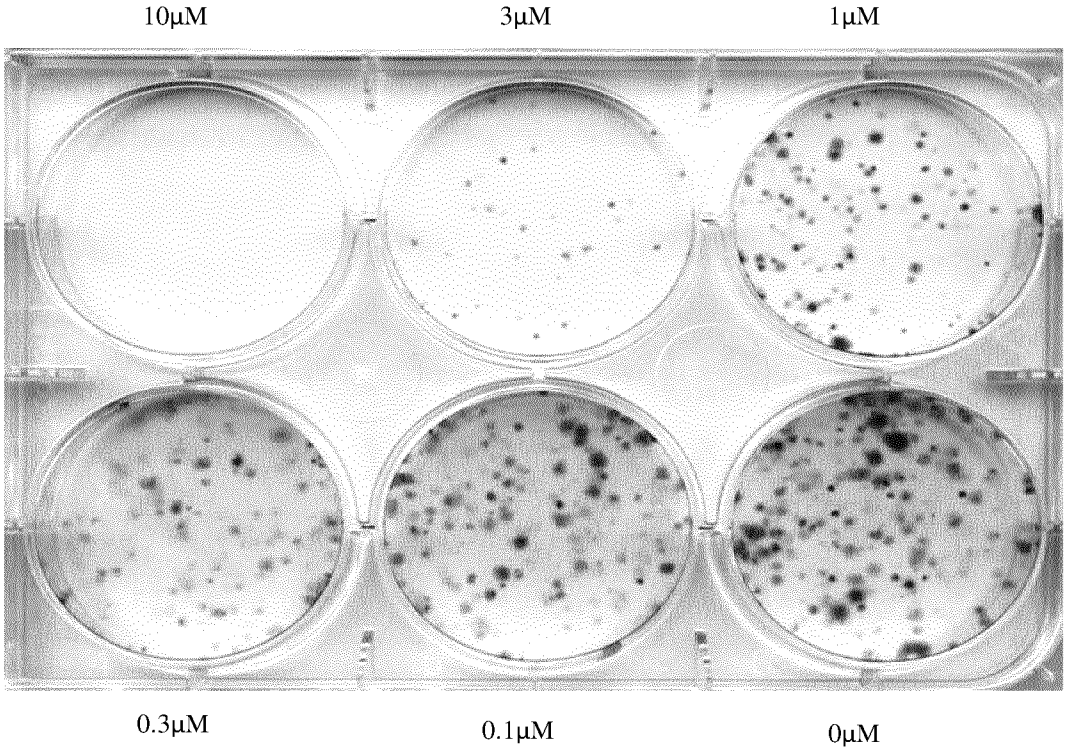


Figure 1b

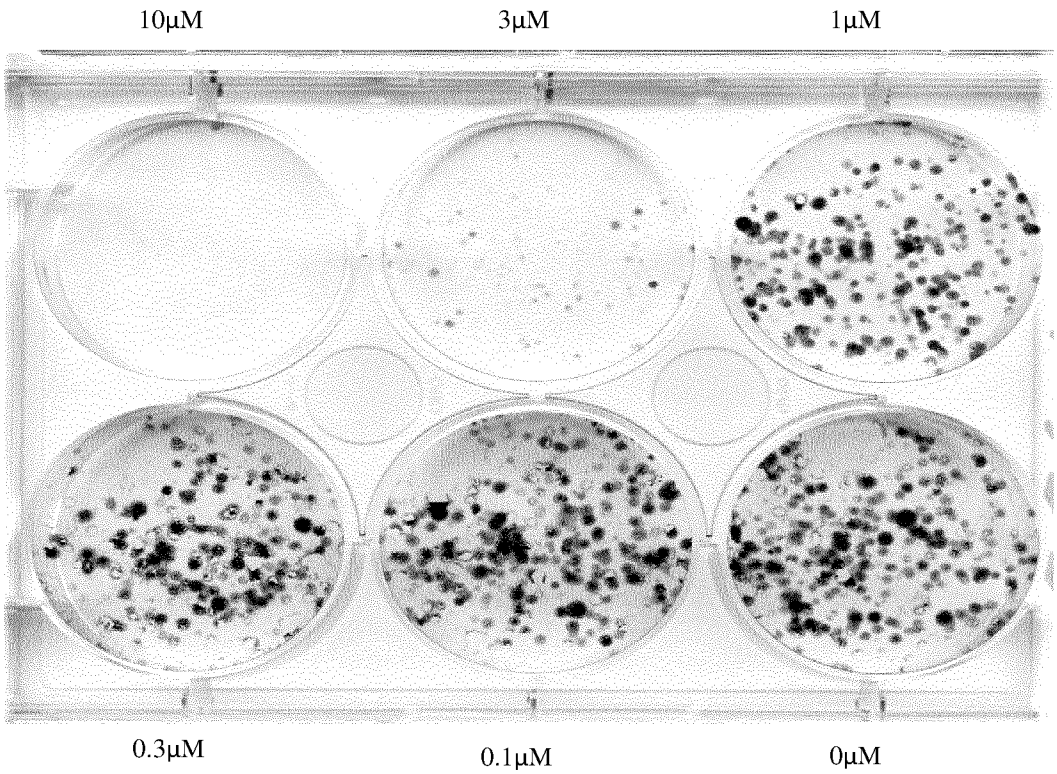


Figure 1c

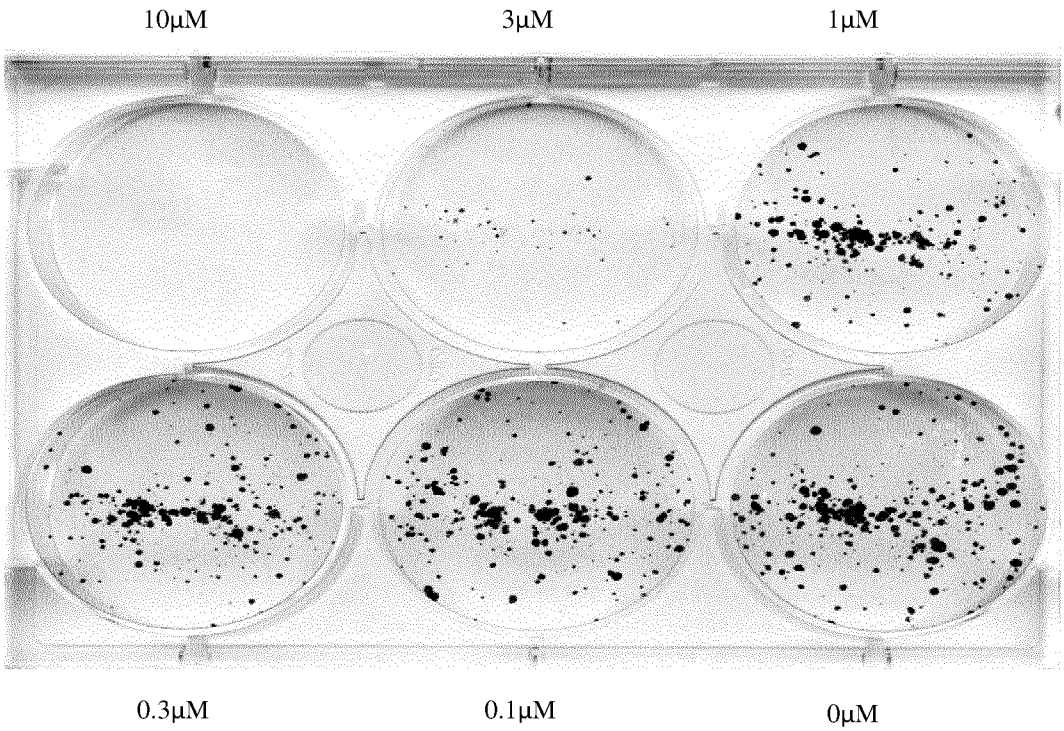


Figure 1d

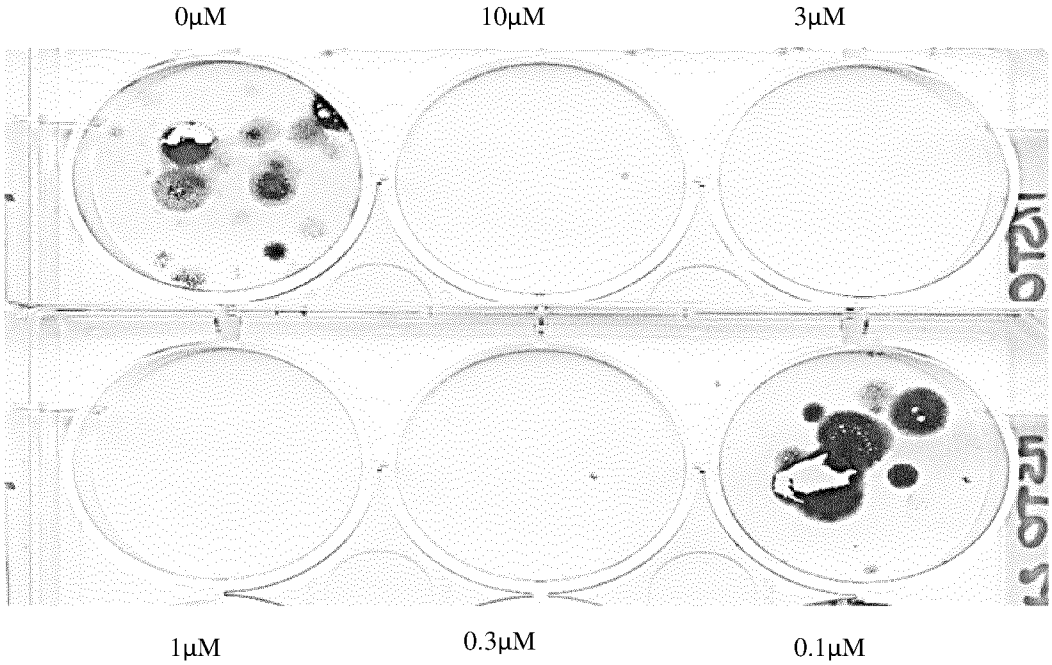


Figure 1e

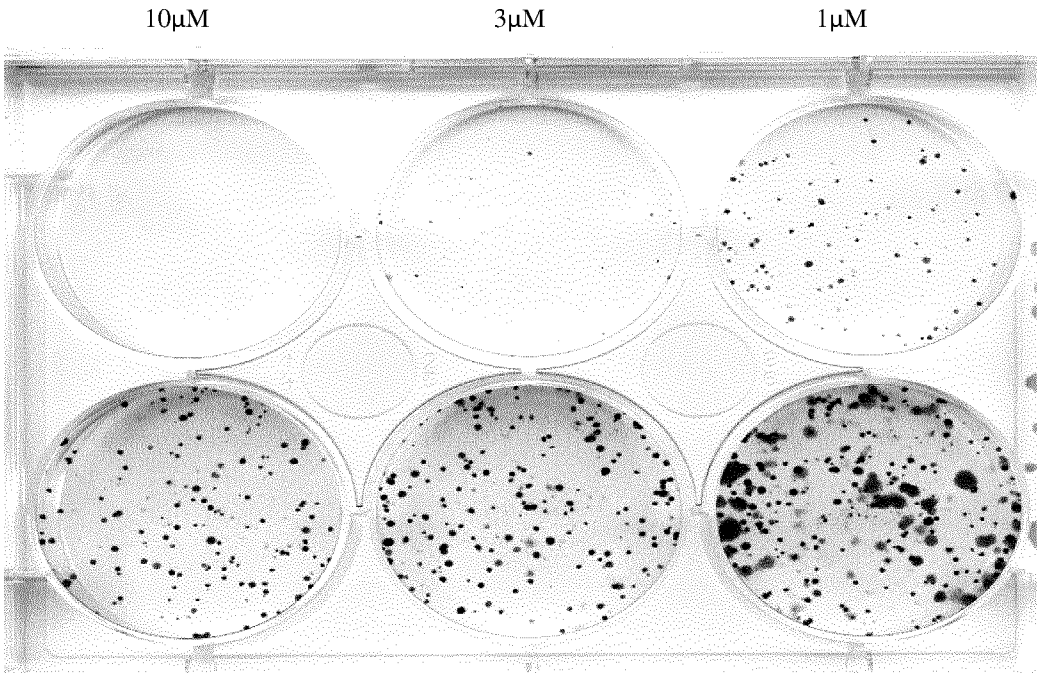


Figure 1f

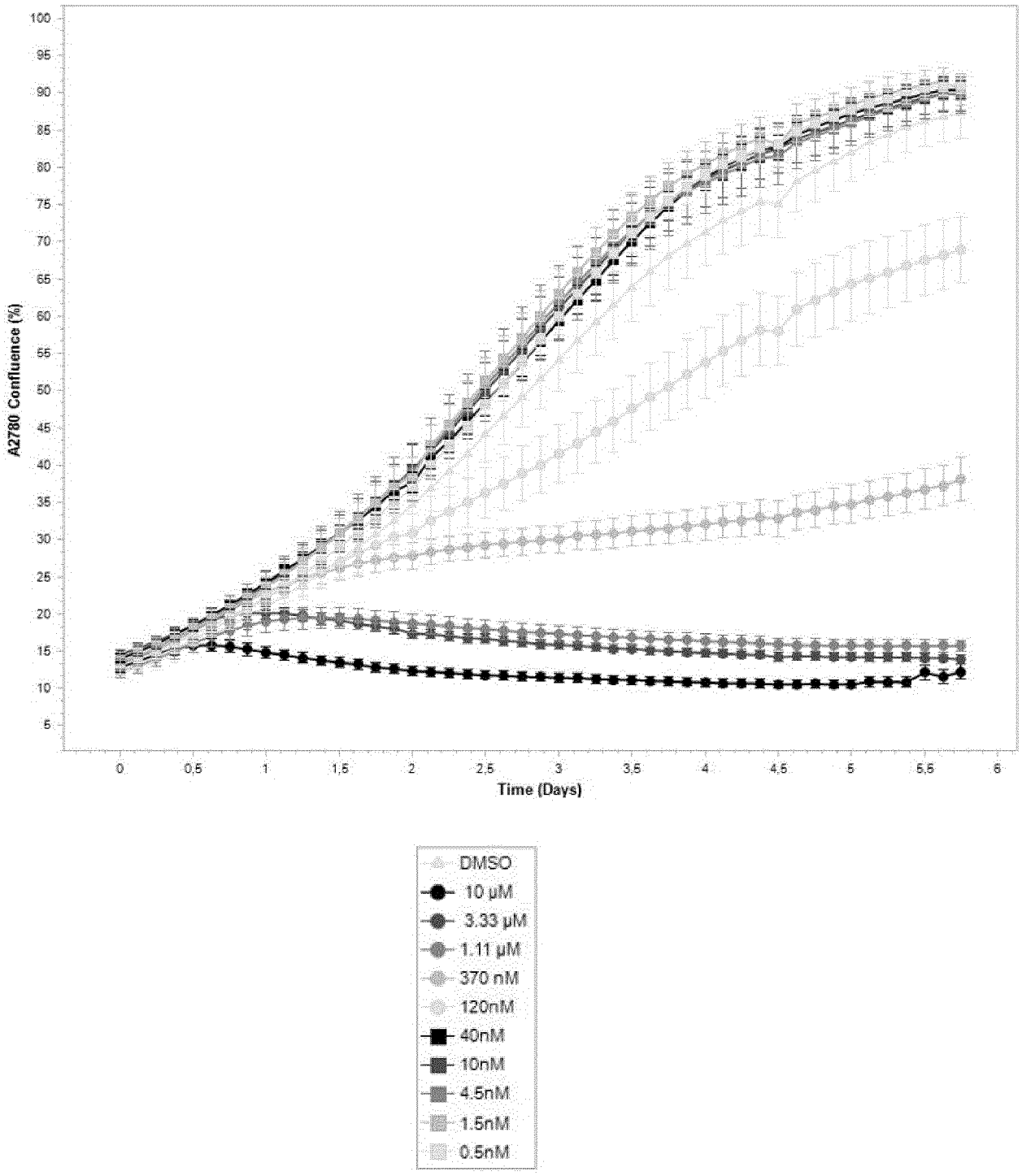

A2780 Confluence (%)
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
0,5
1
1,5
2
2,5
3
3,5
4
4,5
5
5,5
6
Time (Days)
DMSO
10 µM
3.33 µM
1.11 µM
370 nM
120nM
40nM
10nM
4.5nM
1.5nM
0.5nM

Figure 2a

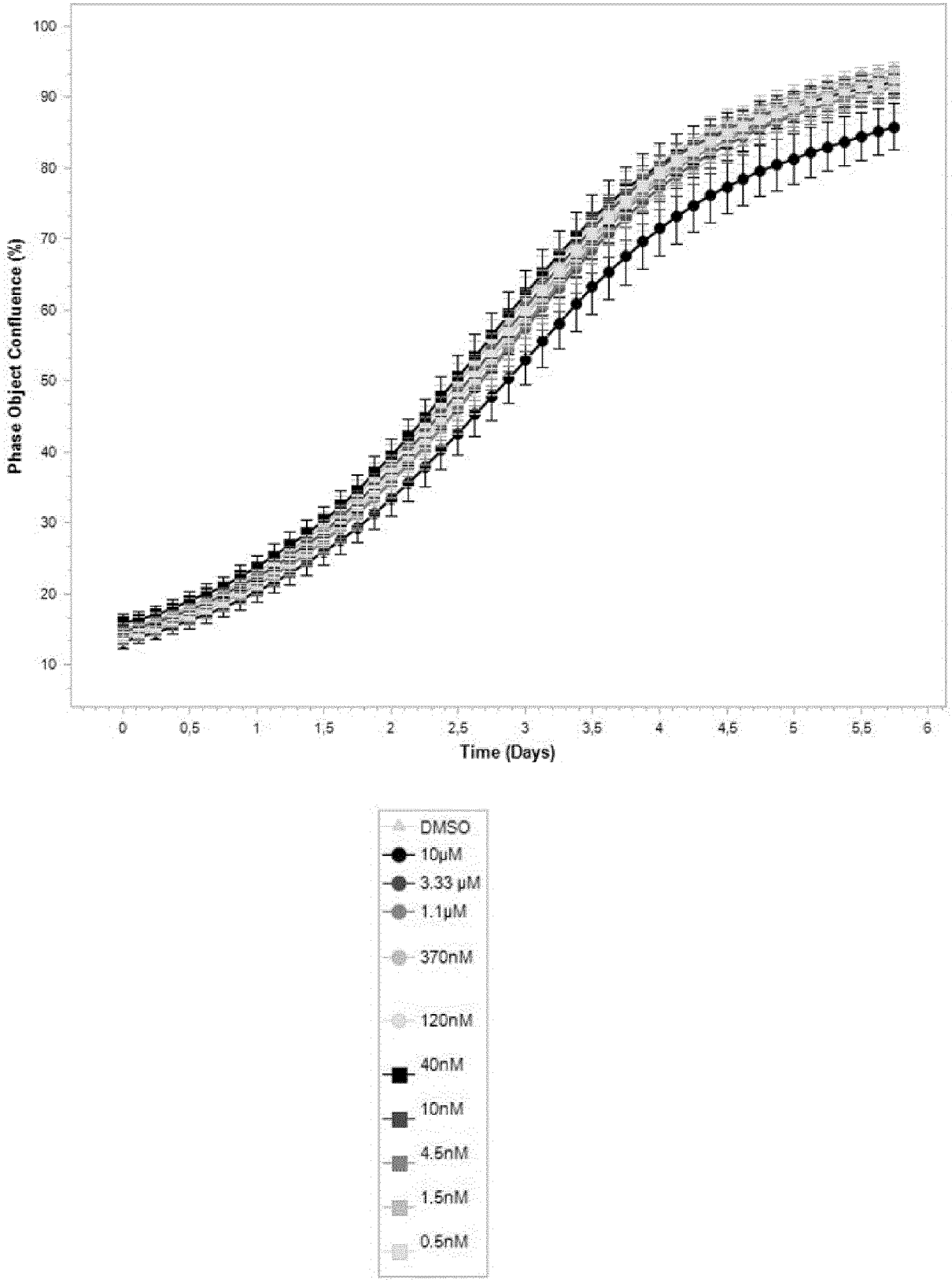

Phase Object Confluence (%)
100
90
80
70
60
50
40
30
20
10
0
0,5
1
1,5
2
2,5
3
3,5
4
4,5
5
5,5
6
Time (Days)
DMSO
10µM
3.33 µM
1.1µM
370nM
120nM
40nM
10nM
4.5nM
1.5nM
0.5nM

Figure 2b

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/058524

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61P25/00 A61P35/00
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 3 851 436 A1 (KAKEN PHARMA CO LTD [JP]) 21 July 2021 (2021-07-21) page 207 - page 208; claim 1	1-11, 14-19
A	WO 2021/222153 A1 (SQUIBB BRISTOL MYERS CO [US]) 4 November 2021 (2021-11-04) page 97	1-11, 14-19
A	WO 2016/010950 A1 (SQUIBB BRISTOL MYERS CO [US]) 21 January 2016 (2016-01-21) Intermediates 138, 139; page 239	1-11, 14-19
A	WO 2015/196086 A1 (UNIV MONTANA MISSOULA MT [US]) 23 December 2015 (2015-12-23) the whole document	1-11, 14-19

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 June 2023	28/07/2023

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

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2023/058524

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims;; it is covered by claims Nos.:

1-11, 14-19

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-11, 14-19

Compounds of formula (I) and process leading to them and corresponding uses, compositions.

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2. claims: 12, 13

Compounds of formulae (II) and (X)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2023/058524

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