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(71) Applicant: **UNIVERSITÉ DE LAUSANNE** [CH/CH]; c/o PACTT Technology Transfer, Biopôle 3, Route de la Corniche 9B, 1066 Epalinges (CH).

(72) Inventor: **JOURDAIN, Alexis**; Le Grand-Chemin 43, 1066 Epalinges (CH).

(74) Agent: **KATZAROV S.A.**; 12 Avenue des Morgines, 1213 Petit-Lancy (CH).

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(54) Title: INHIBITORS OF URIDINE CATABOLISM AND/OR TRANSPORT FOR THERAPY

(57) Abstract: The invention relates to a screening method for the identification of inhibitors of nucleotide catabolism, such as uridine catabolism, to the inhibitors identified by the screening method and use thereof in oncology, immune modulation and metabolic disorders.

INHIBITORS OF URIDINE CATABOLISM AND/OR TRANSPORT FOR THERAPY

FIELD OF THE INVENTION

The invention relates to a screening method for the identification of inhibitors of nucleotide catabolism, such as uridine catabolism, to the inhibitors identified by the screening method and use thereof in oncology, immune modulation and metabolic disorder.

BACKGROUND OF THE INVENTION

Glucose is vital for life, serving both as a source of energy and carbon building block for growth. When glucose is limiting, alternative nutrients are used by cells. It has been recently reported that catabolism of uridine or RNA enables cells to grow in the complete absence of glucose. Indeed, uridine can be salvaged to support pyrimidine synthesis in the setting of mitochondrial electron transport chain deficiency, and the ribose moiety of uridine or RNA can be salvaged to fulfill energy requirements via uridine catabolism pathway defined as: (1) the phosphorylytic cleavage of uridine by uridine phosphorylase UPP1/2 into uracil and ribose-1-phosphate (R1P), (2) the conversion of R1P into fructose-6-P and glyceraldehyde-3-P by the non-oxidative branch of the pentose phosphate pathway (non-oxPPP), and (3) their glycolytic utilization to fuel ATP production, biosynthesis and gluconeogenesis. Such catabolism of uridine appears widespread, and its activity can be found in liver, activated macrophages, and certain cancer lineages. An interesting property of such uridine catabolism is that uridine enters downstream of the initial, highly regulated steps of glucose transport and glycolysis.

The clinical development of metabolic inhibitors is a new, highly attractive area of research for oncology, immune and metabolic modulation. Currently, dozens of drugs are approved or in clinical trials (I to III) for multiple types of cancers. Those drugs generally target energy producing pathway such as glycolysis, mitochondrial respiration, glutaminolysis, fatty acid oxidation and more. However, those drugs may fail due to the metabolic flexibility of cells. Metabolic flexibility is usually defined by the ability that cells have to switch from one energy source to another. For example, the action of an inhibitor of glycolysis may be bypassed by fatty acids oxidation. Thus, identifying and drugging alternative pathways for energy production is of high interest for cancer research, but also immune modulation and metabolic syndromes.

Nucleotides are abundant in human diet, and every living organism ingested by humans, whether animal- or plant-based, contains DNA and RNA. It has been recently reported that organisms can assimilate and derive energy from nucleotides and nucleic acids, as described above. It has been shown that cells deprived of glucose (or genetically, or chemically, unable to perform glycolysis) can use nucleotides and nucleic acids as energy producing substrates. Thus, nucleotides play a critical role in maintaining cellular function and energy metabolism. Uridine, a pyrimidine nucleotide characterized by its high abundance and solubility is one of the most commonly used nucleotides for energy production. Uridine is mostly present in blood and cerebrospinal fluid, where it contributes to the maintenance of basic cellular functions affected by uridine phosphorylase 1 and 2 (UPP1 and UPP2) enzyme activities, feeding habits, and ATP depletion. Uridine is also highly abundant in organs and in the diet. Uridine metabolism depends mainly on three stages: (1) *de novo* synthesis, (2) salvage, and (3) catabolism, all of which are tightly relating to glucose homeostasis, and lipid and amino acid metabolism.

Due to the important roles of uridine, especially as an alternative energy source, there is a need for efficient and simple methods that can identify inhibitors of nucleotides catabolism, preferably uridine catabolism, and thereby prevent use of nucleotides as energy source by cells.

SUMMARY OF THE INVENTION

An aspect of the present invention provides a use of an inhibitor for in-vitro inhibiting uridine catabolism and/or for in-vitro inhibiting uridine transport, wherein the inhibitor is selected from the group comprising

- 2-Methoxy-N-[(2E)-3-[4-[[3-methyl-4-[(6-methyl-3-pyridinyl)oxy]phenyl]amino]-6-quinazolinyl]-2-propen-1-yl]acetamide
  (CP-724714) (CAS: 383432-38-0)
- N-(1,3-Benzodioxol-5-ylmethyl)-4-benzofuro[3,2-d]pyrimidin-4-yl-1-piperazinecarbothioamide (Amuvatinib, MP-470) (CAS: 850879-09-3)
- 1-[4-[4-[[2-[(1E)-2-[4-(Trifluoromethyl)phenyl]ethenyl]-4-oxazolyl]methoxy]phenyl]butyl]-1H-1,2,3-triazole
  (Mubritinib, TAK 165) (CAS: 366017-09-6)
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-(styryl)oxazole, Mubritinib derivative 2

- (*E*)−4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methyl)styryl)oxazole, Mubritinib derivative 3
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methoxy)styryl)oxazole, Mubritinib derivative 4
- (*E*)-4-((4-(4-(1*H*-imidazol-1-yl)butyl)phenoxy)methyl)-2-(4-(trifluoromethyl)styryl)oxazole, Mubritinib derivative 7
- N-[[2-(4-Morpholinylmethyl)phenyl]methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 924234-99-1)
- N-[[4-(1-Pyrrolidinylmethyl)phenyl]methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 930943-65-0)
- N-[(1-Phenylcyclopropyl)methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1110937-38-6)
- N-[2-(2-Chlorophenyl)ethyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1241587-59-6)
- N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[3,2-d]pyrimidin-4-amine (CAS: 930038-39-4)
- N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1015153-83-9)
- 2-[[4-(4-Methoxyphenyl)-3-phenyl-2(3H)-thiazolylidene]amino]ethanol (CAS: 303787-45-3)
- 4-[4-[(4-Chlorophenyl)sulfonyl]-1-piperazinyl]-2-methylquinoline (CAS: 433248-90-9)
- N-(4-Ethylphenyl)-2,3-dihydro-2-methyl-1-(1-oxopropyl)-1H-indole-5-sulfonamide (CAS: 901008-80-8)
- N-(3,4-Dimethylphenyl)-2,3-dihydro-2-methyl-1-(1-oxopropyl)-1H-indole-5-sulfonamide (CAS: 901009-05-0)
- 4-[4-[(2-Fluorophenyl)methoxy]-3-methoxyphenyl]-1,4,5,7-tetrahydro-3-methyl-6H-pyrazolo[3,4-b]pyridin-6-one (CAS: 1110976-91-4)

- N-(8-Methoxy-5-quinolinyl)-1-naphthaleneacetamide (CAS: 942850-72-8)
- N-(3-Ethylphenyl)-α-methyl-3-oxo-1,2-benzisothiazole-2(3H)-acetamide (CAS: 902841-23-0)
- 4-Acetyl-3,4-dihydro-2-methyl-N-(1,2,3,4-tetrahydro-1-naphthalenyl)-2H-1,4-benzothiazine-6-sulfonamide (CAS: 891932-93-7)
- N-[(4-Fluorophenyl)methyl]-1-(3-methylisoxazolo[5,4-d]pyrimidin-4-yl)-4-piperidinecarboxamide (CAS: 932292-32-5)
- 4-Acetyl-3,4-dihydro-2-methyl-N-[(3-methylphenyl)methyl]-2H-1,4-benzothiazine-6-sulfonamide (CAS: 1113123-97-9)
- [1-(5,6-Dimethylfuro[2,3-d]pyrimidin-4-yl)-3-piperidinyl](4-ethyl-1-piperazinyl)methanone (CAS: 1111019-76-1)
- N-[(2,6-Dimethylimidazo[2,1-b]-1,3,4-thiadiazol-5-yl)methyl]-4-(trifluoromethyl)benzamide (CAS: 1341006-76-5)
- 1-{5H,6H,7H-cyclopenta[d]pyrimidin-4-yl}-4-phenylpiperazine (CAS: 1340813-43-5)
- 4-[[(2-Chloro-6-fluorophenyl)methyl]methylamino]-3-nitrobenzamide (CAS: 877974-11-3)
- 1-(4-Acetyl-3,5-dimethyl-1H-pyrrol-2-yl)-2-[2-(2-thienyl)-1-pyrrolidinyl]-1-propanone (CAS: 878911-41-2)
- 4-[2-(2-Thienyl)-1-pyrrolidinyl]thieno[2,3-d]pyrimidine (CAS: 924219-03-4)
- 2,3-Dihydro-1-[(2-methylphenyl)methyl]-1H-indole-5-sulfonamide (CAS: 923778-03-4)
- N-[(2,3-Dihydro-1,4-benzodioxin-2-yl)methyl]-N-propylthieno[2,3-d]pyrimidin-4-amine (CAS: 1090372-48-7)
- 4-[2-[4-(2,3-Dimethylphenyl)-1-piperazinyl]ethoxy]benzenesulfonamide (CAS: 1110869-85-6)
- 2-(Benzofuro[3,2-d]pyrimidin-4-ylamino)-1-butanol (CAS: 844649-81-6)

- [4-(Hydroxyphenylmethyl)-1-piperidinyl][3-methyl-5-(methylamino)-4-isothiazolyl]methanone (CAS: 1197739-15-3)
- 6-(2,3-Dihydro-1H-indol-1-yl)-9-β-D-ribofuranosyl-9H-purine (CAS: 402724-46-3)
- 4-[[6-[Ethyl(tetrahydro-2,2-dimethyl-2H-pyran-4-yl)amino]-9H-purin-9-yl]methyl]tetrahydro-2H-pyran-4-methanol (CAS: 2324334-92-9)
- Tetrahydro-4-[[6-[4-(3-methylbutoxy)-1-piperidinyl]-9H-purin-9-yl]methyl]-2H-pyran-4-ol CAS: 2188639-44-1)
- 7-Ethyl-3,7-dihydro-1,3-dimethyl-8-[[4-(phenylmethyl)-1-piperidinyl]methyl]-1H-purine-2,6-dione (CAS: 878441-28-2)
- N-(1-Butyl-1,2,3,4-tetrahydro-2-oxo-6-quinolinyl)-2,4-dimethoxybenzenesulfonamide (CAS: 941906-49-6)
- Tetrahydro-N-[2-[[4-methyl-6-(1-piperidinyl)-2-pyrimidinyl]amino]ethyl]-2-furancarboxamide (CAS: 1207002-37-6)
- 2,2′,2″,2‴-[(4,8-Di-1-piperidinylpyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetrakis[ethanol] (Dipyridamole) (CAS: 58-32-2)
- 1-(3,4-Diethoxybenzyl)-6,7-diethoxyisoquinoline (Ethaverine hydrochloride) (CAS: 486-47-5)

Another aspect of the present invention provides an inhibitor of the invention for use in a method for treating a disease associated with uridine catabolism selected from cancer and immune disorders, and wherein the cancer expresses high level of Uridine phosphorylase 1 (UPP1) or Uridine phosphorylase 2 (UPP2).

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows method for identifying inhibitors of uridine catabolism for energy production. (I) A cell line with high ability to grow on uridine is selected. (II) Cells are transferred to glucose-free media. (III) Cells are divided in two, and each half is supplemented with an equal concentration of glucose or of uridine. (IV) Cells are then plated on multi-well plates, themselves pre-coated with the drug library. (V) Cells are incubated for a few days. (VI) A

viability dye, such as Prestoblue, is added to each well. (VII) The viability of cells is estimated based on the signal of the viability dye in glucose or in uridine.

Figure 2 shows screen results for uridine catabolism inhibitors. UACC-257 cells were diluted in glucose-free media supplemented with 10mM glucose or 10mM uridine. Supplemented cells were then plated on 384-well plates pre-coated with compounds from the Prestwick library (Prestwick, 1'280 compounds), a kinase inhibitor library (Sellekchem, 258 compounds), or a nucleoside library (Enamine, 320 compounds) as shown in Figure 2A, or compounds from a chemically diverse collection (7'678 compounds) as shown in Figure 2B. The final concentration of inhibitors is 10µM. Prestoblue was added after 72h. Relative Prestoblue fluorescence was measured after 2h and Z-scores were calculated. Compounds were selected for further investigation based on their Z-scores.

Figure 3 shows uridine promotes cell survival and energy metabolism, illustrated here by lactate production, in Primary Peripheral Blood Mononuclear Cells (PBMC).

Figure 4 shows validation of the compounds (identified with CAS numbers) in AsPC1 pancreatic cancer cells. Cells were diluted in glucose-free media supplemented with 10mM glucose or 10mM uridine, and treated with the drugs of interest at a 10µM concentration. After 72h, Prestoblue was added. Relative Prestoblue fluorescence was measured after 2h. Fold change in viability compared to untreated control cells.

Figure 5 shows validation of the compounds (identified with CAS numbers) in SW480 colon cancer cells. Cells were diluted in glucose-free media supplemented with 10M glucose or 10mM uridine, and treated with the drugs of interest at a 10µM concentration. After 72h, Prestoblue was added. Relative Prestoblue fluorescence was measured after 2h. Fold change in viability compared to untreated control cells.

Figure 6 shows validation of the compounds (identified with CAS numbers) in U937 histiocytic lymphoma monocytic cells. Cells were diluted in glucose-free media supplemented with 100nM phorbol-12-myristate-13-acetate (PMA) and with 10M glucose or 10mM uridine, and treated with the drugs of interest at a 10µM concentration. After 72h, Prestoblue was added. Relative Prestoblue fluorescence was measured after 2h. Fold change of viability compared to untreated control cells.

Figure 7 shows validation of the compounds (identified with CAS numbers) in UACC-257 melanoma cells. Cells were diluted in glucose-free media supplemented with 10mM uridine. Extracellular acidification rates (ECAR), an indicator of the glycolytic activity of cells, was recorded at baseline. The drugs of interest at a 10μM concentration were then acutely injected, and ECAR was measured again after 2h. Fold change in ECAR compared to DMSO treated cells.

Figure 8 shows validation of the compounds (identified with CAS numbers) in an *in vitro* system containing recombinant human UPP1 enzyme (2ng/μL), phosphate buffer (0.1M), uridine (2mM final) and the drugs of interest at a 10μM concentration. Absorbance at 280nm is proportional to the catabolism of uridine and was measured over 1h. Fold change in activity compared to DMSO.

Figure 9 shows validation of Mubritinib derivatives in UACC-257 melanoma cells. Cells were diluted in glucose-free media supplemented with 10M glucose (grey) or 10mM uridine (blue), and treated with the drugs of interest at a 10μM concentration. After 72h, Prestoblue was added. Relative Prestoblue fluorescence was measured after 2h. Fold change in viability compared to untreated control cells.

Figure 10 shows a bioinformatic analysis of UPP1 expression levels across 1,479 cancer cell lines from the Cancer Cell Line Encyclopedia (CCLE), corresponding to 33 cancer lineages and 76 sub-lineages. Highlighted in red are cancers with high UPP1 expression, such as pancreatic cancers and melanoma. High UPP1 expression is defined as $\log_2(TPM+1) > 5$. "HC + IC" corresponds to "Hepatocellular Carcinoma plus Intrahepatic Cholangiocarcinoma". "UPS/MFH/HGSCS" corresponds to "Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma."

DETAILED DESCRIPTION OF THE INVENTION

All documents, patents, patent applications, publications, product descriptions, and protocols which are cited throughout this application are incorporated herein by reference in their entireties for all purposes. The publications and applications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such

publication by virtue of prior invention. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting.

In the case of conflict, the present specification, including definitions, will control. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the subject matter herein belongs. As used herein, the following definitions are supplied in order to facilitate the understanding of the present invention.

The term “comprise” is generally used in the sense of include, that is to say permitting the presence of one or more features or components. Also as used in the specification and claims, the language "comprising" can include analogous embodiments described in terms of "consisting of“ and/or "consisting essentially of”.

As used in the specification and claims, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise.

As used in the specification and claims, the term "and/or" used in a phrase such as "A and/or B" herein is intended to include "A and B", "A or B", "A", and "B".

As used herein, "nucleotides” refer to (1) desoxyadenosine, adenosine, thymidine, desoxyuridine, uridine, deoxypseudoruridine, pseudouridine, deoxyguanosine, guanosine, deoxycytidine, cytidine, deoxyinosine and inosine, in non-, mono-, di-, or tri-phosphorylated forms. Non-phosphorylated nucleotides are also called "nucleosides"; (2) nucleotide polymers (nucleic acids in general and in particular DNA and RNA); (3) nucleotide derivative (adenine, guanine, cytosine, uracil, thymine, pseudouracil, hypoxantine, xanthine, ribose-1-phosphate, ribose-5-phosphate, phosphoribosylpyrophosphate); (4) dinucleotides such as nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH).

As used herein, "catabolism" refers to the breakdown of complex molecules in living organisms to form simpler ones, in certain cases accompanied by the release of energy. It includes, but is not limited to, the breakdown (catabolism) of nucleotides, such as uridine that typically includes (1) the phosphorylytic cleavage of uridine by uridine phosphorylase UPP1/2 into uracil and ribose-1-phosphate (R1P); (2) the conversion of R1P into ribose-5-phosphate (R5P) by a

phosphoglucomutase; (3) the conversion of R5P into fructose-6-P and glyceraldehyde-3-P by the non-oxidative branch of the pentose phosphate pathway (non-oxPPP); and (4) their glycolytic utilization to fuel ATP production, biosynthesis and gluconeogenesis.

As used herein, the term “inhibitor of nucleotide catabolism“, such as inhibitor of uridine catabolism, refers to a compound, a gene or an antibody which, when tested in the screening method of the present invention, prevents or reduces the growth of cells in the presence of a nucleotide, such as uridine, but not in the presence of glucose and that prevents or reduces the growth of cells in comparison with the blank incubation.

As used herein, the terms "subject" and “patient” are well-recognized in the art, and, are used herein to refer to a mammal, and most preferably a human. In some embodiments, the subject is a subject in need of treatment and/or a subject having a disease selected from a cancer, immune disorders and metabolic disorders. The term does not denote a particular age or sex. Thus, individuals of all ages, from newborn to adult, whether male or female, are intended to be covered.

As used herein, an "effective amount" of an agent, e.g., a pharmaceutical formulation, or an inhibitor, refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result. An effective amount can be provided in one or more administrations.

As used herein, a "therapeutically effective amount" is at least the minimum concentration required to effect a measurable improvement of a particular disorder (e.g., a cancer, immune disorders and metabolic disorders). A therapeutically effective amount herein may vary according to factors such as the disease state, age, sex, and weight of the patient, and the ability of the inhibitors of the present invention to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the inhibitors of the present invention are outweighed by the therapeutically beneficial effects.

As used herein, the term "treatment" (and grammatical variations thereof such as "treat" or "treating") refers to clinical intervention designed to alter the natural course of the individual or cell being treated during the course of clinical pathology. Desirable effects of treatment include, but are not limited to, alleviation of symptoms, diminishment of any direct or indirect

pathological consequences of the disease, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. In some embodiments, the inhibitors of the present invention are used to delay development of a disease or to slow the progression of a disease. In some embodiments, the disease is cancer, immune disorder or metabolic disorder. An individual is successfully "treated", for example, if one or more symptoms associated with a cancer, immune disorder and/or metabolic disorder are mitigated or eliminated.

The catabolism of uridine typically includes (1) the phosphorylytic cleavage of uridine by uridine phosphorylase UPP1/2 into uracil and ribose-1-phosphate (R1P); (2) the conversion of R1P into fructose-6-P and glyceraldehyde-3-P by the non-oxidative branch of the pentose phosphate pathway (non-oxPPP); (3) the conversion of R5P into fructose-6-P and glyceraldehyde-3-P by the non-oxidative branch of the pentose phosphate pathway (non-oxPPP); and (4) their glycolytic utilization to fuel ATP production, biosynthesis and gluconeogenesis.

To identify inhibitors of nucleotide catabolism, such as inhibitors of uridine catabolism, a system based on the growth of cells in media containing glucose or nucleotide, such as uridine, as sole source of sugar was established. This system is described in Figure 1.

Thus, an aspect of the present invention provides a screening method for identification of inhibitors of nucleotide catabolism, said method comprising the steps of

(i) providing a cell line that has ability to grow on glucose-free media comprising a nucleotide;

(ii) incubating the cell line of step (i) on glucose-free media comprising a nucleotide and a test compound;

(iii) incubating the cell line of step (i) on nucleotide-free media comprising glucose and a test compound;

(iv) incubating the cell line of step (i) on glucose-free media comprising the nucleotide without a test compound (blank incubation);

(v) measuring the growth of cells in steps (ii) to (iv);

(vi) selecting the test compound that

- reduces the growth of cells in step (ii), but not in step (iii),

- reduces the growth of cells in step (ii) comparing to the blank incubation of step (iv)

(vii) optionally determining the half maximal inhibitory concentration (IC_{50}) of the compounds selected in step (vi).

In some embodiments of the screening method of the present invention, the nucleotide is selected from the group comprising adenosine, uridine, pseudouridine, guanosine, cytidine and inosine.

An embodiment of the screening method of present invention provides a screening method for identification of inhibitors of uridine catabolism, said method comprising the steps of

(i) providing a cell line that either has a natural or artificial high expression of the UPP1 or UPP2 gene and/or has ability to grow on glucose-free media comprising uridine;

(ii) incubating the cell line of step (i) on glucose-free media comprising uridine and a test compound;

(iii) incubating the cell line of step (i) on uridine-free media comprising glucose and a test compound;

(iv) incubating the cell line of step (i) on glucose-free media comprising uridine without a test compound (blank incubation);

(v) measuring the growth of cells in steps (ii) to (iv);

(vi) selecting the test compound that

- reduces the growth of cells in step (ii), but not in step (iii),
- reduces the growth of cells in step (ii) comparing to the blank incubation of step (iv)

(vii) optionally determining the half maximal inhibitory concentration (IC_{50}) of the compounds selected in step (vi).

In some embodiments of the screening method of the present invention, the growth of cells in step (ii) is at least 2-fold less comparing to step (iii) and/or step (iv).

According to an embodiment of the screening method of the present invention, optionally determining IC_{50} in step (vii) is carried out

1) first by selecting the test compound according to step (vi). The concentration of the test compound being typically 10 μM.

2) then by varying the concentrations of the selected test compound (typically 10 different concentrations), IC_{50} can be determined. IC_{50} is a concentration of an inhibitor that causes 50% inhibition of the growth of cells.

In an embodiment of the screening method of the present invention, the cell line of step (i) is UACC-257, UACC-57, A2058, SK-MEL5, SK-MEL30, MDA-MB-435S, LOX-IMVI, SH4 melanoma cells, AsPC1 pancreatic cancer, SW480 colon cancer, U937 monocytic cells, or any cell line with detectable levels of UPP1 or UPP2 gene expression and/or ability to grow using a nucleotide, such as uridine, as an energy source ; or a cell line engineered to express UPP1 or UPP2; or a cell line with natural or artificial high level expression of the UPP1 or UPP2 gene.

In another embodiment of the screening method of the present invention, the duration of the incubation of steps (ii), (iii), and (iv) is typically 72 hours, in some embodiments the incubation time is 24 hours, 36 hours, 48 hours, 60 hours, 72 hours, 84 hours, or selected within 24 hours to 84 hours, or 48 hours to 84 hours.

In some embodiments of the screening method of the present invention, a suitable glucose-free media comprising uridine is typically glucose-free RPMI (Roswell Park Memorial Institute) medium supplemented with a nucleotide, such as uridine, or glucose-free DMEM (Dulbecco's Modified Eagle's Medium) supplemented with a nucleotide, such as uridine. In other embodiments of the screening method of the present invention, a glucose-free media supplemented with a nucleotide, such as uridine, generally comprise a nucleotide, such as uridine, as a sole source of sugar and compounds which promote the growth and replication of cells. A typical glucose-free culture medium is composed of a complement of amino acids, vitamins, inorganic salts, a nucleotide, such as uridine, and dialyzed serum as a source of growth factors, hormones, and attachment factors.

In some embodiments of the screening method of the present invention, a suitable nucleotide-free media, such as uridine-free media, comprising glucose is typically nucleotide free, such as uridine-free, RPMI (Roswell Park Memorial Institute) medium supplemented with glucose or nucleotide-free, such as uridine-free, DMEM (Dulbecco's Modified Eagle's Medium) supplemented with glucose. In other embodiments of the screening method of the present invention, a nucleotide-free, such as uridine-free, media supplemented with glucose generally comprise glucose as a sole source of sugar and compounds which promote the growth and

replication of cells. A typical nucleotide-free, such as uridine-free, culture medium is composed of a complement of amino acids, vitamins, inorganic salts, glucose and dialyzed serum as a source of growth factors, hormones, and attachment factors.

In some embodiments of the screening method of the present invention, incubation of cell lines is typically carried out in an incubator with a tightly regulated temperature and CO_2 concentration. Cell lines typically grow at 37°C and 5% CO_2 with saturating humidity.

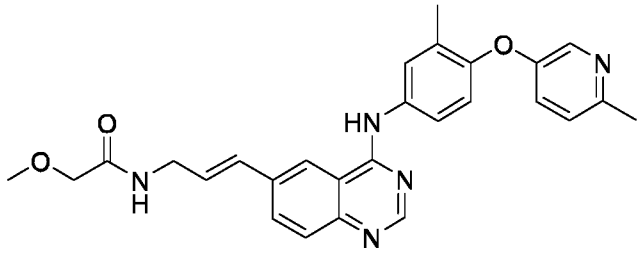
In some embodiments of the screening method of the present invention, measuring the growth of cells in steps (ii), (iii), (iv) and/or (v) is carried out by addition of a cell viability dye, such as Prestoblue.

Another aspect of the present invention provides an inhibitor of nucleotide catabolism, such as uridine catabolism, and/or nucleotide transport, such as uridine transport, identified by the screening method of the present invention. The preferred embodiments of the present invention provide an inhibitor of uridine catabolism and/or uridine transport, identified by the screening method of the present invention.

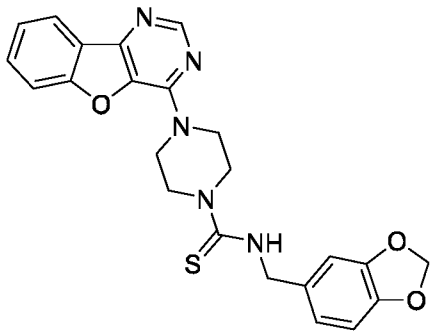
Another aspect of the present invention provides an inhibitor of nucleotide transport, identified by the screening method of the present invention. The preferred embodiments of the present invention provide an inhibitor of uridine transport, identified by the screening method of the present invention.

Another aspect of the present invention provides an inhibitor, that can be identified by the screening method of the present invention, selected from the group comprising

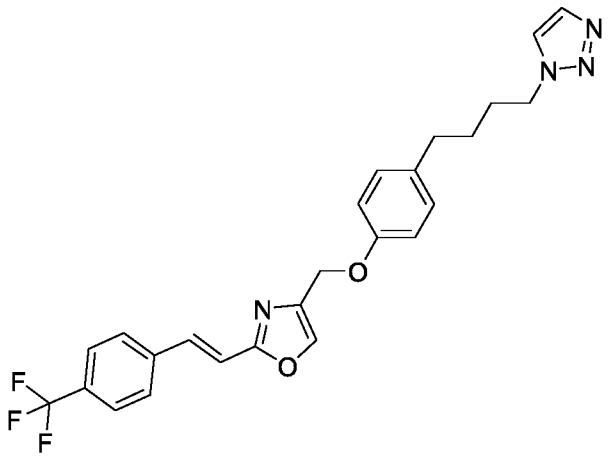
- 2-Methoxy-N-[(2E)-3-[4-[[3-methyl-4-[(6-methyl-3-pyridinyl)oxy]phenyl]amino]-6-quinazolinyl]-2-propen-1-yl]acetamide
  (CP-724714) (CAS: 383432-38-0)



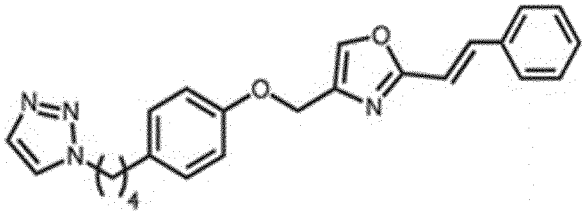
- N-(1,3-Benzodioxol-5-ylmethyl)-4-benzofuro[3,2-d]pyrimidin-4-yl-1-piperazinecarbothioamide
(Amuvatinib, MP-470) (CAS: 850879-09-3)



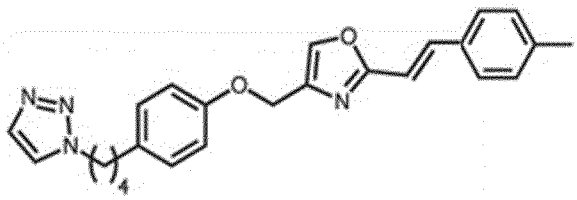
- 1-[4-[4-[[2-[(1E)-2-[4-(Trifluoromethyl)phenyl]ethenyl]-4-oxazolyl]methoxy]phenyl]butyl]-1H-1,2,3-triazole, synonym (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-trifluoromethyl)styryl)oxa-zole
(Mubritinib, TAK 165) (CAS: 366017-09-6)



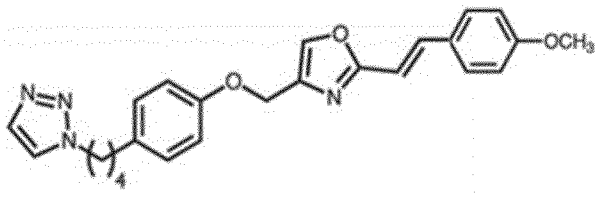
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-(styryl)oxazole, Mubritinib derivative 2



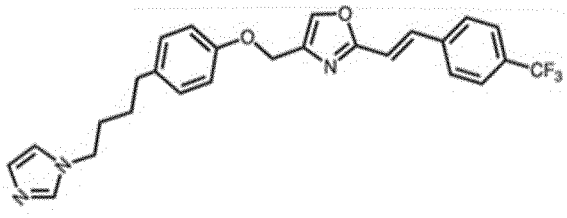
- (*E*)−4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methyl)styryl)oxazole, Mubritinib derivative 3



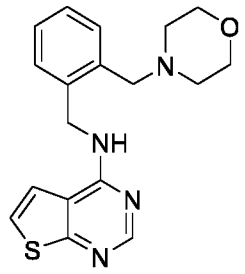
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methoxy)styryl)oxazole, Mubritinib derivative 4



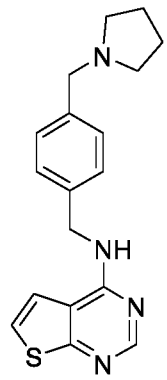
- (*E*)-4-((4-(4-(1*H*-imidazol-1-yl)butyl)phenoxy)methyl)-2-(4-(trifluoromethyl)styryl)oxazole, Mubritinib derivative 7



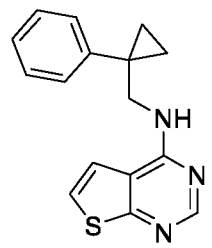
- N-[[2-(4-Morpholinylmethyl)phenyl]methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 924234-99-1)



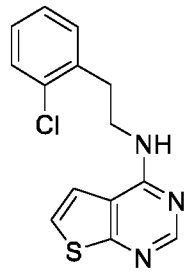
- N-[[4-(1-Pyrrolidinylmethyl)phenyl]methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 930943-65-0)



- N-[(1-Phenylcyclopropyl)methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1110937-38-6)

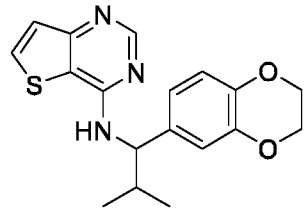


- N-[2-(2-Chlorophenyl)ethyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1241587-59-6)



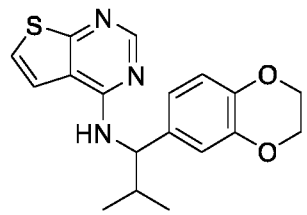
- N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[3,2-d]pyrimidin-4-amine

(CAS: 930038-39-4)



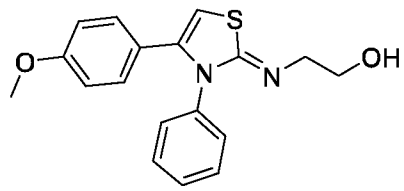
- N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[2,3-d]pyrimidin-4-amine

(CAS: 1015153-83-9)

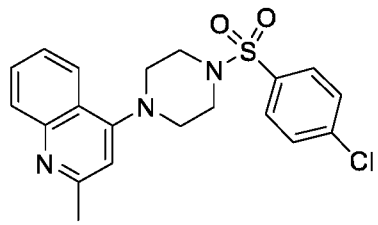


- 2-[[4-(4-Methoxyphenyl)-3-phenyl-2(3H)-thiazolylidene]amino]ethanol

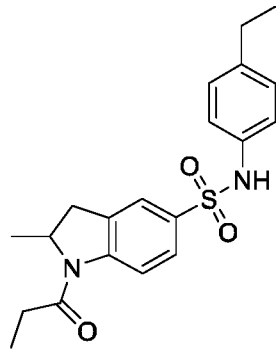
(CAS: 303787-45-3)



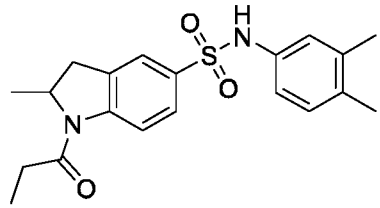
- 4-[4-[(4-Chlorophenyl)sulfonyl]-1-piperazinyl]-2-methylquinoline
(CAS: 433248-90-9)



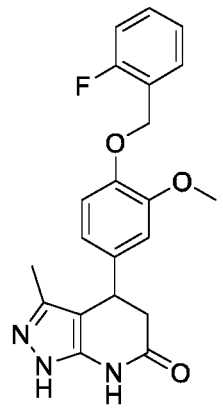
- N-(4-Ethylphenyl)-2,3-dihydro-2-methyl-1-(1-oxopropyl)-1H-indole-5-sulfonamide
(CAS: 901008-80-8)



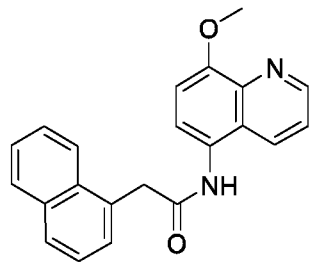
- N-(3,4-Dimethylphenyl)-2,3-dihydro-2-methyl-1-(1-oxopropyl)-1H-indole-5-sulfonamide (CAS: 901009-05-0)



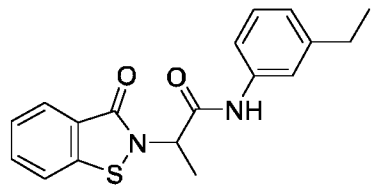
- 4-[4-[(2-Fluorophenyl)methoxy]-3-methoxyphenyl]-1,4,5,7-tetrahydro-3-methyl-6H-pyrazolo[3,4-b]pyridin-6-one (CAS: 1110976-91-4)



- N-(8-Methoxy-5-quinolinyl)-1-naphthaleneacetamide (CAS: 942850-72-8)

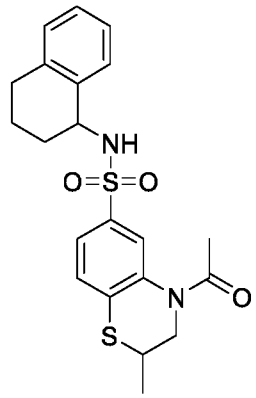


- N-(3-Ethylphenyl)-α-methyl-3-oxo-1,2-benzisothiazole-2(3H)-acetamide (CAS: 902841-23-0)



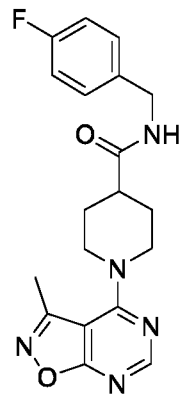
- 4-Acetyl-3,4-dihydro-2-methyl-N-(1,2,3,4-tetrahydro-1-naphthalenyl)-2H-1,4-benzothiazine-6-sulfonamide

(CAS: 891932-93-7)



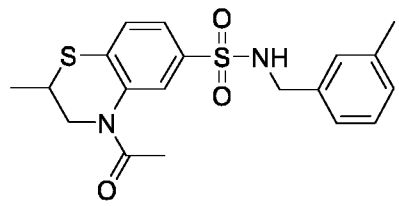
- N-[(4-Fluorophenyl)methyl]-1-(3-methylisoxazolo[5,4-d]pyrimidin-4-yl)-4-piperidinecarboxamide

(CAS: 932292-32-5)



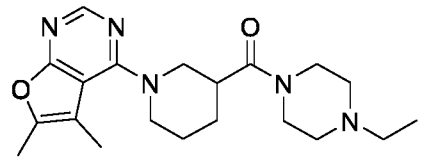
- 4-Acetyl-3,4-dihydro-2-methyl-N-[(3-methylphenyl)methyl]-2H-1,4-benzothiazine-6-sulfonamide

(CAS: 1113123-97-9)

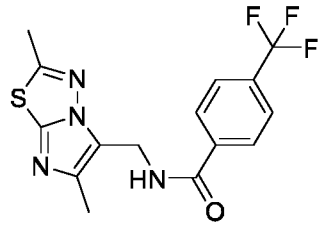


- [1-(5,6-Dimethylfuro[2,3-d]pyrimidin-4-yl)-3-piperidinyl](4-ethyl-1-piperazinyl)methanone

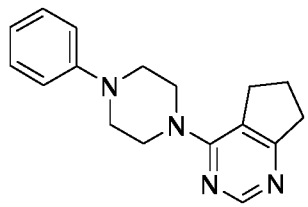
(CAS: 1111019-76-1)



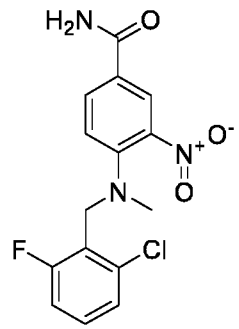
- N-[(2,6-Dimethylimidazo[2,1-b]-1,3,4-thiadiazol-5-yl)methyl]-4-(trifluoromethyl)benzamide
(CAS: 1341006-76-5)



- 1-{5H,6H,7H-cyclopenta[d]pyrimidin-4-yl}-4-phenylpiperazine
(CAS: 1340813-43-5)

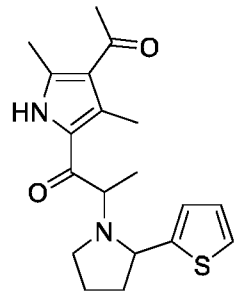


- 4-[[(2-Chloro-6-fluorophenyl)methyl]methylamino]-3-nitrobenzamide
(CAS: 877974-11-3)



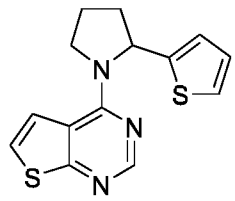
- 1-(4-Acetyl-3,5-dimethyl-1H-pyrrol-2-yl)-2-[2-(2-thienyl)-1-pyrrolidinyl]-1-propanone

(CAS: 878911-41-2)



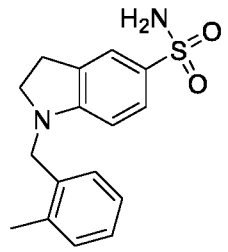
- 4-[2-(2-Thienyl)-1-pyrrolidinyl]thieno[2,3-d]pyrimidine

(CAS: 924219-03-4)



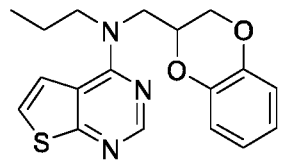
- 2,3-Dihydro-1-[(2-methylphenyl)methyl]-1H-indole-5-sulfonamide

(CAS: 923778-03-4)

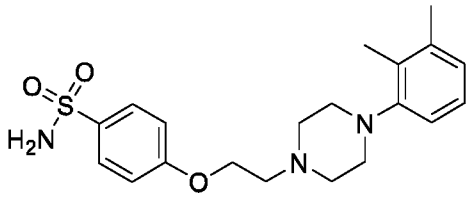


- N-[(2,3-Dihydro-1,4-benzodioxin-2-yl)methyl]-N-propylthieno[2,3-d]pyrimidin-4-amine

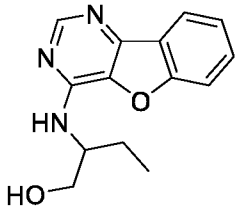
(CAS: 1090372-48-7)



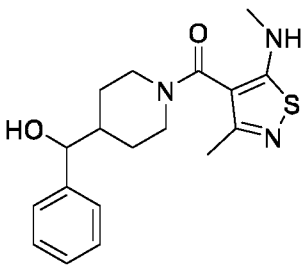
- 4-[2-[4-(2,3-Dimethylphenyl)-1-piperazinyl]ethoxy]benzenesulfonamide
  (CAS: 1110869-85-6)



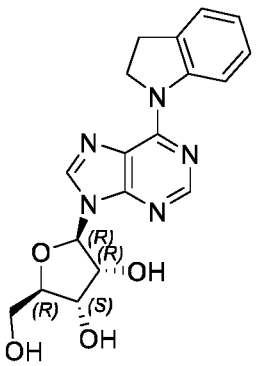
- 2-(Benzofuro[3,2-d]pyrimidin-4-ylamino)-1-butanol
  (CAS: 844649-81-6)



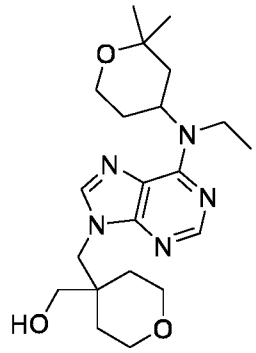
- [4-(Hydroxyphenylmethyl)-1-piperidinyl][3-methyl-5-(methylamino)-4-isothiazolyl]methanone
  (CAS: 1197739-15-3)



- 6-(2,3-Dihydro-1H-indol-1-yl)-9-β-D-ribofuranosyl-9H-purine
  (CAS: 402724-46-3)

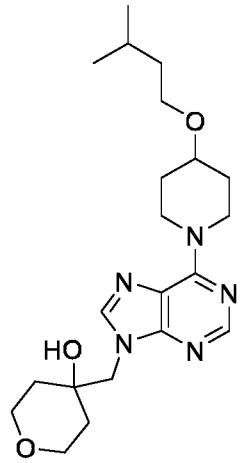


- 4-[[6-[Ethyl(tetrahydro-2,2-dimethyl-2H-pyran-4-yl)amino]-9H-purin-9-yl]methyl]tetrahydro-2H-pyran-4-methanol
  (CAS: 2324334-92-9)



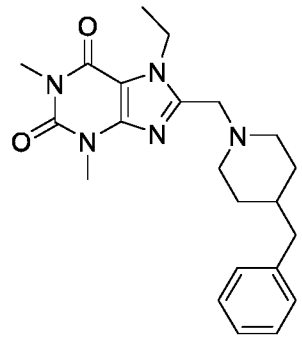
- Tetrahydro-4-[[6-[4-(3-methylbutoxy)-1-piperidinyl]-9H-purin-9-yl]methyl]-2H-pyran-4-ol

  (CAS: 2188639-44-1)

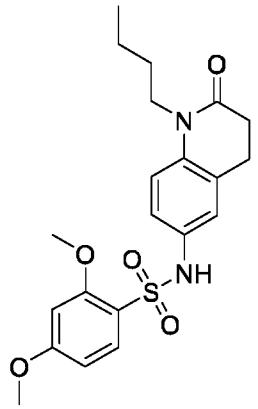


- 7-Ethyl-3,7-dihydro-1,3-dimethyl-8-[[4-(phenylmethyl)-1-piperidinyl]methyl]-1H-purine-2,6-dione

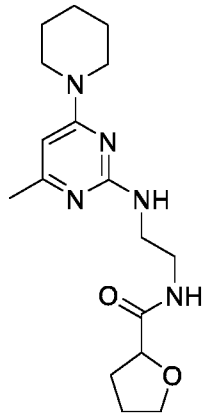
(CAS: 878441-28-2)



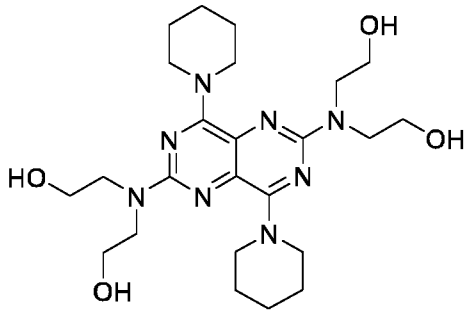
- N-(1-Butyl-1,2,3,4-tetrahydro-2-oxo-6-quinolinyl)-2,4-dimethoxybenzenesulfonamide
(CAS: 941906-49-6)



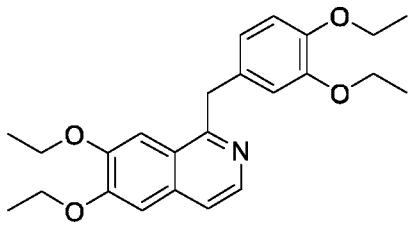
- Tetrahydro-N-[2-[[4-methyl-6-(1-piperidinyl)-2-pyrimidinyl]amino]ethyl]-2-furancarboxamide
(CAS: 1207002-37-6)



- 2,2′,2″,2‴-[(4,8-Di-1-piperidinylpyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetrakis[ethanol]
(Dipyridamole) (CAS: 58-32-2)



- 1-(3,4-Diethoxybenzyl)-6,7-diethoxyisoquinoline
(Ethaverine hydrochloride) (CAS: 486-47-5)



that is used for inhibiting nucleotide catabolism, preferably uridine catabolism and/or for inhibiting nucleotide transport, preferably uridine transport. According to some embodiments, the inhibitors are used for in-vitro inhibiting nucleotide catabolism, preferably uridine catabolism and/or for in-vitro inhibiting nucleotide transport, preferably uridine transport. According to some preferred embodiments, the inhibitors are used for in-vitro inhibiting uridine catabolism and/or in-vitro inhibiting uridine transport.

In a preferred embodiment, the present invention provides an inhibitor, that can be identified by the screening method of the present invention, selected from the group comprising

- 1-[4-[4-[[2-[(1E)-2-[4-(Trifluoromethyl)phenyl]ethenyl]-4-oxazolyl]methoxy]phenyl]butyl]-1H-1,2,3-triazole (Mubritinib, TAK 165) (CAS: 366017-09-6)
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-(styryl)oxazole, Mubritinib derivative 2

- (*E*)−4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methyl)styryl)oxazole, Mubritinib derivative 3
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methoxy)styryl)oxazole, Mubritinib derivative 4
- (*E*)-4-((4-(4-(1*H*-imidazol-1-yl)butyl)phenoxy)methyl)-2-(4-(trifluoromethyl)styryl)oxazole, Mubritinib derivative 7
- N-[(1-Phenylcyclopropyl)methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1110937-38-6)
- N-[2-(2-Chlorophenyl)ethyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1241587-59-6)
- 7-Ethyl-3,7-dihydro-1,3-dimethyl-8-[[4-(phenylmethyl)-1-piperidinyl]methyl]-1H-purine-2,6-dione (CAS: 878441-28-2)
- N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1015153-83-9)
- N-[(2,6-Dimethylimidazo[2,1-b]-1,3,4-thiadiazol-5-yl)methyl]-4-(trifluoromethyl)benzamide (CAS: 1341006-76-5)
- N-(8-Methoxy-5-quinolinyl)-1-naphthaleneacetamide (CAS: 942850-72-8)
- N-[(4-Fluorophenyl)methyl]-1-(3-methylisoxazolo[5,4-d]pyrimidin-4-yl)-4-piperidinecarboxamide (CAS: 932292-32-5)
- 2-Methoxy-N-[(2E)-3-[4-[[3-methyl-4-[(6-methyl-3-pyridinyl)oxy]phenyl]amino]-6-quinazolinyl]-2-propen-1-yl]acetamide (CP-724714) (CAS: 383432-38-0)
- 4-[[(2-Chloro-6-fluorophenyl)methyl]methylamino]-3-nitrobenzamide (CAS: 877974-11-3)
- 4-[4-[(2-Fluorophenyl)methoxy]-3-methoxyphenyl]-1,4,5,7-tetrahydro-3-methyl-6H-pyrazolo[3,4-b]pyridin-6-one (CAS: 1110976-91-4)
- N-(1,3-Benzodioxol-5-ylmethyl)-4-benzofuro[3,2-d]pyrimidin-4-yl-1-piperazinecarbothioamide (Amuvatinib, MP-470) (CAS: 850879-09-3)
- N-[[2-(4-Morpholinylmethyl)phenyl]methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 924234-99-1)

- N-[[4-(1-Pyrrolidinylmethyl)phenyl]methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 930943-65-0)
- N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[3,2-d]pyrimidin-4-amine (CAS: 930038-39-4)

that is used for inhibiting nucleotide catabolism, preferably uridine catabolism and/or for inhibiting nucleotide transport, preferably uridine transport. According to some embodiments, the inhibitors are used for in-vitro inhibiting nucleotide catabolism, preferably uridine catabolism and/or for in-vitro inhibiting nucleotide transport, preferably uridine transport. According to some preferred embodiments, the inhibitors are used for in-vitro inhibiting uridine catabolism and/or for in-vitro inhibiting uridine transport.

In another preferred embodiment, the present invention provides an inhibitor, that can be identified by the screening method of the present invention, selected from the group comprising

- 1-[4-[4-[[2-[(1E)-2-[4-(Trifluoromethyl)phenyl]ethenyl]-4-oxazolyl]methoxy]phenyl]butyl]-1H-1,2,3-triazole (Mubritinib, TAK 165) (CAS: 366017-09-6)
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-(styryl)oxazole, Mubritinib derivative 2
- (*E*)−4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methyl)styryl)oxazole, Mubritinib derivative 3
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methoxy)styryl)oxazole, Mubritinib derivative 4
- (*E*)-4-((4-(4-(1*H*-imidazol-1-yl)butyl)phenoxy)methyl)-2-(4-(trifluoromethyl)styryl)oxazole, Mubritinib derivative 7
- N-[(1-Phenylcyclopropyl)methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1110937-38-6)
- N-[2-(2-Chlorophenyl)ethyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1241587-59-6)
- 7-Ethyl-3,7-dihydro-1,3-dimethyl-8-[[4-(phenylmethyl)-1-piperidinyl]methyl]-1H-purine-2,6-dione (CAS: 878441-28-2)

- N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1015153-83-9)
- N-[(2,6-Dimethylimidazo[2,1-b]-1,3,4-thiadiazol-5-yl)methyl]-4-(trifluoromethyl)benzamide (CAS: 1341006-76-5)
- N-(8-Methoxy-5-quinolinyl)-1-naphthaleneacetamide (CAS: 942850-72-8)
- N-[(4-Fluorophenyl)methyl]-1-(3-methylisoxazolo[5,4-d]pyrimidin-4-yl)-4-piperidinecarboxamide (CAS: 932292-32-5)
- N-(1,3-Benzodioxol-5-ylmethyl)-4-benzofuro[3,2-d]pyrimidin-4-yl-1-piperazinecarbothioamide (Amuvatinib, MP-470) (CAS: 850879-09-3)
- 2-Methoxy-N-[(2E)-3-[4-[[3-methyl-4-[(6-methyl-3-pyridinyl)oxy]phenyl]amino]-6-quinazolinyl]-2-propen-1-yl]acetamide (CP-724714) (CAS: 383432-38-0)

that is used for inhibiting nucleotide catabolism, preferably uridine catabolism and/or for inhibiting nucleotide transport, preferably uridine transport. According to some embodiments, the inhibitors are used for in-vitro inhibiting nucleotide catabolism, preferably uridine catabolism and/or for in-vitro inhibiting nucleotide transport, preferably uridine transport. According to some preferred embodiments, the inhibitors are used for in-vitro inhibiting uridine catabolism and/or for in-vitro inhibiting uridine transport.

In another preferred embodiment, the present invention provides an inhibitor, that can be identified by the screening method of the present invention, selected from the group comprising

- N-[(1-Phenylcyclopropyl)methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1110937-38-6)
- N-[2-(2-Chlorophenyl)ethyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1241587-59-6)
- N-[[4-(1-Pyrrolidinylmethyl)phenyl]methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 930943-65-0
- N-[[2-(4-Morpholinylmethyl)phenyl]methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 924234-99-1)

that is used for inhibiting nucleotide catabolism, preferably uridine catabolism and/or for inhibiting nucleotide transport, preferably uridine transport. According to some embodiments, the inhibitors are used for in-vitro inhibiting nucleotide catabolism, preferably uridine catabolism and/or for in-vitro inhibiting nucleotide transport, preferably uridine transport.

According to some preferred embodiments, the inhibitors are used for in-vitro inhibiting uridine catabolism and/or in-vitro inhibiting uridine transport.

In another preferred embodiment, the present invention provides an inhibitor, that can be identified by the screening method of the present invention, selected from the group comprising

- N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1015153-83-9)
- N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[3,2-d]pyrimidin-4-amine (CAS: 930038-39-4)

that is used for inhibiting nucleotide catabolism, preferably uridine catabolism and/or for inhibiting nucleotide transport, preferably uridine transport. According to some embodiments, the inhibitors are used for in-vitro inhibiting nucleotide catabolism, preferably uridine catabolism and/or for in-vitro inhibiting nucleotide transport, preferably uridine transport. According to some preferred embodiments, the inhibitors are used for in-vitro inhibiting uridine catabolism and/or for in-vitro inhibiting uridine transport.

In another preferred embodiment, the present invention provides an inhibitor, that can be identified by the screening method of the present invention, selected from the group comprising

- 1-[4-[4-[[2-[(1E)-2-[4-(Trifluoromethyl)phenyl]ethenyl]-4-oxazolyl]methoxy]phenyl]butyl]-1H-1,2,3-triazole (Mubritinib, TAK 165) (CAS: 366017-09-6)
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-(styryl)oxazole, Mubritinib derivative 2
- (*E*)−4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methyl)styryl)oxazole, Mubritinib derivative 3
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methoxy)styryl)oxazole, Mubritinib derivative 4
- (*E*)-4-((4-(4-(1*H*-imidazol-1-yl)butyl)phenoxy)methyl)-2-(4-(trifluoromethyl)styryl)oxazole, Mubritinib derivative 7

that is used for inhibiting nucleotide catabolism, preferably uridine catabolism and/or for inhibiting nucleotide transport, preferably uridine transport. According to some embodiments, the inhibitors are used for in-vitro inhibiting nucleotide catabolism, preferably uridine

catabolism and/or for in-vitro inhibiting nucleotide transport, preferably uridine transport. According to some preferred embodiments, the inhibitors are used for in-vitro inhibiting uridine catabolism and/or for in-vitro inhibiting uridine transport.

Such in-vitro inhibiting is helpful in setting-up assays, screening methods or evaluating the inhibition of different inhibitors. Further, such an in-vitro inhibiting involves an in-vitro method comprising a cell incubation.

Another aspect of the present invention provides an inhibitor of nucleotide catabolism, preferably uridine catabolism, of the present invention for use in a method for treating a disease associated with nucleotide catabolism, preferably uridine catabolism. In some embodiments, the disease associated with nucleotide catabolism, preferably uridine catabolism, is selected from the group comprising cancer, immune disorders and metabolic disorders, wherein the cancer expresses high level of Uridine phosphorylase 1 (UPP1) or Uridine phosphorylase 2 (UPP2). See for example Figure 10. In preferred embodiments, the disease associated with uridine catabolism, is selected from cancer and immune disorders, wherein the cancer expresses high level of Uridine phosphorylase 1 (UPP1) or Uridine phosphorylase 2 (UPP2). In further preferred embodiments, the cancer is selected from the group comprising pancreatic ductal adenocarcinoma (PDA), melanoma and colon cancer. In another preferred embodiment, the disease associated with uridine catabolism, is cancer expressing high level of Uridine phosphorylase 1 (UPP1) or Uridine phosphorylase 2 (UPP2). In further preferred embodiments, the cancer is selected from the group comprising pancreatic ductal adenocarcinoma (PDA), melanoma and colon cancer.

As herein used, "high level", "high level expression" or "high UPP1 expression" is defined as $\log_2(TPM+1) > 5$, wherein TPM are “transcripts per million”. TPM are a standard way to measure gene expression, and are calculated as follows:

1) Read counts are divided by the length of each gene in kilobases. This gives “reads per kilobase” (RPK).
2) RPK values in a sample are counted up, and divided by 1,000,000. This number is the “per million” scaling factor.
3) RPK values are divided by the “per million” scaling factor to obtain TPM.

In some embodiments, the present invention provides a method for treating a disease associated with nucleotide catabolism, preferably uridine catabolism, in a subject, the method comprising administering an inhibitor of the nucleotide catabolism, preferably uridine catabolism, of the present invention to the subject. In some embodiments, the disease associated with nucleotide catabolism, preferably uridine catabolism, is selected from the group comprising cancer, immune disorders and metabolic disorders. In preferred embodiments, the disease associated with uridine catabolism, is selected from cancer and immune disorders. In an embodiment, the inhibitor of nucleotide catabolism, preferably uridine catabolism, is administered in a therapeutically effective amount.

In some embodiments, the inhibitors of nucleotide catabolism, preferably uridine catabolism, of the present invention are used in methods for treating a cancer either alone, as monotherapy, or in combination with other types of therapies such as immunotherapy, radiotherapy and/or chemotherapy. Thus in some embodiments, the method for treating a cancer further comprises administering to a subject one or more cancer immunotherapeutic agents selected from the group comprising an immune checkpoint inhibitor, a TCR-T cells, and a CAR-T cells. In other embodiments, the method for treating a cancer further comprises providing radiotherapy to a subject. In other embodiments, the method for treating a cancer further comprises administering to a subject one or more chemotherapeutic agents selected from the group comprising alkylating agents, nitrosoureas, antimetabolites, anti-tumor antibiotics, topoisomerase inhibitors, and mitotic inhibitors.

In some embodiments, the inhibitors of nucleotide catabolism, preferably uridine catabolism, of the present invention are indicated in monotherapy or combined therapy for the treatment of subjects having a cancer expressing high level of Uridine phosphorylase 1 (UPP1) or Uridine phosphorylase 2 (UPP2). Such a cancer is for example pancreatic ductal adenocarcinoma (PDA) cancers, melanoma or colon cancers that express high level of UPP1. Thus before starting a treatment, a test can be carried out to determine whether the cancer to be treated in a subject expresses high level of Uridine phosphorylase 1 (UPP1) or Uridine phosphorylase 2 (UPP2).

In some embodiments, the present invention provides the inhibitors of nucleotide catabolism, preferably uridine catabolism, of the present invention for use in the treatment of a cancer expressing high level of Uridine phosphorylase 1 (UPP1) or Uridine phosphorylase 2 (UPP2).

Optionally the treatment further comprises administering one or more cancer immunotherapeutic agents or one or more chemotherapeutic agents or further providing radiotherapy (to the subject).

In other embodiments, the present invention provides the inhibitors of nucleotide catabolism, preferably uridine catabolism, of the present invention for use in a method of treating a subject with cancer, wherein the method comprises:

(i) determining whether a cancer sample from the subject expresses high level of Uridine phosphorylase 1 (UPP1) or Uridine phosphorylase 2 (UPP2);

(ii) if the cancer sample from the subject expresses high level of Uridine phosphorylase 1 (UPP1) or Uridine phosphorylase 2 (UPP2) administering to the subject an effective amount of the inhibitors of nucleotide catabolism, preferably uridine catabolism, of the present invention; and

(iii) optionally further administering to the subject one or more cancer immunotherapeutic agents or one or more chemotherapeutic agents or further providing radiotherapy to the subject.

In other embodiments, the immune disorders are selected from inflammation disorders, auto-inflammatory disorders and auto-immune disorders. In some embodiments, the inflammation disorders are selected from Rheumatoid Arthritis (RA), Inflammatory Bowel Disease (IBD), Atherosclerosis and Cardiovascular Disease. In some embodiments, the auto-inflammatory disorders are selected from TNF Receptor-Associated Periodic Syndrome (TRAPS), Cryopyrin-Associated Periodic Syndromes (CAPS) and Familial Mediterranean Fever (FMF). In some embodiments, the auto-immune disorders are selected from Systemic Lupus Erythematosus (SLE), Type 1 Diabetes Mellitus, Multiple Sclerosis (MS) and Celiac Disease. The inhibitors of nucleotide catabolism, preferably uridine catabolism, of the present invention can be used in immune modulation. Indeed, the inhibitors of nucleotide catabolism, preferably uridine catabolism, of the present invention can be used to decrease the activity of "over-active" immune cells involved in inflammation disorders, auto-inflammatory disorders and auto-immune disorders, and thus decrease inflammation and prevent auto-inflammatory/auto-immune disorders. Inhibiting (blocking) uridine catabolism can starve those "over-active" immune cells by blocking the access to uridine as energy source and thereby disrupt or reduce their activity. The inventors explored nucleotide catabolism, such as uridine catabolism, in Primary Peripheral Blood Mononuclear Cells (PBMC) and found secretion of lactate (indicative

of uridine catabolism for energy production) and survival of the cells in the presence of uridine (see Figure 3). Further, the inventors investigated the efficacy of the compounds of the invention in monocytes-derived macrophages U937 (see Figure 6 that shows that the compounds are active in this context). U937 cells were used as model cells for monocytes (white blood cell), that can be differentiated into macrophages with PMA.

In further embodiments, the metabolic disorders are selected from fatty liver, obesity and diabetes. Indeed, it is established that a nucleotide-rich diet leads to fatty liver, obesity and diabetes. Thus blocking nucleotide, such as uridine, catabolism decreases energy absorption and helps prevent metabolic disorders.

In further embodiments of the present invention, the inhibitors of nucleotide catabolism, preferably uridine catabolism, of the present invention are also nucleotide transport inhibitors and are used for treating a disease associated with nucleotide transport. In some embodiments, the disease associated with nucleotide transport is selected from the group comprising cancer, viral diseases, bacterial diseases, cardiovascular disorders, inflammatory disorders, diabetes, pregnancy diseases, muscular diseases, impotence and parasitic infections. In some other embodiments, the disease associated with nucleotide transport is selected from the group comprising cancer, viral diseases, bacterial diseases, cardiovascular disorders, inflammatory disorders, diabetes, muscular diseases, impotence and parasitic infections.

Nucleotide transport inhibitors can be used in (i) antimetabolite potentiation, (ii) adenosine potentiation, and (iii) host tissue protection. Indeed, nucleotide transport, such as uridine transport, is crucial to ensure nucleotide homeostasis, such as uridine homeostasis, and due to the importance of nucleotide transport in many physiological processes, the alteration of nucleotide transport can be the origin of some pathological conditions. According to some embodiments, nucleotide transport inhibitors, such as uridine transport inhibitors, are important to disrupt, interrupt, or reduce the transport of nucleotide, preferably uridine, into cancer cells and/or into immune cells, preferably into cancer cells.

According to some embodiments, the inhibitors of nucleotide catabolism, preferably uridine catabolism, of the present invention are also inhibitors of nucleotide transport, preferably uridine transport. Thus according to further embodiments of the present invention, the inhibitors

of the present invention inhibit both nucleotide catabolism, preferably uridine catabolism, and nucleotide transport, preferably uridine transport.

Another aspect of the present invention provides an inhibitor of nucleotide catabolism, preferably uridine catabolism, of the present invention for use in a method for treating a disease associated with nucleotide transport, preferably uridine transport. A disease associated with nucleotide transport, preferably uridine transport, is a disease wherein inhibition of the nucleotide transport, preferably uridine transport, is beneficial for the treatment of said disease.

In some embodiments, the present invention provides a method for treating a disease associated with nucleotide transport in a subject, the method comprising administering an inhibitor of nucleotide catabolism, preferably uridine catabolism, of the present invention to the subject.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications without departing from the spirit or essential characteristics thereof. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations or any two or more of said steps or features. The present disclosure is therefore to be considered as in all aspects illustrated and not restrictive, the scope of the invention being indicated by the appended claims, and all changes which come within the meaning and range of equivalency are intended to be embraced therein.

The foregoing description will be more fully understood with reference to the following Examples. Such Examples, are, however, exemplary of methods of practicing the present invention and are not intended to limit the application and the scope of the invention.

EXAMPLES

Screening method

(1) Selection of a cell line of interest, define as:

a. A cell line with natural or artificial high expression of the UPP1 or UPP2 gene, and/or

b. A cell line with ability to grow on media where glucose has been replaced by uridine. For example UACC-257 melanoma cells, AsPC1 cells, SW480 cells or U937 cells.

(2) Transfer of the cell line to glucose-free media. For example glucose-free RPMI for UACC-257.

(3) Supplementation of the media with glucose or uridine. For example at a 10mM concentration.

(4) Plating of the cells to multi-well plates (for example 384-well plates) in duplicate. The multi-well plates are pre-plated with drugs from the libraries.

(5) Growth of the cells for a given amount of time, for example 72h.

(6) Addition of a cell viability dye, for example Prestoblue.

(7) Quantification of the signal and determination of IC50.

For screening:

UACC-257 cells were diluted in glucose-free media supplemented with 10mM glucose or 10mM uridine. Supplemented cells were then plated on 384-well plates pre-coated with compounds from the Prestwick library (Prestwick, 1'280 compounds), a kinase inhibitor library (Sellekchem, 258 compounds), a nucleoside library (Enamine, 320 compounds), or a chemically diverse collection (EPFL, 7'678 compounds) see below. The final concentration of inhibitors is 10µM. Prestoblue was added after 72h. Relative Prestoblue fluorescence was measured after 2h and Z-scores were calculated. Compounds were selected for further investigation based on their Z-scores. See Figure 2.

For validation:

UACC-257 cells were diluted in glucose-free media supplemented with 10mM glucose or 10mM uridine. Supplemented cells were then plated on 384-well plates pre-coated with the 96 best compounds from the screen, at 10 concentrations. The final concentration of inhibitors is 10^{-4} to $10^{-8.5}$ M. Prestoblue was added after 72h. Relative Prestoblue fluorescence was measured after 2h and IC50 were calculated. Compounds were selected for further investigation based on their IC50. See Table 2.

Validation in additional cell types:

AsPC1 were diluted in glucose-free media supplemented with 10mM glucose or 10mM uridine. Supplemented cells were then plated on 96-well plates pre-coated with the 30 best compounds from the validation. The final concentration of inhibitors is 10µM. Prestoblue was added after 72h. Relative Prestoblue fluorescence was measured after 2h and fold changes were calculated.

SW480 were diluted in glucose-free media supplemented with 10mM glucose or 10mM uridine. Supplemented cells were then plated on 96-well plates pre-coated with the 30 best compounds from the validation. The final concentration of inhibitors is 10µM. Prestoblue was added after 72h. Relative Prestoblue fluorescence was measured after 2h and fold changes were calculated.

U937 were diluted in glucose-free media supplemented with 10mM glucose or 10mM uridine, and 100 nM PMA (phorbol-12-myristate-13-acetate). Supplemented cells were then plated on 96-well plates pre-coated with the 30 best compounds from the validation. The final concentration of inhibitors is 10µM. Prestoblue was added after 72h. Relative Prestoblue fluorescence was measured after 2h and fold changes were calculated.

See Figures 4, 5 and 6 for results.

Identified inhibitors

The small molecule inhibitors were identified using the screening method of the invention. 1'280 compounds from the Prestwick library, 320 nucleosides analogs, 258 known kinase inhibitors and 7'678 compounds from a chemically diverse collection were used.

UACC-257 melanoma cells were used for the primary screen. Cells were grown on RPMI media supplemented with dialyzed FBS and either of 10mM glucose or 10mM uridine, for 72h in the presence of the small molecule inhibitors. The screen readout was performed using a Prestoblue assay (Life Technologies). The same protocol was applied to AsPC1 cells, SW480 cells and U937 cells.

Results of the screening are presented in Figures 2A, 2B and 7. Inhibitors with interesting profiles were then selected based on their ability to prevent the growth of cells on uridine but not on glucose. In a second independent experiment, cells were plated on increasing concentration of the compounds of interest for IC50 determination.

As a result of screening, the following inhibitors were validated:

CAS number	Chemical name
303787-45-3	2-[[4-(4-Methoxyphenyl)-3-phenyl-2(3H)-thiazolylidene]amino]ethanol
433248-90-9	4-[4-[(4-Chlorophenyl)sulfonyl]-1-piperazinyl]-2-methylquinoline
901008-80-8	N-(4-Ethylphenyl)-2,3-dihydro-2-methyl-1-(1-oxopropyl)-1H-indole-5-sulfonamide
901009-05-0	N-(3,4-Dimethylphenyl)-2,3-dihydro-2-methyl-1-(1-oxopropyl)-1H-indole-5-sulfonamide
1110976-91-4	4-[4-[(2-Fluorophenyl)methoxy]-3-methoxyphenyl]-1,4,5,7-tetrahydro-3-methyl-6H-pyrazolo[3,4-b]pyridin-6-one
942850-72-8	N-(8-Methoxy-5-quinolinyl)-1-naphthaleneacetamide
902841-23-0	N-(3-Ethylphenyl)-α-methyl-3-oxo-1,2-benzisothiazole-2(3H)-acetamide
891932-93-7	4-Acetyl-3,4-dihydro-2-methyl-N-(1,2,3,4-tetrahydro-1-naphthalenyl)-2H-1,4-benzothiazine-6-sulfonamide
932292-32-5	N-[(4-Fluorophenyl)methyl]-1-(3-methylisoxazolo[5,4-d]pyrimidin-4-yl)-4-piperidinecarboxamide
1113123-97-9	4-Acetyl-3,4-dihydro-2-methyl-N-[(3-methylphenyl)methyl]-2H-1,4-benzothiazine-6-sulfonamide
1111019-76-1	[1-(5,6-Dimethylfuro[2,3-d]pyrimidin-4-yl)-3-piperidinyl](4-ethyl-1-piperazinyl)methanone
1341006-76-5	N-[(2,6-Dimethylimidazo[2,1-b]-1,3,4-thiadiazol-5-yl)methyl]-4-(trifluoromethyl)benzamide
1340813-43-5	1-{5H,6H,7H-cyclopenta[d]pyrimidin-4-yl}-4-phenylpiperazine
877974-11-3	4-[[(2-Chloro-6-fluorophenyl)methyl]methylamino]-3-nitrobenzamide
878911-41-2	1-(4-Acetyl-3,5-dimethyl-1H-pyrrol-2-yl)-2-[2-(2-thienyl)-1-pyrrolidinyl]-1-propanone
924234-99-1	N-[[2-(4-Morpholinylmethyl)phenyl]methyl]thieno[2,3-d]pyrimidin-4-amine
930038-39-4	N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[3,2-d]pyrimidin-4-amine
924219-03-4	4-[2-(2-Thienyl)-1-pyrrolidinyl]thieno[2,3-d]pyrimidine

923778-03-4	2,3-Dihydro-1-[(2-methylphenyl)methyl]-1H-indole-5-sulfonamide
930943-65-0	N-[[4-(1-Pyrrolidinylmethyl)phenyl]methyl]thieno[2,3-d]pyrimidin-4-amine
1090372-48-7	N-[(2,3-Dihydro-1,4-benzodioxin-2-yl)methyl]-N-propylthieno[2,3-d]pyrimidin-4-amine
1110869-85-6	4-[2-[4-(2,3-Dimethylphenyl)-1-piperazinyl]ethoxy]benzenesulfonamide
1110937-38-6	N-[(1-Phenylcyclopropyl)methyl]thieno[2,3-d]pyrimidin-4-amine
844649-81-6	2-(Benzofuro[3,2-d]pyrimidin-4-ylamino)-1-butanol
1197739-15-3	[4-(Hydroxyphenylmethyl)-1-piperidinyl][3-methyl-5-(methylamino)-4-isothiazolyl]methanone
1241587-59-6	N-[2-(2-Chlorophenyl)ethyl]thieno[2,3-d]pyrimidin-4-amine
1015153-83-9	N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[2,3-d]pyrimidin-4-amine
402724-46-3	6-(2,3-Dihydro-1H-indol-1-yl)-9-β-D-ribofuranosyl-9H-purine
2324334-92-9	4-[[6-[Ethyl(tetrahydro-2,2-dimethyl-2H-pyran-4-yl)amino]-9H-purin-9-yl]methyl]tetrahydro-2H-pyran-4-methanol
2188639-44-1	Tetrahydro-4-[[6-[4-(3-methylbutoxy)-1-piperidinyl]-9H-purin-9-yl]methyl]-2H-pyran-4-ol
878441-28-2	7-Ethyl-3,7-dihydro-1,3-dimethyl-8-[[4-(phenylmethyl)-1-piperidinyl]methyl]-1H-purine-2,6-dione
941906-49-6	N-(1-Butyl-1,2,3,4-tetrahydro-2-oxo-6-quinolinyl)-2,4-dimethoxybenzenesulfonamide
1207002-37-6	Tetrahydro-N-[2-[[4-methyl-6-(1-piperidinyl)-2-pyrimidinyl]amino]ethyl]-2-furancarboxamide
58-32-2	2,2′,2″,2‴-[(4,8-Di-1-piperidinylpyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetrakis[ethanol] (Dipyridamole)
486-47-5	1-(3,4-Diethoxybenzyl)-6,7-diethoxyisoquinoline (Ethaverine hydrochloride)
383432-38-0	2-Methoxy-N-[(2E)-3-[4-[[3-methyl-4-[(6-methyl-3-pyridinyl)oxy]phenyl]amino]-6-quinazolinyl]-2-propen-1-yl]acetamide (CP-724714)
850879-09-3	N-(1,3-Benzodioxol-5-ylmethyl)-4-benzofuro[3,2-d]pyrimidin-4-yl-1-piperazinecarbothioamide (Amuvatinib (MP-470))

366017-09-6	1-[4-[4-[[2-[(1E)-2-[4-(Trifluoromethyl)phenyl]ethenyl]-4-oxazolyl]methoxy]phenyl]butyl]-1H-1,2,3-triazole (Mubritinib (TAK 165))

Table 1: validated inhibitors

CAS number	IC50 glucose	IC50 uridine	Fold change
303787-45-3	8.42E-05	6.34E-06	13.3
433248-90-9	5.94E-05	2.75E-06	21.6
901008-80-8	3.15E-05	7.02E-06	4.5
901009-05-0	3.25E-05	3.45E-06	9.4
1110976-91-4	1.75E-04	5.01E-06	35.0
942850-72-8	3.00E-04	1.89E-06	158.9
902841-23-0	1.56E-04	1.09E-05	14.3
891932-93-7	3.96E-05	2.74E-06	14.5
932292-32-5	2.43E-04	2.57E-06	94.4
1113123-97-9	4.30E-05	7.08E-06	6.1
1111019-76-1	1.20E-04	6.62E-06	18.1
1341006-76-5	3.25E-04	1.56E-06	208.4
1340813-43-5	3.42E-05	7.45E-06	4.6
877974-11-3	3.17E-04	5.86E-06	54.1
878911-41-2	5.67E-05	5.86E-06	9.7
924234-99-1	2.68E-05	2.74E-06	9.8
930038-39-4	3.61E-05	1.37E-06	26.3
924219-03-4	2.67E-05	2.46E-06	10.9
923778-03-4	2.74E-05	5.67E-06	4.8
930943-65-0	4.31E-05	3.03E-06	14.3
1090372-48-7	3.29E-05	5.99E-06	5.5
1110869-85-6	2.48E-05	5.98E-06	4.2
1110937-38-6	4.69E-04	6.11E-07	767.3
844649-81-6	3.17E-05	3.11E-06	10.2
1197739-15-3	8.71E-05	3.89E-06	22.4
1241587-59-6	2.98E-04	4.66E-07	639.3
1015153-83-9	2.29E-04	1.07E-06	213.8

402724-46-3	3.46E-05	1.50E-05	2.3
2324334-92-9	6.33E-05	2.26E-05	2.8
2188639-44-1	3.76E-05	5.39E-06	7.0
878441-28-2	3.80E-04	9.57E-07	396.8
941906-49-6	2.52E-05	7.12E-06	3.5
1207002-37-6	3.45E-05	6.81E-06	5.1
58-32-2	8.40E-05	3.24E-06	25.9
486-47-5	4.92E-05	4.80E-06	10.2
383432-38-0	3.35E-04	3.81E-06	88.0
850879-09-3	3.58E-05	1.13E-06	31.8
366017-09-6	1.49E-04	2.80E-08	5329.3

Table 2: IC50 values (M) of tested compounds. IC50 values are given in molar (M).

As shown in Table 2, the tested compounds are able to prevent the growth of cells on uridine but not on glucose. This is demonstrated by a strong difference between IC50 values obtained on uridine and on glucose.

From Figures 3, 4, 5, 6, 7, 8 and Table 2, it can be concluded that the compounds of the invention are active to prevent the use of uridine as an energy source in several cancer cell lines. Thus the compounds of the invention are active against cancers with high UPP1/2 expression/activity.

Immunity

Primary Peripheral Blood Mononuclear Cells (PBMC) were isolated from the buffy coat of blood donors and cultured. After 24h, the cells were harvested for viability determination, and the concentration of lactate in the media was measured (see Figure 3).

U937 were diluted in glucose-free media supplemented with 10mM glucose or 10mM uridine, and 100 nM PMA (phorbol-12-myristate-13-acetate). Supplemented cells were then plated on 96-well plates pre-coated with the 30 best compounds from the validation. The final concentration of inhibitors is 10µM. Prestoblue was added after 72h. Relative Prestoblue fluorescence was measured after 2h and fold changes were calculated.

Validation of Mubritinib derivatives

Mubritinib and some derivatives thereof have been tested in UACC-257 melanoma cells (see Figure 9 for results).

Tested compounds:

- Mubritinib (1): (E)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-trifluoromethyl)styryl)oxa-zole;
- Mubritinib derivative 2: (E)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-(styryl)oxazole;
- Mubritinib derivative 3: (E)−4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methyl)styryl)oxazole;
- Mubritinib derivative 4: (E)-4-((4-(4-(1 H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methoxy)styryl)oxazole;
- Mubritinib derivative 5: 4-(4'-methylphenoxymethyl)-2-[(E)-2-(4-trifluoromethylphenyl)ethenyl]-1,3-oxazole;
- Mubritinib derivative 7: (E)-4-((4-(4-(1H-imidazol-1-yl)butyl)phenoxy)methyl)-2-(4-(trifluoromethyl)styryl)oxazole;
- Mubritinib derivative 8: (E)-4-((4-(4-(1H-pyrrol-1-yl)butyl)phenoxy)methyl)-2-(4-(trifluoromethyl)styryl)oxazole.

Cells were diluted in glucose-free media supplemented with 10M glucose (grey in Figure 9) or 10mM uridine (blue in Figure 9), and treated with the drugs of interest at a 10μM concentration. After 72h, Prestoblue was added. Relative Prestoblue fluorescence was measured after 2h. Fold change in viability compared to untreated control cells.

CLAIMS

1. Use of an inhibitor for in-vitro inhibiting uridine catabolism and/or for in-vitro inhibiting uridine transport, wherein the inhibitor is selected from the group comprising

- 2-Methoxy-N-[(2E)-3-[4-[[3-methyl-4-[(6-methyl-3-pyridinyl)oxy]phenyl]amino]-6-quinazolinyl]-2-propen-1-yl]acetamide
  (CP-724714) (CAS: 383432-38-0)
- N-(1,3-Benzodioxol-5-ylmethyl)-4-benzofuro[3,2-d]pyrimidin-4-yl-1-piperazinecarbothioamide (Amuvatinib, MP-470) (CAS: 850879-09-3)
- 1-[4-[4-[[2-[(1E)-2-[4-(Trifluoromethyl)phenyl]ethenyl]-4-oxazolyl]methoxy]phenyl]butyl]-1H-1,2,3-triazole
  (Mubritinib, TAK 165) (CAS: 366017-09-6)
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-(styryl)oxazole, Mubritinib derivative 2
- (*E*)−4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methyl)styryl)oxazole, Mubritinib derivative 3
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methoxy)styryl)oxazole, Mubritinib derivative 4
- (*E*)-4-((4-(4-(1*H*-imidazol-1-yl)butyl)phenoxy)methyl)-2-(4-(trifluoromethyl)styryl)oxazole, Mubritinib derivative 7
- N-[[2-(4-Morpholinylmethyl)phenyl]methyl]thieno[2,3-d]pyrimidin-4-amine
  (CAS: 924234-99-1)
- N-[[4-(1-Pyrrolidinylmethyl)phenyl]methyl]thieno[2,3-d]pyrimidin-4-amine
  (CAS: 930943-65-0)
- N-[(1-Phenylcyclopropyl)methyl]thieno[2,3-d]pyrimidin-4-amine
  (CAS: 1110937-38-6)
- N-[2-(2-Chlorophenyl)ethyl]thieno[2,3-d]pyrimidin-4-amine
  (CAS: 1241587-59-6)
- N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[3,2-d]pyrimidin-4-amine (CAS: 930038-39-4)

- N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1015153-83-9)
- 2-[[4-(4-Methoxyphenyl)-3-phenyl-2(3H)-thiazolylidene]amino]ethanol (CAS: 303787-45-3)
- 4-[4-[(4-Chlorophenyl)sulfonyl]-1-piperazinyl]-2-methylquinoline (CAS: 433248-90-9)
- N-(4-Ethylphenyl)-2,3-dihydro-2-methyl-1-(1-oxopropyl)-1H-indole-5-sulfonamide (CAS: 901008-80-8)
- N-(3,4-Dimethylphenyl)-2,3-dihydro-2-methyl-1-(1-oxopropyl)-1H-indole-5-sulfonamide (CAS: 901009-05-0)
- 4-[4-[(2-Fluorophenyl)methoxy]-3-methoxyphenyl]-1,4,5,7-tetrahydro-3-methyl-6H-pyrazolo[3,4-b]pyridin-6-one (CAS: 1110976-91-4)
- N-(8-Methoxy-5-quinolinyl)-1-naphthaleneacetamide (CAS: 942850-72-8)
- N-(3-Ethylphenyl)-α-methyl-3-oxo-1,2-benzisothiazole-2(3H)-acetamide (CAS: 902841-23-0)
- 4-Acetyl-3,4-dihydro-2-methyl-N-(1,2,3,4-tetrahydro-1-naphthalenyl)-2H-1,4-benzothiazine-6-sulfonamide (CAS: 891932-93-7)
- N-[(4-Fluorophenyl)methyl]-1-(3-methylisoxazolo[5,4-d]pyrimidin-4-yl)-4-piperidinecarboxamide (CAS: 932292-32-5)
- 4-Acetyl-3,4-dihydro-2-methyl-N-[(3-methylphenyl)methyl]-2H-1,4-benzothiazine-6-sulfonamide (CAS: 1113123-97-9)
- [1-(5,6-Dimethylfuro[2,3-d]pyrimidin-4-yl)-3-piperidinyl](4-ethyl-1-piperazinyl)methanone (CAS: 1111019-76-1)
- N-[(2,6-Dimethylimidazo[2,1-b]-1,3,4-thiadiazol-5-yl)methyl]-4-(trifluoromethyl)benzamide (CAS: 1341006-76-5)
- 1-{5H,6H,7H-cyclopenta[d]pyrimidin-4-yl}-4-phenylpiperazine (CAS: 1340813-43-5)

- 4-[[(2-Chloro-6-fluorophenyl)methyl]methylamino]-3-nitrobenzamide (CAS: 877974-11-3)
- 1-(4-Acetyl-3,5-dimethyl-1H-pyrrol-2-yl)-2-[2-(2-thienyl)-1-pyrrolidinyl]-1-propanone (CAS: 878911-41-2)
- 4-[2-(2-Thienyl)-1-pyrrolidinyl]thieno[2,3-d]pyrimidine (CAS: 924219-03-4)
- 2,3-Dihydro-1-[(2-methylphenyl)methyl]-1H-indole-5-sulfonamide (CAS: 923778-03-4)
- N-[(2,3-Dihydro-1,4-benzodioxin-2-yl)methyl]-N-propylthieno[2,3-d]pyrimidin-4-amine (CAS: 1090372-48-7)
- 4-[2-[4-(2,3-Dimethylphenyl)-1-piperazinyl]ethoxy]benzenesulfonamide (CAS: 1110869-85-6)
- 2-(Benzofuro[3,2-d]pyrimidin-4-ylamino)-1-butanol (CAS: 844649-81-6)
- [4-(Hydroxyphenylmethyl)-1-piperidinyl][3-methyl-5-(methylamino)-4-isothiazolyl]methanone (CAS: 1197739-15-3)
- 6-(2,3-Dihydro-1H-indol-1-yl)-9-β-D-ribofuranosyl-9H-purine (CAS: 402724-46-3)
- 4-[[6-[Ethyl(tetrahydro-2,2-dimethyl-2H-pyran-4-yl)amino]-9H-purin-9-yl]methyl]tetrahydro-2H-pyran-4-methanol (CAS: 2324334-92-9)
- Tetrahydro-4-[[6-[4-(3-methylbutoxy)-1-piperidinyl]-9H-purin-9-yl]methyl]-2H-pyran-4-ol CAS: 2188639-44-1)
- 7-Ethyl-3,7-dihydro-1,3-dimethyl-8-[[4-(phenylmethyl)-1-piperidinyl]methyl]-1H-purine-2,6-dione (CAS: 878441-28-2)
- N-(1-Butyl-1,2,3,4-tetrahydro-2-oxo-6-quinolinyl)-2,4-dimethoxybenzenesulfonamide (CAS: 941906-49-6)
- Tetrahydro-N-[2-[[4-methyl-6-(1-piperidinyl)-2-pyrimidinyl]amino]ethyl]-2-furancarboxamide (CAS: 1207002-37-6)
- 2,2′,2″,2‴-[(4,8-Di-1-piperidinylpyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetrakis[ethanol] (Dipyridamole) (CAS: 58-32-2)

- 1-(3,4-Diethoxybenzyl)-6,7-diethoxyisoquinoline (Ethaverine hydrochloride) (CAS: 486-47-5)

2. The use of claim 1, wherein the inhibitor selected from the group comprising

- 1-[4-[4-[[2-[(1E)-2-[4-(Trifluoromethyl)phenyl]ethenyl]-4-oxazolyl]methoxy]phenyl]butyl]-1H-1,2,3-triazole (Mubritinib, TAK 165) (CAS: 366017-09-6)
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-(styryl)oxazole, Mubritinib derivative 2
- (*E*)−4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methyl)styryl)oxazole, Mubritinib derivative 3
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methoxy)styryl)oxazole, Mubritinib derivative 4
- (*E*)-4-((4-(4-(1*H*-imidazol-1-yl)butyl)phenoxy)methyl)-2-(4-(trifluoromethyl)styryl)oxazole, Mubritinib derivative 7
- N-[(1-Phenylcyclopropyl)methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1110937-38-6)
- N-[2-(2-Chlorophenyl)ethyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1241587-59-6)
- 7-Ethyl-3,7-dihydro-1,3-dimethyl-8-[[4-(phenylmethyl)-1-piperidinyl]methyl]-1H-purine-2,6-dione (CAS: 878441-28-2)
- N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1015153-83-9)
- N-[(2,6-Dimethylimidazo[2,1-b]-1,3,4-thiadiazol-5-yl)methyl]-4-(trifluoromethyl)benzamide (CAS: 1341006-76-5)
- N-(8-Methoxy-5-quinolinyl)-1-naphthaleneacetamide (CAS: 942850-72-8)
- N-[(4-Fluorophenyl)methyl]-1-(3-methylisoxazolo[5,4-d]pyrimidin-4-yl)-4-piperidinecarboxamide (CAS: 932292-32-5)

- 2-Methoxy-N-[(2E)-3-[4-[[3-methyl-4-[(6-methyl-3-pyridinyl)oxy]phenyl]amino]-6-quinazolinyl]-2-propen-1-yl]acetamide (CP-724714) (CAS: 383432-38-0)
- 4-[[(2-Chloro-6-fluorophenyl)methyl]methylamino]-3-nitrobenzamide (CAS: 877974-11-3)
- 4-[4-[(2-Fluorophenyl)methoxy]-3-methoxyphenyl]-1,4,5,7-tetrahydro-3-methyl-6H-pyrazolo[3,4-b]pyridin-6-one (CAS: 1110976-91-4)
- N-(1,3-Benzodioxol-5-ylmethyl)-4-benzofuro[3,2-d]pyrimidin-4-yl-1-piperazinecarbothioamide (Amuvatinib, MP-470) (CAS: 850879-09-3)
- N-[[2-(4-Morpholinylmethyl)phenyl]methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 924234-99-1)
- N-[[4-(1-Pyrrolidinylmethyl)phenyl]methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 930943-65-0)
- N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[3,2-d]pyrimidin-4-amine (CAS: 930038-39-4)

3. The use of claim 1, wherein the inhibitor is selected from the group comprising

- 1-[4-[4-[[2-[(1E)-2-[4-(Trifluoromethyl)phenyl]ethenyl]-4-oxazolyl]methoxy]phenyl]butyl]-1H-1,2,3-triazole (Mubritinib, TAK 165) (CAS: 366017-09-6)
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-(styryl)oxazole, Mubritinib derivative 2
- (*E*)−4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methyl)styryl)oxazole, Mubritinib derivative 3
- (*E*)-4-((4-(4-(1H-1,2,3-triazol-1-yl)butyl)phenoxy)methyl)-2-((4-methoxy)styryl)oxazole, Mubritinib derivative 4
- (*E*)-4-((4-(4-(1*H*-imidazol-1-yl)butyl)phenoxy)methyl)-2-(4-(trifluoromethyl)styryl)oxazole, Mubritinib derivative 7
- N-[(1-Phenylcyclopropyl)methyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1110937-38-6)

- N-[2-(2-Chlorophenyl)ethyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1241587-59-6)
- 7-Ethyl-3,7-dihydro-1,3-dimethyl-8-[[4-(phenylmethyl)-1-piperidinyl]methyl]-1H-purine-2,6-dione (CAS: 878441-28-2)
- N-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-2-methylpropyl]thieno[2,3-d]pyrimidin-4-amine (CAS: 1015153-83-9)
- N-[(2,6-Dimethylimidazo[2,1-b]-1,3,4-thiadiazol-5-yl)methyl]-4-(trifluoromethyl)benzamide (CAS: 1341006-76-5)
- N-(8-Methoxy-5-quinolinyl)-1-naphthaleneacetamide (CAS: 942850-72-8)
- N-[(4-Fluorophenyl)methyl]-1-(3-methylisoxazolo[5,4-d]pyrimidin-4-yl)-4-piperidinecarboxamide (CAS: 932292-32-5)
- 2-Methoxy-N-[(2E)-3-[4-[[3-methyl-4-[(6-methyl-3-pyridinyl)oxy]phenyl]amino]-6-quinazolinyl]-2-propen-1-yl]acetamide (CP-724714) (CAS: 383432-38-0)
- N-(1,3-Benzodioxol-5-ylmethyl)-4-benzofuro[3,2-d]pyrimidin-4-yl-1-piperazinecarbothioamide (Amuvatinib, MP-470) (CAS: 850879-09-3)

4. An inhibitor according to any one of claims 1 to 3 for use in a method for treating a disease associated with uridine catabolism selected from cancer and immune disorders, and wherein the cancer expresses high level of Uridine phosphorylase 1 (UPP1) or Uridine phosphorylase 2 (UPP2).

5. The inhibitor for use of claim 4, wherein the cancer is selected from the group comprising pancreatic ductal adenocarcinoma (PDA) cancers, melanoma and colon cancers.

6. The inhibitor for use of claim 4 or claim 5, wherein the disease is cancer and wherein the method for treating further comprises immunotherapy, radiotherapy and/or chemotherapy.

7. The inhibitor for use of claim 4, wherein the immune disorders are selected from inflammation, auto-inflammatory disorders and auto-immune disorders.

8. The inhibitor for use of claim 4, wherein the metabolic disorders are selected from fatty liver, obesity and diabetes.

Figure 1

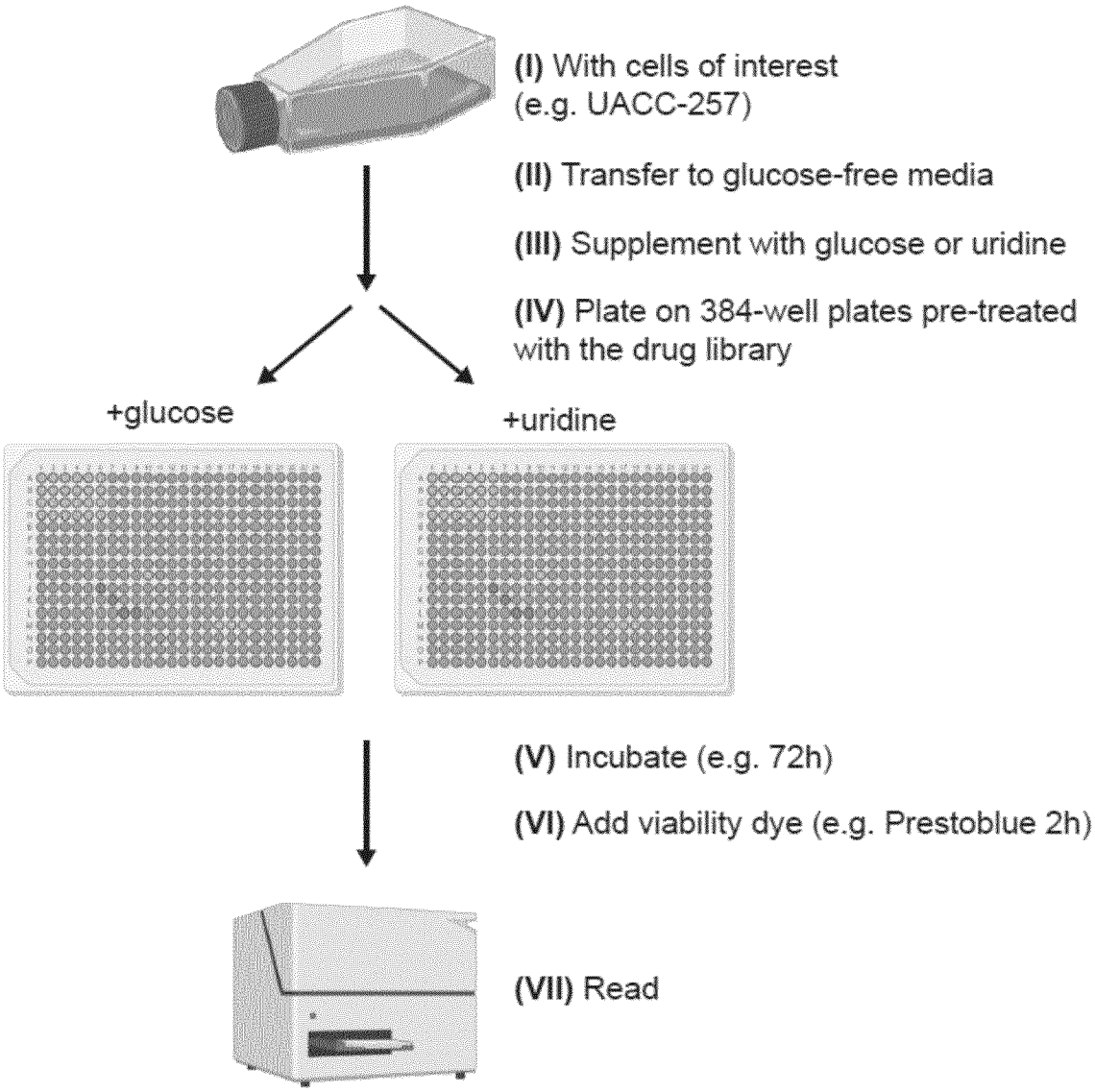

(I) With cells of interest
(e.g. UACC-257)
(II) Transfer to glucose-free media
(III) Supplement with glucose or uridine
(IV) Plate on 384-well plates pre-treated with the drug library
+glucose
+uridine
(V) Incubate (e.g. 72h)
(VI) Add viability dye (e.g. Prestoblue 2h)
(VII) Read

Figure 2A

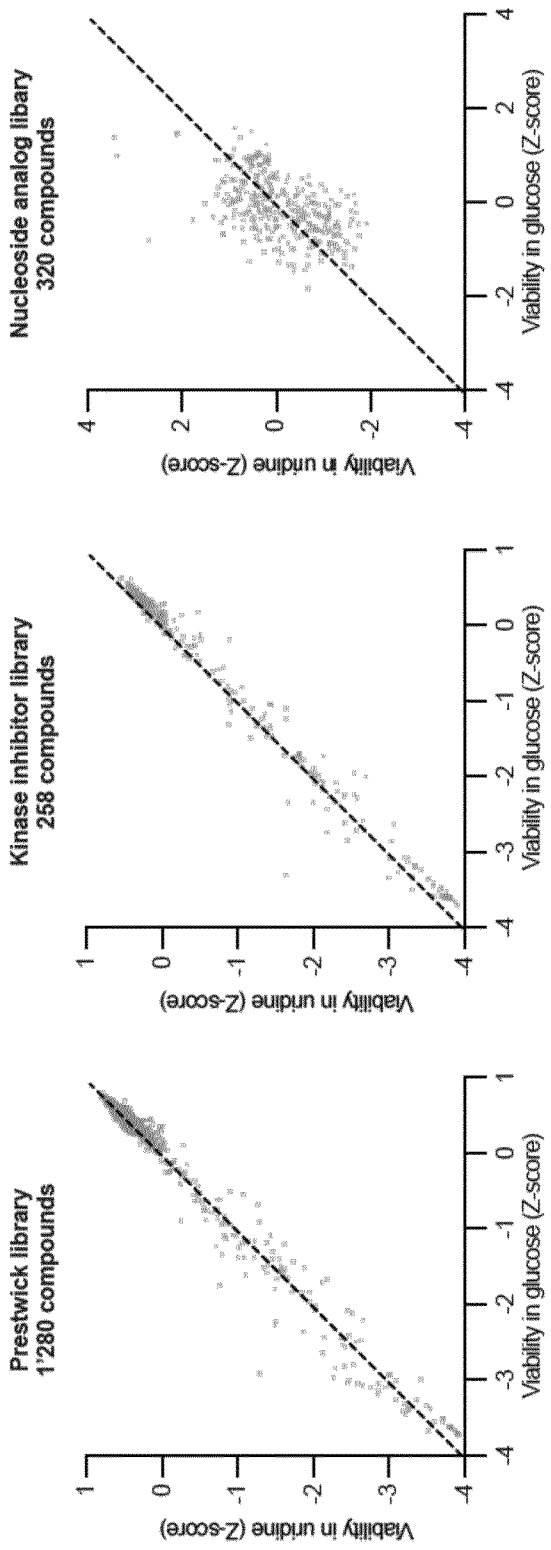

Nucleoside analog libary
320 compounds
Viability in uridine (Z-score)
Viability in glucose (Z-score)
Kinase inhibitor library
258 compounds
Viability in uridine (Z-score)
Viability in glucose (Z-score)
Prestwick library
1'280 compounds
Viability in uridine (Z-score)
Viability in glucose (Z-score)

Figure 2B

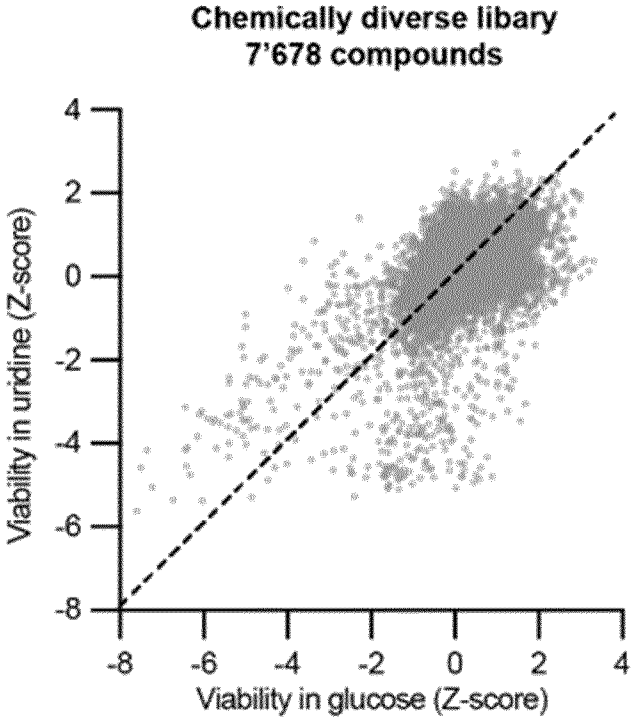

Chemically diverse libary
7'678 compounds
Viability in uridine (Z-score)
Viability in glucose (Z-score)
4
2
0
-2
-4
-6
-8
-8
-6
-4
-2
0
2
4

Figure 3

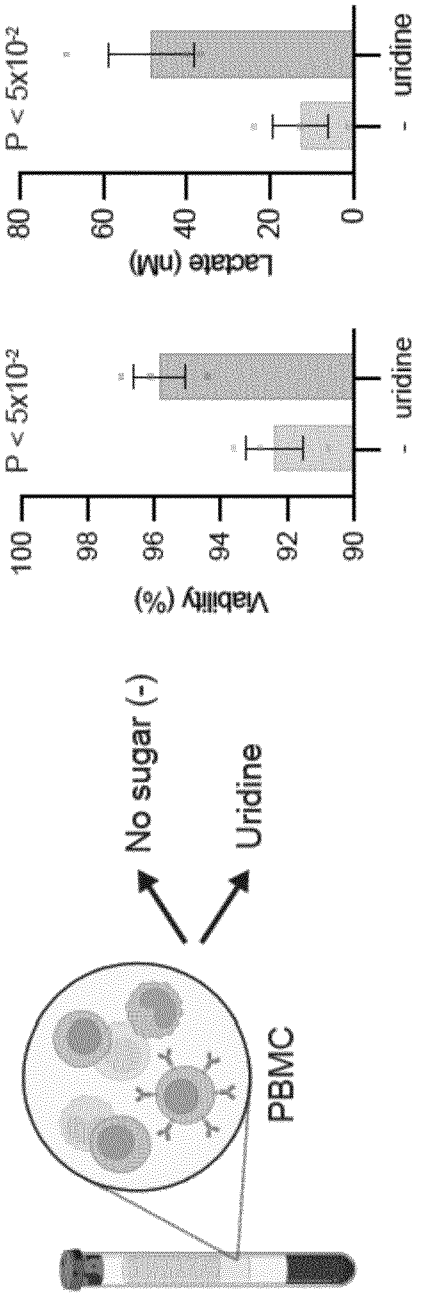

Lactate (nM)
80
60
40
20
0
P < 5x10-2
- uridine
Viability (%)
100
98
96
94
92
90
P < 5x10-2
- uridine
No sugar (-)
Uridine
PBMC

Figure 4

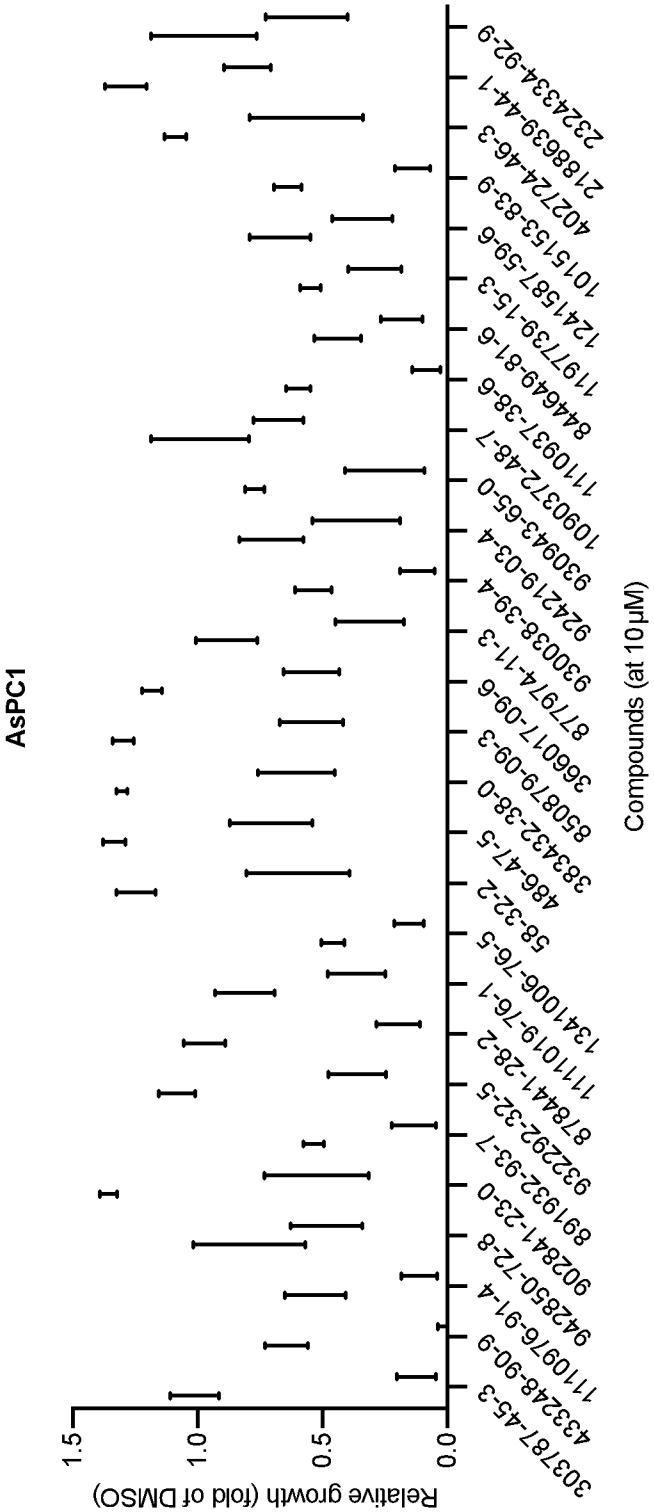

AsPC1
Relative growth (fold of DMSO)
1.5
1.0
0.5
0.0
Compounds (at 10 µM)
3037874-5-3
4332481-90-9
11109768-91-4
9428506-72-8
9028417-23-0
8919321-93-7
9322929-32-5
8784471-28-2
11110191-76-1
13410061-76-5
58-32-2
486-47-5
38343285-38-0
8508793-09-3
36601709-09-6
8779741-11-3
9300381-39-4
9242191-03-4
9309431-65-0
10903721-48-7
11109371-38-6
8446491-81-6
11977391-15-3
12415871-59-6
10151531-83-9
4027241-46-3
21886391-44-1
23243434-92-9

Figure 5

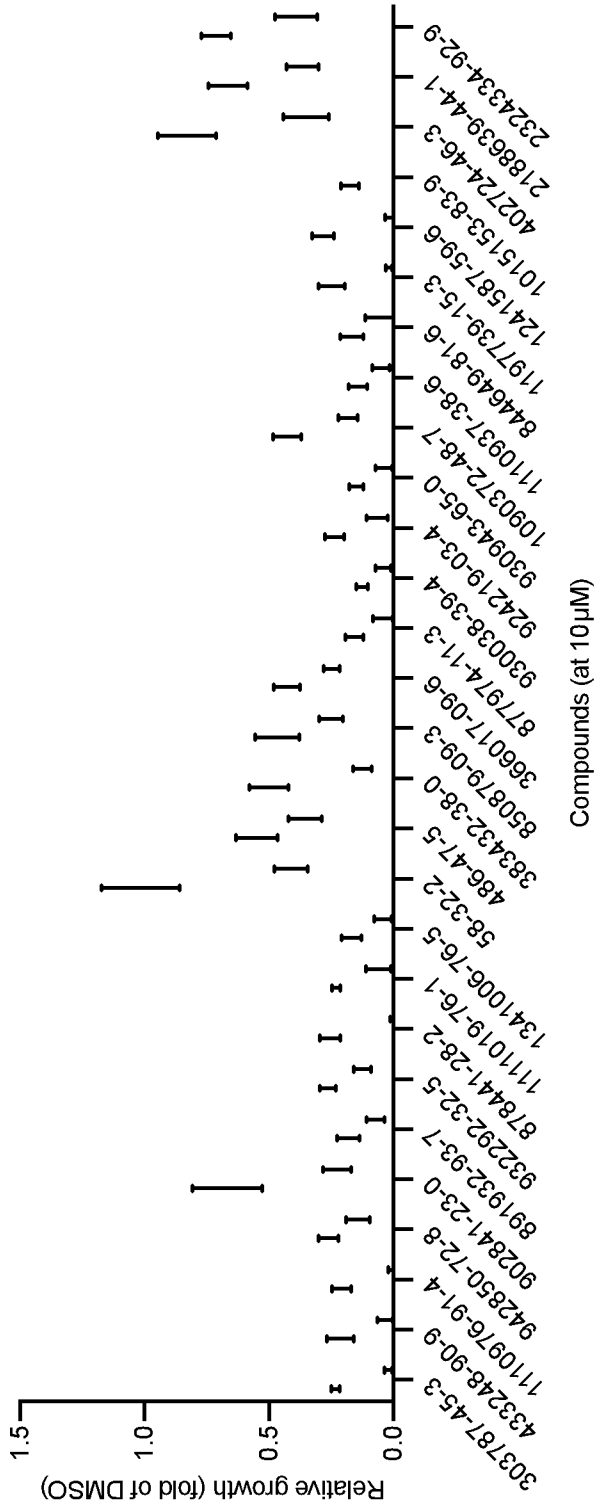

SW480
Relative growth (fold of DMSO)
1.5
1.0
0.5
0.0
Compounds (at 10µM)
303787-45-3
432248-90-9
1110976-90-9
942850-72-8
902847-23-0
891932-93-7
932292-32-5
878441-28-2
1711019-76-1
1341006-76-5
58-32-2
486-47-5
3834432-38-0
850879-09-3
3660117-09-6
877974-11-3
930038-39-4
924219-03-4
930943-65-0
1090372-48-7
1110937-38-6
844649-81-6
1197739-15-3
1241587-59-6
1015153-83-9
402724-46-3
2188639-44-1
2324334-92-9

Figure 6

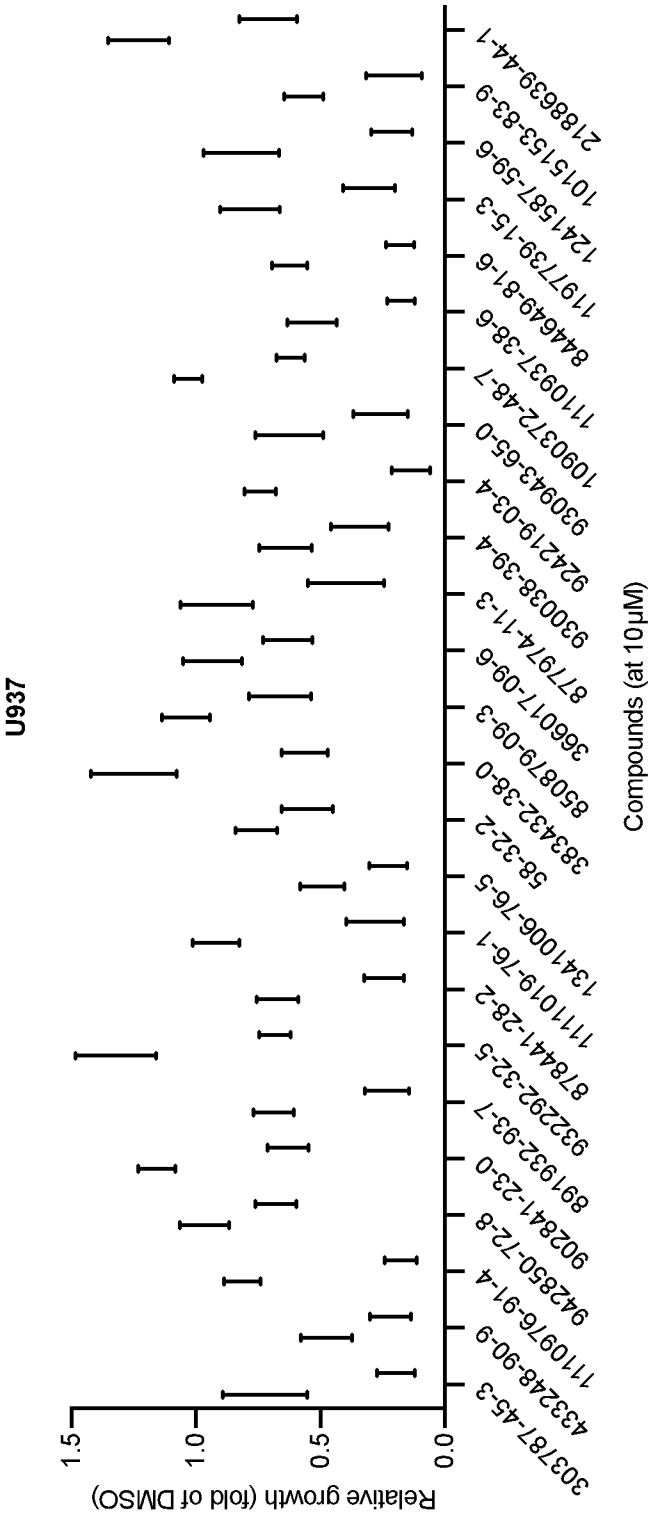

U937
Relative growth (fold of DMSO)
1.5
1.0
0.5
0.0
Compounds (at 10µM)
303787-45-3
433248-90-9
1110976-90-9
942850-72-8
902841-23-0
891932-93-7
932292-32-5
878441-28-2
1110119-76-1
1341006-76-5
58-32-2
383432-38-0
850879-09-3
366017-09-6
877974-11-3
930038-39-4
924219-03-4
930943-65-0
1109372-48-7
1110937-38-6
844649-81-6
1197739-15-3
1241587-59-6
1015153-83-9
2188639-44-1

Figure 7

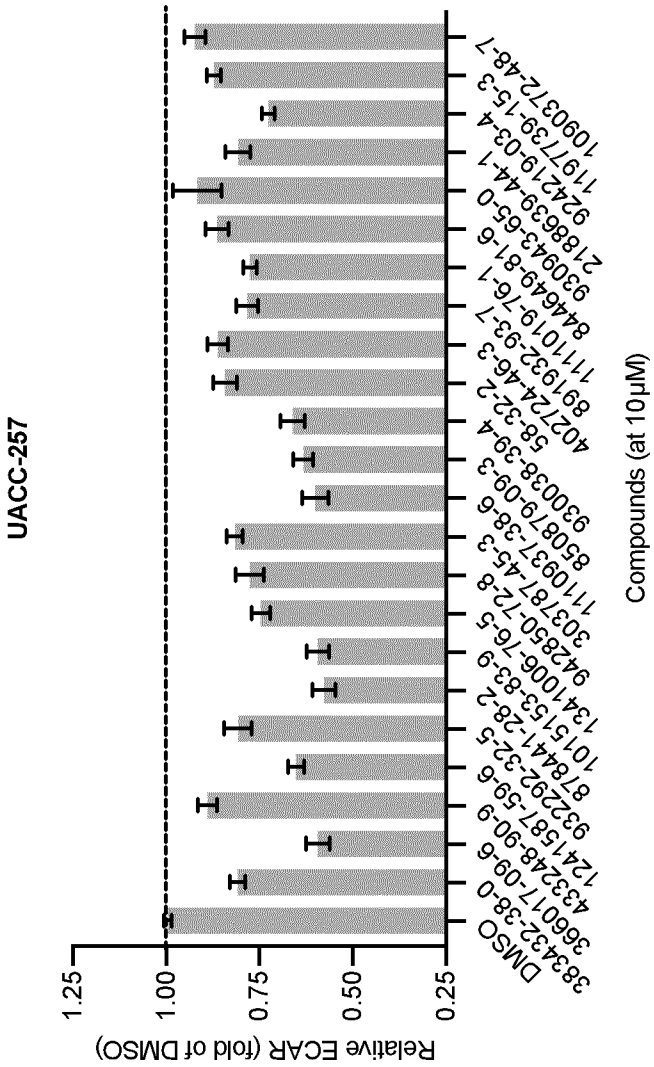

UACC-257
Relative ECAR (fold of DMSO)
1.25
1.00
0.75
0.50
0.25
Compounds (at 10µM)
DMSO
3834232-38-0
3660172-38-0
4332487-09-6
1241587-90-9
9322292-32-6
8784447-28-5
1015153-28-2
1341006-83-9
9428506-76-5
3037867-12-8
1710937-45-3
8508079-38-6
9300038-09-3
4027247-58-32-2
8919324-46-3
1711019-93-7
8446491-76-1
9309437-81-6
2188639-65-0
9242194-44-1
1197739-03-4
1090372-15-3
1090372-48-7

Figure 8

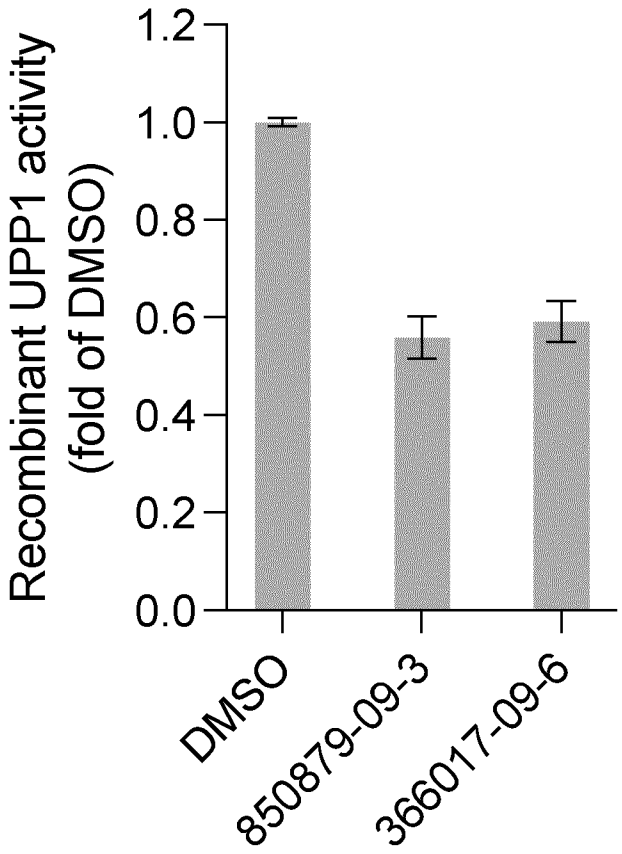

Recombinant UPP1 activity
(fold of DMSO)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
DMSO
850879-09-3
366017-09-6

Figure 9

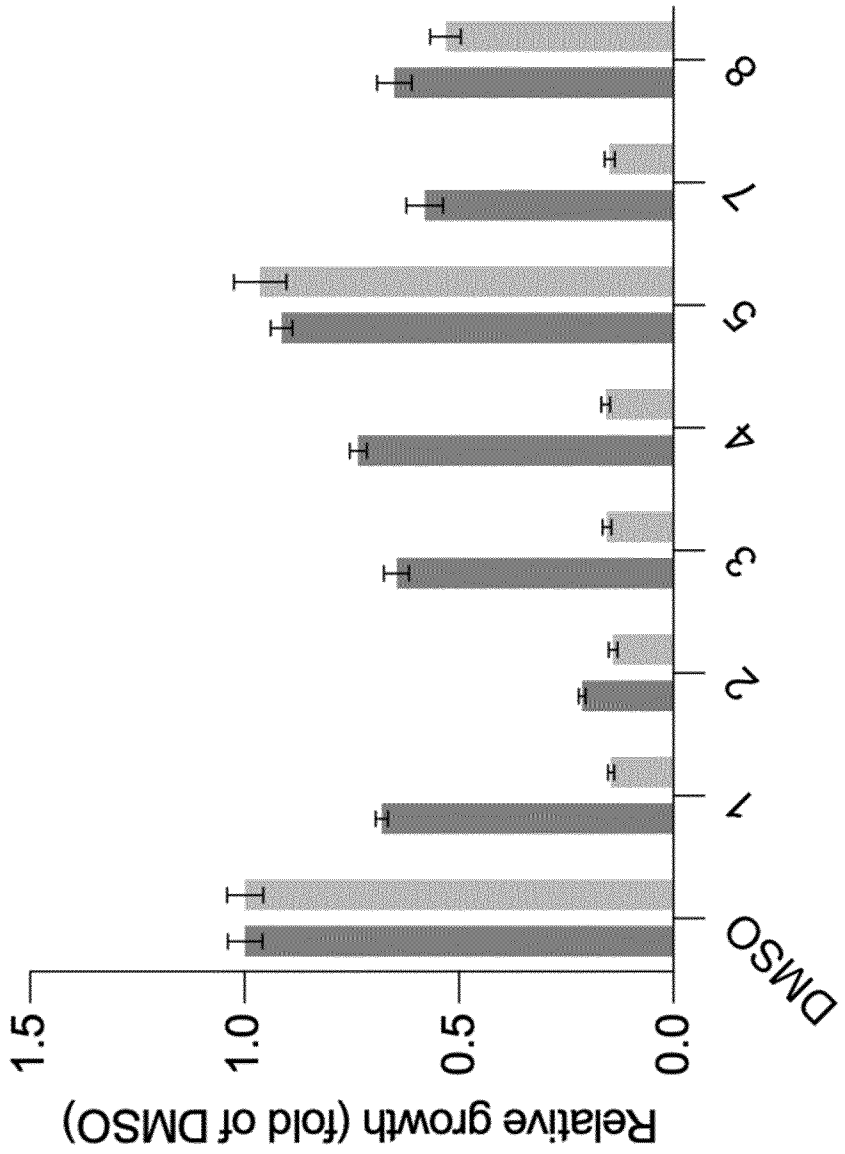


Figure 10

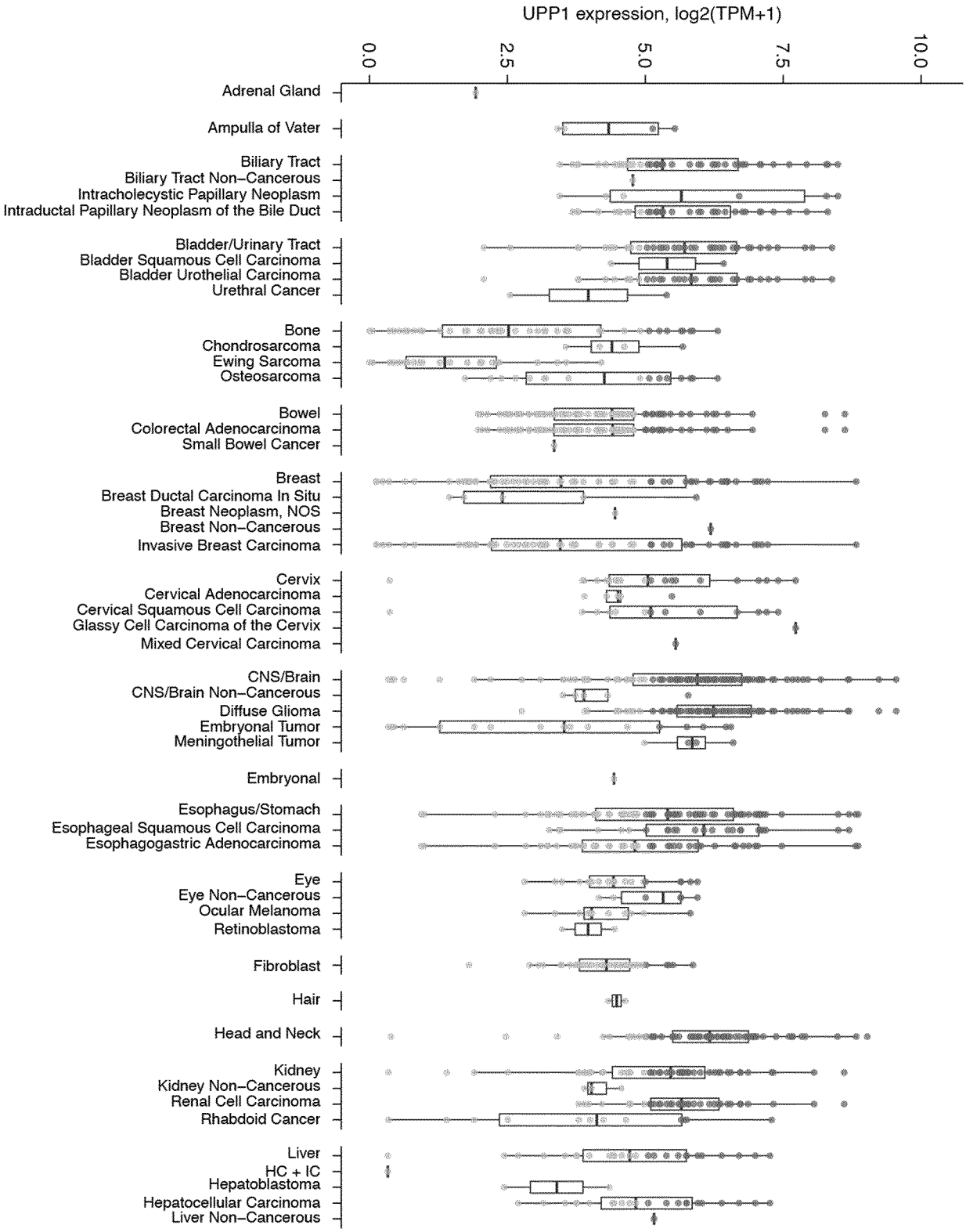
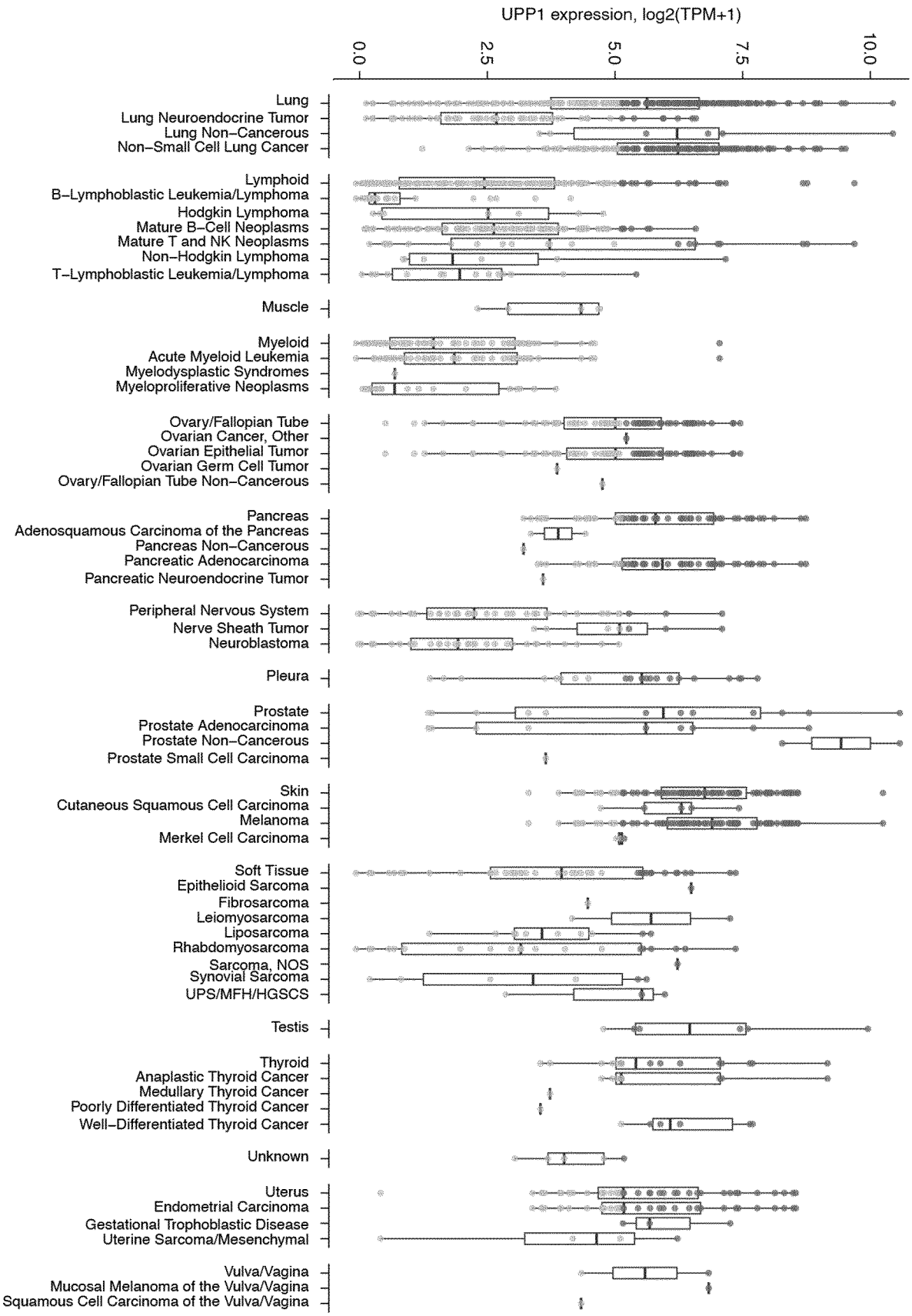

UPP1 expression, log2(TPM+1)
0.0
2.5
5.0
7.5
10.0
Adrenal Gland
Ampulla of Vater
Biliary Tract
Biliary Tract Non–Cancerous
Intracholecystic Papillary Neoplasm
Intraductal Papillary Neoplasm of the Bile Duct
Bladder/Urinary Tract
Bladder Squamous Cell Carcinoma
Bladder Urothelial Carcinoma
Urethral Cancer
Bone
Chondrosarcoma
Ewing Sarcoma
Osteosarcoma
Bowel
Colorectal Adenocarcinoma
Small Bowel Cancer
Breast
Breast Ductal Carcinoma In Situ
Breast Neoplasm, NOS
Breast Non–Cancerous
Invasive Breast Carcinoma
Cervix
Cervical Adenocarcinoma
Cervical Squamous Cell Carcinoma
Glassy Cell Carcinoma of the Cervix
Mixed Cervical Carcinoma
CNS/Brain
CNS/Brain Non–Cancerous
Diffuse Glioma
Embryonal Tumor
Meningothelial Tumor
Embryonal
Esophagus/Stomach
Esophageal Squamous Cell Carcinoma
Esophagogastric Adenocarcinoma
Eye
Eye Non–Cancerous
Ocular Melanoma
Retinoblastoma
Fibroblast
Hair
Head and Neck
Kidney
Kidney Non–Cancerous
Renal Cell Carcinoma
Rhabdoid Cancer
Liver
HC + IC
Hepatoblastoma
Hepatocellular Carcinoma
Liver Non–Cancerous

Figure 10 – continues



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/058419

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/422 A61K31/513 A61K31/517 A61K31/519 A61K31/52
A61K45/06 A61P1/16 A61P3/00 A61P3/04 A61P3/10
A61P9/00 A61P15/10 A61P21/00 A61P31/04 A61P31/12

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91/16315 A1 (UNIV BROWN RES FOUND [US]) 31 October 1991 (1991-10-31) abstract page 3, line 1 - line 19 page 14, line 9 - line 20 page 31, line 1 - line 10 page 32, Table I claims 14, 15 -----	1-3
X	WO 02/18404 A2 (HOFFMANN LA ROCHE [CH]) 7 March 2002 (2002-03-07) abstract page 102, third compound page 118, line 18 - line 21 page 120, line 4 - page 122, line 35 claims 49-53 ----- -/--	4-8

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

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

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

"L" 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

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Date of the actual completion of the international search	Date of mailing of the international search report
4 June 2024	10/06/2024

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	Taylor, Mark

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021/214475 A1 (AIVIVO LTD [GB]) 28 October 2021 (2021-10-28) abstract page 11, Table 1 page 11, line 2 - line 7 page 28, line 1 - line 18 claims 1-43	4-8
X	QI WENQING ET AL: "MP470, a novel receptor tyrosine kinase inhibitor, in combination with Erlotinib inhibits the HER family/PI3K/Akt pathway and tumor growth in prostate cancer", BMC CANCER, BIOMED CENTRAL, LONDON, GB, vol. 9, no. 1, 11 May 2009 (2009-05-11), page 142, XP021049017, ISSN: 1471-2407, DOI: 10.1186/1471-2407-9-142 the whole document	4-8
X	NAGASAWA JOJI ET AL: "Novel HER2 selective tyrosine kinase inhibitor, TAK-165, inhibits bladder, kidney and androgen-independent prostate cancer in vitro and in vivo", INTERNATIONAL JOURNAL OF UROLOGY, vol. 13, no. 5, 8 June 2006 (2006-06-08), pages 587-592, XP093073532, JP ISSN: 0919-8172, DOI: 10.1111/j.1442-2042.2006.01342.x abstract	4-8
X	WO 2019/084662 A1 (UNIV MONTREAL [CA]) 9 May 2019 (2019-05-09) abstract page 2, line 6 - page 6, line 5 page 48, Compound 32 page 116, Compound 32 example 7 page 214, Table 4 claims 1-135	4-8
X	ZOE A STEPHENSON: "Identification of a novel toxicophore in anti-cancer chemotherapeutics that targets mitochondrial respiratory complex I", ELIFE, vol. 9, 20 May 2020 (2020-05-20), page e55845, XP093164561, GB ISSN: 2050-084X, DOI: 10.7554/eLife.55845 abstract figure 2	4-8

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/058419

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZHANG YUMEI ET AL: "Uridine Metabolism and Its Role in Glucose, Lipid, and Amino Acid Homeostasis", BIOMED RESEARCH INTERNATIONAL, vol. 2020, 7091718, 15 April 2020 (2020-04-15), pages 1-7, XP093073449, ISSN: 2314-6133, DOI: 10.1155/2020/7091718 abstract -----	1-8
A,P	OWEN S. SKINNER: "Salvage of ribose from uridine or RNA supports glycolysis in nutrient-limited conditions", NATURE METABOLISM, vol. 5, no. 5, 17 May 2023 (2023-05-17), pages 765-776, XP093164435, ISSN: 2522-5812, DOI: 10.1038/s42255-023-00774-2 the whole document -----	1-8

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/058419

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9116315 A1	31-10-1991	AT E124936 T1	15-07-1995
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		CA 2080343 A1	13-10-1991
		DE 69111232 T2	21-12-1995
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		JP 3001972 B2	24-01-2000
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		BR 0113611 A	24-06-2003
		CA 2419399 A1	07-03-2002
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		EP 1315736 A2	04-06-2003
		JP 2004513083 A	30-04-2004
		KR 20030061792 A	22-07-2003
		MX PA03001775 A	04-06-2003
		PA 8528001 A1	30-07-2002
		PE 20020410 A1	28-05-2002
		US 2003008841 A1	09-01-2003
		US 2004110718 A1	10-06-2004
		UY 26914 A1	28-02-2002
		WO 0218404 A2	07-03-2002
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		WO 2021214475 A1	28-10-2021
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		BR 112020008767 A2	03-11-2020
		CA 2995617 A1	03-05-2019
		CN 111886234 A	03-11-2020
		EP 3704111 A1	09-09-2020
		IL 274353 A	30-06-2020
		JP 7355392 B2	03-10-2023
		JP 2021501770 A	21-01-2021
		KR 20200095482 A	10-08-2020
		SG 11202003998X A	28-05-2020
		US 2021387980 A1	16-12-2021
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