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(54) Title: COMBINATION TREATMENTS COMPRISING A CTPS1 INHIBITOR AND A WEE1 INHIBITOR

(57) Abstract: The invention provides *inter alia* methods of treating cancer comprising administering to a subject a cytidine triphosphate synthase 1 (CTPS1) inhibitor and a WEE1 inhibitor.

COMBINATION TREATMENTS COMPRISING A CTPS1 INHIBITOR AND A WEE1 INHIBITOR

Field of the invention

The invention relates to combinations, in particular the combination of a CTPS1 inhibitor and a WEE1 inhibitor, pharmaceutical compositions and kits comprising such combinations which may be of use in the treatment of cancer and to related aspects.

Background of the invention

Cancer can affect multiple cell types and tissues but the underlying cause is a breakdown in the control of cell division. This process is highly complex, requiring careful coordination of multiple pathways, many of which remain to be fully characterised. Cell division requires the effective replication of the cell's DNA and other constituents. Interfering with a cell's ability to replicate by targeting nucleic acid synthesis has been a core approach in cancer therapy for many years. Examples of therapies acting in this way are 6-thioguanine, 6-mecaptopurine, 5-fluorouracil, cytarabine, gemcitabine and pemetrexed.

Cancer therapeutics against a wide array of specific targets are available. Small molecule targeted therapy drugs are generally inhibitors of enzymatic domains on mutated, overexpressed, or otherwise critical proteins within the cancer cell. Monoclonal antibody therapy is another strategy in which the therapeutic agent is an antibody which specifically binds to a protein on the surface of the cancer cells.

All proliferating cells, including neoplastic cells, are reliant on a ready source of purine and pyrimidine nucleotides for DNA and RNA synthesis. Whilst salvage pathways may be sufficient for steady state metabolism, DNA replication to enable cell division is dependent on synthesis of nucleotides via the *de novo* pathway. A key bottleneck in the *de novo* pyrimidine synthesis pathway is the enzyme cytidine triphosphate synthase (CTPS) which catalyses the conversion of UTP to CTP (van Kuilenburg 2000). CTPS also has two isoforms in humans (CTPS1 and CTPS2; see Fig. 1). Both isoforms are ubiquitously expressed in normal and malignant human cells (BioGPS and EMBL-EBI Expression Atlas). Human genetic studies have identified an essential and non-redundant role for CTPS1 in the proliferation of normal immune (B and T) cells (Martin 2014; Martin 2020).

Whilst cancer cells are dependent on CTPS activity in order to proliferate, the precise role that CTPS1 and CTPS2 play in cancer is currently not completely clear. Several CTPS inhibitors that inhibit both CTPS1 and CTPS2 have been developed for oncology indications up to phase I/II clinical trials, but were stopped due to toxicity and efficacy issues. Most of the developed inhibitors are nucleoside-analogue prodrugs (3-deazauridine (DAU), CPEC, carbodine, gemcitabine), which are converted to the active triphosphorylated metabolite by the kinases involved in pyrimidine biosynthesis: uridine/cytidine kinase, nucleoside monophosphate-

kinase (NMP-kinase) and nucleoside diphosphatekinase (NDP-kinase). The remaining inhibitors (acivicin, DON) are reactive analogues of glutamine, which irreversibly inhibit the glutaminase domain of CTPS. Importantly, none of the inhibitors of CTPS developed to date are selective for one isoform of CTPS over the other. As such, available CTPS inhibitors block all CTPS activity and, therefore, block the ability of all cells in the body to undergo cell division.

The DNA damage response (DDR) is a complex cellular pathway that is activated in response to direct damage to a cell's DNA, and in situations where DNA damage is likely to occur, for example nucleotide deficiency, stalled replication forks and other causes of replication stress. DDR activation is a feature of different cancer types, and its exploitation is a current area of interest in oncology drug development (Gorecki 2021). The biological purpose of the DDR pathway is to prevent cells entering the cell cycle whilst harbouring DNA damage, by inducing a cell cycle arrest and thus providing the opportunity to carry out DNA repair ensuring an error free copy of the genome is replicated once the cell cycle resumes.

The DDR pathway has been shown to be activated across a diverse range of cancer types. Inhibition of this pathway may be of therapeutic benefit in cancer. The role of the DDR pathway is to pause cell cycle and allow time for DNA damage to be repaired, such that inhibition of this pathway may result in cancer cells entering mitosis prematurely resulting in mitotic catastrophe and cell death (Gorecki 2021). Small molecule inhibitors have been developed against different components of the DDR pathway, including ATR, CHEK1 and WEE1.

WEE1 inhibits the entry of cells into mitosis (M phase). Activation of WEE1 in cancer cells allows the cells to pause in G2 in order to repair DNA damage. Inhibition of WEE1 in cancer cells may promote premature entry into mitosis, resulting in mitotic catastrophe and cell death (Gorecki 2021).

There remains a need for new approaches to cancer therapies, such approaches may demonstrate high *in vivo* efficacy, reduction in the dose required for effect *in vivo*, an improved safety profile/reduced side effects, or the like.

Summary of the invention

The invention provides a CTPS1 inhibitor for use in the treatment of cancer with a WEE1 inhibitor.

In a further aspect the invention provides a WEE1 inhibitor for use in the treatment of cancer with a CTPS1 inhibitor.

In a further aspect the invention provides a CTPS1 inhibitor and a WEE1 inhibitor for use in the treatment of cancer.

In a further aspect the invention provides the use of a CTPS1 inhibitor in the manufacture of a medicament for the treatment of cancer with a WEE1 inhibitor.

In a further aspect the invention provides the use of a WEE1 inhibitor in the manufacture of a medicament for the treatment of cancer with a CTPS1 inhibitor.

In a further aspect the invention provides the use of a CTPS1 inhibitor and a WEE1 inhibitor in the manufacture of a medicament for the treatment of cancer.

In a further aspect the invention provides a method of treating cancer in a subject which method comprises administering to the subject a CTPS1 inhibitor and a WEE1 inhibitor.

In a further aspect the invention provides a pharmaceutical composition comprising a CTPS1 inhibitor and a WEE1 inhibitor.

In a further aspect the invention provides a kit of parts comprising:

a) a first container comprising a CTPS1 inhibitor; and

b) a second container comprising a WEE1 inhibitor.

Summary of the sequences

SEQ ID NO: 1 FLAG-His_8-tag

SEQ ID NO: 2 FLAG-His-Avi tag

Summary of the figures

Fig. 1 *De novo* CTP production pathway

Fig. 2 Impact of deletion of different genes in the pyrimidine synthesis pathway

Fig. 3 Bliss scores for cancer cell lines exposed to the CTPS1 inhibitor CTPS1-IA in combination with either a standard of care drug or a WEE1 inhibitor

Fig. 4 Bliss scores for human cancer cell lines derived from solid tumours exposed to the CTPS1 inhibitor CTPS1-IA in combination with either a WEE1 inhibitor

Fig. 5 A comparison of Bliss scores for 2 human colorectal cancer cell lines and 2 human ovarian cancer cell lines exposed to a WEE1 inhibitor (adavosertib) in combination with either the CTPS1 inhibitor CTPS1-IA or a chemotherapy drug (irinotecan, cisplatin or gemcitabine); in 11 of the 12 combinations tested, synergy observed with the adavosertib CTPS1-IA combination exceeded that observed with the adavosertib chemotherapy combination.

Detailed description of the invention

CTPS1 inhibitors

In one aspect of the invention there is provided a CTPS1 inhibitor for use in the treatment of cancer with a WEE1 inhibitor.

A CTPS1 inhibitor, as used herein, is an agent which directly inhibits the enzymatic activity of the CTPS1 enzyme through interaction with the enzyme. Direct inhibition of the

CTPS1 enzyme may be quantified using any suitable assay procedure, though is suitably performed using the procedure set out in Example 1.

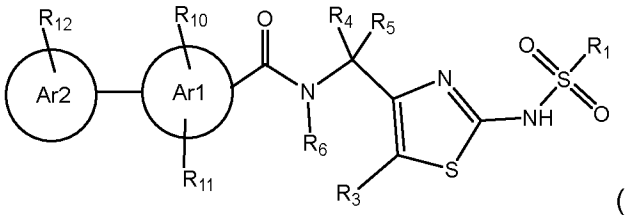
CTPS1 inhibitors may demonstrate an IC_{50} of 10 uM or lower, such as 1uM or lower, especially 100nM or lower, in respect of CTPS1 enzyme. CTPS1 inhibitors of particular interest are those demonstrating an IC_{50} of 10 uM or lower, such as 1uM or lower, especially 100nM or lower, in respect of CTPS1 enzyme using the assay procedure set out in Example 1.

CTPS1 inhibitors may demonstrate a selectivity for CTPS1 over CTPS2. Suitably the inhibitors demonstrate a selectivity of at least 2-fold, such as at least 30-fold, especially at least 60-fold and in particular at least 1000-fold. CTPS1 inhibitors of particular interest are those demonstrating a selectivity for CTPS1 over CTPS2, suitably of at least 2-fold, such as at least 30-fold, especially at least 60-fold and in particular at least 1000-fold using the assay procedure set out in Example 2. Desirably the selectivity is for human CTPS1 over human CTPS2.

In the case of medicaments intended for human use, CTPS1 inhibition and CTPS1 vs CTPS2 selectivity should be based on human forms of the enzymes.

Suitably the CTPS1 inhibitor may be selected from the following compounds:

A compound of formula (I)



(I)

wherein

R_1 is C_{1-5}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, C_{1-3}alkyleneOC_{1-2}alkyl, or CF_3;

R_3 is H, CH_3, halo, OC_{1-2}alkyl or CF_3;

R_4 and R_5 are each independently H, C_{1-6}alkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, C_{1-6}alkylOH or C_{1-6}haloalkyl,

or R_4 and R_5 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl ring;

R_6 is H or C_{1-3}alkyl;

Ar1 is a 6-membered aryl or heteroaryl;

Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to the amide;

R_{10} is H, halo, C_{1-3}alkyl, OC_{1-2}alkyl, C_{1-2}haloalkyl, OC_{1-2}haloalkyl or CN;

R_{11} is H, F, Cl, CH_3, ethyl, OCH_3, CF_3, OCF_3 or CN;

R_{12} is attached to Ar2 in the meta or ortho position relative to Ar1 and R_{12} is H, halo, C_{1-4}alkyl, C_{2-4}alkynyl, $C(=O)C_{1-2}$alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, C_{1-}

$_3$alkyleneOC$_{1-3}$alkyl, C$_{1-4}$haloalkyl, OC$_{1-4}$haloalkyl, CN, OC$_{0-2}$alkyleneC$_{3-5}$cycloalkyl, OCH$_2$CH$_2$N(CH$_3$)$_2$, OH, C$_{1-4}$alkylOH, NR$_{23}$R$_{24}$, SO$_2$CH$_3$, C(O)N(CH$_3$)$_2$, NHC(O)C$_{1-3}$alkyl, or a C$_{3-6}$heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2, or R$_{12}$ together with a nitrogen atom to which it is attached forms an N-oxide (N$^+$-O$^-$);

R$_{23}$ is H or C$_{1-2}$alkyl;

R$_{24}$ is H or C$_{1-2}$alkyl;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

More suitably the CTPS1 inhibitor is selected from the following ('List A') compounds:

N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-5-phenylpicolinamide;

N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-4-(pyridin-3-yl)benzamide;

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide;

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide (R enantiomer);

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide (S enantiomer);

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;

N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide;

N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-methoxybenzamide;

N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-[1,1'-biphenyl]-4-carboxamide;

N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;

N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide;

N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;

N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-4-(6-isopropoxypyrazin-2-yl)benzamide;

N-((2-(cyclopropanesulfonamido)thiazol-4-yl)methyl)-4-(6-ethoxypyrazin-2-yl)benzamide;

N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide;

N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)-4-(5-fluoropyridin-3-yl)benzamide;

N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)-4-(5-methylpyridin-3-yl)benzamide;

N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)-4-(pyridin-3-yl)benzamide;

N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;
4-(6-chloropyrazin-2-yl)-N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)benzamide;
N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)-4-(6-methylpyrazin-2-yl)benzamide;
N-(3-(2-(cyclopropanesulfonamido)thiazol-4-yl)pentan-3-yl)-4-(pyrazin-2-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-5-(6-ethoxypyrazin-2-yl)-3-fluoropicolinamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-5-(6-(trifluoromethyl)pyrazin-2-yl)picolinamide;
5-(6-chloropyrazin-2-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)picolinamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-5-(6-ethoxypyrazin-2-yl)picolinamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-[2,2'-bipyridine]-5-carboxamide;
4-(5-chloropyridin-3-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-fluoro-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide;
4-(5-chloropyridin-3-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-fluorobenzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-fluoro-4-(5-fluoropyridin-3-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methoxy-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide;
4-(5-acetylpyridin-3-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(5-fluoropyridin-3-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(5-methylpyridin-3-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(5-methoxypyridin-3-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(pyridin-3-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-3'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethylpyrazin-2-yl)-2-fluorobenzamide;

N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-fluoro-4-(6-isopropoxypyrazin-2-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-fluoro-4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methyl-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-methylbenzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-(trifluoromethyl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methoxy-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;
4-(6-chloropyrazin-2-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methoxybenzamide;
4-(6-cyanopyrazin-2-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methoxybenzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;
4-(6-chloropyrazin-2-yl)-N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-methylpyrazin-2-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-methoxypyrazin-2-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-isopropoxypyrazin-2-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(pyrazin-2-yl)benzamide;
N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-fluoropyridin-3-yl)benzamide;
N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-methylpyridin-3-yl)benzamide;
N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(pyridin-3-yl)benzamide;
N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide;

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(6-ethoxypyrazin-2-yl)-2-fluoro-N-methylbenzamide;
N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-2-fluoro-4-(6-isopropoxypyrazin-2-yl)benzamide;
4-(6-chloropyrazin-2-yl)-N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)benzamide;
N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(6-methylpyrazin-2-yl)benzamide;
N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(pyrazin-2-yl)benzamide;
N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-fluoropyridin-3-yl)benzamide (R enantiomer);
N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(5-fluoropyridin-3-yl)benzamide (S enantiomer);
N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide (R enantiomer);
N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)propyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide (S enantiomer);
N-(2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)propan-2-yl)-5-(6-ethoxypyrazin-2-yl)picolinamide;
N-(2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-5-(6-ethoxypyrazin-2-yl)picolinamide;
N-(2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide;
N-(2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide;
N-(2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)propan-2-yl)-2-methyl-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;
N-(2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-2-methyl-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)propan-2-yl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;
N-(2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)propan-2-yl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;
N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)-5-(6-ethoxypyrazin-2-yl)picolinamide;
N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)-4-(pyridin-3-yl)benzamide;
N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide;

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)-2-methyl-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropyl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-4-(5-fluoropyridin-3-yl)benzamide;

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-4-(6-ethylpyrazin-2-yl)-2-fluorobenzamide;

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide;

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-2-fluoro-4-(6-isopropoxypyrazin-2-yl)benzamide;

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-4-(6-ethoxypyrazin-2-yl)benzamide;

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)ethyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide;

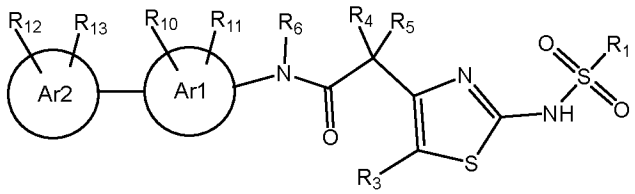
N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide (R enantiomer); and

N-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methoxypropyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide (S enantiomer);

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Such CTPS1 inhibitors are disclosed in PCT publication number WO2019106146 which is incorporated by reference in its entirety for the purpose of the CTPS1 inhibitors disclosed therein. In particular a CTPS1 inhibitor may be a compound described in any one of clauses 1 to 110 of WO2019106146 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof, in particular a compound R1 to R93 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Alternatively, the CTPS1 inhibitor is compound of formula (II):



(II)

wherein

R_1 is C_{1-5}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, C_{1-3}alkyleneOC_{1-2}alkyl, or CF_3;

R_3 is H, halo, CH_3, OC_{1-2}alkyl or CF_3;

or R_3 together with R_5 forms a 5- or 6-membered cycloalkyl or 5 or 6 membered oxygen-containing heterocycloalkyl;

R_4 and R_5 are each independently H, halo, C_{1-6}alkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-6}alkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, C_{1-6}alkylOH, C_{1-6}haloalkyl, OC_{1-6}haloalkyl or $NR_{21}R_{22}$,

or R_4 is H and R_5 together with R_3 form a 5- or 6-membered cycloalkyl or 5 or 6 membered oxygen-containing heterocycloalkyl,

or R_4 and R_5 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl,

or R_4 is H and R_5 and R_6 are a C_{2-3}alkylene chain forming a 5- or 6-membered ring;

or R_4 is O and R_5 is absent;

R_6 is H or C_{1-3}alkyl,

or R_6 together with R_{11} when in the ortho-position to the amide are a C_2alkylene chain forming a 5-membered ring,

or R_5 and R_6 are a C_{2-3}alkylene chain forming a 5- or 6-membered ring and R_4 is H;

Ar1 is 6-membered aryl or heteroaryl;

Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to the amide;

R_{10} is H, halo, C_{1-3}alkyl, OC_{1-2}alkyl, C_{1-2}haloalkyl, OC_{1-2}haloalkyl or CN;

R_{11} is H, F, Cl, CH_3, ethyl, OCH_3, CF_3, OCF_3 or CN,

or R_{11}, when in the ortho-position to the amide, together with R_6 are a C_2alkylene chain forming a 5-membered ring;

R_{12} is attached to Ar2 in the ortho or meta position relative to Ar1 and R_{12} is H, halo, C_{1-4}alkyl, C_{2-4}alkynyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, OC_{0-2}alkyleneC_{3-5}cycloalkyl, $OCH_2CH_2N(CH_3)_2$, OH, C_{1-4}alkylOH, CN, C_{1-3}alkyleneOC_{1-3}alkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, $C(=O)C_{1-2}$alkyl, $NR_{23}R_{24}$, SO_2C_{1-4}alkyl, SOC_{1-4}alkyl, SC_{1-4}alkyl, SH, $C(O)N(CH_3)_2$, $NHC(O)C_{1-3}$alkyl, C_{3-6}heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2, or R_{12} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

R_{13} is H, halo, CH_3 or OCH_3;

R_{21} is H, C_{1-5}alkyl, $C(O)C_{1-5}$alkyl, $C(O)OC_{1-5}$alkyl;

R_{22} is H or CH_3;

R_{23} is H or C_{1-2}alkyl; and

R_{24} is H or C_{1-2}alkyl;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

More suitably the CTPS1 inhibitor is selected from the following ('List B') compounds:

N-([1,1'-biphenyl]-4-yl)-2-(2-(methylsulfonamido)thiazol-4-yl)acetamide;
N-([1,1'-biphenyl]-4-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-ethyl-N-(5-(pyrazin-2-yl)pyridin-2-yl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(pyrimidin-2-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(pyridin-3-yl)phenyl)butanamide (racemic);
(R)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(pyridin-3-yl)phenyl)butanamide;
(S)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(pyridin-3-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-fluoropyridin-3-yl)phenyl)butanamide (racemic);
(R)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-fluoropyridin-3-yl)phenyl)butanamide;
(S)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-fluoropyridin-3-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methyl-N-(4-(pyrimidin-5-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methyl-N-(4-(pyridin-3-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-methoxypyridin-3-yl)phenyl)-2-methylpropanamide;
N-(2-chloro-4-(pyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)acetamide;
2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)-2-methyl-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(pyrimidin-5-yl)phenyl)propanamide;
6-(4-(2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamido)phenyl)-N,N-dimethylpyrazine-2-carboxamide;
N-(5-(5-cyanopyridin-3-yl)pyrimidin-2-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-([1,1'-biphenyl]-4-yl)-2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethynylpyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(6-(pyrimidin-5-yl)pyridin-3-yl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-phenylpyridin-2-yl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4'-fluoro-[1,1'-biphenyl]-4-yl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-methyl-N-(4-(pyridin-3-yl)phenyl)acetamide;
N-([2,3'-bipyridin]-5-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(3'-methoxy-[1,1'-biphenyl]-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(pyridin-3-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(5-methylpyridin-3-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(pyridazin-4-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(pyrazin-2-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-methoxypyrazin-2-yl)phenyl)butanamide;
N-(3-cyano-4-(pyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2,3-difluoro-4-(pyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5-(pyridin-3-yl)pyrimidin-2-yl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5-(6-propoxypyrazin-2-yl)pyridin-2-yl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(3-fluoro-4-(pyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(pyridin-3-yl)-2-(trifluoromethoxy)phenyl)propanamide;
N-(2-chloro-4-(pyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(pyridin-3-yl)phenyl)-2-methylpropanamide ;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(3-methoxy-4-(pyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(2-methoxypyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-(hydroxymethyl)pyridin-3-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-methoxypyridin-3-yl)phenyl)-2-methylpropanamide;
N-(4-(5-cyanopyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(5-(trifluoromethyl)pyridin-3-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(5-(methylsulfonyl)pyridin-3-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-methoxy-4-(5-methoxypyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5'-(trifluoromethyl)-[3,3'-bipyridin]-6-yl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(6-morpholinopyrazin-2-yl)phenyl)propanamide;
N-(4-(6-cyclobutoxypyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(6-propoxypyrazin-2-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(5-methoxypyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methoxy-N-(4-(6-methoxypyrazin-2-yl)phenyl)acetamide;
N-(4-(5-chloropyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-isopropoxyacetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-4-methoxy-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)butanamide;
N-([1,1'-biphenyl]-4-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2,2-difluoroacetamide;
2-(2-(cyclobutanesulfonamido)thiazol-4-yl)-N-(4-(6-methoxypyrazin-2-yl)phenyl)acetamide;
N-([3,3'-bipyridin]-6-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5-phenylpyridin-2-yl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(pyrimidin-5-yl)pyridin-2-yl)acetamide;
N-([3,3'-bipyridin]-6-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(6-phenylpyridin-3-yl)acetamide;
N-([2,3'-bipyridin]-5-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(pyridazin-3-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(pyridazin-4-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(pyrazin-2-yl)phenyl)butanamide;

N-(4-(5-chloropyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-4-methoxybutanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-fluoropyridin-3-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methyl-N-(4-(pyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-propoxypyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-isopropoxypyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-cyclopropoxypyrazin-2-yl)phenyl)butanamide;
N-(4-(6-chloropyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;
N-(4-(6-cyanopyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-methoxypyrazin-2-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(pyrazin-2-yl)phenyl)acetamide;
N-([1,1'-biphenyl]-4-yl)-2-(cyclopropanesulfonamido)-4,5,6,7-tetrahydrobenzo[d]thiazole-4-carboxamide;
2-(cyclopropanesulfonamido)-N-(4-(pyridin-3-yl)phenyl)-4,5,6,7-tetrahydrobenzo[d]thiazole-4-carboxamide;
N-([1,1'-biphenyl]-4-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;
N-([1,1'-biphenyl]-4-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-3-methylbutanamide;
N-(3'-chloro-[1,1'-biphenyl]-4-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(3'-cyano-[1,1'-biphenyl]-4-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2,2-difluoro-N-(4-(pyridin-3-yl)phenyl)acetamide;
N-(4-(5-fluoropyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-ethyl-N-(4-(pyridin-3-yl)phenyl)butanamide;
N-(4-(5-cyanopyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-ethylbutanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-ethoxypyridin-3-yl)phenyl)propanamide;
N-(4-(5-chloropyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-ethoxypyridin-3-yl)phenyl)butanamide;
N-([1,1'-biphenyl]-4-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(4-methylpyridin-3-yl)phenyl)acetamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-methylpyridin-3-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(2-methylpyridin-3-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-methylpyridin-3-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(pyridin-3-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(2-methylpyridin-3-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-oxo-N-(4-(pyridin-3-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(6-methylpyridin-3-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)butanamide;
(R)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methoxy-N-(4-(6-methoxypyrazin-2-yl)phenyl)acetamide;
(S)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methoxy-N-(4-(6-methoxypyrazin-2-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)pyridin-2-yl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(3-fluoro-5-(pyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)-3-fluoropyridin-2-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(3-fluoro-5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;
N-(5-(6-cyanopyrazin-2-yl)-3-fluoropyridin-2-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5'-(2,2,2-trifluoroethoxy)-[3,3'-bipyridin]-6-yl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5'-(difluoromethoxy)-[3,3'-bipyridin]-6-yl)-2-methylpropanamide;
N-([2,3'-bipyridin]-5-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(6-(pyrimidin-5-yl)pyridin-3-yl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-(difluoromethoxy)pyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-ethyl-N-(4-(6-methoxypyrazin-2-yl)phenyl)butanamide;

N-(4-(5-chloropyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-ethylbutanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-ethyl-N-(2-fluoro-4-(pyridin-3-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-ethyl-N-(4-(pyrazin-2-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-ethyl-N-(4-(6-propoxypyrazin-2-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-ethoxypyridin-3-yl)-2-fluorophenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(5-fluoropyridin-3-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)phenyl)propanamide;

N-(4-(5-chloropyridin-3-yl)-2-fluorophenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

N-(4-(5-cyanopyridin-3-yl)-2-fluorophenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-methoxypyrazin-2-yl)phenyl)cyclopentane-1-carboxamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(5-(2,2,2-trifluoroethoxy)pyridin-3-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(5-(trifluoromethyl)pyridin-3-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(5-(2,2,2-trifluoroethoxy)pyridin-3-yl)phenyl)propanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethynylpyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-methylphenyl)-2-methylpropanamide;

N-(4-(6-chloropyrazin-2-yl)-2-methylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-(difluoromethoxy)pyridin-3-yl)-2-fluorophenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5-(pyrazin-2-yl)pyridin-2-yl)propanamide;
N-(5-(6-cyclobutoxypyrazin-2-yl)pyridin-2-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-cyclopropoxypyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-isopropoxypyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;
N-([3,3'-bipyridin]-6-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-ethylbutanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5'-ethoxy-[3,3'-bipyridin]-6-yl)-2-ethylbutanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5'-propoxy-[3,3'-bipyridin]-6-yl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-ethyl-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)butanamide;
N-([3,3'-bipyridin]-6-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-methoxy-4-(pyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(3-methoxy-4-(pyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(3-fluoro-4-(pyridin-3-yl)phenyl)-2-methylpropanamide;
N-(3-cyano-4-(pyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(3-chloro-4-(pyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(4-(6-cyanopyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(4-(6-chloropyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-ethyl-N-(4-(5-fluoropyridin-3-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(5-propoxypyridin-3-yl)phenyl)propanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-isopropoxypyridin-3-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(5-isopropoxypyridin-3-yl)phenyl)-2-methylpropanamide;

N-(4-(6-chloropyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-ethylbutanamide;

N-(4-(6-cyanopyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-ethylbutanamide;

2-methyl-2-(2-(methylsulfonamido)thiazol-4-yl)-N-(4-(pyridin-3-yl)phenyl)propanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N,2-dimethyl-N-(4-(pyridin-3-yl)phenyl)propanamide;

2-(cyclopropanesulfonamido)-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)-5,6-dihydro-4H-cyclopenta[d]thiazole-4-carboxamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-4-methoxy-N-(5-(pyrazin-2-yl)pyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-4-methoxy-N-(5'-methoxy-[3,3'-bipyridin]-6-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-isopropoxy-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)acetamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-propoxypyrazin-2-yl)pyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-isopropoxypyrazin-2-yl)pyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-methoxypyrazin-2-yl)pyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)butanamide;

N-(5-(6-cyanopyrazin-2-yl)pyridin-2-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5'-fluoro-[3,3'-bipyridin]-6-yl)butanamide;

N-(5'-cyano-[3,3'-bipyridin]-6-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-phenylpyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)pyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)-3-fluoropyridin-2-yl)butanamide;

N-(5-(6-cyanopyrazin-2-yl)-3-fluoropyridin-2-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5'-(2,2,2-trifluoroethoxy)-[3,3'-bipyridin]-6-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5'-(difluoromethoxy)-[3,3'-bipyridin]-6-yl)butanamide;

N-(5-(6-chloropyrazin-2-yl)pyridin-2-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2,3-difluoro-4-(pyridin-3-yl)phenyl)acetamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)butanamide (racemic);

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-4-methoxy-N-(4-(6-methoxypyrazin-2-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-fluoropyridin-3-yl)phenyl)-4-methoxybutanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)propanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-(trifluoromethyl)pyridin-3-yl)phenyl)butanamide;

N-(4-(5-cyanopyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(pyrazin-2-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-ethoxypyridin-3-yl)-2-fluorophenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(5-fluoropyridin-3-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(pyridin-3-yl)phenyl)butanamide;

N-(4-(5-cyanopyridin-3-yl)-2-fluorophenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;

N-(4-(5-chloropyridin-3-yl)-2-fluorophenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;

(R)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)butanamide;
(S)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)butanamide;
N-(4-(1-(5-(6-ethoxypyrazin-2-yl)indolin-1-yl)-1-oxobutan-2-yl)thiazol-2-yl)cyclopropanesulfonamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-methoxypyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-(difluoromethoxy)pyridin-3-yl)-2-fluorophenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-(difluoromethoxy)pyridin-3-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-(2,2,2-trifluoroethoxy)pyridin-3-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(5-(2,2,2-trifluoroethoxy)pyridin-3-yl)phenyl)butanamide;
2-(cyclopropanesulfonamido)-N-(4-(pyridin-3-yl)phenyl)-5,6-dihydro-4H-cyclopenta[d]thiazole-4-carboxamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methoxy-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-methoxy-4-(pyridin-3-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(pyridin-3-yl)phenyl)acetamide;
N-(4-(5-cyanopyridin-3-yl)phenyl)-2-(cyclopropanesulfonamido)-5,6-dihydro-4H-cyclopenta[d]thiazole-4-carboxamide;
2-(cyclopropanesulfonamido)-N-(4-(5-fluoropyridin-3-yl)phenyl)-5,6-dihydro-4H-cyclopenta[d]thiazole-4-carboxamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methoxy-N-(4-(pyridin-3-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(pyridin-3-yl)phenyl)-2-methoxyacetamide;
N-(2-chloro-4-(pyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5'-methoxy-[3,3'-bipyridin]-6-yl)-2-methylpropanamide;
N-(5'-chloro-[3,3'-bipyridin]-6-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(5'-cyano-[3,3'-bipyridin]-6-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-fluoro-[3,3'-bipyridin]-6-yl)-2-methylpropanamide;
N-(5'-cyano-5-fluoro-[3,3'-bipyridin]-6-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(5'-chloro-5-fluoro-[3,3'-bipyridin]-6-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5,5'-difluoro-[3,3'-bipyridin]-6-yl)-2-methylpropanamide;
N-(5-(3-chloro-5-methylphenyl)pyridin-2-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(3-methoxyphenyl)pyridin-2-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(3-fluoro-5-methoxyphenyl)pyridin-2-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(3,5-dimethoxyphenyl)pyridin-2-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5-(3-(trifluoromethoxy)phenyl)pyridin-2-yl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(3-(2-hydroxypropan-2-yl)phenyl)pyridin-2-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5-(3-morpholinophenyl)pyridin-2-yl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(6-phenylpyridin-3-yl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(2-fluoropyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-(hydroxymethyl)pyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(2-methoxypyrimidin-5-yl)phenyl)acetamide;
N-(4'-(tert-butyl)-[1,1'-biphenyl]-4-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)acetamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(pyridin-3-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(pyridin-4-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2'-methoxy-[1,1'-biphenyl]-4-yl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(pyrimidin-5-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(2-(trifluoromethyl)pyridin-3-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5'-methyl-[3,3'-bipyridin]-6-yl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(2-methoxy-4-methylpyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-methoxy-5-methylpyridin-3-yl)phenyl)-2-methylpropanamide;
N-(4-(5-chloropyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-fluoropyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(4-methylpyridin-3-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(4-(trifluoromethyl)pyridin-3-yl)phenyl)propanamide;
N-(4-(5-chloropyridin-3-yl)-2-methoxyphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-(dimethylamino)pyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-methoxy-4-(5-methylpyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-methoxy-4-(5-(trifluoromethyl)pyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-methoxypyridin-3-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5'-fluoro-[3,3'-bipyridin]-6-yl)-2-methylpropanamide;
N-(5-(6-chloropyrazin-2-yl)pyridin-2-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(5-(6-cyanopyrazin-2-yl)pyridin-2-yl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5-(pyrimidin-5-yl)pyridin-2-yl)propanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-methoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(6-methylpyrazin-2-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;
N-(4-(6-chloropyridin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-methoxypyridin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(6-(trifluoromethyl)pyridin-2-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(4-methoxypyridin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-isopropoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-cyclopropoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(pyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-methoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
N-(4-(6-chloro-3-methylpyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(4-(6-chloro-5-methylpyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(6-(pyrrolidin-1-yl)pyrazin-2-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-(2-(dimethylamino)ethoxy)pyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(3-methylpyrazin-2-yl)phenyl)propanamide;
N-(4-(6-acetamidopyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5,6-dimethylpyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-(hydroxymethyl)pyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(3,6-dimethylpyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-methoxypyridin-3-yl)-2-methylphenyl)-2-methylpropanamide;
N-(4-(5-cyanopyridin-3-yl)-2-methylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-fluoropyridin-3-yl)-2-methylphenyl)-2-methylpropanamide;
N-(4-(5-chloropyridin-3-yl)-3-methylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(4-(5-cyanopyridin-3-yl)-3-ethoxyphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-ethoxypyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-cyclopropylpyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(5-methoxypyridin-3-yl)pyrimidin-2-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(5-fluoropyridin-3-yl)pyrimidin-2-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5-(5-(trifluoromethyl)pyridin-3-yl)pyrimidin-2-yl)propanamide;
N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-methyl-2-(2-((2-methylpropyl)sulfonamido)thiazol-4-yl)propanamide;
N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methyl-2-(2-((trifluoromethyl)sulfonamido)thiazol-4-yl)propanamide;
2-methyl-2-(2-((1-methylethyl)sulfonamido)thiazol-4-yl)-N-(4-(pyridin-3-yl)phenyl)propanamide;
N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methyl-2-(2-((1-methylethyl)sulfonamido)thiazol-4-yl)propanamide;
2-methyl-2-(2-((1-methylcyclopropane)-1-sulfonamido)thiazol-4-yl)-N-(4-(pyridin-3-yl)phenyl)propanamide;
N-(4-(5-chloropyridin-3-yl)phenyl)-2-methyl-2-(2-((1-methylcyclopropane)-1-sulfonamido)thiazol-4-yl)propanamide;
N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methyl-2-(2-((1-methylcyclopropane)-1-sulfonamido)thiazol-4-yl)propanamide;

2-methyl-2-(2-((1-methylcyclopropane)-1-sulfonamido)thiazol-4-yl)-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;
2-(2-((1,1-dimethylethyl)sulfonamido)thiazol-4-yl)-2-methyl-N-(4-(pyridin-3-yl)phenyl)propanamide;
2-(2-((1,1-dimethylethyl)sulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-((1,1-dimethylethyl)sulfonamido)thiazol-4-yl)-2-methyl-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;
2-(2-(cyclobutanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(pyridin-3-yl)phenyl)propanamide;
2-(2-(cyclobutanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclobutanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;
N-(4-(5-cyanopyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N,2-dimethylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N,2-dimethyl-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;
2-methyl-2-(2-((2-methylpropyl)sulfonamido)thiazol-4-yl)-N-(4-(pyridin-3-yl)phenyl)propanamide;
N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methyl-2-(2-((2-methylpropyl)sulfonamido)thiazol-4-yl)propanamide;
2-methyl-2-(2-((2-methylpropyl)sulfonamido)thiazol-4-yl)-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;
N-(4-(5-chloropyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-methyl-N-(4-(pyridin-3-yl)phenyl)butanamide;
N-(4-(5-cyanopyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-methylbutanamide;
2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
N-(4-(5-chloropyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N,2-dimethylpropanamide;
2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)-2-methyl-N-(4-(pyridin-3-yl)phenyl)propanamide;
N-(4-(5-cyanopyridin-3-yl)-2,6-dimethylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

N-(4-(5-chloropyridin-3-yl)-2,6-dimethylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

N-(4-(5-cyanopyridin-3-yl)-3-methylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(pyridin-3-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-fluoropyridin-3-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methoxy-N-(4-(6-methoxypyrazin-2-yl)phenyl)acetamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)butanamide;

2-amino-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)acetamide;

2-acetamido-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)acetamide;

methyl(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-((4-(6-ethoxypyrazin-2-yl)phenyl) amino)-2-oxoethyl)carbamate;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-(dimethylamino)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)acetamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-4-hydroxybutanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methoxyacetamide;

(R)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methoxyacetamide;

(S)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methoxyacetamide;

2-(2-((2-methoxyethyl)sulfonamido)thiazol-4-yl)-2-methyl-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)propanamide;

2-(2-(cyclopentanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(pyridin-3-yl)phenyl)propanamide;

2-(2-(cyclopentanesulfonamido)thiazol-4-yl)-2-methyl-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;

2-(2-(cyclopentanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-isopropylpyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5'-ethoxy-[3,3'-bipyridin]-6-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-(2-hydroxypropan-2-yl)pyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-(2-methoxypropan-2-yl)pyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)-2-methyl-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)propanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;

N-(4-(5-chloropyridin-3-yl)-2-(trifluoromethyl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

N-(4-(5-cyanopyridin-3-yl)-2-(trifluoromethyl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-fluoropyridin-3-yl)-2-(trifluoromethyl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(2-(trifluoromethyl)-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-(trifluoromethyl)phenyl)-2-methylpropanamide;

N-(4-(5-chloropyridin-3-yl)-2,6-diethylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

N-(4-(5-cyanopyridin-3-yl)-2,6-diethylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)-N-(2-fluoro-4-(5-(trifluoromethyl)pyridin-3-yl)phenyl)-2-methylpropanamide;

N-(4-(5-chloropyridin-3-yl)-2,6-difluorophenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

N-(4-(5-chloropyridin-3-yl)-2-fluoro-5-methylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-(2-methoxypropan-2-yl)pyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)-N-(2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)-2-methylpropanamide;

N-(4-(6-cyanopyrazin-2-yl)-2-fluorophenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethylpyrazin-2-yl)-2-fluorophenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-isopropoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)-2-methylpropanamide;
N-(4-(5-chloropyridin-3-yl)-2-isopropylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(4-(5-cyanopyridin-3-yl)-2-isopropylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-isopropyl-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-isopropylphenyl)-2-methylpropanamide;
N-(4-(5-chloropyridin-3-yl)-3-fluoro-2-methylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(4-(5-chloropyridin-3-yl)-5-fluoro-2-methylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(4-(5-chloropyridin-3-yl)-2,3-dimethylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(4-(5-chloropyridin-3-yl)-2,5-dimethylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(4-(5-cyanopyridin-3-yl)-3-fluoro-2-methylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(2-methyl-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;
N-(4-(5-chloropyridin-3-yl)-5-fluoro-2-methoxyphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(4-(5-chloropyridin-3-yl)-3-(trifluoromethyl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-3-methylphenyl)-2-methylpropanamide;
N-(4-(5-chloropyridin-3-yl)-3-ethoxyphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
N-(4-(5-chloropyridin-3-yl)phenyl)-1-(2-(cyclopropanesulfonamido)thiazol-4-yl)cyclopropane-1-carboxamide;

N-(4-(5-cyanopyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)-5-methylthiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-(2-methoxypropan-2-yl)pyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(5-chloro-2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)-5-methoxythiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
N-(4-(6-(cyclopentylmethoxy)pyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-hydroxypyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(ethylsulfonamido)thiazol-4-yl)-2-methyl-N-(5'-(trifluoromethyl)-[3,3'-bipyridin]-6-yl)propanamide;
2-(2-(ethylsulfonamido)thiazol-4-yl)-2-methyl-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)propanamide;
N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-(2-(ethylsulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(ethylsulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-isopropoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
N-(4-(5-cyanopyridin-3-yl)phenyl)-2-(2-(ethylsulfonamido)thiazol-4-yl)-2-methylpropanamide;
2-(2-(ethylsulfonamido)thiazol-4-yl)-N-(4-(5-fluoropyridin-3-yl)phenyl)-2-methylpropanamide;
2-(2-(ethylsulfonamido)thiazol-4-yl)-2-methyl-N-(4-(pyridin-3-yl)phenyl)propanamide;
2-(2-(ethylsulfonamido)thiazol-4-yl)-2-methyl-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;
2-(2-(ethylsulfonamido)thiazol-4-yl)-N-(4-(6-isopropoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
2-methyl-2-(2-(methylsulfonamido)thiazol-4-yl)-N-(5'-(trifluoromethyl)-[3,3'-bipyridin]-6-yl)propanamide;
N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-methyl-2-(2-(methylsulfonamido)thiazol-4-yl)propanamide;
N-(2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)-2-methyl-2-(2-(methylsulfonamido)thiazol-4-yl)propanamide;
N-(2-fluoro-4-(6-isopropoxypyrazin-2-yl)phenyl)-2-methyl-2-(2-(methylsulfonamido)thiazol-4-yl)propanamide;
N-(4-(5-chloropyridin-3-yl)phenyl)-2-methyl-2-(2-(methylsulfonamido)thiazol-4-yl)propanamide;

2-methyl-2-(2-(methylsulfonamido)thiazol-4-yl)-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;

N-(4-(6-isopropoxypyrazin-2-yl)phenyl)-2-methyl-2-(2-(methylsulfonamido)thiazol-4-yl)propanamide;

2-(2-((cyclopropylmethyl)sulfonamido)thiazol-4-yl)-2-methyl-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)propanamide;

1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)cyclopropane-1-carboxamide;

1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)cyclopropane-1-carboxamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)-4-methoxybutanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-isopropoxypyrazin-2-yl)phenyl)-4-methoxybutanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-isopropylpyrazin-2-yl)pyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-(2-methoxypropan-2-yl)pyrazin-2-yl)pyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-(2-methoxypropan-2-yl)pyrazin-2-yl)phenyl)butanamide;

N-(4-(6-cyanopyrazin-2-yl)-2-fluorophenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethylpyrazin-2-yl)-2-fluorophenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-(2-methoxypropan-2-yl)pyrazin-2-yl)phenyl)butanamide;

tert-butyl-(1-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-((4-(6-ethoxypyrazin-2-yl)phenyl)amino)-2-oxoethyl)carbamate;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)-2-methoxyacetamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)-2-methoxyacetamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methoxyacetamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-isopropoxypyrazin-2-yl)phenyl)-2-methoxyacetamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)butanamide;
(R)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)butanamide;
(S)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)butanamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(5-(trifluoromethyl)pyridin-3-yl)phenyl)butanamide;
(R)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(5-(trifluoromethyl)pyridin-3-yl)phenyl)butanamide;
(S)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(5-(trifluoromethyl)pyridin-3-yl)phenyl)butanamide;
2-Amino-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-*N*-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)acetamide hydrochloride;
2-Amino-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-*N*-(2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)acetamide;
2-Amino-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-*N*-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)acetamide hydrochloride;
2-(2-(Cyclopropanesulfonamido)thiazol-4-yl)-2-(dimethylamino)-*N*-(2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)acetamide;
2-(2-(Cyclopropanesulfonamido)thiazol-4-yl)-2-(dimethylamino)-*N*-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2,2-difluoroacetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)acetamide;
2-methyl-2-(2-(methylsulfonamido)thiazol-4-yl)-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)propanamide;
N-(2-fluoro-4-(5-(trifluoromethyl)pyridin-3-yl)phenyl)-2-methyl-2-(2-(methylsulfonamido)thiazol-4-yl)propanamide;
2-(2-((cyclopropylmethyl)sulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(5-(trifluoromethyl)pyridin-3-yl)phenyl)-2-methylpropanamide;
N-(4-(5-chloro-4-methylpyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

N-(4-(6-ethoxypyrazin-2-yl)-2-(trifluoromethyl)phenyl)-2-methyl-2-(2-(methylsulfonamido)thiazol-4-yl)propanamide;

2-(2-((cyclopropylmethyl)sulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)-2-methylpropanamide;

N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)-2-methyl-2-(2-(methylsulfonamido)thiazol-4-yl)propanamide;

N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)-2-(2-((2-methoxyethyl)sulfonamido)thiazol-4-yl)-2-methylpropanamide;

2-(2-((cyclopropylmethyl)sulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)-2-methylpropanamide;

N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methyl-2-(2-(methylsulfonamido)thiazol-4-yl)propanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)-3-fluoropyridin-2-yl)-4-methoxybutanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-methoxybutanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-4-methoxy-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)-3-methylpyridin-2-yl)butanamide;

N-(2-chloro-4-(6-ethoxypyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;

N-(2-cyano-4-(6-ethoxypyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-methylphenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-(trifluoromethoxy)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-methoxyphenyl)butanamide;

2-(2-(Cyclopropanesulfonamido)thiazol-4-yl)-*N*-(4-(6-(ethylamino)pyrazin-2-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)-3-fluoropyridin-2-yl)-2-methoxyacetamide;

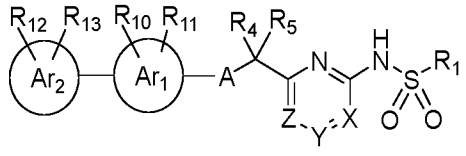
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-methoxyacetamide;

2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(5-fluoropyridin-3-yl)-2-(trifluoromethyl)phenyl)-2-methoxyacetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(5-(trifluoromethyl)pyridin-3-yl)phenyl)-2-methoxyacetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-(trifluoromethyl)phenyl)-2-methoxyacetamide;
N-(2-chloro-4-(6-ethoxypyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methoxyacetamide;
N-(2-cyano-4-(6-ethoxypyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methoxyacetamide;
N-(2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)-2-methoxy-2-(2-(methylsulfonamido)thiazol-4-yl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2,6-difluorophenyl)-2-methoxyacetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-(trifluoromethoxy)phenyl)-2-methoxyacetamide;
N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methoxy-2-(2-(methylsulfonamido)thiazol-4-yl)acetamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)-3-fluoropyridin-2-yl)butanamide (R enantiomer);
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)-3-fluoropyridin-2-yl)butanamide (S enantiomer);
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)-2-methoxyacetamide (R enantiomer);
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)-2-methoxyacetamide (S enantiomer);
4-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)tetrahydro-2H-pyran-4-carboxamide;
4-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide;
4-(2-(cyclopropanesulfonamido)thiazol-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide;
N-(4-(1-(4-(5-methoxypyridin-3-yl)phenyl)-2-oxopyrrolidin-3-yl)thiazol-2-yl)cyclopropanesulfonamide;
2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methyl-N-(5-(6-methylpyrazin-2-yl)pyridin-2-yl)propanamide; and
N-(4-(6-cyanopyrazin-2-yl)-2-methylphenyl)-2-(2-(cyclopropanesulfonamido)thiazol-4-yl)-2-methylpropanamide;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Such CTPS1 inhibitors are disclosed in PCT publication number WO2019106156, which is incorporated by reference in its entirety for the purpose of the CTPS1 inhibitors disclosed therein. In particular a CTPS1 inhibitor may be a compound described in any one of clauses 1 to 118 of WO2019106156, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof, in particular a compound T1 to T465 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Alternatively, the CTPS1 inhibitor is a compound formula (III):



(III)

wherein

A is an amide linker having the following structure: -C(=O)NH- or -NHC(=O)-;

X is N or CH;

Y is N or CR_2;

Z is N or CR_3;

with the proviso that when at least one of X or Z is N, Y cannot be N;

R_1 is C_{1-5}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, or CF_3;

R_2 is H, halo, C_{1-2}alkyl, OC_{1-2}alkyl, C_{1-2}haloalkyl or OC_{1-2}haloalkyl;

R_3 is H, halo, CH_3, OCH_3, CF_3 or OCF_3;

wherein at least one of R_2 and R_3 is H;

R_4 and R_5 are each independently H, C_{1-6}alkyl, C_{1-6}alkylOH, C_{1-6}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, or R_4 and R_5 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl; and

when A is -NHC(=O)-:

R_4 and R_5 may additionally be selected from halo, OC_{1-6}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-6}alkyl and $NR_{21}R_{22}$;

Ar1 is a 6-membered aryl or heteroaryl;

Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to the amide;

R_{10} is H, halo, C_{1-3}alkyl, C_{1-2}haloalkyl, OC_{1-2}alkyl, OC_{1-2}haloalkyl or CN;

R_{11} is H, F, Cl, C_{1-2}alkyl, CF_3, OCH_3 or CN;

R_{12} is attached to Ar2 in the ortho or meta position relative to Ar1 and R_{12} is H, halo, C_{1-4}alkyl, C_{2-4}alkenyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, OC_{0-2}alkyleneC_{3-5}cycloalkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, hydroxy, C_{1-4}alkylOH, SO_2C_{1-2}alkyl, $C(O)N(C_{1-2}alkyl)_2$, $NHC(O)C_{1-3}$alkyl or $NR_{23}R_{24}$; and

when A is -NHC(=O)-:

R_{12} may additionally be selected from CN, $OCH_2CH_2N(CH_3)_2$ and a C_{3-6}heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2, or R_{12} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

R_{13} is H or halo;

R_{21} is H, C_{1-5}alkyl, $C(O)C_{1-5}$alkyl, $C(O)OC_{1-5}$alkyl;

R_{22} is H or CH_3;

R_{23} is H or C_{1-2}alkyl; and

R_{24} is H or C_{1-2}alkyl;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

More suitably, the CTPS1 inhibitor is selected from the following ('List C') compounds:

N-(4-(5-chloropyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)butanamide;

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)cyclopentanecarboxamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-methoxypyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methyl-N-(4-(5-(trifluoromethyl)pyridin-3-yl)phenyl)propanamide;

2-methyl-N-(2-methyl-4-(6-methylpyrazin-2-yl)phenyl)-2-(2-(methylsulfonamido)pyrimidin-4-yl)propanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(pyrazin-2-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(5-(trifluoromethyl)pyridin-3-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)acetamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-isopropoxypyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-ethylbutanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)acetamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(6-isopropoxypyrazin-2-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(5-(trifluoromethyl)pyridin-3-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(5-(2,2,2-trifluoroethoxy)pyridin-3-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)-5-fluoropyrimidin-4-yl)-N-(4-(pyridin-3-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(pyridin-3-yl)phenyl)acetamide;
N-([1,1'-biphenyl]-4-yl)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)acetamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-methoxypyrazin-2-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)phenyl)acetamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-isopropoxypyrazin-2-yl)phenyl)acetamide;
2-(2-(cyclobutanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;
2-(2-(cyclobutanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(6-isopropoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclobutanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-methylphenyl)-2-methylpropanamide;
2-(2-(cyclobutanesulfonamido)pyrimidin-4-yl)-N-(4-(6-methoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclobutanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)-3-fluoropyridin-2-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5'-ethoxy-[3,3'-bipyridin]-6-yl)-2-methylpropanamide;
N-([3,3'-bipyridin]-6-yl)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methyl-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)propanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-cyclopropoxypyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;

N-(2-chloro-4-(6-ethoxypyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methylpropanamide;

N-(2-cyano-4-(6-ethoxypyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(5-isopropoxypyridin-3-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(pyridin-3-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(6-isopropoxypyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluoro-5-methylphenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2,6-difluorophenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(pyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methyl-N-(2-methyl-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2,3-dimethylphenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-5-fluoro-2-methylphenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2,5-dimethylphenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-(trifluoromethoxy)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-5-fluoro-2-methoxyphenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-methoxyphenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methyl-N-(4-(pyrimidin-5-yl)phenyl)propanamide;

N-(4-(5-chloropyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methylpropanamide;

N-(4-(5-cyanopyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(5-fluoropyridin-3-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methyl-N-(4-(5-methylpyridin-3-yl)phenyl)propanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(5-(difluoromethoxy)pyridin-3-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(5-methoxypyridin-3-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(5-ethoxypyridin-3-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(5-isopropoxypyridin-3-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methyl-N-(4-(pyridin-3-yl)phenyl)propanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methyl-N-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)propanamide;

N-(3'-chloro-[1,1'-biphenyl]-4-yl)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methylpropanamide;

N-(3'-cyano-[1,1'-biphenyl]-4-yl)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(3'-ethoxy-[1,1'-biphenyl]-4-yl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methyl-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-cyclopropoxypyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-isopropoxypyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)-5-fluoropyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;

N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methyl-2-(2-((1-methylcyclopropane)-1-sulfonamido)pyrimidin-4-yl)propanamide;

2-(2-(cyclopropanesulfonamido)-5-methylpyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methyl-N-(4-(pyrazin-2-yl)phenyl)propanamide;

N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)-2-(2-(ethylsulfonamido)pyrimidin-4-yl)-2-methylpropanamide;

2-(2-(ethylsulfonamido)pyrimidin-4-yl)-2-methyl-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;

N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-(2-(ethylsulfonamido)pyrimidin-4-yl)-2-methylpropanamide;

N-(5-(6-ethoxypyrazin-2-yl)-3-fluoropyridin-2-yl)-2-methyl-2-(2-(methylsulfonamido)pyrimidin-4-yl)propanamide;

N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-methyl-2-(2-(methylsulfonamido)pyrimidin-4-yl)propanamide;

N-(2-fluoro-4-(5-isopropoxypyridin-3-yl)phenyl)-2-methyl-2-(2-(methylsulfonamido)pyrimidin-4-yl)propanamide;

N-(2-fluoro-4-(6-isopropoxypyrazin-2-yl)phenyl)-2-methyl-2-(2-(methylsulfonamido)pyrimidin-4-yl)propanamide;

2-methyl-N-(2-methyl-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)-2-(2-(methylsulfonamido)pyrimidin-4-yl)propanamide;

2-methyl-2-(2-(methylsulfonamido)pyrimidin-4-yl)-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;

N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methyl-2-(2-(methylsulfonamido)pyrimidin-4-yl)propanamide;

2-(2-((1,1-dimethylethyl)sulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)cyclopropanecarboxamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5'-(trifluoromethyl)-[3,3'-bipyridin]-6-yl)butanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5'-(2,2,2-trifluoroethoxy)-[3,3'-bipyridin]-6-yl)butanamide;

N-([3,3'-bipyridin]-6-yl)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)butanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-isopropoxypyrazin-2-yl)pyridin-2-yl)butanamide;
N-(4-(5-chloropyridin-3-yl)-2-fluorophenyl)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(5-(2,2,2-trifluoroethoxy)pyridin-3-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(5-isopropoxypyridin-3-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(pyridin-3-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(6-methoxypyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(6-isopropoxypyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(2-fluoro-4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)phenyl)butanamide;
N-(4-(5-cyanopyridin-3-yl)phenyl)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(5-(2,2,2-trifluoroethoxy)pyridin-3-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(5-isopropoxypyridin-3-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(pyridin-3-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)butanamide;
N-(4-(6-chloropyrazin-2-yl)phenyl)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-methoxypyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-isopropoxypyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)phenyl)butanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(pyrazin-2-yl)phenyl)butanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-4-methoxybutanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(pyridin-3-yl)phenyl)propenamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-(*R*)-fluorobutanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-(*S*)-fluorobutanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-fluorobutanamide;
4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-isopropylpyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)-2,2-difluoroacetamide;
N-((2-(cyclopropanesulfonamido)pyrimidin-4-yl)methyl)-4-(6-ethoxypyrazin-2-yl)benzamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methyl-N-(5-(6-(prop-1-en-2-yl)pyrazin-2-yl)pyridin-2-yl)propanamide;
2-(2-(cyclopropanesulfonamido)-6-methylpyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)-6-(trifluoromethyl)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-cyclopropylpyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(6-(6-ethoxypyrazin-2-yl)pyridin-3-yl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-cyclopropylpyrazin-2-yl)-2-fluorophenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)-6-methylpyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)-6-(trifluoromethyl)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)-2-methylpropanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-methyl-N-(4-(6-(prop-1-en-2-yl)pyrazin-2-yl)phenyl)propanamide;
2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-isopropylpyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-(dimethylamino)pyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)-6-methylpyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)-6-(trifluoromethyl)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;

2-(2-(cyclopropanesulfonamido)-6-methoxypyrimidin-4-yl)-2-methyl-N-(4-(pyridin-3-yl)phenyl)propanamide;

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)cyclopentane-1-carboxamide;

4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)tetrahydro-2H-pyran-4-carboxamide;

N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(2-(methylsulfonamido)pyrimidin-4-yl)piperidine-4-carboxamide;

tert-butyl 4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-4-((5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)carbamoyl)piperidine-1-carboxylate;

4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)piperidine-4-carboxamide;

tert-butyl 3-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-3-((5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)carbamoyl)azetidine-1-carboxylate;

tert-butyl 4-((5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)carbamoyl)-4-(2-(methylsulfonamido)pyrimidin-4-yl)piperidine-1-carboxylate;

4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)tetrahydro-2H-pyran-4-carboxamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)-3-fluoropyridin-2-yl)-4-methoxybutanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-methoxybutanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)-4-methoxybutanamide;

N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-methoxy-2-methyl-2-(2-(methylsulfonamido)pyrimidin-4-yl)butanamide;

N-(5'-chloro-[3,3'-bipyridin]-6-yl)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)butanamide;

N-(5'-chloro-[3,3'-bipyridin]-6-yl)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-2-fluorobutanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-cyclopropylpyrazin-2-yl)pyridin-2-yl)-2-fluorobutanamide;

N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-fluoro-2-(2-(methylsulfonamido)pyrimidin-4-yl)butanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)-3-methylpyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-cyclopropylpyrazin-2-yl)pyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-(2,2,2-trifluoroethoxy)pyrazin-2-yl)pyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(3-fluoro-5-(6-methoxypyrazin-2-yl)pyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-methoxypyrazin-2-yl)pyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-cyclopropylpyrazin-2-yl)-2-fluorophenyl)butanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-methylphenyl)butanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)-3-fluoropyridin-2-yl)butanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-methylbutanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-fluoro-3-methylbutanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)-3-methylbutanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-3-methylbutanamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methoxyacetamide;

N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-fluoro-2-(2-(methylsulfonamido)pyrimidin-4-yl)-(*R*)-butanamide;

N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-fluoro-2-(2-(methylsulfonamido)pyrimidin-4-yl)-(*S*)-butanamide;

N-(4-(5-chloropyridin-3-yl)phenyl)-2-(6-(cyclopropanesulfonamido)pyridin-2-yl)acetamide;

N-(4-(5-cyanopyridin-3-yl)phenyl)-2-(6-(cyclopropanesulfonamido)pyridin-2-yl)acetamide;

2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(4-(5-fluoropyridin-3-yl)phenyl)acetamide;

2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(4-(5-methoxypyridin-3-yl)phenyl)acetamide;

2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(4-(pyridin-3-yl)phenyl)acetamide;

2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)acetamide;
2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(4-(6-methoxypyrazin-2-yl)phenyl)acetamide;
2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(4-(pyrazin-2-yl)phenyl)acetamide;
N-([3,3'-bipyridin]-6-yl)-2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-2-methylpropanamide;
N-(4-(5-chloropyridin-3-yl)phenyl)-2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-2-methylpropanamide;
2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(4-(5-fluoropyridin-3-yl)phenyl)-2-methylpropanamide;
2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(4-(5-ethoxypyridin-3-yl)phenyl)-2-methylpropanamide;
2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-2-methyl-N-(4-(pyridin-3-yl)phenyl)propanamide;
2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(2-fluoro-4-(pyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-2-methyl-N-(4-(6-(trifluoromethyl)pyrazin-2-yl)phenyl)propanamide;
N-(4-(6-chloropyrazin-2-yl)phenyl)-2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-2-methylpropanamide;
2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(4-(6-methoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-2-methyl-N-(4-(pyrazin-2-yl)phenyl)propanamide;
4-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide;
2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(5-(6-(trifluoromethyl)pyrazin-2-yl)pyridin-2-yl)butanamide;
2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)butanamide;
N-(4-(5-chloropyridin-3-yl)phenyl)-2-(6-(cyclopropanesulfonamido)pyridin-2-yl)butanamide;
2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)butanamide;
2-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)butanamide;
2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(4-(pyridin-3-yl)phenyl)acetamide;
2-(6-(ethylsulfonamido)pyrazin-2-yl)-N-(4-(pyridin-3-yl)phenyl)acetamide;
2-(6-(methylsulfonamido)pyrazin-2-yl)-N-(4-(pyridin-3-yl)phenyl)acetamide;

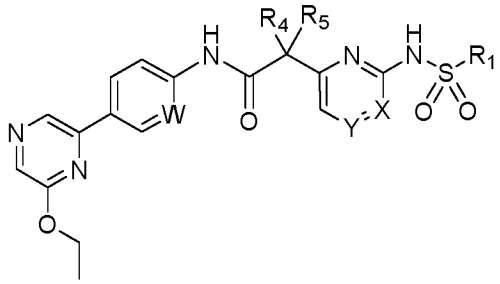
2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-methylpropanamide;
2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methylpropanamide;
4-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide;
2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-methoxy-2-methylbutanamide;
N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-methoxy-2-methyl-2-(6-(methylsulfonamido)pyrazin-2-yl)butanamide;
2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-fluorobutanamide;
2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)butanamide;
2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)butanamide;
2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-methoxyacetamide;
2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)-2-methoxyacetamide;
2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-methoxypropanamide;
2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-(*R*)-fluorobutanamide;
2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-(*S*)-fluorobutanamide;
2-(4-(cyclopropanesulfonamido)pyrimidin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)butanamide;
N-(1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)cyclopropyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide;
N-(1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)propyl)-5-(6-ethoxypyrazin-2-yl)picolinamide;
N-(1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)propyl)-2-fluoro-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide;
4-(5-chloropyridin-3-yl)-N-(1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)propyl)-2-fluorobenzamide;
N-(1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)propyl)-4-(5-(trifluoromethyl)pyridin-3-yl)benzamide;
4-(5-chloropyridin-3-yl)-N-(1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)propyl)benzamide;

N-(1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)propyl)-4-(6-ethoxypyrazin-2-yl)-2-(trifluoromethyl)benzamide;
N-(1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)propyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide;
N-(1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)propyl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;
N-(1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)propyl)-4-(6-isopropoxypyrazin-2-yl)benzamide;
N-(1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)propyl)-4-(6-ethoxypyrazin-2-yl)benzamide;
N-(2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)butan-2-yl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide;
N-(2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)propan-2-yl)-2-fluoro-4-(6-isopropoxypyrazin-2-yl)benzamide;
N-(2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)propan-2-yl)-4-(6-(trifluoromethyl)pyrazin-2-yl)benzamide;
N-(1-(6-(cyclopropanesulfonamido)pyrazin-2-yl)propyl)-4-(6-ethoxypyrazin-2-yl)-2-fluorobenzamide;
N-(1-(6-(cyclopropanesulfonamido)pyrazin-2-yl)propyl)-4-(6-ethoxypyrazin-2-yl)-2-(*R*)-fluorobenzamide; and
N-(1-(6-(cyclopropanesulfonamido)pyrazin-2-yl)propyl)-4-(6-ethoxypyrazin-2-yl)-2-(*S*)-fluorobenzamide;
or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Such CTPS1 inhibitors are disclosed in PCT publication number WO2019179652 which is incorporated by reference in its entirety for the purpose of the CTPS1 inhibitors disclosed therein. In particular a CTPS1 inhibitor may be a compound described in any one of clauses 1 to 148 of WO2019179652 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof, in particular a compound P1 to P225 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Such CTPS1 inhibitors are also disclosed in PCT publication number WO2019180244 which is incorporated by reference in its entirety for the purpose of the CTPS1 inhibitors disclosed therein. In particular a CTPS1 inhibitor may be a compound described in any one of clauses 1 to 148 of WO2019180244 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof, in particular a compound P1 to P225 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

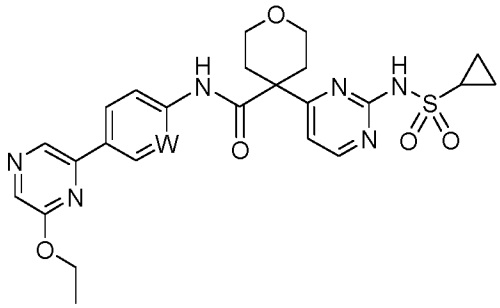
More suitably, the CTPS1 inhibitor is a compound of formula (IV):



(IV)

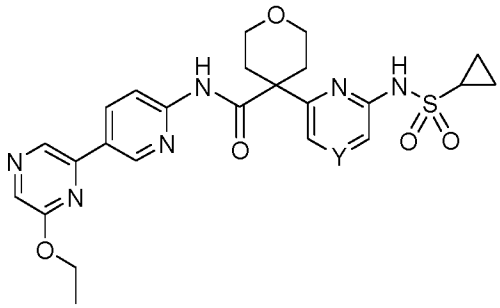
wherein:

(a) when R_4, R_5, X, Y and R_1 are as follows:



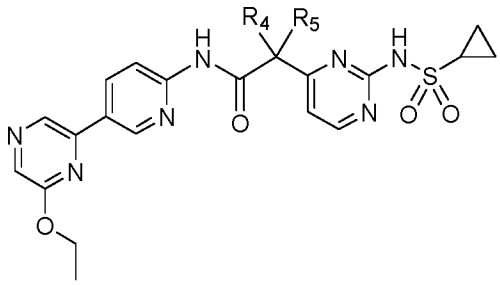
then W is N, CH or CF;

(b) when R_4, R_5, X, W and R_1 are as follows:

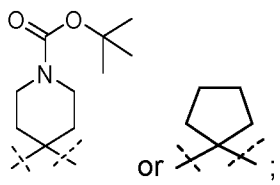


then Y is CH or N;

(c) when W, X, Y and R_1 are as follows:

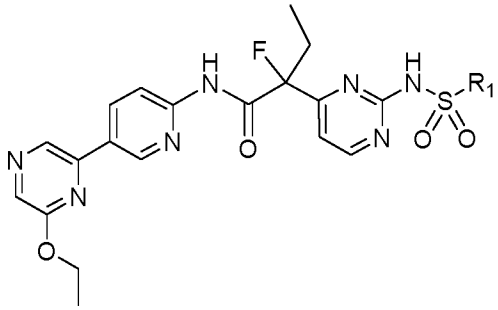


then R_4 and R_5 are joined to form the following structures:



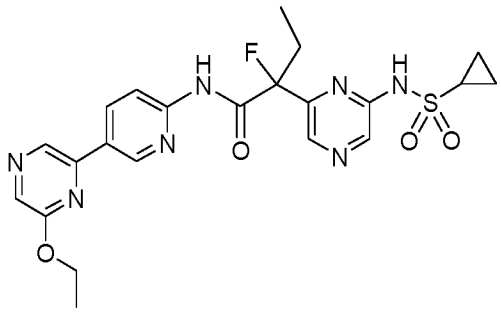
or ;

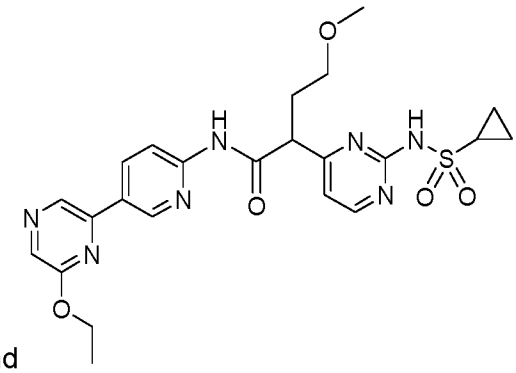
(d) when W, R_4, R_5, X and Y are as follows:



then R_1 is methyl or cyclopropyl; and

(e) the compound is selected from the group consisting of:





and

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

More suitably the CTPS1 inhibitor is selected from the following ('List D') compounds:

(*R*)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-fluorobutanamide;

(*S*)-2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-fluorobutanamide;

4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide;

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)cyclopentane-1-carboxamide;

4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)phenyl)tetrahydro-2H-pyran-4-carboxamide;

tert-butyl 4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-4-((5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)carbamoyl)piperidine-1-carboxylate;

4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(4-(6-ethoxypyrazin-2-yl)-2-fluorophenyl)tetrahydro-2H-pyran-4-carboxamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-methoxybutanamide;

(*R*)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-fluoro-2-(2-(methylsulfonamido)pyrimidin-4-yl)butanamide;

(*S*)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-fluoro-2-(2-(methylsulfonamido)pyrimidin-4-yl)butanamide;

4-(6-(cyclopropanesulfonamido)pyridin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide;

4-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide;

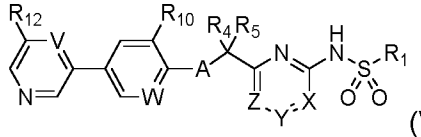
(*R*)-2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-fluorobutanamide; and

(*S*)-2-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-fluorobutanamide;

or a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof.

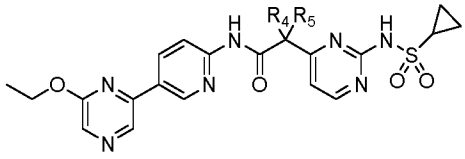
Such CTPS1 inhibitors are disclosed in PCT publication number WO2020083975 which is incorporated by reference in its entirety for the purpose of the CTPS1 inhibitors disclosed therein. In particular a CTPS1 inhibitor may be a compound selected from P112, P113, P114, P115, P136, P137, P139, P143, P145, P165, P166, P186, P197, P206 and P207 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Alternatively, the CTPS1 inhibitor is a compound of formula (V):



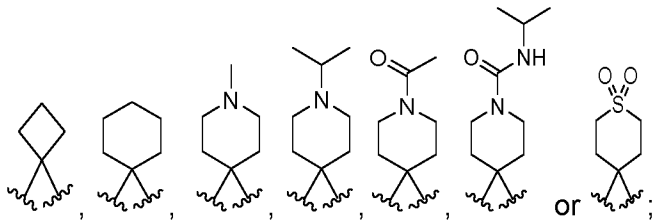
(V)

(a) when A, V, W, X, Y, Z, R_1, R_{10} and R_{12} are as follows:



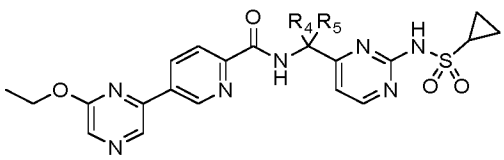
,

then R_4 and R_5 together with the carbon atom to which they attached form:



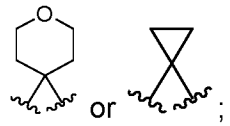
or

(b) when A, V, W, X, Y, Z, R_1, R_{10} and R_{12} are as follows:



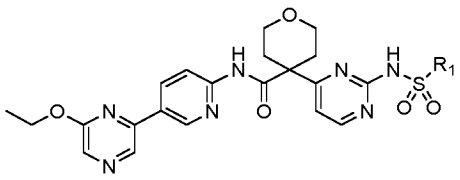
,

then R_4 and R_5 together with the carbon atom to which they are attached form:

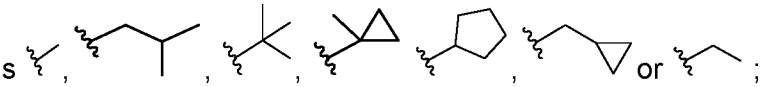


or

(c) when A, V, W, X, Y, Z, R_4, R_5, R_{10} and R_{12} are as follows:

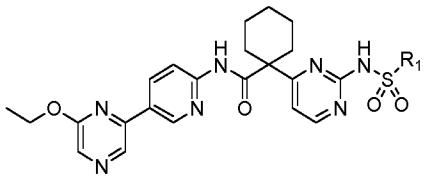


:

then R_1 is  ;

or

(d) when A, V, W, X, Y, Z, R_4, R_5, R_{10} and R_{12} are as follows:

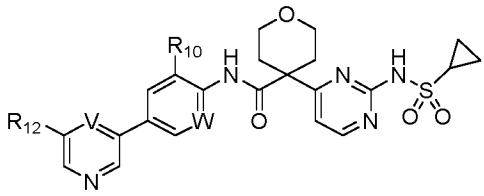


,

then R_1 is  ;

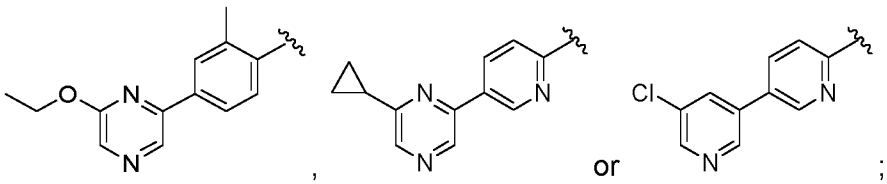
or

(e) when A, X, Y, Z, R_1, R_4 and R_5 are as follows:



,

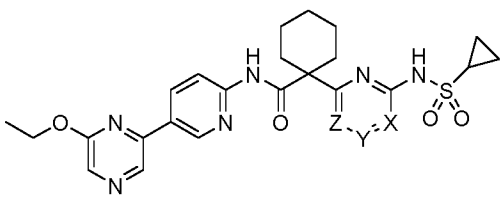
then V, W, R_{10} and R_{12} are:



;

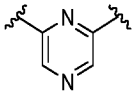
or

(f) when A, V, W, R_1, R_4, R_5, R_{10} and R_{12} are as follows:



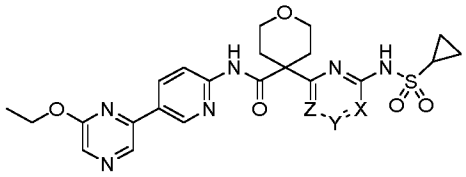
,

then Z, X and Y are

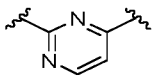

;

or

(g) when A, V, W, R_1, R_4, R_5, R_{10} and R_{12} are as follows:

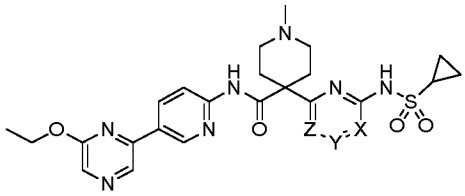

,

then Z, X and Y are

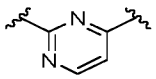

;

or

(h) when A, V, W, R_1, R_4, R_5, R_{10} and R_{12} are as follows



then Z, X and Y are


;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

More suitably the CTPS1 inhibitor is selected from the following ('List E') compounds:

N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(2-(methylsulfonamido)pyrimidin-4-yl)tetrahydro-2*H*-pyran-4-carboxamide;

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)cyclohexane-1-carboxamide;

N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-1-(2-(methylsulfonamido)pyrimidin-4-yl)cyclohexane-1-carboxamide;

1-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)cyclohexane-1-carboxamide;

4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(4-(6-ethoxypyrazin-2-yl)-2-methylphenyl)tetrahydro-2H-pyran-4-carboxamide;

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)cyclobutane-1-carboxamide;

4-(4-(cyclopropanesulfonamido)pyrimidin-2-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2*H*-pyran-4-carboxamide;

4-(2-(cyclopentanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2*H*-pyran-4-carboxamide;

N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(2-((1-methylcyclopropane)-1-sulfonamido)pyrimidin-4-yl)tetrahydro-2*H*-pyran-4-carboxamide;

4-(2-(Cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-1-methylpiperidine-4-carboxamide;

4-(2-(Cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-1-isopropylpiperidine-4-carboxamide;

4-(2-(Cyclopropanesulfonamido)pyrimidin-4-yl)-*N*4-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-*N*1-isopropylpiperidine-1,4-dicarboxamide;

4-(2-((1,1-dimethylethyl)sulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide;

N-(4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)tetrahydro-2H-pyran-4-yl)-5-(6-ethoxypyrazin-2-yl)picolinamide;

1-Acetyl-4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)piperidine-4-carboxamide;

N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(2-((2-methylpropyl)sulfonamido)pyrimidin-4-yl)tetrahydro-2*H*-pyran-4-carboxamide;

4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-cyclopropylpyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide;

N-(5'-chloro-[3,3'-bipyridin]-6-yl)-4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)tetrahydro-2H-pyran-4-carboxamide;

N-(1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)cyclopropyl)-5-(6-ethoxypyrazin-2-yl)picolinamide;

4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide;

N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(2-(ethylsulfonamido)pyrimidin-4-yl)tetrahydro-2*H*-pyran-4-carboxamide;

4-(2-(cyclopropylmethylsulfonamido) pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2*H*-pyran-4-carboxamide and

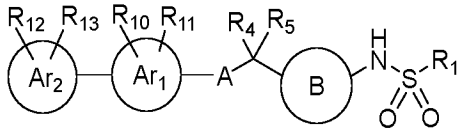
4-(4-(cyclopropanesulfonamido)pyrimidin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-1-methylpiperidine-4-carboxamide;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Such CTPS1 inhibitors are disclosed in PCT publication number WO2020245664 which is incorporated by reference in its entirety for the purpose of the CTPS1 inhibitors disclosed therein. In particular a CTPS1 inhibitor may be a compound selected from P319, P231 to P234, P236, P237, P238, P239, P240, P241, P243, P245, P246, P247, P249, P250, P252,

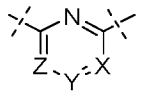
P253, P257, P259, P262, P263 and P140 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Alternatively, the CTPS1 inhibitor is a compound of formula (VI):



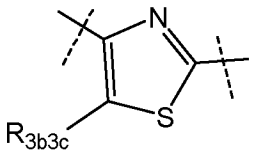
(VI)

wherein ring B is selected from the group consisting of:



(B-a)

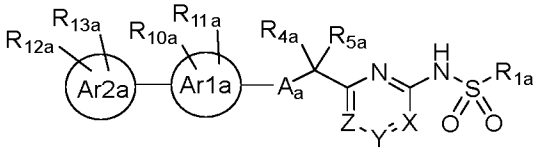
wherein X, Y and Z are as defined below; and



(B-bc);

wherein R_{3b3c} is R_{3b} or R_{3c} as defined below;

wherein when B is (B-a) the compound of formula (VI) is a compound of formula (VI-a):



(VI-a)

wherein:

A_a is A_{aa} or A_{ba};

wherein:

A_{aa} is an amine linker having the following structure: -NH-, -CH_2NH- or -NHCH_2-;

A_{ba} is an amide linker having the following structure: -C(=O)NH- or -NHC(=O)-;

X is N or CH;

Y is N or CR_{2a};

Z is N or CR_{3a};

with the proviso that when at least one of X or Z is N, Y cannot be N;

R_{2a} is H, halo, $C_{1\text{-}2}$alkyl, $OC_{1\text{-}2}$alkyl, $C_{1\text{-}2}$haloalkyl or $OC_{1\text{-}2}$haloalkyl; and

R_{3a} is H, halo, CH_3, OCH_3, CF_3 or OCF_3;

wherein at least one of R_{2a} and R_{3a} is H;

R_{1a} is R_{1aa} or R_{1ba};

wherein:

R_{1aa} is $NR_{32a}R_{33a}$;

R_{1ba} is C_{1-5}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, or CF_3;

R_{4a} and R_{5a} are R_{4aa} and R_{5aa}, or R_{4ba} and R_{5ba};

wherein:

R_{4aa} and R_{5aa} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl which is:

substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl, oxo, OH, C_{1-3}alkylOH, C_{1-3}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, halo, OC_{1-3}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-3}alkyl and $NR_{21a}R_{22a}$; or

one of the carbons of the C_{3-6}cycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}cycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}cycloalkyl formed by R_{4aa} and R_{5aa} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4aa} and R_{5aa} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl wherein one of the carbons of the C_{3-6}heterocycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}heterocycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}heterocycloalkyl formed by R_{4aa} and R_{5aa} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4aa} and R_{5aa} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl comprising one nitrogen atom, wherein said nitrogen atom is substituted by $-S(O)_2R_{29a}$; or

R_{4ba} and R_{5ba} are each independently H, C_{1-6}alkyl, C_{1-6}alkylOH, C_{1-6}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, or R_{4ba} and R_{5ba} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl; and

when A_a is $-NHC(=O)-$ or $-NHCH_2-$:

R_{4ba} and R_{5ba} may additionally be selected from halo, OC_{1-6}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-6}alkyl and $NR_{21a}R_{22a}$;

Ar1a is a 6-membered aryl or heteroaryl;

Ar2a is a 6-membered aryl or heteroaryl and is attached to Ar1a in the para position relative to group A_a;

R_{10a} is H, halo, C_{1-3}alkyl, C_{1-2}haloalkyl, OC_{1-2}alkyl, OC_{1-2}haloalkyl or CN;

R_{11a} is H, F, Cl, C_{1-2}alkyl, CF_3, OCH_3 or CN;

R_{12a} is attached to Ar2 in the ortho or meta position relative to Ar1a and R_{12a} is H, halo, C_{1-4}alkyl, C_{2-4}alkenyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, OC_{0-2}alkyleneC_{3-5}cycloalkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, hydroxy, C_{1-4}alkylOH, SO_2C_{1-2}alkyl, $C(O)N(C_{1-2}alkyl)_2$, $NHC(O)C_{1-3}$alkyl or $NR_{23a}R_{24a}$; and

when A_a is -NHC(=O)-, -NH- or -$NHCH_2$-:

R_{12a} may additionally be selected from CN, $OCH_2CH_2N(CH_3)_2$ and a C_{3-6}heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2a, or R_{12a} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

R_{13a} is H or halo;

R_{21a} is H, C_{1-5}alkyl, $C(O)C_{1-5}$alkyl, $C(O)OC_{1-5}$alkyl, C_{1-3}alkylOC_{1-2}alkyl, C_{1-4}haloalkyl, or C_{4-6}heterocycloalkyl;

R_{22a} is H or CH_3;

R_{23a} is H or C_{1-2}alkyl; and

R_{24a} is H or C_{1-2}alkyl

R_{29a} is C_{1-3}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, CF_3, $N(C_{1-3}alkyl)_2$, or a 5 or 6 membered heteroaryl wherein the 5 or 6 membered heteroaryl is optionally substituted by methyl;

R_{32a} is C_{1-3}alkyl and R_{33} is C_{1-3}alkyl; or

R_{32a} and R_{33a} together with the nitrogen atom to which they are attached form a C_{3-5}heterocycloalkyl;

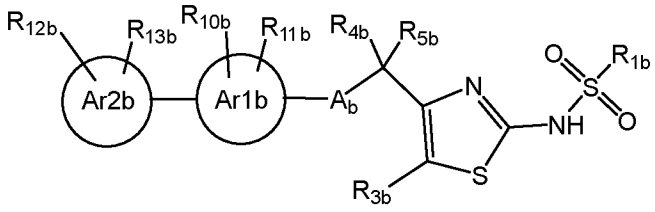
wherein

R_{1a} is R_{1aa}; and/or

R_{4a} and R_{5a} are R_{4aa} and R_{5aa}; and/or

A_a is A_{aa}; and

wherein when B is (B-bc) and R_{3b3c} is R_{3b}, the compound of formula (VI) is a compound of formula (VI-b):



(VI-b)

wherein:

A_b is A_{ab} or A_{bb};

wherein:

A_{ab} is $-NR_{6b}CH_2-$ or $-NR_{6b}-$;

A_{bb} is $-NR_{6b}C(=O)-$;

R_{1b} is R_{1ab} or R_{1bb};

wherein:

R_{1ab} is $NR_{32b}R_{33b}$;

R_{1bb} is C_{1-5}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, C_{1-3}alkyleneOC_{1-2}alkyl, or CF_3;

R_{3b} is H, halo, CH_3, OC_{1-2}alkyl or CF_3;

or R_{3b} together with R_{5bb} forms a 5- or 6-membered cycloalkyl or 5 or 6 membered oxygen-containing heterocycloalkyl;

R_{4b} and R_{5b} are either R_{4ab} and R_{5ab} or R_{4bb} and R_{5bb};

wherein:

R_{4ab} and R_{5ab} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl which is:

substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl, oxo, OH, C_{1-3}alkylOH, C_{1-3}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, halo, OC_{1-3}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-3}alkyl and $NR_{21b}R_{22b}$; or

one of the carbons of the C_{3-6}cycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}cycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}cycloalkyl formed by R_{4ab} and R_{5ab} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4ab} and R_{5ab} together with the carbon atom to which they are attached form a C_{3-6}heteroycloalkyl wherein one of the carbons of the C_{3-6}heterocycloalkyl is a spiro

centre such that a spirocyclic ring system is formed by the C_{3-6}heterocycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}heteroycloalkyl formed by R_{4ab} and R_{5ab} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4ab} and R_{5ab} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl comprising one nitrogen atom, wherein said nitrogen atom is substituted by $-S(O)_2R_{29b}$; or

R_{4bb} and R_{5bb} are each independently H, halo, C_{1-6}alkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-6}alkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, C_{1-6}alkylOH, C_{1-6}haloalkyl, OC_{1-6}haloalkyl or $NR_{21b}R_{22b}$,

or R_{4bb} is H and R_{5bb} together with R_{3b} form a 5- or 6-membered cycloalkyl or 5 or 6 membered oxygen-containing heterocycloalkyl,

or R_{4bb} and R_{5bb} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl,

or R_{4bb} is H and R_{5bb} and R_{6b} are a C_{2-3}alkylene chain forming a 5- or 6-membered ring;

or R_{4bb} is O and R_{5bb} is absent;

R_{6b} is H or C_{1-3}alkyl,

or R_{6b} together with R_{11b} when in the ortho-position to group A_b are a C_2alkylene chain forming a 5-membered ring,

or R_{5bb} and R_{6b} are a C_{2-3}alkylene chain forming a 5- or 6-membered ring and R_{4bb} is H;

Ar1b is 6-membered aryl or heteroaryl;

Ar2b is a 6-membered aryl or heteroaryl and is attached to Ar1b in the para position relative to group A_b;

R_{10b} is H, halo, C_{1-3}alkyl, OC_{1-2}alkyl, C_{1-2}haloalkyl, OC_{1-2}haloalkyl or CN;

R_{11b} is H, F, Cl, CH_3, ethyl, OCH_3, CF_3, OCF_3 or CN,

or R_{11b}, when in the ortho-position to group A_b, together with R_{6b} are a C_2alkylene chain forming a 5-membered ring;

R_{12b} is attached to Ar2b in the ortho or meta position relative to Ar1b and R_{12b} is H, halo, C_{1-4}alkyl, C_{2-4}alkynyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, OC_{0-2}alkyleneC_{3-5}cycloalkyl, $OCH_2CH_2N(CH_3)_2$, OH, C_{1-4}alkylOH, CN, C_{1-3}alkyleneOC_{1-3}alkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, $C(=O)C_{1-2}$alkyl, $NR_{23b}R_{24b}$, SO_2C_{1-4}alkyl, SOC_{1-4}alkyl, SC_{1-4}alkyl, SH, $C(O)N(CH_3)_2$, $NHC(O)C_{1-3}$alkyl, C_{3-6}heterocycloalkyl comprising one nitrogen located at

the point of attachment to Ar2b, or R_{12b} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

R_{13b} is H, halo, CH_3 or OCH_3;

R_{21b} is H, $C_{1\text{-}5}$alkyl, $C(O)C_{1\text{-}5}$alkyl, $C(O)OC_{1\text{-}5}$alkyl, $C_{1\text{-}3}$alkyl$OC_{1\text{-}2}$alkyl, $C_{1\text{-}4}$haloalkyl, or $C_{4\text{-}6}$heterocycloalkyl;

R_{22b} is H or CH_3;

R_{23b} is H or $C_{1\text{-}2}$alkyl;

R_{24b} is H or $C_{1\text{-}2}$alkyl;

R_{29b} is $C_{1\text{-}3}$alkyl, $C_{0\text{-}2}$alkylene$C_{3\text{-}5}$cycloalkyl which cycloalkyl is optionally substituted by CH_3, CF_3, $N(C_{1\text{-}3}alkyl)_2$, or a 5 or 6 membered heteroaryl wherein the 5 or 6 membered heteroaryl is optionally substituted by methyl; and

R_{32b} is $C_{1\text{-}3}$alkyl and R_{33b} is $C_{1\text{-}3}$alkyl; or

R_{32b} and R_{33b} together with the nitrogen atom to which they are attached form a $C_{3\text{-}5}$heterocycloalkyl;

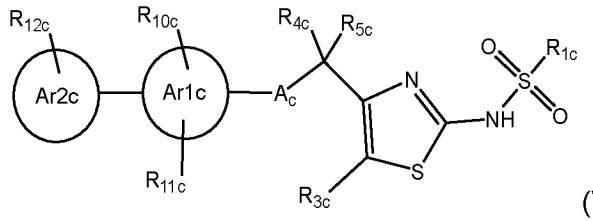
wherein:

R_{1b} is R_{1ab}; and/or

R_{4b} and R_{5b} are R_{4ab} and R_{5ab}; and/or

A is A_{ab}; or

wherein when B is (B-bc) and R_{3b3c} is R_{3c}, the compound of formula (VI) is a compound of formula (VI-c):



(VI-c)

wherein:

A_c is A_{ac} or A_{bc};

wherein:

A_{ac} is $-CH_2NR_{6c}-$;

A_{bc} is $-C(=O)NR_{6c}-$;

R_{1c} is R_{1ac} or R_{1bc};

wherein:

R_{1ac} is $NR_{32c}R_{33c}$;

R_{1bc} is $C_{1\text{-}5}$alkyl, $C_{0\text{-}2}$alkylene$C_{3\text{-}5}$cycloalkyl which cycloalkyl is optionally substituted by CH_3, $C_{1\text{-}3}$alkylene$OC_{1\text{-}2}$alkyl, or CF_3;

R_{3c} is H, CH_3, halo, $OC_{1\text{-}2}$alkyl or CF_3;

R_{4c} and R_{5c} are either R_{4ac} and R_{5ac} or R_{4bc} and R_{5bc};

wherein:

R_{4ac} and R_{5ac} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl which is:

substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl, oxo, OH, C_{1-3}alkylOH, C_{1-3}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, halo, OC_{1-3}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-3}alkyl and $NR_{21c}R_{22c}$; or

one of the carbons of the C_{3-6}cycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}cycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}cycloalkyl formed by R_{4ac} and R_{5ac} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4ac} and R_{5ac} together with the carbon atom to which they are attached form a C_{3-6}heteroycloalkyl wherein one of the carbons of the C_{3-6}heterocycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}cheterocycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}heteroycloalkyl formed by R_{4ac} and R_{5ac} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4ac} and R_{5ac} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl comprising one nitrogen atom, wherein said nitrogen atom is substituted by $-S(O)_2R_{29c}$; or

R_{4bc} and R_{5bc} are each independently H, C_{1-6}alkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, C_{1-6}alkylOH or C_{1-6}haloalkyl,

or R_{4bc} and R_{5bc} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl ring;

R_{6c} is H or C_{1-3}alkyl;

Ar1c is a 6-membered aryl or heteroaryl;

Ar2c is a 6-membered aryl or heteroaryl and is attached to Ar1c in the para position relative to group A_c;

R_{10c} is H, halo, C_{1-3}alkyl, OC_{1-2}alkyl, C_{1-2}haloalkyl, OC_{1-2}haloalkyl or CN;

R_{11c} is H, F, Cl, CH_3, ethyl, OCH_3, CF_3, OCF_3 or CN;

R_{12c} is attached to Ar2c in the meta or ortho position relative to Ar1c and R_{12c} is H, halo, C_{1-4}alkyl, C_{2-4}alkynyl, $C(=O)C_{1-2}$alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, C_{1-3}alkyleneOC_{1-3}alkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, CN, OC_{0-2}alkyleneC_{3-5}cycloalkyl, $OCH_2CH_2N(CH_3)_2$, OH, C_{1-4}alkylOH, $NR_{23c}R_{24c}$, SO_2CH_3, $C(O)N(CH_3)_2$, $NHC(O)C_{1-3}$alkyl, or a C_{3-6}heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2c, or R_{12c} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

R_{21c} is H, C_{1-5}alkyl, $C(O)C_{1-5}$alkyl, $C(O)OC_{1-5}$alkyl, C_{1-3}alkylOC_{1-2}alkyl, C_{1-4}haloalkyl, or C_{4-6}heterocycloalkyl;

R_{22c} is H or CH_3;

R_{23c} is H or C_{1-2}alkyl;

R_{24c} is H or C_{1-2}alkyl;

R_{29c} is C_{1-3}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, CF_3, $N(C_{1-3}alkyl)_2$, or a 5 or 6 membered heteroaryl wherein the 5 or 6 membered heteroaryl is optionally substituted by methyl; and

R_{32c} is C_{1-3}alkyl and R_{33c} is C_{1-3}alkyl; or

R_{32c} and R_{33c} together with the nitrogen atom to which they are attached form a C_{3-5}heterocycloalkyl;

wherein:

R_{1c} is R_{1ac}; and/or

R_{4c} and R_{5c} are R_{4ac} and R_{5ac}; and/or

A_c is A_{ac};

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

More suitably the CTPS1 inhibitor is selected from the following ('List F') compounds:

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-oxocyclohexanecarboxamide;

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-hydroxycyclohexanecarboxamide;

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-hydroxycyclohexanecarboxamide (diastereomer 1);

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-hydroxycyclohexanecarboxamide (diastereomer 2);

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-4-(dimethylamino)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)cyclohexane-1-carboxamide;

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-4-(dimethylamino)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)cyclohexane-1-carboxamide (diastereomer 1);

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-4-(dimethylamino)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)cyclohexane-1-carboxamide (diastereomer 2);

N-(4-(1-((4-(6-Ethoxypyrazin-2-yl)-2-fluorobenzyl)amino)propyl)pyrimidin-2-yl)cyclopropanesulfonamide;

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4,4-difluorocyclohexane-1-carboxamide;

8-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-1,4-dioxaspiro[4.5]decane-8-carboxamide;

4-(2-((*N*,*N*-dimethylsulfamoyl)amino)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2*H*-pyran-4-carboxamide;

4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-1-(methylsulfonyl)piperidine-4-carboxamide;

N-(4-(1-(((5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)methyl)amino)cyclopropyl)pyrimidin-2-yl)cyclopropanesulfonamide;

N-(4-(1-((4-(6-ethoxypyrazin-2-yl)-2-fluorobenzyl)amino)cyclopropyl)pyrimidin-2-yl)cyclopropanesulfonamide;

N-(4-(4-(((4-(6-ethoxypyrazin-2-yl)phenyl)amino)methyl)tetrahydro-2H-pyran-4-yl)pyrimidin-2-yl)cyclopropanesulfonamide;

2-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-5,8-dioxaspiro[3.4]octane-2-carboxamide;

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-methoxycyclohexane-1-carboxamide;

N-(4-(1-((4-(6-ethoxypyrazin-2-yl)phenyl)amino)propyl)pyrimidin-2-yl)cyclopropanesulfonamidearboxamide;

4-(2-(Cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-1-(2-methoxyacetyl)piperidine-4-carboxamide;

4-(2-(Cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-1-(ethylsulfonyl)piperidine-4-carboxamide;

4-(2-(Cyclopropanesulfonamido)pyrimidin-4-yl)-1-(cyclopropylsulfonyl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)piperidine-4-carboxamide;

4-(2-(Cyclopropanesulfonamido)pyrimidin-4-yl)-1-(*N*,*N*-dimethylsulfamoyl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)piperidine-4-carboxamide;

4-(2-(Cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-1-((trifluoromethyl)sulfonyl)piperidine-4-carboxamide;

4-(2-(Cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-1-((1-methyl-1*H*-pyrazol-3-yl)sulfonyl)piperidine-4-carboxamide;

1-(cyanomethyl)-4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)piperidine-4-carboxamide;

ethyl 2-(4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-4-((5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)carbamoyl)piperidin-1-yl)acetate;

N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(2-(ethylsulfonamido)pyrimidin-4-yl)-1-(2-methoxyacetyl)piperidine-4-carboxamide;

N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(2-(ethylsulfonamido)pyrimidin-4-yl)-1-(methylsulfonyl)piperidine-4-carboxamide;

N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(2-(ethylsulfonamido)pyrimidin-4-yl)-1-(ethylsulfonyl)piperidine-4-carboxamide;

1-(Cyclopropylsulfonyl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(2-(ethylsulfonamido)pyrimidin-4-yl)piperidine-4-carboxamide;

N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(2-(ethylsulfonamido)pyrimidin-4-yl)-1-((1-methyl-1*H*-pyrazol-3-yl)sulfonyl)piperidine-4-carboxamide;

1-(2-(Cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-cyclopropylpyrazin-2-yl)pyridin-2-yl)-4-methoxycyclohexane-1-carboxamide (diastereomer 1);

1-(2-(Cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-cyclopropylpyrazin-2-yl)pyridin-2-yl)-4-methoxycyclohexane-1-carboxamide (diastereomer 2);

1-(2-(Cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(pyrrolidin-1-yl)cyclohexane-1-carboxamide (diastereomer 1);

1-(2-(Cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(pyrrolidin-1-yl)cyclohexane-1-carboxamide (diastereomer 2);

4-amino-1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)cyclohexane-1-carboxamide (diastereomer 1);

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-morpholinocyclohexane-1-carboxamide (diastereomer 1);

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-morpholinocyclohexane-1-carboxamide (diastereomer 2);

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(methyl(oxetan-3-yl)amino)cyclohexane-1-carboxamide (diastereomer 1);

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-((2-methoxyethyl)(methyl)amino)cyclohexane-1-carboxamide (diastereomer 1);

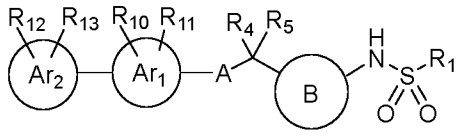
1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-((2-methoxyethyl)(methyl)amino)cyclohexane-1-carboxamide (diastereomer 2);

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-4-((2,2-difluoroethyl)(methyl)amino)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)cyclohexane-1-carboxamide (diastereomer 1);

1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(4-methylpiperazin-1-yl)cyclohexane-1-carboxamide (diastereomer 1);
1-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(4-methylpiperazin-1-yl)cyclohexane-1-carboxamide (diastereomer 2);
4-(6-(cyclopropanesulfonamido)pyrazin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-1-(methylsulfonyl)piperidine-4-carboxamide;
4-(4-(cyclopropanesulfonamido)pyrimidin-2-yl)-N-(5-(6-cyclopropylpyrazin-2-yl)pyridin-2-yl)-1-(methylsulfonyl)piperidine-4-carboxamide;
4-(4-(cyclopropanesulfonamido)pyrimidin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-1-(methylsulfonyl)piperidine-4-carboxamide;
4-(4-(cyclopropanesulfonamido)pyrimidin-2-yl)-N-(5-(6-cyclopropylpyrazin-2-yl)pyridin-2-yl)-1-(ethylsulfonyl)piperidine-4-carboxamide; and
4-(4-(cyclopropanesulfonamido)pyrimidin-2-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-1-(ethylsulfonyl)piperidine-4-carboxamide;
or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Such CTPS1 inhibitors are disclosed in PCT publication number WO2020245665 which is incorporated by reference in its entirety for the purpose of the CTPS1 inhibitors disclosed therein. In particular a CTPS1 inhibitor may be a compound described in any one of clauses 1 to 204 of WO2020245665 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof, in particular a compound selected from P226, P227, P228, P229, P230, P235, P242, P244, P248, P251, P254, P255, P256, P258, P260, P261, P288, P289, P290, P291, P292, P293, P294, P295, P296, P297, P298, P299, P300, P301, P302, P303, P304, P305, P306, P307, P308, P309, P310, P311, P312, P313, P314, P315, P316, P317 and P318 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Alternatively, the CTPS1 inhibitor is a compound of formula (VII):



(VII)

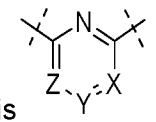
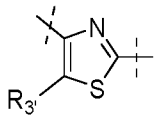
wherein

A is A_a or A_b;

wherein

A_a is an amine linker having the following structure: -NH-, -CH_2NH- or -NHCH_2-;

A_b is an amide linker having the following structure: -C(=O)NH- or -NHC(=O)-;

B is  or  ;

X is N or CH;

Y is N or CR_2;

Z is N or CR_3;

with the proviso that when at least one of X or Z is N, Y cannot be N;

R_1 is C_{1-5}fluoroalkyl, with the proviso that R_1 is not CF_3;

R_2 is H, halo, C_{1-2}alkyl, OC_{1-2}alkyl, C_{1-2}haloalkyl or OC_{1-2}haloalkyl;

R_3 is H, halo, CH_3, OCH_3, CF_3 or OCF_3;

wherein at least one of R_2 and R_3 is H;

$R_{3'}$ is H, halo, CH_3, OC_{1-2}alkyl or CF_3; and

when A is -NHC(=O)-, additionally $R_{3'}$ together with R_5 forms a 5- or 6-membered cycloalkyl or 5 or 6 membered oxygen-containing heterocycloalkyl;

R_4 and R_5 are R_{4a} and R_{5a}, or R_{4b} and R_{5b};

wherein

R_{4a} and R_{5a} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl which is:

substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl, oxo, OH, C_{1-3}alkylOH, C_{1-3}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, halo, OC_{1-3}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-3}alkyl and $NR_{21}R_{22}$; or

one of the carbons of the C_{3-6}cycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}cycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}cycloalkyl formed by R_{4a} and R_{5a} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4a} and R_{5a} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl wherein one of the carbons of the C_{3-6}heterocycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}heterocycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}heterocycloalkyl formed by R_{4a} and R_{5a} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4a} and R_{5a} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl comprising one nitrogen atom, wherein said nitrogen atom is substituted by $-S(O)_2R_{29}$; or

R_{4b} and R_{5b} are each independently H, C_{1-6}alkyl, C_{1-6}alkylOH, C_{1-6}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, or R_{4b} and R_{5b} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl; and

when A is -NHC(=O)- or $-NHCH_2-$:

R_{4b} and R_{5b} may additionally be selected from halo, OC_{1-6}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-6}alkyl and $NR_{21}R_{22}$;

Ar1 is a 6-membered aryl or heteroaryl;

Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to group A;

R_{10} is H, halo, C_{1-3}alkyl, C_{1-2}haloalkyl, OC_{1-2}alkyl, OC_{1-2}haloalkyl or CN;

R_{11} is H, F, Cl, C_{1-2}alkyl, CF_3, OCH_3 or CN;

R_{12} is attached to Ar2 in the ortho or meta position relative to Ar1 and R_{12} is H, halo, C_{1-4}alkyl, C_{2-4}alkenyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, OC_{0-2}alkyleneC_{3-5}cycloalkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, hydroxy, C_{1-4}alkylOH, SO_2C_{1-2}alkyl, $C(O)N(C_{1-2}alkyl)_2$, $NHC(O)C_{1-3}$alkyl or $NR_{23}R_{24}$; and

when A is -NHC(=O)-, -NH- or $-NHCH_2-$:

R_{12} may additionally be selected from CN, $OCH_2CH_2N(CH_3)_2$ and a C_{3-6}heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2, or R_{12} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

R_{13} is H or halo;

R_{21} is H, C_{1-5}alkyl, $C(O)C_{1-5}$alkyl, $C(O)OC_{1-5}$alkyl;

R_{22} is H or CH_3;

R_{23} is H or C_{1-2}alkyl; and

R_{24} is H or C_{1-2}alkyl;

R_{29} is C_{1-3}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, or CF_3;

R_{32} is C_{1-3}alkyl and R_{33} is C_{1-3}alkyl; or

R_{32} and R_{33} together with the nitrogen atom to which they are attached form a C_{3-5}heterocycloalkyl;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

More suitably the CTPS1 inhibitor is selected from the following ('List G') compounds:

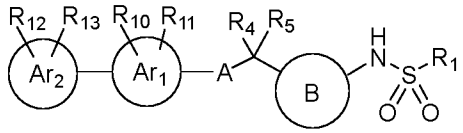
4-(2-((2,2-difluoroethyl)sulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide; and

2-(2-((2,2-difluoroethyl)sulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-2-fluorobutanamide;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Such CTPS1 inhibitors are disclosed in PCT publication number WO2021053403 which is incorporated by reference in its entirety for the purpose of the CTPS1 inhibitors disclosed therein. In particular a CTPS1 inhibitor may be a compound described in any one of clauses 1 to 191 of WO2021053403 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof, in particular a compound selected from P271 and P284 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Alternatively, the CTPS1 inhibitor is compound of formula (VIII):



(VIII)

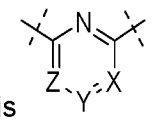
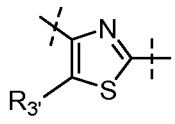
wherein

A is A_a or A_b;

wherein

A_a is an amine linker having the following structure: -NH-, -CH_2NH- or -NHCH_2-;

A_b is an amide linker having the following structure: -C(=O)NH- or -NHC(=O)-;

B is  or  ;

X is N or CH;

Y is N or CR_2;

Z is N or CR_3;

with the proviso that when at least one of X or Z is N, Y cannot be N;

R_1 is $C_{1\text{-}5}$alkyl or $C_{0\text{-}2}$alkylene$C_{3\text{-}5}$cycloalkyl, which alkyl or (alkylene)cycloalkyl is substituted by CN;

R_2 is H, halo, $C_{1\text{-}2}$alkyl, $OC_{1\text{-}2}$alkyl, $C_{1\text{-}2}$haloalkyl or $OC_{1\text{-}2}$haloalkyl;

R_3 is H, halo, CH_3, OCH_3, CF_3 or OCF_3;

wherein at least one of R_2 and R_3 is H;

$R_{3'}$ is H, halo, CH_3, $OC_{1\text{-}2}$alkyl or CF_3; and

when A is -NHC(=O)-, additionally $R_{3'}$ together with R_5 forms a 5- or 6-membered cycloalkyl or 5 or 6 membered oxygen-containing heterocycloalkyl;

R_4 and R_5 are R_{4a} and R_{5a}, or R_{4b} and R_{5b};

wherein

R_{4a} and R_{5a} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl which is:

substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl, oxo, OH, C_{1-3}alkylOH, C_{1-3}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, halo, OC_{1-3}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-3}alkyl and $NR_{21}R_{22}$; or

one of the carbons of the C_{3-6}cycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}cycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}cycloalkyl formed by R_{4a} and R_{5a} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4a} and R_{5a} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl wherein one of the carbons of the C_{3-6}heterocycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}heterocycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}heterocycloalkyl formed by R_{4a} and R_{5a} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4a} and R_{5a} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl comprising one nitrogen atom, wherein said nitrogen atom is substituted by $-S(O)_2R_{29}$; or

R_{4b} and R_{5b} are each independently H, C_{1-6}alkyl, C_{1-6}alkylOH, C_{1-6}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, or R_{4b} and R_{5b} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl; and

when A is -NHC(=O)- or $-NHCH_2-$:

R_{4b} and R_{5b} may additionally be selected from halo, OC_{1-6}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-6}alkyl and $NR_{21}R_{22}$;

Ar1 is a 6-membered aryl or heteroaryl;

Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to group A;

R_{10} is H, halo, C_{1-3}alkyl, C_{1-2}haloalkyl, OC_{1-2}alkyl, OC_{1-2}haloalkyl or CN;

R_{11} is H, F, Cl, C_{1-2}alkyl, CF_3, OCH_3 or CN;

R_{12} is attached to Ar2 in the ortho or meta position relative to Ar1 and R_{12} is H, halo, C_{1-4}alkyl, C_{2-4}alkenyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, OC_{0-2}alkyleneC_{3-5}cycloalkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, hydroxy, C_{1-4}alkylOH, SO_2C_{1-2}alkyl, $C(O)N(C_{1-2}alkyl)_2$, $NHC(O)C_{1-3}$alkyl or $NR_{23}R_{24}$; and

when A is -NHC(=O)-, -NH- or -$NHCH_2$-:

R_{12} may additionally be selected from CN, $OCH_2CH_2N(CH_3)_2$ and a C_{3-6}heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2, or R_{12} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

R_{13} is H or halo;

R_{21} is H, C_{1-5}alkyl, $C(O)C_{1-5}$alkyl, $C(O)OC_{1-5}$alkyl;

R_{22} is H or CH_3;

R_{23} is H or C_{1-2}alkyl; and

R_{24} is H or C_{1-2}alkyl;

R_{29} is C_{1-3}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, or CF_3;

R_{32} is C_{1-3}alkyl and R_{33} is C_{1-3}alkyl; or

R_{32} and R_{33} together with the nitrogen atom to which they are attached form a C_{3-5}heterocycloalkyl;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

More suitably the CTPS1 inhibitor is selected from the following ('List H') compounds:

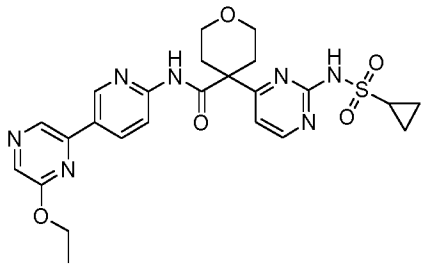
4-(2-((1-cyanocyclopropane)-1-sulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide; and

4-(2-((cyanomethyl)sulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2*H*-pyran-4-carboxamide;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Such CTPS1 inhibitors are disclosed in PCT publication number WO2021053402 which is incorporated by reference in its entirety for the purpose of the CTPS1 inhibitors disclosed therein. In particular a CTPS1 inhibitor may be a compound described in any one of clauses 1 to 191 of WO2021053402 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof, in particular a compound selected from P285 and P287 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

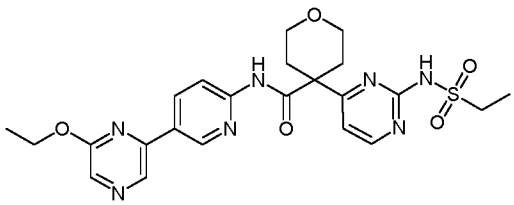
The CTPS1 inhibitor may be 4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide (referred to herein as 'CTPS-IA'):



,

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Alternatively, the CTPS1 inhibitor may be *N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(2-(ethylsulfonamido)pyrimidin-4-yl)tetrahydro-2*H*-pyran-4-carboxamide (referred to herein as 'CTPS-IB'):

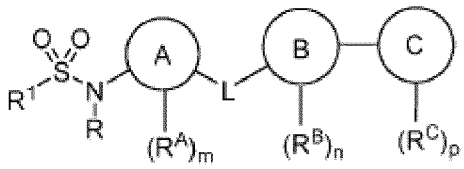


,

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

The compounds described above (and methods for making these compounds) are disclosed in PCT publication numbers WO2019106156, WO2019180244, WO2019106146, WO2019179652, WO2020245665, WO2020245664, WO2021053403, WO2021053402 or WO2020083975.

The CTPS1 inhibitor may be a compound of formula (IX):

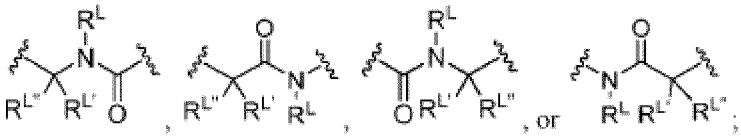


(IX)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from C_{1-6} aliphatic; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; and a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with q instances of R^A;

Ring A is selected from phenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 7-11 membered fused bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L is  ;

wherein each of R^L, $R^{L'}$, and $R^{L''}$ is independently hydrogen, -CN, halogen, or an optionally substituted group selected from C_{1-6} aliphatic; phenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two of R^L, $R^{L'}$, and $R^{L''}$ groups are taken together with the atoms to which each is attached, to form an optionally substituted 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

any one of R^L, $R^{L'}$, and $R^{L''}$, together with R^B forms a 7-10 membered saturated or partially unsaturated fused bicyclic ring;

Ring B is selected from phenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-11 membered saturated or partially unsaturated fused, bridged, or spiro, bicyclic carbocyclic ring; a 7-11 membered fused bicyclic aryl ring; a 7-11 membered saturated or partially unsaturated fused, bridged, or spiro, bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 7-11 membered fused bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring C is selected from a phenyl, 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 7-11 membered fused bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

the bond between Ring B and Ring C is absent, and Ring B and Ring C together form a 7-11 membered saturated or partially unsaturated fused, bridged, or spiro, bicyclic carbocyclic ring; a 7-11 membered fused bicyclic aryl ring; a 7-11 membered saturated or partially unsaturated fused, bridged, or spiro, bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-11 membered fused bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^A, R^B, and R^C is independently oxo, halogen, –CN, $–NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-S(O)NR_2$, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $–N(R)NR_2$, $-N(R)S(O)_2NR_2$, $–N(R)S(O)_2R$, $–N=S(O)R_2$, –S(NR)(O)R, –N(R)S(O)R, –N(R)CN, $–P(O)(R)NR_2$, –P(O)(R)OR or $–P(O)R_2$; or each instance of R^C is independently an optionally substituted group selected from C_{1-6} aliphatic; phenyl; naphthalenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, phosphorous, silicon and sulfur; or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-8 membered

saturated or partially unsaturated bridged bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-10 membered saturated or partially unsaturated spirocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 6-11 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with r instances of R and s instances of R^D; or two R^C groups are optionally taken together with the atoms to which each R^C is attached, to form an optionally substituted 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-7 membered heteroaryl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^D is independently oxo, halogen, –CN, $–NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-S(O)NR_2$, -C(O)R, -C(O)OR, $–C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $–N(R)NR_2$, $-N(R)S(O)_2NR_2$, $–N(R)S(O)_2R$, $–N=S(O)R_2$, –S(NR)(O)R, –N(R)S(O)R, –N(R)CN, $–P(O)(R)NR_2$, –P(O)(R)OR or $–P(O)R_2$;

each R is independently hydrogen, -CN, halogen, or an optionally substituted group selected from C_{1-6} aliphatic; phenyl; naphthalenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-8 membered saturated or partially unsaturated bridged bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-10 membered saturated or partially unsaturated spirocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-11 membered saturated or partially unsaturated bicyclic carbocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or:

two R groups are taken together with the atoms to which each R is attached, to form an optionally substituted 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

m is 0, 1, or 2;

n is 0, 1, or 2;

p is 0, 1, or 2;

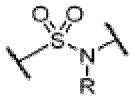
each q is independently 0, 1, 2, 3, or 4;

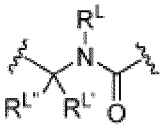
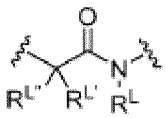
each r is independently 0, 1, 2, 3, or 4; and

each s is independently 0, 1, 2, 3, or 4;

provided that when:

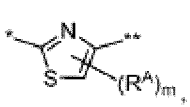
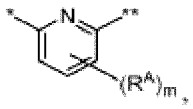
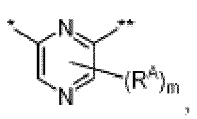
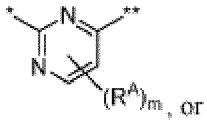
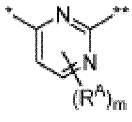
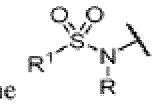
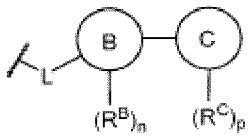
R^1 is C_{1-6} aliphatic or a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring;

the R group of the sulfonamide moiety  is hydrogen or para-methoxybenzyl;

L is  and the R^L and $R^{L'}$ or R^L and $R^{L''}$ groups are not taken together with the atoms to which each is attached to form an optionally substituted 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or L is  ;

Ring B is phenyl or a 6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

Ring C is phenyl or a 6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and is attached to Ring B in the para position relative to the L group;

then Ring A and its R^A substituents are other than  ,  ,  ,  , or  , where * denotes attachment to the  moiety and ** denotes attachment to the  moiety.

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

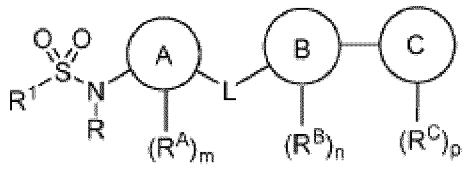
Such CTPS1 inhibitors are disclosed in PCT publication number WO2022087634 which is incorporated by reference in its entirety for the purpose of the CTPS1 inhibitors disclosed therein. In particular a CTPS1 inhibitor may be a compound described in any one of claims 1 to 31 of WO2022087634 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof. A CTPS1 inhibitor may be a compound selected from compounds I-1 to I-286 of WO2022087634, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof. A CTPS1 inhibitor may be a compound selected from compounds Z-1 to Z-10 of WO2022087634, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

In one embodiment the CTPS1 inhibitor is not a CTPS1 inhibitor disclosed in PCT publication number WO2022087634. In a further embodiment, the CTPS1 inhibitor is not (i) a compound described in any one of claims 1 to 31 of WO2022087634 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof, (ii) a compound selected from compounds I-1 to I-286 of WO2022087634, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof, or (iii) a compound selected from compounds Z-1 to Z-10 of WO2022087634, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

CTPS1 inhibitors are disclosed in WO2022/087634, which is incorporated by reference in its entirety for the purpose of defining CTPS1 inhibitors. In some embodiments the CTPS1 inhibitor is as described in WO2022/087634, such as any of compounds I-1 to I-286 or Z-1 to Z-10, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof. In other embodiments the CTPS1 inhibitor is not described in WO2022/087634.

Suitably, the CTPS1 inhibitor is not:

1. A compound of formula **I**:

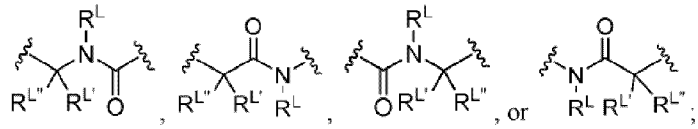


I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from C_{1-6} aliphatic; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; and a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with q instances of R^A;

Ring A is selected from phenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 7-11 membered fused bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L is  ;

wherein each of R^L, $R^{L'}$, and $R^{L''}$ is independently hydrogen, -CN, halogen, or an optionally substituted group selected from C_{1-6} aliphatic; phenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

two of R^L, $R^{L'}$, and $R^{L''}$ groups are taken together with the atoms to which each is attached, to form an optionally substituted 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

any one of R^L, $R^{L'}$, and $R^{L''}$, together with R^B forms a 7-10 membered saturated or partially unsaturated fused bicyclic ring;

Ring B is selected from phenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-11 membered saturated or partially unsaturated fused, bridged, or spiro, bicyclic carbocyclic ring; a 7-11 membered fused bicyclic aryl ring; a 7-11 membered saturated or partially unsaturated fused, bridged, or spiro, bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 7-11 membered fused bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

Ring C is selected from a phenyl, 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a 7-11 membered fused bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

the bond between Ring B and Ring C is absent, and Ring B and Ring C together form a 7-11 membered saturated or partially unsaturated fused, bridged, or spiro, bicyclic carbocyclic ring; a 7-11 membered fused bicyclic aryl ring; a 7-11 membered saturated or partially unsaturated fused, bridged, or spiro, bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-11 membered fused bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^A, R^B, and R^C is independently oxo, halogen, –CN, $–NO_2$, –OR, -SR, $-NR_2$, $-S(O)_2R$,

$-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, $-N=S(O)R_2$, $-S(NR)(O)R$, $-N(R)S(O)R$, $-N(R)CN$, $-P(O)(R)NR_2$, $-P(O)(R)OR$ or $-P(O)R_2$; or each instance of R^C is independently an optionally substituted group selected from C_{1-6} aliphatic; phenyl; naphthalenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, phosphorous, silicon and sulfur; or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-8 membered saturated or partially unsaturated bridged bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-10 membered saturated or partially unsaturated spirocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 6-11 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is substituted with r instances of R and s instances of R^D; or two R^C groups are optionally taken together with the atoms to which each R^C is attached, to form an optionally substituted 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 5-7 membered heteroaryl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^D is independently oxo, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-S(O)NR_2$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)C(NR)NR_2$, $-N(R)NR_2$, $-N(R)S(O)_2NR_2$, $-N(R)S(O)_2R$, $-N=S(O)R_2$, $-S(NR)(O)R$, $-N(R)S(O)R$, $-N(R)CN$, $-P(O)(R)NR_2$, $-P(O)(R)OR$ or $-P(O)R_2$;

each R is independently hydrogen, -CN, halogen, or an optionally substituted group selected from C_{1-6} aliphatic; phenyl; naphthalenyl; a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic

heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5-8 membered saturated or partially unsaturated bridged bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-10 membered saturated or partially unsaturated spirocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 6-11 membered saturated or partially unsaturated bicyclic carbocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or:

two R groups are taken together with the atoms to which each R is attached, to form an optionally substituted 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or

m is 0, 1, or 2;

n is 0, 1, or 2;

p is 0, 1, or 2;

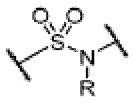
each q is independently 0, 1, 2, 3, or 4;

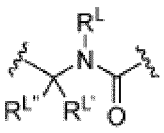
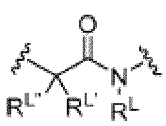
each r is independently 0, 1, 2, 3, or 4; and

each s is independently 0, 1, 2, 3, or 4;

provided that when:

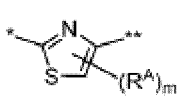
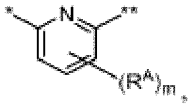
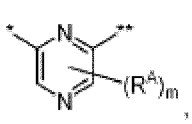
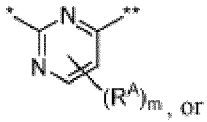
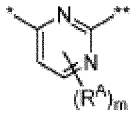
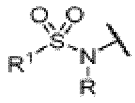
R^1 is C_{1-6} aliphatic or a 3-7 membered saturated or partially unsaturated monocyclic carbocyclic ring;

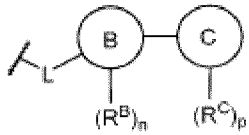
the R group of the sulfonamide moiety  is hydrogen or para-methoxybenzyl;

L is  and the R^L and $R^{L'}$ or R^L and $R^{L''}$ groups are not taken together with the atoms to which each is attached to form an optionally substituted 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or L is  ;

Ring B is phenyl or a 6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

Ring C is phenyl or a 6-membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur and is attached to Ring B in the para position relative to the L group;

then Ring A and its R^A substituents are other than  ,  ,  ,  , or  , where * denotes attachment to the 



moiety and ** denotes attachment to the moiety.

Suitably, the CTPS1 inhibitor is not a CTPS1 inhibitor as defined in claim 1 of WO2022/087634. Suitably, the CTPS1 inhibitor is not a CTPS1 inhibitor as defined in WO2022/087634.

Depending on the nature of the specific CTPS1 inhibitor, the CTPS1 inhibitor may be provided in the form of a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate. In some embodiments the CTPS1 inhibitor is provided in the form of a pharmaceutically acceptable salt and pharmaceutically acceptable solvate. In other embodiments the CTPS1 inhibitor is provided in the form of a pharmaceutically acceptable salt. In further embodiments the CTPS1 inhibitor is provided in the form of a pharmaceutically acceptable solvate. In some embodiments the CTPS1 inhibitor is provided in free form (i.e. not a salt or solvate).

Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art. Pharmaceutically acceptable salts include those *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p.1418. Such pharmaceutically acceptable salts include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Pharmaceutically acceptable salts may also be formed with metal ions such as metal salts, such as sodium or potassium salts, and organic bases such as basic amines e.g. with ammonia, meglumine, tromethamine, piperazine, arginine, choline, diethylamine, benzathine or lysine.

The CTPS1 inhibitor may form acid or base addition salts with one or more equivalents of the acid or base. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The CTPS1 inhibitor may be prepared in crystalline or non-crystalline form and, if crystalline, may optionally be solvated, e.g. as the hydrate. This invention includes within its scope stoichiometric solvates (e.g. hydrates) as well as compounds containing variable amounts of solvent (e.g. water).

The CTPS1 inhibitor encompasses all isomers of the CTPS1 inhibitors disclosed herein including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present, the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The CTPS1 inhibitor encompasses all isotopic forms of the CTPS1 inhibitors provided herein, whether in a form (i) wherein all atoms of a given atomic number have a mass number (or mixture of mass numbers) which predominates in nature (referred to herein as the “natural isotopic form”) or (ii) wherein one or more atoms are replaced by atoms having the same atomic number, but a mass number different from the mass number of atoms which predominates in nature (referred to herein as an “unnatural variant isotopic form”). It is understood that an atom may naturally exist as a mixture of mass numbers. The term “unnatural variant isotopic form” also includes embodiments in which the proportion of an atom of given atomic number having a mass number found less commonly in nature (referred to herein as an “uncommon isotope”) has been increased relative to that which is naturally occurring e.g. to the level of >20%, >50%, >75%, >90%, >95% or >99% by number of the atoms of that atomic number (the latter embodiment referred to as an "isotopically enriched variant form"). The term “unnatural variant isotopic form” also includes embodiments in which the proportion of an uncommon isotope has been reduced relative to that which is naturally occurring. Isotopic forms may include radioactive forms (i.e. they incorporate radioisotopes) and non-radioactive forms. Radioactive forms will typically be isotopically enriched variant forms.

Unnatural variant isotopic forms comprising radioisotopes may, for example, be used for drug and/or substrate tissue distribution studies.

In one embodiment, the CTPS1 inhibitor is provided in a natural isotopic form.

In one embodiment, the CTPS1 inhibitor is provided in an unnatural variant isotopic form. In one embodiment, the CTPS1 inhibitor is provided whereby a single atom of the compound exists in an unnatural variant isotopic form. In another embodiment, the CTPS1 inhibitor is provided whereby two or more atoms exist in an unnatural variant isotopic form.

The CTPS1 inhibitor administered to a subject should be safe and effective, i.e. a CTPS1 inhibitor providing an acceptable balance of desired benefits and undesired side effects. “Safe and effective" is intended to include a compound that is effective to achieve a desirable effect in

treatment of cancer. A desirable effect is typically clinically significant and/or measurable, for instance in the context of (a) inhibiting the disease-state, i.e., slowing or arresting its development; and/or (b) relieving the disease-state, i.e., causing regression of the disease state or a reduction in associated symptoms.

For avoidance of doubt, "safe and effective" as recited herein can be achieved by any suitable dosage regimen. Hence, for example, references herein to administering a safe and effective CTPS1 inhibitor, such as by a particular administration route, include achieving the safe and effective amount via a single dose or by plural doses, such as administered by the specified administration route. For instance, orally administering a safe and effective CTPS1 inhibitor includes both orally administering a single dose and orally administering any plural number of doses, provided that a safe and effective dose of CTPS1 inhibitor is thereby achieved by oral administration.

WEE1 inhibitors

In one aspect of the invention there is provided a WEE1 inhibitor for use in the treatment of cancer with a CTPS1 inhibitor.

A WEE1 inhibitor, as used herein, is an agent which directly inhibits WEE1 activity, such as WEE1 induced phosphorylation of CDC2. Direct inhibition of WEE1 may be quantified using any suitable assay procedure, though is suitably performed using the WEE1 kinase assay procedure or the CDC2 phosphorylation assay procedure set out in Example 3. In one embodiment inhibition of WEE1 may be quantified using the WEE1 kinase assay procedure set out in Example 3. In one embodiment inhibition of WEE1 may be quantified using the CDC2 phosphorylation assay procedure set out in Example 3.

WEE1 inhibitors of particular interest are those demonstrating Ki values for binding to WEE1 of 50 nM or lower, such as 20 nM or lower, such as 10 nM or lower, such as 5 nM or lower, such as 1 nM or lower.

WEE1 inhibitors of particular interest are those demonstrating Ki values for binding to WEE1 of 50 nM or lower, such as 20 nM or lower, such as 10 nM or lower, such as 5 nM or lower, such as 1 nM or lower, using the WEE1 kinase assay or WEE1 CDC2 phosphorylation assay procedure set out in Example 3.

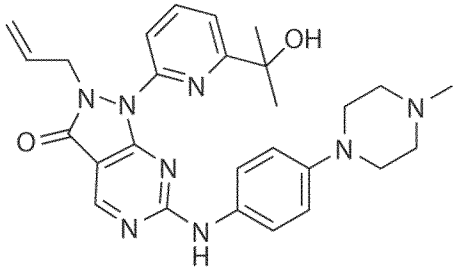
WEE1 inhibitors of particular interest are those demonstrating a selectivity for WEE1 over CHEK1 of >2-fold, such as >5-fold, such as >10-fold, for example a selectivity for WEE1 over CHEK1 of >2-fold, such as >5-fold, such as >10-fold using the assay procedure set out in Example 4.

In the case of medicaments intended for human use, WEE1 inhibition and WEE1 vs CHEK1 selectivity should be based on human forms of the proteins.

Particular WEE1 inhibitors include the following:

Adavosertib

The structure of adavosertib (1-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]-6-[4-(4-methylpiperazin-1-yl)anilino]-2-prop-2-enylpyrazolo[3,4-d]pyrimidin-3-one, CAS number 955365-80-7, also known as AZD1775 or MK-1775) is provided below.

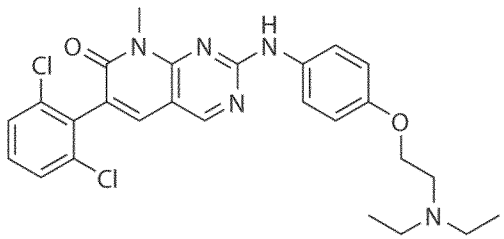


The WEE1 inhibitor may be adavosertib or a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof. In one embodiment the WEE1 inhibitor is adavosertib. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable salt of adavosertib. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable solvate of adavosertib. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable salt and a pharmaceutically acceptable solvate of adavosertib. In one embodiment, the WEE1 inhibitor is not adavosertib. In one embodiment, the WEE1 inhibitor is not adavosertib or a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof.

Adavosertib is disclosed in Hirai 2009, which is incorporated herein by reference in its entirety for the purpose of defining the WEE1 inhibitor.

PD0166285

The structure of PD0166285 (6-(2,6-dichlorophenyl)-2-[4-[2-(diethylamino)ethoxy]anilino]-8-methylpyrido[2,3-d]pyrimidin-7-one, CAS number 212391-63-4) is provided below.

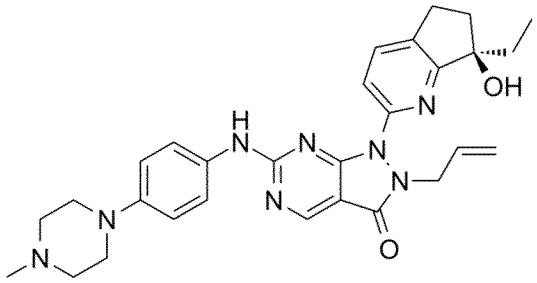


The WEE1 inhibitor may be PD0166285 or a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof. In one embodiment the WEE1 inhibitor is PD0166285. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable salt of PD0166285. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable solvate of PD0166285. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable salt and a pharmaceutically acceptable solvate of PD0166285.

PD0166285 is disclosed in Wang 2001, which is incorporated herein by reference in its entirety for the purpose of defining the WEE1 inhibitor.

ZN-c3

The structure of ZN-c3 (CAS number 2376146-48-2) is provided below.

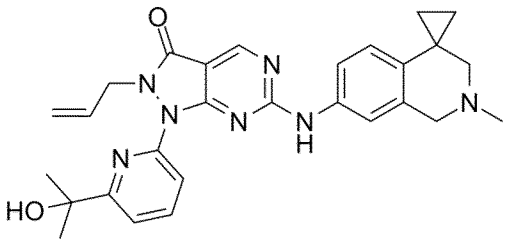


The WEE1 inhibitor may be ZN-c3 or a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof. In one embodiment the WEE1 inhibitor is ZN-c3. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable salt of ZN-c3. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable solvate of ZN-c3. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable salt and a pharmaceutically acceptable solvate of ZN-c3.

ZN-c3 is disclosed in Huang 2021, which is incorporated herein by reference in its entirety for the purpose of defining the WEE1 inhibitor.

WEE1-IN-3

The structure of WEE1-IN-3 (CAS number 2272976-28-8) is provided below.

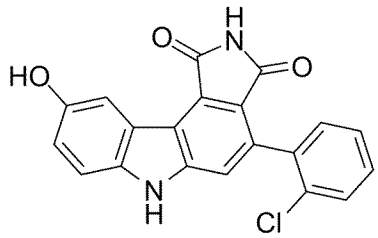


The WEE1 inhibitor may be WEE1-IN-3 or a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof. In one embodiment the WEE1 inhibitor is WEE1-IN-3. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable salt of WEE1-IN-3. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable solvate of WEE1-IN-3. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable salt and a pharmaceutically acceptable solvate of WEE1-IN-3.

WEE1-IN-3 is disclosed in PCT Publication Number WO2019028008, which is incorporated herein by reference in its entirety for the purpose of defining the WEE1 inhibitor.

WEE1-IN-4

The structure of WEE1-IN-4 (CAS number 622855-37-2) is provided below.

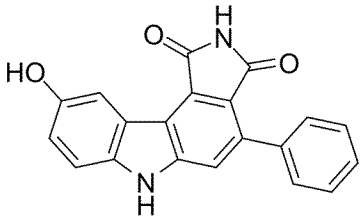


The WEE1 inhibitor may be WEE1-IN-4 or a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof. In one embodiment the WEE1 inhibitor is WEE1-IN-4. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable salt of WEE1-IN-4. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable solvate of WEE1-IN-4. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable salt and a pharmaceutically acceptable solvate of WEE1-IN-4.

WEE1-IN-4 is disclosed in Wichapong 2009, which is incorporated herein by reference in its entirety for the purpose of defining the WEE1 inhibitor.

PD 407824

The structure of PD 407824 (9-hydroxy-4-phenyl-6H-pyrrolo[3,4-c]carbazole-1,3-dione, CAS number 622864-54-4) is provided below.

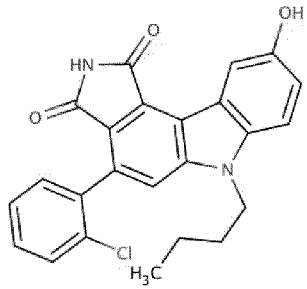


The WEE1 inhibitor may be PD 407824 or a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof. In one embodiment the WEE1 inhibitor is PD 407824. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable salt of PD 407824. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable solvate of PD 407824. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable salt and a pharmaceutically acceptable solvate of PD 407824.

PD 407824 is disclosed in Palmer 2006, which is incorporated herein by reference in its entirety for the purpose of defining the WEE1 inhibitor.

WEE1 Inhibitor II

The structure of WEE1 Inhibitor II (6-butyl-4-(2-chlorophenyl)-9-hydroxypyrrolo[3,4-c]carbazole-1,3-dione, CAS number 622855-50-9) is provided below.



The WEE1 inhibitor may be WEE1 Inhibitor II or a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof. In one embodiment the WEE1 inhibitor is WEE1 Inhibitor II. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable salt of WEE1 Inhibitor II. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable solvate of WEE1 Inhibitor II. In one embodiment the WEE1 inhibitor is a pharmaceutically acceptable salt and a pharmaceutically acceptable solvate of WEE1 Inhibitor II.

WEE1 Inhibitor II is disclosed in Palmer 2006, which is incorporated herein by reference in its entirety for the purpose of defining the WEE1 inhibitor.

In one embodiment, the WEE1 inhibitor is selected from the group consisting of adavosertib, PD0166285, ZN-c3, WEE1-IN-3, WEE1-IN-4, PD 407824 and WEE1 Inhibitor II, pharmaceutically acceptable salts and/or pharmaceutically acceptable solvates thereof. More suitably the WEE1 inhibitor is adavosertib, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Depending on the nature of the specific WEE1 inhibitor, the WEE1 inhibitor may be provided in the form of a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate. In some embodiments the WEE1 inhibitor is provided in the form of a pharmaceutically acceptable salt and pharmaceutically acceptable solvate. In other embodiments the WEE1 inhibitor is provided in the form of a pharmaceutically acceptable salt. In further embodiments the WEE1 inhibitor is provided in the form of a pharmaceutically acceptable solvate. In some embodiments the WEE1 inhibitor is provided in free form (i.e. not a salt or solvate).

Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art. Pharmaceutically acceptable salts include those *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p.1418. Such pharmaceutically acceptable salts include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Pharmaceutically acceptable salts may also be formed with metal ions such as metal salts, such

as sodium or potassium salts, and organic bases such as basic amines e.g. with ammonia, meglumine, tromethamine, piperazine, arginine, choline, diethylamine, benzathine or lysine.

The WEE1 inhibitor may form acid or base addition salts with one or more equivalents of the acid or base. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The WEE1 inhibitor may be prepared in crystalline or non-crystalline form and, if crystalline, may optionally be solvated, e.g. as the hydrate. This invention includes within its scope stoichiometric solvates (e.g. hydrates) as well as compounds containing variable amounts of solvent (e.g. water).

The WEE1 inhibitor encompasses all isomers of the WEE1 inhibitors disclosed herein including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). Where additional chiral centres are present, the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The WEE1 inhibitor encompasses all isotopic forms of the WEE1 inhibitors provided herein, whether in a form (i) wherein all atoms of a given atomic number have a mass number (or mixture of mass numbers) which predominates in nature (referred to herein as the “natural isotopic form”) or (ii) wherein one or more atoms are replaced by atoms having the same atomic number, but a mass number different from the mass number of atoms which predominates in nature (referred to herein as an “unnatural variant isotopic form”). It is understood that an atom may naturally exist as a mixture of mass numbers. The term “unnatural variant isotopic form” also includes embodiments in which the proportion of an atom of given atomic number having a mass number found less commonly in nature (referred to herein as an “uncommon isotope”) has been increased relative to that which is naturally occurring e.g. to the level of >20%, >50%, >75%, >90%, >95% or >99% by number of the atoms of that atomic number (the latter embodiment referred to as an "isotopically enriched variant form"). The term “unnatural variant isotopic form” also includes embodiments in which the proportion of an uncommon isotope has been reduced relative to that which is naturally occurring. Isotopic forms may include radioactive forms (i.e. they incorporate radioisotopes) and non-radioactive forms. Radioactive forms will typically be isotopically enriched variant forms.

Unnatural variant isotopic forms comprising radioisotopes may, for example, be used for drug and/or substrate tissue distribution studies.

In one embodiment, the WEE1 inhibitor is provided in a natural isotopic form.

In one embodiment, the WEE1 inhibitor is provided in an unnatural variant isotopic form.

In one embodiment, the WEE1 inhibitor is provided whereby a single atom of the compound exists in an unnatural variant isotopic form. In another embodiment, the WEE1 inhibitor is provided whereby two or more atoms exist in an unnatural variant isotopic form.

In general, the WEE1 inhibitors disclosed herein may be made according to the organic synthesis techniques known to those skilled in this field. For example, preparation of adavosertib is described in Hirai 2009 and preparation of PD0166285 is disclosed in Wang 2001. These references are incorporated herein by reference in their entirety for the purpose of methods of producing the WEE1 inhibitors adavosertib and PD0166285 as disclosed therein.

The WEE1 inhibitor administered to a subject should be safe and effective, i.e. a WEE1 inhibitor providing an acceptable balance of desired benefits and undesired side effects. “Safe and effective" is intended to include a compound that is effective to achieve a desirable effect in treatment of cancer. A desirable effect is typically clinically significant and/or measurable, for instance in the context of (a) inhibiting the disease-state, i.e., slowing or arresting its development; and/or (b) relieving the disease-state, i.e., causing regression of the disease state or a reduction in associated symptoms.

For avoidance of doubt, “safe and effective” as recited herein can be achieved by any suitable dosage regimen. Hence, for example, references herein to administering a safe and effective WEE1 inhibitor, such as by a particular administration route, include achieving the safe and effective amount via a single dose or by plural doses, such as administered by the specified administration route. For instance, orally administering a safe and effective WEE1 inhibitor includes both orally administering a single dose and orally administering any plural number of doses, provided that a safe and effective dose of WEE1 inhibitor is thereby achieved by oral administration.

Administration

The invention is typically intended for use with mammalian subjects, in particular human subjects. The combination treatment will typically be administered to a subject in need thereof, in particular a mammalian subject, in particular a human subject.

In a further aspect the invention provides a CTPS1 inhibitor and a WEE1 inhibitor for use in the treatment of cancer.

One aspect of the invention provides the use of a CTPS1 inhibitor in the manufacture of a medicament for the treatment of cancer with a WEE1 inhibitor.

A further aspect of the invention provides the use of a WEE1 inhibitor in the manufacture of a medicament for the treatment of cancer with a CTPS1 inhibitor.

A further aspect of the invention provides the use of a CTPS1 inhibitor and a WEE1 inhibitor in the manufacture of a medicament for the treatment of cancer.

A further aspect of the invention provides a method of treating cancer in a subject which method comprises administering to the subject a CTPS1 inhibitor and a WEE1 inhibitor.

A further aspect of the invention provides a pharmaceutical composition comprising a CTPS1 inhibitor and a WEE1 inhibitor, suitably for use in the treatment of cancer.

Suitably the CTPS1 inhibitor and the WEE1 inhibitor act synergistically in treating the cancer. The CTPS1 inhibitor and the WEE1 inhibitor act 'synergistically' if their combined administration results in a beneficial effect greater than the sum of the beneficial effects of each agent administered alone. Suitably the CTPS1 inhibitor and the WEE1 inhibitor act synergistically if they achieve a Bliss score (Bliss 1939; Zheng 2021) of ≥10 when applied to a cancer cell line as set out in Example 6.

Administration of the CTPS1 inhibitor

The CTPS1 inhibitor may be administered by any suitable route, which may depend on the nature of the specific agent. Exemplary routes include oral, parenteral, buccal, sublingual, nasal or rectal administration. Conveniently, the CTPS1 inhibitor is administered orally.

The CTPS1 inhibitor may be provided in the form of a pharmaceutical composition comprising the CTPS1 inhibitor and a pharmaceutically acceptable carrier or excipient.

If delivered orally, the CTPS1 inhibitor may suitably be delivered in a solid pharmaceutical composition (such as a tablet, capsule or lozenge) or in a liquid pharmaceutical composition (such as a suspension, emulsion or solution). Suitably the CTPS1 inhibitor is administered orally in a solid pharmaceutical composition.

A liquid formulation will generally consist of a suspension or solution of the CTPS1 inhibitor in a suitable liquid carrier e.g. an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A tablet formulation can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

Suitably, the pharmaceutical composition is in unit dose form, such as a tablet, capsule or ampoule. Suitably the unit dose form is for oral delivery.

The pharmaceutical composition may for example contain from 0.1% to 99.99% by weight, for example from 10 to 60% by weight, of the active material, depending on the method of administration. The pharmaceutical composition may contain from 0.01% to 99% by weight, for example 40% to 90% by weight, of the carrier, depending on the method of administration. The pharmaceutical composition may contain from 0.05 mg to 2000 mg of the active material, for example from 1.0 mg to 500 mg, depending on the method of administration. The

pharmaceutical composition may contain from 50 mg to 1000 mg of the carrier, for example from 100 mg to 400 mg, depending on the method of administration.

The dose of the compound used will vary in the usual way with the seriousness of the cancer, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 mg to 1000 mg, more suitably 1.0 mg to 500 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks, months or longer. A plurality of unit does, such as a plurality of tablets, may be taken together.

The dose provided to a subject will typically be a safe and effective dose, i.e. an amount providing an acceptable balance of desired benefits and undesired side effects. A “safe and effective amount" is intended to include an amount of a compound that is effective to achieve a desirable effect in treatment of a disease-state. A desirable effect is typically clinically significant and/or measurable, for instance in the context of (a) inhibiting the disease-state, i.e., slowing or arresting its development; and/or (b) relieving the disease-state, i.e., causing regression of the disease state or a reduction in associated symptoms. The safe and effective amount is one that is sufficient to achieve the desirable effect when the CTPS1 inhibitor is administered with the WEE1 inhibitor.

For avoidance of doubt, a “safe and effective amount” as recited herein can be achieved by any suitable dosage regimen. Hence, for example, references herein to administering a safe and effective amount of a compound, such as by a particular administration route, include achieving the safe and effective amount via a single dose or by plural doses, such as administered by the specified administration route. For instance, orally administering a safe and effective amount includes both orally administering a single dose and orally administering any plural number of doses, provided that a safe and effective amount is thereby achieved by oral administration.

Administration of the WEE1 inhibitor

The WEE1 inhibitor may be administered by any suitable route, which may depend on the nature of the specific agent. Exemplary routes include oral, parenteral, buccal, sublingual, nasal or rectal administration. Conveniently, the WEE1 inhibitor is administered orally. The WEE1 inhibitor may be provided in the form of a pharmaceutical composition comprising the WEE1 inhibitor and a pharmaceutically acceptable carrier or excipient.

If delivered orally, the WEE1 inhibitor may suitably be delivered in a solid pharmaceutical composition (such as a tablet, capsule or lozenge) or in a liquid pharmaceutical composition (such as a suspension, emulsion or solution).

A liquid formulation will generally consist of a suspension or solution of the WEE1 inhibitor in a suitable liquid carrier e.g. an aqueous solvent such as water, ethanol or glycerine,

or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A tablet formulation can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

Suitably, the pharmaceutical composition is in unit dose form, such as a tablet, capsule or ampoule. Suitably the unit dose form is for oral delivery.

The pharmaceutical composition may for example contain from 0.1% to 99.99% by weight, for example from 10 to 60% by weight, of the active material, depending on the method of administration. The pharmaceutical composition may contain from 0.01% to 99% by weight, for example 40% to 90% by weight, of the carrier, depending on the method of administration. The pharmaceutical composition may contain from 0.05 mg to 2000 mg of the active material, for example from 1.0 mg to 500 mg, suitably 5 mg to 15 mg, such as 10 mg, depending on the method of administration. For oral administration, 10 mg may be desirable. The pharmaceutical composition may contain from 50 mg to 1000 mg of the carrier, for example from 100 mg to 400 mg, depending on the method of administration.

The dose of the compound used will vary in the usual way with the seriousness of the cancer, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 mg to 1000 mg, more suitably 1.0 mg to 500 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks, months or longer. A plurality of unit does, such as a plurality of tablets, may be taken together. If the WEE1 inhibitor is adavosertib (or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof) then this WEE1 inhibitor will typically be administered at a dose of 300 mg administered orally, suitably once daily on days 1 to 5 and days 8 to 12 of a 21-day treatment cycle. Suitably the WEE1 inhibitor is administered orally at a daily dose of up to 300 mg, suitably once daily on days 1 to 5 and days 8 to 12 of a 21-day treatment cycle. Suitably, the WEE1 inhibitor is administered orally, such as orally in a solid pharmaceutical composition.

The dose provided to a subject will typically be a safe and effective dose, i.e. an amount providing an acceptable balance of desired benefits and undesired side effects. A “safe and effective amount" is intended to include an amount of a compound that is effective to achieve a desirable effect in treatment of a disease-state. A desirable effect is typically clinically significant and/or measurable, for instance in the context of (a) inhibiting the disease-state, i.e., slowing or arresting its development; and/or (b) relieving the disease-state, i.e., causing regression of the disease state or a reduction in associated symptoms. The safe and effective amount is one that is sufficient to achieve the desirable effect when the CTPS1 inhibitor is administered with the WEE1 inhibitor.

For avoidance of doubt, a "safe and effective amount" as recited herein can be achieved by any suitable dosage regimen. Hence, for example, references herein to administering a safe and effective amount of a compound, such as by a particular administration route, include achieving the safe and effective amount via a single dose or by plural doses, such as administered by the specified administration route. For instance, orally administering a safe and effective amount includes both orally administering a single dose and orally administering any plural number of doses, provided that a safe and effective amount is thereby achieved by oral administration.

Administration regimes

The CTPS1 inhibitor and WEE1 inhibitor may be administered separately, sequentially or simultaneously.

The CTPS1 inhibitor may be administered before the WEE1 inhibitor. Alternatively, the WEE1 inhibitor may be administered before the CTPS1 inhibitor.

To maintain therapeutic efficacy whilst controlling toxicity, the CTPS1 inhibitor and/or WEE1 inhibitor may be administered intermittently. Intermittently in this context means that the CTPS1 inhibitor and/or the WEE1 inhibitor are not administered every day of a treatment cycle (e.g. the CTPS1 inhibitor and/or the WEE1 inhibitor are administered for 4 days in each 7 day period of a treatment cycle; e.g. the WEE1 inhibitor is administered for 5 days in each 7 day period of a treatment cycle). It will be understood that when the CTPS1 inhibitor and WEE1 inhibitor are both administered intermittently, they need not be administered according to the same schedule.

Suitably, the CTPS1 inhibitor and/or WEE1 inhibitor may be administered continuously i.e. administered at least daily in a treatment cycle (e.g. the CTPS1 inhibitor and/or the WEE1 inhibitor are administered each day of a treatment cycle).

Suitably, the CTPS1 inhibitor is administered intermittently and the WEE1 inhibitor is administered intermittently. Suitably, the CTPS1 inhibitor is administered continuously and the WEE1 inhibitor is administered continuously. Suitably, the CTPS1 inhibitor is administered intermittently and the WEE1 inhibitor is administered continuously. Suitably, the CTPS1 inhibitor is administered continuously and the WEE1 inhibitor is administered intermittently.

The CTPS1 inhibitor and the WEE1 inhibitor may be delivered in co-formulation (where compatible with co-formulation and whether the dosage regimes of the two agents allow) or in separate formulations. Most suitably the CTPS1 inhibitor and the WEE1 inhibitor are delivered in co-formulation or in separate formulations which are simultaneously administered. Alternatively, if delivered in separate formulations, the CTPS1 inhibitor and the WEE1 inhibitor may be delivered at different times.

If separately formulated, the CTPS1 inhibitor (or a pharmaceutical composition comprising such, such as a tablet or capsule) and WEE1 inhibitor (or a pharmaceutical composition comprising such, such as a tablet or capsule) may be provided in separate containers.

If separately formulated, the CTPS1 inhibitor and WEE1 inhibitor may be provided in the form of a kit of parts comprising:

a) a first container comprising a CTPS1 inhibitor; and

b) a second container comprising a WEE1 inhibitor.

More suitably, the CTPS1 inhibitor and WEE1 inhibitor may be provided in the form of a kit of parts comprising a first container comprising a CTPS1 inhibitor (or a pharmaceutical composition comprising such, such as a tablet or capsule) and a second container comprising a WEE1 inhibitor (or a pharmaceutical composition comprising such, such as a tablet or capsule).

Combinations with further agents

Treatment with the CTPS1 inhibitor and WEE1 inhibitor may be combined with one or more further pharmaceutically acceptable active ingredients, which may be selected from: anti-mitotic agents such as vinblastine, paclitaxel and docetaxel; alkylating agents, for example cisplatin, carboplatin, dacarbazine and cyclophosphamide; antimetabolites, for example 5-fluorouracil, cytosine arabinoside and hydroxyurea; intercalating agents for example adriamycin and bleomycin; topoisomerase inhibitors for example etoposide, topotecan and irinotecan; thymidylate synthase inhibitors for example raltitrexed; PI3 kinase inhibitors for example idelalisib; mTor inhibitors for example everolimus and temsirolimus; proteasome inhibitors for example bortezomib; histone deacetylase inhibitors for example panobinostat or vorinostat; and hedgehog pathway blockers such as vismodegib.

The CTPS1 inhibitor, WEE1 inhibitor and the additional pharmaceutically acceptable active ingredients may each be administered in any combination of separate, sequential or simultaneous dosing. If administered simultaneously, the CTPS1 inhibitor and WEE1 inhibitor may be e.g. (a) formulated together but separately from the further pharmaceutically acceptable active ingredient, (b) formulated separately from each other and separately from the further pharmaceutically acceptable active ingredient (c) formulated together with the further pharmaceutically acceptable active ingredient.

The CTPS1 inhibitor, the WEE1 inhibitor and the additional pharmaceutically acceptable active ingredients may each be administered in any combination of separate, sequential or simultaneous dosing. The CTPS1 inhibitor, WEE1 inhibitor and the additional pharmaceutically acceptable active ingredients may be e.g. (a) formulated together but separately from the further pharmaceutically acceptable active ingredient, (b) formulated separately from each other and separately from the further pharmaceutically acceptable active ingredient, (c) formulated

together with the further pharmaceutically acceptable active ingredient; (d) formulated separately from each other, but one of the CTPS1 inhibitor or WEE1 inhibitor formulated together with the further pharmaceutically acceptable active ingredient.

The further pharmaceutically acceptable active ingredient may be selected from tyrosine kinase inhibitors such as, for example, axitinib, dasatinib, erlotinib, imatinib, nilotinib, pazopanib and sunitinib. Alternatively, the further pharmaceutically acceptable active ingredient may be selected from azacitidine, decitabine, or cytarabine.

Further pharmaceutically acceptable active ingredients also include anticancer antibodies, such as those selected from the group consisting of anti-CD20 antibodies (such as obinutuzumab, ofatumumab, tositumomab or rituximab) or other antibodies such as olaratumab, daratumumab, necitumumab, dinutuximab, traztuzumab emtansine, pertuzumab, brentuximab, panitumumab, catumaxomab, bevacizumab, cetuximab, traztuzumab and gentuzumab ozogamycin.

The CTPS1 inhibitor and WEE1 inhibitor may also be administered in combination with radiotherapy, surgery, hyperthermia therapy or cryotherapy.

Cancer

Potential biomarkers of response to WEE1 inhibition include genomic alterations associated with replication stress (including *CCNE1* amplification, *MYC* amplification and *FBXW7* mutation), TP53 deficiency, markers of double stranded DNA breakage such as γH2AX, and activation of CHEK1 (measured by pCHEK1 protein, Cleary (2020).

Biomarkers currently being used to select patients for clinical trials of WEE1 inhibitors include mutation of *TP53*, *BRCA1* or *BRCA2*, amplification of *CCNE1* or *MYC* family genes, or loss of *CDKN2A*.

Accordingly, the invention may be expected to be particularly effective in treating cancers comprising these markers.

In one embodiment, the cancer displays *CCNE1* amplification. In a further embodiment, the cancer displays *MYC* amplification. In a further embodiment, the cancer displays the *FBXW7* mutation. In a further embodiment, the cancer displays TP53 deficiency. In a further embodiment, the cancer displays markers of double stranded DNA breakage (such as γH2AX), and activation of CHEK1 (suitably measured by pCHEK1 protein (Cleary 2020)).

In one embodiment the cancer comprises a mutation of *TP53*, *BRCA1* or *BRCA2*, amplification of *CCNE1* or *MYC* family genes, or loss of *CDKN2A*.

In one embodiment the cancer is a cancer which is susceptible to replication stress or has high pre-existing levels of replication stress. By a 'high' level it is meant that the cancer has a pre-existing level of replication stress which is higher than an average cancer.

Suitably the cancer is a haematological cancer, such as acute myeloid leukemia, angioimmunoblastic T-cell lymphoma, B-cell acute lymphoblastic leukemia, Sweet syndrome, T-cell non-Hodgkin lymphoma (including natural killer/T-cell lymphoma, adult T-cell leukaemia/lymphoma, enteropathy type T-cell lymphoma, hepatosplenic T-cell lymphoma and cutaneous T-cell lymphoma), T-cell acute lymphoblastic leukemia, B-cell non-Hodgkin lymphoma (including Burkitt lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma), hairy cell leukemia, Hodgkin lymphoma, lymphoblastic lymphoma, lymphoplasmacytic lymphoma, mucosa-associated lymphoid tissue lymphoma, multiple myeloma, myelodysplastic syndrome, plasma cell myeloma, primary mediastinal large B-cell lymphoma, chronic myeloproliferative disorders (such as chronic myeloid leukemia, primary myelofibrosis, essential thrombocythemia, polycythemia vera) or chronic lymphocytic leukemia. Most suitably, T cell lymphoma, diffuse large B cell lymphoma, plasma cell myeloma, acute myeloid leukaemia, chronic lymphocytic leukaemia or peripheral T cell lymphoma. A further haematological cancer of interest is T-cell prolymphocytic leukemia. Other haematological cancers of interest are myelodysplastic syndromes (MDS), such as MDS with single lineage dysplasia, MDS with multilineage dysplasia or MDS with excess blasts.

Alternatively, the cancer is a non-haematological cancer, such as selected from the group consisting of colorectal cancer, bile duct cancer, endometrial cancer, hepatic cancer, gastric cancer, oesophageal cancer, sarcoma, bladder cancer, pancreatic cancer, ovarian cancer, lung cancer, mesothelioma, melanoma, bone cancer, head and neck cancer, breast cancer, brain cancers, prostate cancer, renal cancer, thyroid cancer and neuroblastoma. More suitably the non-haematological cancer is selected from colorectal cancer, bile duct cancer, endometrial cancer, hepatic cancer, gastric cancer, oesophageal cancer, sarcoma, bladder cancer, pancreatic cancer, ovarian cancer, lung cancer, mesothelioma and melanoma. More suitably the non-haematological cancer is selected from colorectal cancer, bile duct cancer, endometrial cancer, hepatic cancer, gastric cancer and oesophageal cancer. The non-haematological cancer may be selected from prostate cancer, pancreatic cancer, ovarian cancer, lung cancer, renal cancer, colorectal cancer or breast cancer, especially prostate cancer, pancreatic cancer, ovarian cancer, renal cancer, colorectal cancer or breast cancer.

The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit of the invention may be for administration to a subject identified as having a cancer expected to be susceptible to treatment by a CTPS1 inhibitor and a WEE1 inhibitor. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit of the invention may be for administration to a subject from whom a sample of cancer cells has been shown to be susceptible to treatment by a CTPS1 inhibitor and a WEE1 inhibitor. A ‘susceptible’ cancer or cancer cell sample in this context is one which is associated with generally demonstrating a benefit from the treatment according to the invention relative to treatment with CTPS1 or WEE1 inhibitors alone, e.g. additive or suitably

synergistic effects - high *in vivo* efficacy, reduction in the dose required for effect *in vivo* and/or an improved safety profile/reduced side effects.

The invention is further exemplified by the following non-limiting examples.

EXAMPLES

Example 1: Human CTPS1 Enzyme Inhibition

Enzyme inhibitory activities of compounds CTPS1-IA and CTPS1-IB

The enzyme inhibitory activities of compounds CTPS1-IA and CTPS1-IB against CTPS1 were determined using the ADP-Glo™ Max assay (Promega, UK).

CTPS1-IA is 4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-N-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide.

CTPS-IB is *N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(2-(ethylsulfonamido)pyrimidin-4-yl)tetrahydro-2*H*-pyran-4-carboxamide.

Assays for human CTPS1 were performed in 1x assay buffer containing 50mM Tris, 10mM $MgCl_2$, 0.01% Tween-20, pH to 8.0 accordingly. Finally, immediately before use, L-cysteine was added to the 1x assay buffer to a final concentration of 2mM. All reagents are from Sigma-Aldrich unless specified otherwise. Human full length active C-terminal FLAG-His_8-tag CTPS1 (UniProtKB - P17812, CTPS[1-591]-GGDYKDDDDKGGHHHHHHHH, SEQ ID NO: 1) was obtained from Proteros biostructures GmbH.

Assay Procedure

3x human CTPS1 protein was prepared in 1x assay buffer to the final working protein concentration required for the reaction. A 2uL volume per well of 3x human CTPS1 protein was mixed with 2uL per well of 3x test compound (compound prepared in 1x assay buffer to an appropriate final 3x compound concentration respective to the concentration response curve designed for the compounds under test) for 10 minutes at 25°C. The enzymatic reaction was then initiated by addition of a 2uL per well volume of a pre-mixed substrate mix (UltraPure ATP from ADP-Glo™ Max kit (0.31mM), GTP (0.034mM), UTP (0.48mM) and L-glutamine (0.186mM)) and the mixture was incubated for an appropriate amount of time within the determined linear phase of the reaction at 25°C under sealed plate conditions with constant agitation at 500 revolutions per minute (rpm). ADP-Glo™ Max reagent was added for 60 minutes (6µL per well) and subsequently ADP-Glo™ Max development reagent was added for 60 minutes (12uL per well) prior to signal detection in a microplate reader (EnVision® Multilabel Reader, Perkin Elmer). Following each reagent addition over the course of the assay, assay plates were pulse centrifuged for 30 seconds at 500rpm.

In all cases, the enzyme converts ATP to ADP and the ADP-Glo™ Max reagent subsequently depletes any remaining endogenous ATP in the reaction system. The ADP-Glo™ Max detection reagent converts the ADP that has been enzymatically produced back into ATP and using ATP as a substrate together with luciferin for the enzyme luciferase, light is generated which produces a detectable luminescence. The luminescent signal measured is directly proportional to the amount of ADP produced by the enzyme reaction and a reduction in this signal upon compound treatment demonstrates enzyme inhibition. The percentage inhibition produced by each concentration of compound was calculated using the equation shown below:

$$\%\ Inhibition = 1 - \frac{(Mean_{Min} - Mean_{Inh})}{(Mean_{Min} - Mean_{Max})}\ x\ 100$$

Percentage inhibition was then plotted against compound concentration, and the 50% inhibitory concentration (IC_{50}) was determined from the resultant concentration-response curve. The data for the tested compounds are presented below.

Table 1: *Human CTPS1 Enzyme Inhibition data*

Compound	IC_{50} (um)	Compound	IC_{50} (um)
CTPS1-IA	≤0.1	CTPS1-IB	≤0.1

Both compounds were found to demonstrate inhibition of CTPS1 enzyme in this assay. Consequently, these compounds may be expected to have utility in the inhibition of CTPS1.

Example 2: RapidFire/MS-based CTPS1 Enzyme Selectivity Assays

Human CTPS1 versus CTPS2 Selectivity Assessment by RapidFire/MS Analysis.

The enzyme inhibitory activities against each target isoform of interest were determined for compounds using an optimised RapidFire high-throughput mass spectrometry (RF/MS) assay format. RF/MS assays for both human CTPS1 and CTPS2 were performed in assay buffer consisting of 50mM HEPES (Merck), 20mM $MgCl_2$, 5mM KCl, 1mM DTT, 0.01% Tween-20, pH to 8.0 accordingly. Human full-length active C-terminal FLAG-His-tag CTPS1 (UniProtKB - P17812, CTPS[1-591]-GGDYKDDDDKGGHHHHHHHH, SEQ ID NO: 1) was obtained from Proteros biostructures GmbH. Human full length active C-terminal FLAG-His-Avi tagged CTPS2 (UniProtKB – Q9NRF8, CTPS2 [1-586]-DYKDDDDKHHHHHHGLNDIFEAQKIEWHE, SEQ ID NO: 2) was obtained from Harker Bio.

Assay Procedure

Human CTPS (1 or 2) protein was prepared in 1x assay buffer to the final working protein concentration required for the reaction. A 2uL volume per well of 2x CTPS (1 or 2) protein was mixed with 40nL of compound using acoustic (ECHO) delivery and incubated for 10 minutes at 25°C. Each isoform enzymatic reaction was subsequently initiated by addition of 2uL per well

of a 2x substrate mix in assay buffer. For hCTPS1: ATP (0.3mM), UTP (0.2mM), GTP (0.07mM) and L-glutamine (0.1mM). For hCTPS2: ATP (0.1mM), UTP (0.04mM), GTP (0.03mM) and L-glutamine (0.1mM). Each mixture was incubated for an appropriate amount of time per isoform within the determined linear phase of the reaction at 25°C. A 60uL volume of stop solution (1% formic acid with 0.5uM $^{13}C_9$-$^{15}N_3$-CTP in H_20) was added and the plate immediately heat-sealed and centrifuged for 10 minutes at 4,000rpm. Following centrifugation, plates were loaded onto the Agilent RapidFire microfluidic solid phase extraction system coupled to an API4000 triple quadrupole mass spectrometer (RF/MS) for analysis.

In all cases, the enzyme converts UTP to CTP. Highly specific and sensitive multiple reaction monitoring (MRM) MS methods may be optimised for the detection of the enzymatic reaction product, CTP, and the stable isotope labelled product standard $^{13}C_9$-$^{15}N_3$-CTP. Readout for data analysis was calculated as the ratio between the peak area of the product CTP and the internal standard $^{13}C_9$-$^{15}N_3$-CTP. For data reporting, the following equation was used:

$$R = \frac{P}{IS}$$

(R = ratio/readout, P = product signal area, IS = internal standard signal area)

For each screening plate, the means of the negative (DMSO) and positive control values were used for the calculation of the respective assay window (S/B) and Z' values. The median of the respective control values was used for calculation of percent inhibition according to the following equation:

$$I = \frac{R_{neg} - R_{sample}}{[R_{neg} - R_{pos}]} \%$$

(I = Inhibition, R_{neg} = median of negative control readout values, R_{pos} = median of positive control readout values, R_{sample} = sample readout value)

Percentage inhibition was then plotted against compound concentration, and the 50% inhibitory concentration (IC_{50}) was determined from the resultant concentration-response curve.

Fold selectivity between CTPS1 and CTPS2 was subsequently calculated according to the following equation:

$$\text{Fold selectivity} = \frac{\text{CTPS2 } IC_{50}}{\text{CTPS1 } IC_{50}}$$

CTPS1-IA and CTPS1-IB were tested for selectivity. The results are presented below.

Table 2: Selectivity data

Compound	Selectivity
CTPS1-IA	>60 fold

Compound	Selectivity
CTPS1-IB	>60 fold

These compounds may be expected to have utility in the treatment of diseases whereby a selective CTPS1 compound is beneficial.

Example 3: Human WEE1 Inhibition

WEE1 kinase assay

Recombinant human WEE1 protein is incubated with radio-labelled ATP ([γ-^{33}P]-ATP), enzyme substrate (poly[Lys, Tyr]) and different concentrations of small molecule inhibitor. Radioactivity incorporated into the substrate, which is a measure of enzymatic activity, is quantified by capturing the substrate on a suitable surface and measuring radioactivity using a liquid scintillation counter.

This protein kinase assay is disclosed in Hirai 2009, which is incorporated herein by reference in its entirety for the purpose of detailing this protein kinase assay.

WEE1 CDC2 phosphorylation assay

Human cancer cell line cells are cultured in 96-well plates and incubated with a DNA-damaging agent, for example doxorubicin or gemcitabine, for 24 h, then with test compound and nocodazole for additional 8 h. Cells are then lysed and subjected in a colorimetric ELISA to determine the amounts of p-CDC2Y15 and total CDC2 using appropriate monoclonal antibodies.

This phosphorylation assay is disclosed in Hirai 2009, which is incorporated herein by reference in its entirety for the purpose of detailing this phosphorylation assay.

Example 4: WEE1 Selectivity

The WEE1 protein kinase assay can be used to assay the ability of test compounds to inhibit the activity of other protein kinases. As an example, the CHEK1 kinase domain could be expressed in Sf9 insect cells, and a biotinylated CDC25C peptide containing the consensus CHEK1 phosphorylation site used as the substrate. A dilution series of test compound could be mixed with a kinase reaction buffer containing unlabelled ATP, plus 5 nmol/L ^{33}P γ-labelled ATP. Radioactivity incorporated into the substrate, which is a measure of enzymatic activity, could be quantified by capturing the substrate on a suitable surface and measuring radioactivity using a liquid scintillation counter. This method could be adapted for other protein kinases such as CHEK2 and CDK2.

Example 5: CTPS1 Involvement in the Proliferation of Cancer Cells

Pathways involved in providing the key building blocks for nucleic acid replication are the purine and pyrimidine synthesis pathways, and pyrimidine biosynthesis has been observed to be up-regulated in tumors and neoplastic cells. CTPS activity is upregulated in a range of tumour types of both haematological and non-haematological origin, although heterogeneity is observed among patients. Linkages have also been made between high enzyme levels and resistance to chemotherapeutic agents. In an analysis of published data, CTPS1 was found by the present inventors to be essential for the proliferation of human cancer cells derived from a broad range of haematological and solid tumour types, whereas CTPS2 was invariably redundant. This analysis used data from the Achilles project where every gene in the human genome was independently deleted using CRIPR technology in each of 324 human cancer cell lines, and the effects of each gene deletion was assessed using an *in vitro* proliferation assay (Behan 2019). This dataset has subsequently been expanded to include data from 1,032 human cancer cell lines (Cancer Dependency Map: https://depmap.org/). The effects of deletion of different genes in the pyrimidine synthesis pathway were assessed (see Fig. 2). Deletion of *CTPS2* had no effect on cancer cell proliferation. Deletion of genes in the salvage pathway (*UCK1, UCK2*) had minimal effect on cell proliferation. Deletion of *CMPK1* had a marked effects on cell proliferation, consistent with *CMPK1* being an essential gene. Deletion of *CTPS1, UMPS, DHODH* or *CAD* inhibited cancer cell proliferation with an effect that is consistent with dependency of cancer cells on the products of these genes; inhibition of *CTPS1* produced the greatest impairment of cancer cell proliferation. These findings indicate that the majority of cancer cells are dependent on CTPS1 for cell proliferation, whereas CTPS2 is not required.

In recent work, the CTPS1 isoform has shown higher enzymatic activity than CTPS2. Taken together with the CRISPR study analysis outlined above, these findings highlight CTPS1 as the more potent CTP synthase enzyme and identify a non-redundant role for CTPS1 in the proliferation of human cancer cells, thus identifying CTPS1 as a potential therapeutic target in a wide range of human malignancies.

Example 6: Effect of Combined Treatment with a CTPS1 inhibitor and a WEE1 Inhibitor

In vitro proliferation assays were performed using human cancer cell lines to investigate any interactions between the antiproliferative effects of CTPS1-IA and (a) WEE1 inhibitor adavosertib or (b) standard of care therapies for myeloma.

Cell lines (available from commercial repositories, such as Deutsche Sammlung von Mikroorganismen und Zellkulturen) were plated in triplicate at a density of $0.2x10^6$ cells/ml in 96 well plates. CTPS1-IA and the second agent were added at prespecified concentrations that were specific to each cell line, covering concentrations above and below the IC_{50} value for the individual agents, and viability was assessed after 72 hours incubation using a tetrazolium salt-based

colourimetric assay. CTPS1-IA and the second agent were tested in a 4x4 matrix (total 16 conditions). Each compound was included at concentrations producing single agent 72 hour viability of 80-90%, 50-60% and 30-40%, as well as a no drug condition.

Fig. 3 shows Bliss scores (Bliss 1939; Zheng 2021) for the interaction between CTPS1-IA combined with WEE1 inhibitor adavosertib, or CTPS1-IA combined with standard of care therapies for myeloma cell lines. A value of -10 to <10 indicates an additive effect and a value of ≥10 indicates synergy. Synergy was observed for CTPS1-IA combined with adavosertib while there was a lack of synergy with standard of care therapies.

Fig. 4 shows data from 24 human cancer lines derived from solid tumours exposed to the CTPS1 inhibitor CTPS1-IA combined with a WEE1 inhibitor (adavosertib). Synergy was observed in 14 of the cell lines (Bliss scores 10 - 27). Synergy was observed for at least one cell line in each of the 6 tumour types tested (prostate, pancreas, ovary, kidney, colorectal, breast).

Fig. 5 shows a comparison of synergy in anti-tumour effects in 2 human colorectal cancer cell lines and 2 human ovarian cancer cell lines elicited by the WEE1 inhibitor adavosertib in combination with either the CTPS1 inhibitor CTPS1-IA or a chemotherapy drug (irinotecan, cisplatin or gemcitabine). In 11 of the 12 combinations tested, the synergy elicited by the adavosertib CTPS1-IA combination exceeded that elicited by the adavosertib chemotherapy combination.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word ‘comprise’, and variations such as ‘comprises’ and ‘comprising’, will be understood to imply the inclusion of a stated integer, step, group of integers or group of steps but not to the exclusion of any other integer, step, group of integers or group of steps.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the claims which follow.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Clauses of the invention

A series of clauses setting out embodiments of the invention are as follows.

Clause 1. A CTPS1 inhibitor for use in the treatment of cancer with a WEE1 inhibitor.

Clause 2. A WEE1 inhibitor for use in the treatment of cancer with a CTPS1 inhibitor.

Clause 3. A CTPS1 inhibitor and a WEE1 inhibitor for use in the treatment of cancer.

Clause 4. Use of a CTPS1 inhibitor in the manufacture of a medicament for the treatment of cancer with a WEE1 inhibitor.

Clause 5. Use of a WEE1 inhibitor in the manufacture of a medicament for the treatment of cancer with a CTPS1 inhibitor.

Clause 6. Use of a CTPS1 inhibitor and a WEE1 inhibitor in the manufacture of a medicament for the treatment of cancer.

Clause 7. A method of treating cancer in a subject which method comprises administering to the subject a CTPS1 inhibitor and a WEE1 inhibitor.

Clause 8. A pharmaceutical composition comprising a CTPS1 inhibitor and a WEE1 inhibitor.

Clause 9. A kit of parts comprising:

a) a first container comprising a CTPS1 inhibitor; and

b) a second container comprising a WEE1 inhibitor.

Clause 10. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 9, wherein the CTPS1 inhibitor has an IC_{50} of 10 uM or lower in respect of human CTPS1 enzyme.

Clause 11. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 10, wherein the CTPS1 inhibitor has an IC_{50} of 1 uM or lower in respect of human CTPS1 enzyme.

Clause 12. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 11, wherein the CTPS1 inhibitor has an IC_{50} of 100nM or lower in respect of human CTPS1 enzyme.

Clause 13. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 10 to 12, wherein the IC_{50} of the CTPS1 inhibitor is established using the assay procedure set out in Example 1.

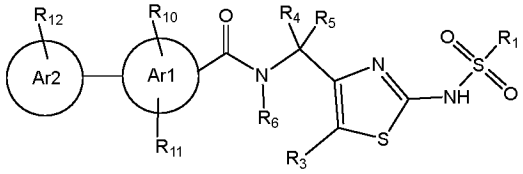
Clause 14. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 13, wherein the CTPS1 inhibitor has a selectivity for human CTPS1 over human CTPS2 of at least 2-fold.

Clause 15. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 14, wherein the CTPS1 inhibitor has a selectivity for human CTPS1 over human CTPS2 of at least 30-fold.

Clause 16. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 15, wherein the CTPS1 inhibitor has a selectivity for human CTPS1 over human CTPS2 of at least 60-fold, such as at least 1000-fold.

Clause 17. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 14 to 16, wherein the selectivity of the CTPS1 inhibitor is established using the assay procedure set out in Example 2.

Clause 18. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 17, wherein the CTPS1 inhibitor is a compound of formula (I)



(I)

wherein

R_1 is C_{1-5}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, C_{1-3}alkyleneOC_{1-2}alkyl, or CF_3;

R_3 is H, CH_3, halo, OC_{1-2}alkyl or CF_3;

R_4 and R_5 are each independently H, C_{1-6}alkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, C_{1-6}alkylOH or C_{1-6}haloalkyl,

or R_4 and R_5 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl ring;

R_6 is H or C_{1-3}alkyl;

Ar1 is a 6-membered aryl or heteroaryl;

Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to the amide;

R_{10} is H, halo, C_{1-3}alkyl, OC_{1-2}alkyl, C_{1-2}haloalkyl, OC_{1-2}haloalkyl or CN;

R_{11} is H, F, Cl, CH_3, ethyl, OCH_3, CF_3, OCF_3 or CN;

R_{12} is attached to Ar2 in the meta or ortho position relative to Ar1 and R_{12} is H, halo, C_{1-4}alkyl, C_{2-4}alkynyl, $C(=O)C_{1-2}$alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, C_{1-3}alkyleneOC_{1-3}alkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, CN, OC_{0-2}alkyleneC_{3-5}cycloalkyl, $OCH_2CH_2N(CH_3)_2$, OH, C_{1-4}alkylOH, $NR_{23}R_{24}$, SO_2CH_3, $C(O)N(CH_3)_2$, $NHC(O)C_{1-3}$alkyl, or a C_{3-6}heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2, or R_{12} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

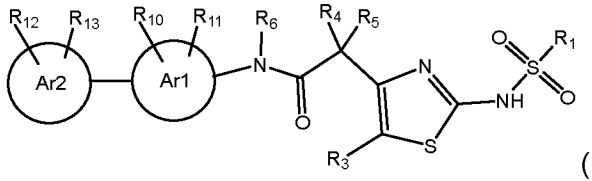
R_{23} is H or C_{1-2}alkyl;

R_{24} is H or C_{1-2}alkyl;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 19. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 18, wherein the CTPS1 inhibitor is selected from the compounds disclosed in List A or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 20. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 17, wherein the CTPS1 inhibitor is a compound of formula (II):



(II)

wherein

R_1 is C_{1-5}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, C_{1-3}alkyleneOC_{1-2}alkyl, or CF_3;

R_3 is H, halo, CH_3, OC_{1-2}alkyl or CF_3;

or R_3 together with R_5 forms a 5- or 6-membered cycloalkyl or 5 or 6 membered oxygen-containing heterocycloalkyl;

R_4 and R_5 are each independently H, halo, C_{1-6}alkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-6}alkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, C_{1-6}alkylOH, C_{1-6}haloalkyl, OC_{1-6}haloalkyl or $NR_{21}R_{22}$,

or R_4 is H and R_5 together with R_3 form a 5- or 6-membered cycloalkyl or 5 or 6 membered oxygen-containing heterocycloalkyl,

or R_4 and R_5 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl,

or R_4 is H and R_5 and R_6 are a C_{2-3}alkylene chain forming a 5- or 6-membered ring;

or R_4 is O and R_5 is absent;

R_6 is H or C_{1-3}alkyl,

or R_6 together with R_{11} when in the ortho-position to the amide are a C_2alkylene chain forming a 5-membered ring,

or R_5 and R_6 are a C_{2-3}alkylene chain forming a 5- or 6-membered ring and R_4 is H;

Ar1 is 6-membered aryl or heteroaryl;

Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to the amide;

R_{10} is H, halo, C_{1-3}alkyl, OC_{1-2}alkyl, C_{1-2}haloalkyl, OC_{1-2}haloalkyl or CN;

R_{11} is H, F, Cl, CH_3, ethyl, OCH_3, CF_3, OCF_3 or CN,

or R_{11}, when in the ortho-position to the amide, together with R_6 are a C_2alkylene chain forming a 5-membered ring;

R_{12} is attached to Ar2 in the ortho or meta position relative to Ar1 and R_{12} is H, halo, C_{1-4}alkyl, C_{2-4}alkynyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, OC_{0-2}alkyleneC_{3-5}cycloalkyl, $OCH_2CH_2N(CH_3)_2$, OH, C_{1-4}alkylOH, CN, C_{1-3}alkyleneOC_{1-3}alkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, $C(=O)C_{1-2}$alkyl, $NR_{23}R_{24}$, SO_2C_{1-4}alkyl, SOC_{1-4}alkyl, SC_{1-4}alkyl, SH, $C(O)N(CH_3)_2$, $NHC(O)C_{1-3}$alkyl, C_{3-6}heterocycloalkyl comprising one nitrogen located at

the point of attachment to Ar2, or R_{12} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

R_{13} is H, halo, CH_3 or OCH_3;

R_{21} is H, C_{1-5}alkyl, $C(O)C_{1-5}$alkyl, $C(O)OC_{1-5}$alkyl;

R_{22} is H or CH_3;

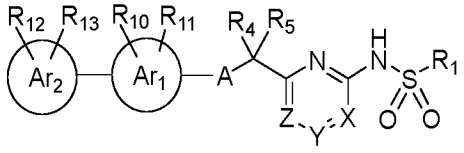
R_{23} is H or C_{1-2}alkyl; and

R_{24} is H or C_{1-2}alkyl;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 21. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 20, wherein the CTPS1 inhibitor is selected from the compounds disclosed in List B or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 22. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 17, wherein the CTPS1 inhibitor is a compound of formula (III):



(III)

wherein

A is an amide linker having the following structure: -C(=O)NH- or -NHC(=O)-;

X is N or CH;

Y is N or CR_2;

Z is N or CR_3;

with the proviso that when at least one of X or Z is N, Y cannot be N;

R_1 is C_{1-5}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, or CF_3;

R_2 is H, halo, C_{1-2}alkyl, OC_{1-2}alkyl, C_{1-2}haloalkyl or OC_{1-2}haloalkyl;

R_3 is H, halo, CH_3, OCH_3, CF_3 or OCF_3;

wherein at least one of R_2 and R_3 is H;

R_4 and R_5 are each independently H, C_{1-6}alkyl, C_{1-6}alkylOH, C_{1-6}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, or R_4 and R_5 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl; and

when A is -NHC(=O)-:

R_4 and R_5 may additionally be selected from halo, OC_{1-6}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-6}alkyl and $NR_{21}R_{22}$;

Ar1 is a 6-membered aryl or heteroaryl;

Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to the amide;

R_{10} is H, halo, C_{1-3}alkyl, C_{1-2}haloalkyl, OC_{1-2}alkyl, OC_{1-2}haloalkyl or CN;

R_{11} is H, F, Cl, C_{1-2}alkyl, CF_3, OCH_3 or CN;

R_{12} is attached to Ar2 in the ortho or meta position relative to Ar1 and R_{12} is H, halo, C_{1-4}alkyl, C_{2-4}alkenyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, OC_{0-2}alkyleneC_{3-5}cycloalkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, hydroxy, C_{1-4}alkylOH, SO_2C_{1-2}alkyl, $C(O)N(C_{1-2}alkyl)_2$, $NHC(O)C_{1-3}$alkyl or $NR_{23}R_{24}$; and

when A is -NHC(=O)-:

R_{12} may additionally be selected from CN, $OCH_2CH_2N(CH_3)_2$ and a C_{3-6}heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2, or R_{12} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

R_{13} is H or halo;

R_{21} is H, C_{1-5}alkyl, $C(O)C_{1-5}$alkyl, $C(O)OC_{1-5}$alkyl;

R_{22} is H or CH_3;

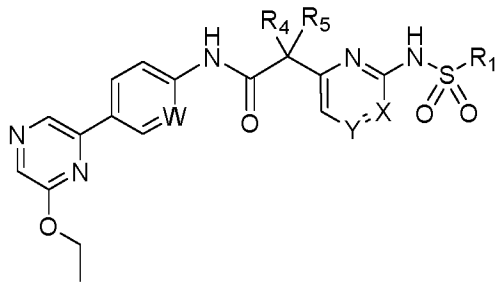
R_{23} is H or C_{1-2}alkyl; and

R_{24} is H or C_{1-2}alkyl;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 23. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 22, wherein the CTPS1 inhibitor is selected from the compounds disclosed in List C or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

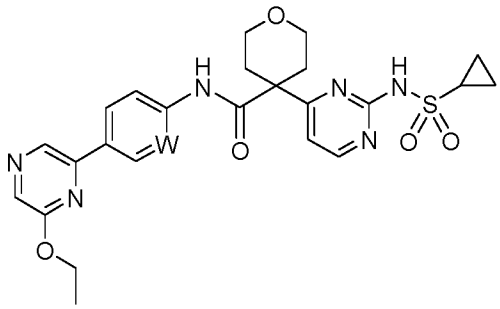
Clause 24. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 22, wherein the CTPS1 inhibitor is a compound of formula (IV):



(IV)

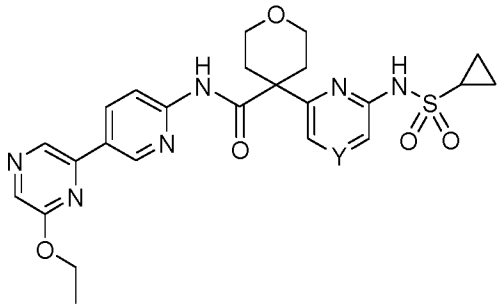
wherein:

(a) when R_4, R_5, X, Y and R_1 are as follows:



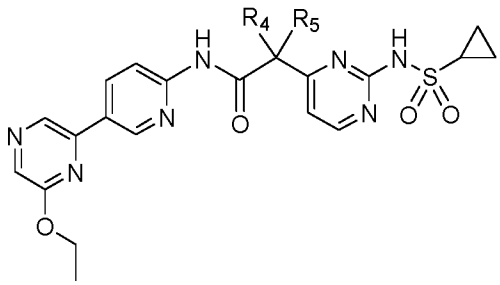
then W is N, CH or CF;

(b) when R_4, R_5, X, W and R_1 are as follows:

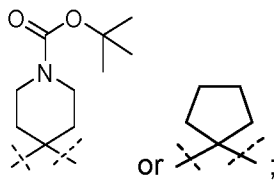


then Y is CH or N;

(c) when W, X, Y and R_1 are as follows:

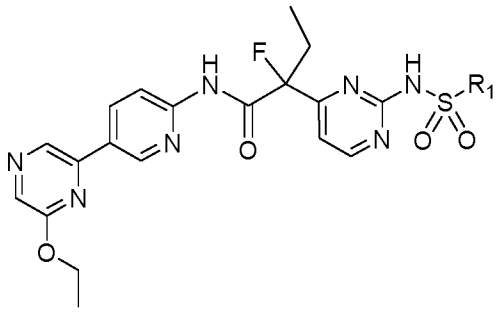


then R_4 and R_5 are joined to form the following structures:



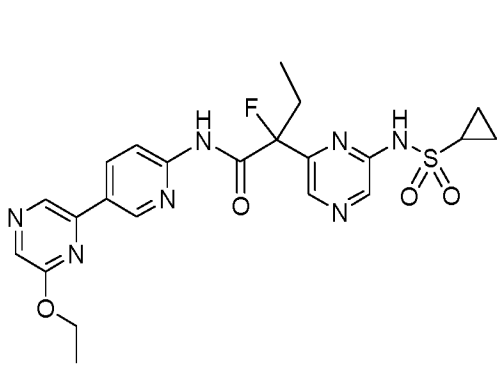
;

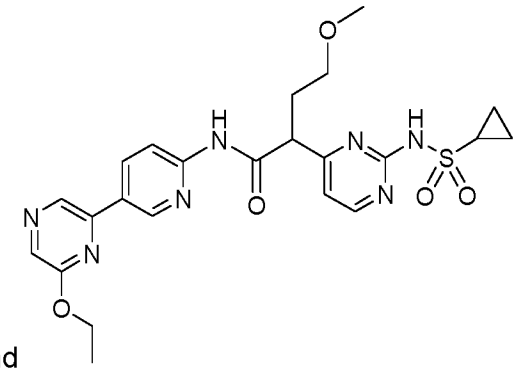
(d) when W, R_4, R_5, X and Y are as follows:



then R_1 is methyl or cyclopropyl; and

(e) the compound is selected from the group consisting of:



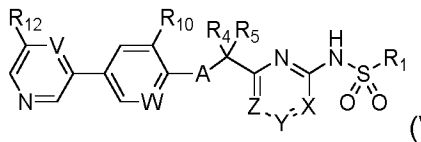


and

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

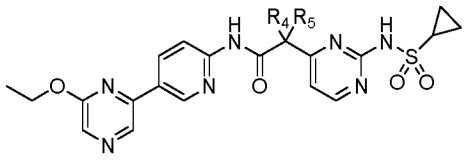
Clause 25. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 24, wherein the CTPS1 inhibitor is selected from the compounds disclosed in List D or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 26. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 22, wherein the CTPS1 inhibitor is a compound of formula (V):



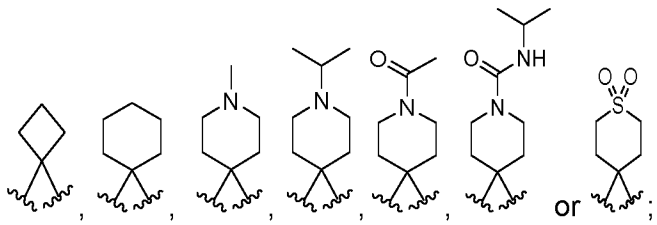
(V)

(a) when A, V, W, X, Y, Z, R_1, R_{10} and R_{12} are as follows:



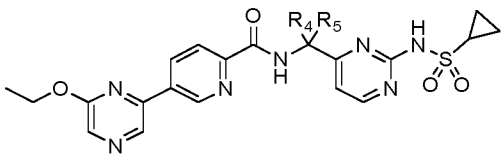
,

then R_4 and R_5 together with the carbon atom to which they attached form:



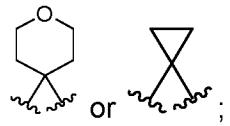
or

(b) when A, V, W, X, Y, Z, R_1, R_{10} and R_{12} are as follows:



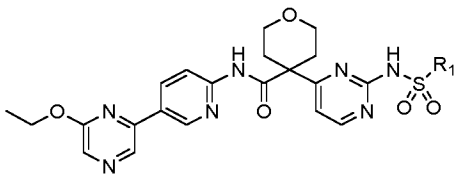
,

then R_4 and R_5 together with the carbon atom to which they are attached form:

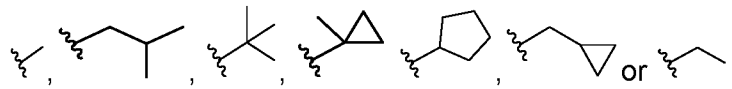


or

(c) when A, V, W, X, Y, Z, R_4, R_5, R_{10} and R_{12} are as follows:

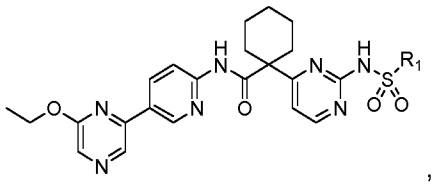


:

then R_1 is  ;

or

(d) when A, V, W, X, Y, Z, R_4, R_5, R_{10} and R_{12} are as follows:

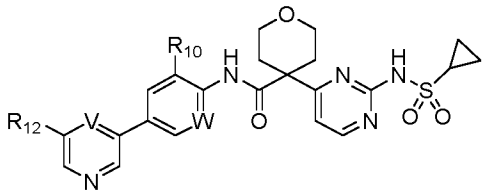


,

then R_1 is  ;

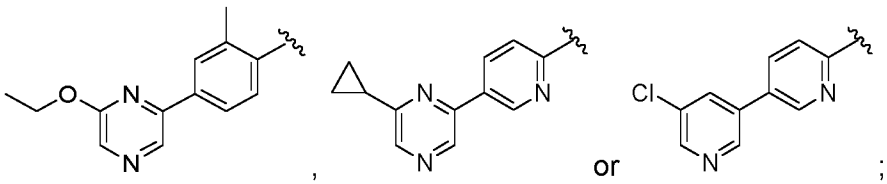
or

(e) when A, X, Y, Z, R_1, R_4 and R_5 are as follows:



,

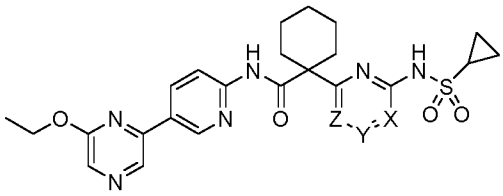
then V, W, R_{10} and R_{12} are:



;

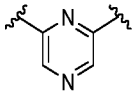
or

(f) when A, V, W, R_1, R_4, R_5, R_{10} and R_{12} are as follows:



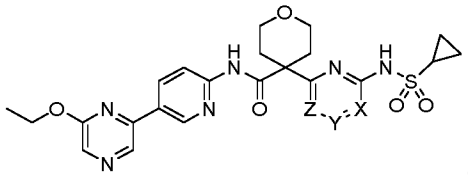
,

then Z, X and Y are

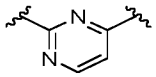

;

or

(g) when A, V, W, R_1, R_4, R_5, R_{10} and R_{12} are as follows:

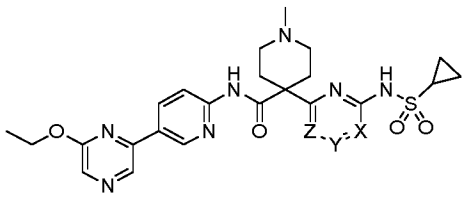

,

then Z, X and Y are

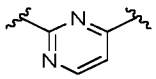

;

or

(h) when A, V, W, R_1, R_4, R_5, R_{10} and R_{12} are as follows



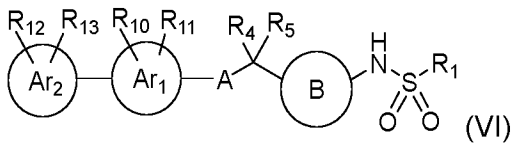
then Z, X and Y are


;

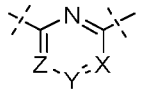
or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 27. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 26, wherein the CTPS1 inhibitor is selected from the compounds disclosed in List E or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

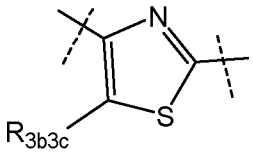
Clause 28. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 17, wherein the CTPS1 inhibitor is a compound of formula (VI):


(VI)

wherein ring B is selected from the group consisting of:


(B-a)

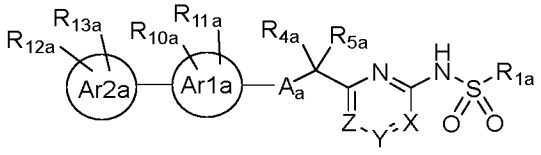
wherein X, Y and Z are as defined below; and



(B-bc);

wherein R_{3b3c} is R_{3b} or R_{3c} as defined below;

wherein when B is (B-a) the compound of formula (VI) is a compound of formula (VI-a):



(VI-a)

wherein:

A_a is A_{aa} or A_{ba};

wherein:

A_{aa} is an amine linker having the following structure: -NH-, -CH_2NH- or -NHCH_2-;

A_{ba} is an amide linker having the following structure: -C(=O)NH- or -NHC(=O)-;

X is N or CH;

Y is N or CR_{2a};

Z is N or CR_{3a};

with the proviso that when at least one of X or Z is N, Y cannot be N;

R_{2a} is H, halo, C_{1-2}alkyl, OC_{1-2}alkyl, C_{1-2}haloalkyl or OC_{1-2}haloalkyl; and

R_{3a} is H, halo, CH_3, OCH_3, CF_3 or OCF_3;

wherein at least one of R_{2a} and R_{3a} is H;

R_{1a} is R_{1aa} or R_{1ba};

wherein:

R_{1aa} is $NR_{32a}R_{33a}$;

R_{1ba} is C_{1-5}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, or CF_3;

R_{4a} and R_{5a} are R_{4aa} and R_{5aa}, or R_{4ba} and R_{5ba};

wherein:

R_{4aa} and R_{5aa} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl which is:

substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl, oxo, OH, C_{1-3}alkylOH, C_{1-3}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, halo, OC_{1-3}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-3}alkyl and $NR_{21a}R_{22a}$; or

one of the carbons of the C_{3-6}cycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}cycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}cycloalkyl formed by R_{4aa} and R_{5aa} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4aa} and R_{5aa} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl wherein one of the carbons of the C_{3-6}heterocycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}heterocycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}heterocycloalkyl formed by R_{4aa} and R_{5aa} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4aa} and R_{5aa} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl comprising one nitrogen atom, wherein said nitrogen atom is substituted by $-S(O)_2R_{29a}$; or

R_{4ba} and R_{5ba} are each independently H, C_{1-6}alkyl, C_{1-6}alkylOH, C_{1-6}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, or R_{4ba} and R_{5ba} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl; and

when A_a is -NHC(=O)- or $-NHCH_2$-:

R_{4ba} and R_{5ba} may additionally be selected from halo, OC_{1-6}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-6}alkyl and $NR_{21a}R_{22a}$;

Ar1a is a 6-membered aryl or heteroaryl;

Ar2a is a 6-membered aryl or heteroaryl and is attached to Ar1a in the para position relative to group A_a;

R_{10a} is H, halo, C_{1-3}alkyl, C_{1-2}haloalkyl, OC_{1-2}alkyl, OC_{1-2}haloalkyl or CN;

R_{11a} is H, F, Cl, C_{1-2}alkyl, CF_3, OCH_3 or CN;

R_{12a} is attached to Ar2 in the ortho or meta position relative to Ar1a and R_{12a} is H, halo, C_{1-4}alkyl, C_{2-4}alkenyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, OC_{0-2}alkyleneC_{3-5}cycloalkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, hydroxy, C_{1-4}alkylOH, SO_2C_{1-2}alkyl, $C(O)N(C_{1-2}alkyl)_2$, $NHC(O)C_{1-3}$alkyl or $NR_{23a}R_{24a}$; and

when A_a is -NHC(=O)-, -NH- or $-NHCH_2$-:

R_{12a} may additionally be selected from CN, $OCH_2CH_2N(CH_3)_2$ and a C_{3-6}heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2a, or R_{12a} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

R_{13a} is H or halo;

R_{21a} is H, C_{1-5}alkyl, $C(O)C_{1-5}$alkyl, $C(O)OC_{1-5}$alkyl, C_{1-3}alkylOC_{1-2}alkyl, C_{1-4}haloalkyl, or C_{4-6}heterocycloalkyl;

R_{22a} is H or CH_3;

R_{23a} is H or C_{1-2}alkyl; and

R_{24a} is H or C_{1-2}alkyl

R_{29a} is C_{1-3}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, CF_3, $N(C_{1-3}alkyl)_2$, or a 5 or 6 membered heteroaryl wherein the 5 or 6 membered heteroaryl is optionally substituted by methyl;

R_{32a} is C_{1-3}alkyl and R_{33} is C_{1-3}alkyl; or

R_{32a} and R_{33a} together with the nitrogen atom to which they are attached form a C_{3-5}heterocycloalkyl;

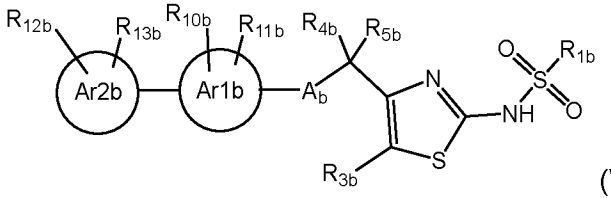
wherein

R_{1a} is R_{1aa}; and/or

R_{4a} and R_{5a} are R_{4aa} and R_{5aa}; and/or

A_a is A_{aa}; and

wherein when B is (B-bc) and R_{3b3c} is R_{3b}, the compound of formula (VI) is a compound of formula (VI-b):



(VI-b)

wherein:

A_b is A_{ab} or A_{bb};

wherein:

A_{ab} is $-NR_{6b}CH_2-$ or $-NR_{6b}-$;

A_{bb} is $-NR_{6b}C(=O)-$;

R_{1b} is R_{1ab} or R_{1bb};

wherein:

R_{1ab} is $NR_{32b}R_{33b}$;

R_{1bb} is C_{1-5}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, C_{1-3}alkyleneOC_{1-2}alkyl, or CF_3;

R_{3b} is H, halo, CH_3, OC_{1-2}alkyl or CF_3;

or R_{3b} together with R_{5bb} forms a 5- or 6-membered cycloalkyl or 5 or 6 membered oxygen-containing heterocycloalkyl;

R_{4b} and R_{5b} are either R_{4ab} and R_{5ab} or R_{4bb} and R_{5bb};

wherein:

R_{4ab} and R_{5ab} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl which is:

substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl, oxo, OH, C_{1-3}alkylOH, C_{1-3}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, halo, OC_{1-3}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-3}alkyl and $NR_{21b}R_{22b}$; or

one of the carbons of the C_{3-6}cycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}cycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}cycloalkyl formed by R_{4ab} and R_{5ab} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4ab} and R_{5ab} together with the carbon atom to which they are attached form a C_{3-6}heteroycloalkyl wherein one of the carbons of the C_{3-6}heterocycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}cheterocycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}heteroycloalkyl formed by R_{4ab} and R_{5ab} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4ab} and R_{5ab} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl comprising one nitrogen atom, wherein said nitrogen atom is substituted by $-S(O)_2R_{29b}$; or

R_{4bb} and R_{5bb} are each independently H, halo, C_{1-6}alkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-6}alkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, C_{1-6}alkylOH, C_{1-6}haloalkyl, OC_{1-6}haloalkyl or $NR_{21b}R_{22b}$,

or R_{4bb} is H and R_{5bb} together with R_{3b} form a 5- or 6-membered cycloalkyl or 5 or 6 membered oxygen-containing heterocycloalkyl,

or R_{4bb} and R_{5bb} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl,

or R_{4bb} is H and R_{5bb} and R_{6b} are a C_{2-3}alkylene chain forming a 5- or 6-membered ring;

or R_{4bb} is O and R_{5bb} is absent;

R_{6b} is H or C_{1-3}alkyl,

or R_{6b} together with R_{11b} when in the ortho-position to group A_b are a C_2alkylene chain forming a 5-membered ring,

or R_{5bb} and R_{6b} are a C_{2-3}alkylene chain forming a 5- or 6-membered ring and R_{4bb} is H;

Ar1b is 6-membered aryl or heteroaryl;

Ar2b is a 6-membered aryl or heteroaryl and is attached to Ar1b in the para position relative to group A_b;

R_{10b} is H, halo, C_{1-3}alkyl, OC_{1-2}alkyl, C_{1-2}haloalkyl, OC_{1-2}haloalkyl or CN;

R_{11b} is H, F, Cl, CH_3, ethyl, OCH_3, CF_3, OCF_3 or CN,

or R_{11b}, when in the ortho-position to group A_b, together with R_{6b} are a C_2alkylene chain forming a 5-membered ring;

R_{12b} is attached to Ar2b in the ortho or meta position relative to Ar1b and R_{12b} is H, halo, C_{1-4}alkyl, C_{2-4}alkynyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, OC_{0-2}alkyleneC_{3-5}cycloalkyl, $OCH_2CH_2N(CH_3)_2$, OH, C_{1-4}alkylOH, CN, C_{1-3}alkyleneOC_{1-3}alkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, $C(=O)C_{1-2}$alkyl, $NR_{23b}R_{24b}$, SO_2C_{1-4}alkyl, SOC_{1-4}alkyl, SC_{1-4}alkyl, SH, $C(O)N(CH_3)_2$, $NHC(O)C_{1-3}$alkyl, C_{3-6}heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2b, or R_{12b} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

R_{13b} is H, halo, CH_3 or OCH_3;

R_{21b} is H, C_{1-5}alkyl, $C(O)C_{1-5}$alkyl, $C(O)OC_{1-5}$alkyl, C_{1-3}alkylOC_{1-2}alkyl, C_{1-4}haloalkyl, or C_{4-6}heterocycloalkyl;

R_{22b} is H or CH_3;

R_{23b} is H or C_{1-2}alkyl;

R_{24b} is H or C_{1-2}alkyl;

R_{29b} is C_{1-3}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, CF_3, $N(C_{1-3}alkyl)_2$, or a 5 or 6 membered heteroaryl wherein the 5 or 6 membered heteroaryl is optionally substituted by methyl; and

R_{32b} is C_{1-3}alkyl and R_{33b} is C_{1-3}alkyl; or

R_{32b} and R_{33b} together with the nitrogen atom to which they are attached form a C_{3-5}heterocycloalkyl;

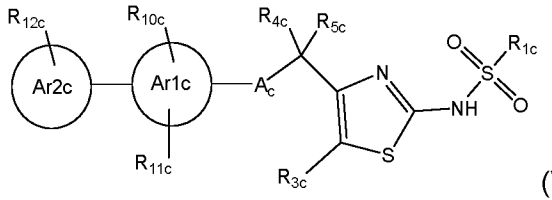
wherein:

R_{1b} is R_{1ab}; and/or

R_{4b} and R_{5b} are R_{4ab} and R_{5ab}; and/or

A is A_{ab}; or

wherein when B is (B-bc) and R_{3b3c} is R_{3c}, the compound of formula (VI) is a compound of formula (VI-c):



(VI-c)

wherein:

A_c is A_{ac} or A_{bc};

wherein:

A_{ac} is $-CH_2NR_{6c}-$;

A_{bc} is $-C(=O)NR_{6c}-$;

R_{1c} is R_{1ac} or R_{1bc};

wherein:

R_{1ac} is $NR_{32c}R_{33c}$;

R_{1bc} is C_{1-5}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, C_{1-3}alkyleneOC_{1-2}alkyl, or CF_3;

R_{3c} is H, CH_3, halo, OC_{1-2}alkyl or CF_3;

R_{4c} and R_{5c} are either R_{4ac} and R_{5ac} or R_{4bc} and R_{5bc};

wherein:

R_{4ac} and R_{5ac} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl which is:

substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl, oxo, OH, C_{1-3}alkylOH, C_{1-3}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, halo, OC_{1-3}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-3}alkyl and $NR_{21c}R_{22c}$; or

one of the carbons of the C_{3-6}cycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}cycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}cycloalkyl formed by R_{4ac} and R_{5ac} together with the carbon atom to which they are attached may be substituted by one or two substituents, each

substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4ac} and R_{5ac} together with the carbon atom to which they are attached form a C_{3-6}heteroycloalkyl wherein one of the carbons of the C_{3-6}heterocycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}cheterocycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}heteroycloalkyl formed by R_{4ac} and R_{5ac} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4ac} and R_{5ac} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl comprising one nitrogen atom, wherein said nitrogen atom is substituted by $-S(O)_2R_{29c}$; or

R_{4bc} and R_{5bc} are each independently H, C_{1-6}alkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, C_{1-6}alkylOH or C_{1-6}haloalkyl, or R_{4bc} and R_{5bc} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl ring;

R_{6c} is H or C_{1-3}alkyl;

Ar1c is a 6-membered aryl or heteroaryl;

Ar2c is a 6-membered aryl or heteroaryl and is attached to Ar1c in the para position relative to group A_c;

R_{10c} is H, halo, C_{1-3}alkyl, OC_{1-2}alkyl, C_{1-2}haloalkyl, OC_{1-2}haloalkyl or CN;

R_{11c} is H, F, Cl, CH_3, ethyl, OCH_3, CF_3, OCF_3 or CN;

R_{12c} is attached to Ar2c in the meta or ortho position relative to Ar1c and R_{12c} is H, halo, C_{1-4}alkyl, C_{2-4}alkynyl, $C(=O)C_{1-2}$alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, C_{1-3}alkyleneOC_{1-3}alkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, CN, OC_{0-2}alkyleneC_{3-5}cycloalkyl, $OCH_2CH_2N(CH_3)_2$, OH, C_{1-4}alkylOH, $NR_{23c}R_{24c}$, SO_2CH_3, $C(O)N(CH_3)_2$, $NHC(O)C_{1-3}$alkyl, or a C_{3-6}heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2c, or R_{12c} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

R_{21c} is H, C_{1-5}alkyl, $C(O)C_{1-5}$alkyl, $C(O)OC_{1-5}$alkyl, C_{1-3}alkylOC_{1-2}alkyl, C_{1-4}haloalkyl, or C_{4-6}heterocycloalkyl;

R_{22c} is H or CH_3;

R_{23c} is H or C_{1-2}alkyl;

R_{24c} is H or C_{1-2}alkyl;

R_{29c} is C_{1-3}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, CF_3, $N(C_{1-3}alkyl)_2$, or a 5 or 6 membered heteroaryl wherein the 5 or 6 membered heteroaryl is optionally substituted by methyl; and

R_{32c} is C_{1-3}alkyl and R_{33c} is C_{1-3}alkyl; or

R_{32c} and R_{33c} together with the nitrogen atom to which they are attached form a C_{3-5}heterocycloalkyl;

wherein:

R_{1c} is R_{1ac}; and/or

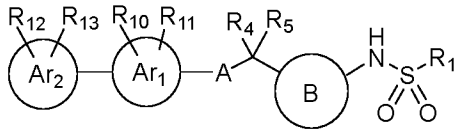
R_{4c} and R_{5c} are R_{4ac} and R_{5ac}; and/or

A_c is A_{ac};

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 29. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 28, wherein the CTPS1 inhibitor is selected from the compounds disclosed in List F or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 30. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 17, wherein the CTPS1 inhibitor is a compound of formula (VII):



(VII)

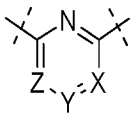
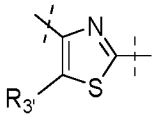
wherein

A is A_a or A_b;

wherein

A_a is an amine linker having the following structure: -NH-, $-CH_2NH-$ or $-NHCH_2-$;

A_b is an amide linker having the following structure: -C(=O)NH- or -NHC(=O)-;

B is  or  ;

X is N or CH;

Y is N or CR_2;

Z is N or CR_3;

with the proviso that when at least one of X or Z is N, Y cannot be N;

R_1 is C_{1-5}fluoroalkyl, with the proviso that R_1 is not CF_3;

R_2 is H, halo, C_{1-2}alkyl, OC_{1-2}alkyl, C_{1-2}haloalkyl or OC_{1-2}haloalkyl;

R_3 is H, halo, CH_3, OCH_3, CF_3 or OCF_3;

wherein at least one of R_2 and R_3 is H;

$R_{3'}$ is H, halo, CH_3, OC_{1-2}alkyl or CF_3; and

when A is -NHC(=O)-, additionally $R_{3'}$ together with R_5 forms a 5- or 6-membered cycloalkyl or 5 or 6 membered oxygen-containing heterocycloalkyl;

R_4 and R_5 are R_{4a} and R_{5a}, or R_{4b} and R_{5b};

wherein

R_{4a} and R_{5a} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl which is:

substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl, oxo, OH, C_{1-3}alkylOH, C_{1-3}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, halo, OC_{1-3}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-3}alkyl and $NR_{21}R_{22}$; or

one of the carbons of the C_{3-6}cycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}cycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}cycloalkyl formed by R_{4a} and R_{5a} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4a} and R_{5a} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl wherein one of the carbons of the C_{3-6}heterocycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}heterocycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}heterocycloalkyl formed by R_{4a} and R_{5a} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4a} and R_{5a} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl comprising one nitrogen atom, wherein said nitrogen atom is substituted by $-S(O)_2R_{29}$; or

R_{4b} and R_{5b} are each independently H, C_{1-6}alkyl, C_{1-6}alkylOH, C_{1-6}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, or R_{4b} and R_{5b} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl; and

when A is -NHC(=O)- or $-NHCH_2-$:

R_{4b} and R_{5b} may additionally be selected from halo, OC_{1-6}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-6}alkyl and $NR_{21}R_{22}$;

Ar1 is a 6-membered aryl or heteroaryl;

Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to group A;

R_{10} is H, halo, C_{1-3}alkyl, C_{1-2}haloalkyl, OC_{1-2}alkyl, OC_{1-2}haloalkyl or CN;

R_{11} is H, F, Cl, C_{1-2}alkyl, CF_3, OCH_3 or CN;

R_{12} is attached to Ar2 in the ortho or meta position relative to Ar1 and R_{12} is H, halo, C_{1-4}alkyl, C_{2-4}alkenyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, OC_{0-2}alkyleneC_{3-5}cycloalkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, hydroxy, C_{1-4}alkylOH, SO_2C_{1-2}alkyl, $C(O)N(C_{1-2}alkyl)_2$, $NHC(O)C_{1-3}$alkyl or $NR_{23}R_{24}$; and

when A is -NHC(=O)-, -NH- or $-NHCH_2-$:

R_{12} may additionally be selected from CN, $OCH_2CH_2N(CH_3)_2$ and a C_{3-6}heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2, or R_{12} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

R_{13} is H or halo;

R_{21} is H, C_{1-5}alkyl, $C(O)C_{1-5}$alkyl, $C(O)OC_{1-5}$alkyl;

R_{22} is H or CH_3;

R_{23} is H or C_{1-2}alkyl; and

R_{24} is H or C_{1-2}alkyl;

R_{29} is C_{1-3}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, or CF_3;

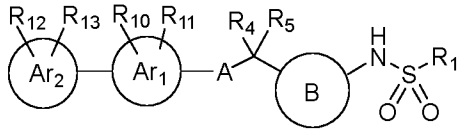
R_{32} is C_{1-3}alkyl and R_{33} is C_{1-3}alkyl; or

R_{32} and R_{33} together with the nitrogen atom to which they are attached form a C_{3-5}heterocycloalkyl;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 31. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 30, wherein the CTPS1 inhibitor is selected from the compounds disclosed in List G or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 32. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 17, wherein the CTPS1 inhibitor is compound of formula (VIII):



(VIII)

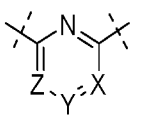
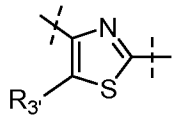
wherein

A is A_a or A_b;

wherein

A_a is an amine linker having the following structure: -NH-, -CH_2NH- or -NHCH_2-;

A_b is an amide linker having the following structure: -C(=O)NH- or -NHC(=O)-;

B is  or  ;

X is N or CH;

Y is N or CR_2;

Z is N or CR_3;

with the proviso that when at least one of X or Z is N, Y cannot be N;

R_1 is C_{1-5}alkyl or C_{0-2}alkyleneC_{3-5}cycloalkyl, which alkyl or (alkylene)cycloalkyl is substituted by CN;

R_2 is H, halo, C_{1-2}alkyl, OC_{1-2}alkyl, C_{1-2}haloalkyl or OC_{1-2}haloalkyl;

R_3 is H, halo, CH_3, OCH_3, CF_3 or OCF_3;

wherein at least one of R_2 and R_3 is H;

$R_{3'}$ is H, halo, CH_3, OC_{1-2}alkyl or CF_3; and

when A is -NHC(=O)-, additionally $R_{3'}$ together with R_5 forms a 5- or 6-membered cycloalkyl or 5 or 6 membered oxygen-containing heterocycloalkyl;

R_4 and R_5 are R_{4a} and R_{5a}, or R_{4b} and R_{5b};

wherein

R_{4a} and R_{5a} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl which is:

substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl, oxo, OH, C_{1-3}alkylOH, C_{1-3}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, halo, OC_{1-3}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-3}alkyl and $NR_{21}R_{22}$; or

one of the carbons of the C_{3-6}cycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}cycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}cycloalkyl formed by R_{4a} and R_{5a} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4a} and R_{5a} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl wherein one of the carbons of the C_{3-6}heterocycloalkyl is a spiro centre such that a spirocyclic ring system is formed by the C_{3-6}heterocycloalkyl ring and a further C_{3-6}cycloalkyl ring or a C_{3-6}heterocycloalkyl ring, and wherein the C_{3-6}heterocycloalkyl formed by R_{4a} and R_{5a} together with the carbon atom to which they are attached may be substituted by one or two substituents, each substituent being independently selected from the group consisting of C_{1-3}alkyl or OC_{1-3}alkyl; or

R_{4a} and R_{5a} together with the carbon atom to which they are attached form a C_{3-6}heterocycloalkyl comprising one nitrogen atom, wherein said nitrogen atom is substituted by $-S(O)_2R_{29}$; or

R_{4b} and R_{5b} are each independently H, C_{1-6}alkyl, C_{1-6}alkylOH, C_{1-6}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, or R_{4b} and R_{5b} together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl; and

when A is -NHC(=O)- or $-NHCH_2-$:

R_{4b} and R_{5b} may additionally be selected from halo, OC_{1-6}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-6}alkyl and $NR_{21}R_{22}$;

Ar1 is a 6-membered aryl or heteroaryl;

Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to group A;

R_{10} is H, halo, C_{1-3}alkyl, C_{1-2}haloalkyl, OC_{1-2}alkyl, OC_{1-2}haloalkyl or CN;

R_{11} is H, F, Cl, C_{1-2}alkyl, CF_3, OCH_3 or CN;

R_{12} is attached to Ar2 in the ortho or meta position relative to Ar1 and R_{12} is H, halo, C_{1-4}alkyl, C_{2-4}alkenyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, OC_{0-2}alkyleneC_{3-5}cycloalkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, hydroxy, C_{1-4}alkylOH, SO_2C_{1-2}alkyl, $C(O)N(C_{1-2}alkyl)_2$, $NHC(O)C_{1-3}$alkyl or $NR_{23}R_{24}$; and

when A is -NHC(=O)-, -NH- or $-NHCH_2-$:

R_{12} may additionally be selected from CN, $OCH_2CH_2N(CH_3)_2$ and a C_{3-6}heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2, or R_{12} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

R_{13} is H or halo;

R_{21} is H, C_{1-5}alkyl, $C(O)C_{1-5}$alkyl, $C(O)OC_{1-5}$alkyl;

R_{22} is H or CH_3;

R_{23} is H or C_{1-2}alkyl; and

R_{24} is H or C_{1-2}alkyl;

R_{29} is C_{1-3}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, or CF_3;

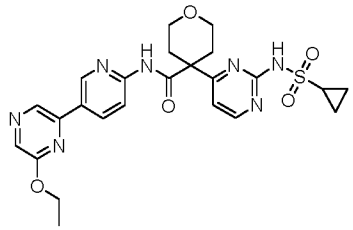
R_{32} is C_{1-3}alkyl and R_{33} is C_{1-3}alkyl; or

R_{32} and R_{33} together with the nitrogen atom to which they are attached form a C_{3-5}heterocycloalkyl;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 33. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 32, wherein the CTPS1 inhibitor is selected from the compounds disclosed in List H or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

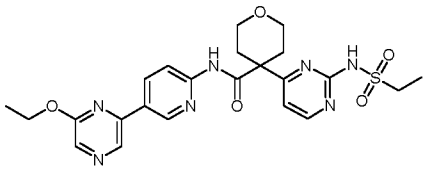
Clause 34. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 17, wherein the CTPS1 inhibitor is 4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide:



,

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 35. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 17, wherein the CTPS1 inhibitor is *N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(2-(ethylsulfonamido)pyrimidin-4-yl)tetrahydro-2*H*-pyran-4-carboxamide:



,

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

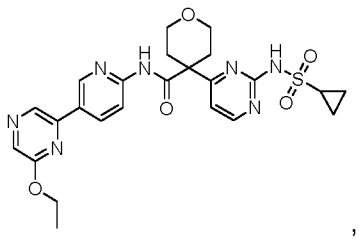
Clause 36. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 35, wherein the CTPS1 inhibitor is in its free form.

Clause 37. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 35, wherein the CTPS1 inhibitor is a pharmaceutically acceptable salt.

Clause 38. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 35, wherein the CTPS1 inhibitor is a pharmaceutically acceptable solvate.

Clause 39. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 35, wherein the CTPS1 inhibitor is a pharmaceutically acceptable salt and a pharmaceutically acceptable solvate.

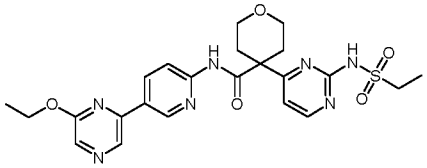
Clause 40. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 17, wherein the CTPS1 inhibitor is 4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide ('CTPS1-IA'):



,

or a pharmaceutically acceptable salt thereof.

Clause 41. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 17, wherein the CTPS1 inhibitor is *N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(2-(ethylsulfonamido)pyrimidin-4-yl)tetrahydro-2*H*-pyran-4-carboxamide ('CTPS1-IB'):



,

or a pharmaceutically acceptable salt thereof.

Clause 42. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 41, wherein the CTPS1 inhibitor is provided in a natural isotopic form.

Clause 43. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 42, wherein the WEE1 inhibitor has a Ki value for binding to human WEE1 of 50 nM or lower.

Clause 44. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 43, wherein the WEE1 inhibitor has a Ki value for binding to human WEE1 of 20 nM or lower.

Clause 45. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 44, wherein the WEE1 inhibitor has a Ki value for binding to human WEE1 of 10 nM or lower.

Clause 46. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 45, wherein the WEE1 inhibitor has a Ki value for binding to human WEE1 of 5 nM or lower.

Clause 47. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 46, wherein the WEE1 inhibitor has a Ki value for binding to human WEE1 of 1 nM or lower.

Clause 48. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 43 to 47, wherein the Ki value of the WEE1 inhibitor for binding to human WEE1 is established using the WEE1 kinase assay procedure set out in Example 3.

Clause 49. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 43 to 47, wherein the Ki value of the WEE1 inhibitor for binding to human WEE1 is established using the WEE1 CDC2 phosphorylation assay procedure set out in Example 3.

Clause 50. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 49, wherein the WEE1 inhibitor has a selectivity for human WEE1 over human CHEK1 of >2-fold.

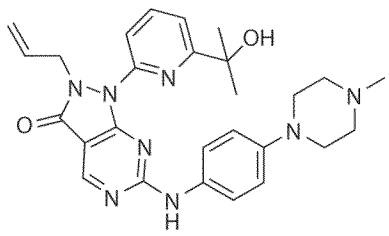
Clause 51. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 50, wherein the WEE1 inhibitor has a selectivity for human WEE1 over human CHEK1 of >5-fold.

Clause 52. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 51, wherein the WEE1 inhibitor has a selectivity for human WEE1 over human CHEK1 of >10-fold.

Clause 53. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 50 to 52, wherein the selectivity of the WEE1 inhibitor is established using the assay procedure set out in Example 4.

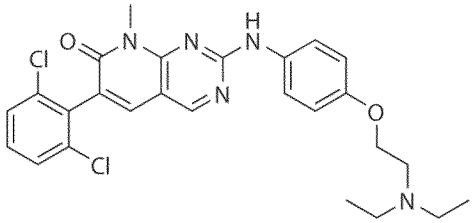
Clause 54. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 53, wherein the WEE1 inhibitor is selected from adavosertib, PD0166285, ZN-c3, WEE1-IN-3, WEE1-IN-4, PD 407824 and WEE1 Inhibitor II, pharmaceutically acceptable salts thereof and/or pharmaceutically acceptable solvates thereof.

Clause 55. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 54, wherein the WEE1 inhibitor is adavosertib:



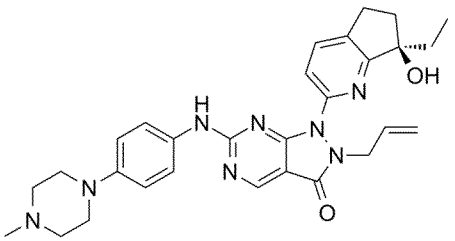
(1-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]-6-[4-(4-methylpiperazin-1-yl)anilino]-2-prop-2-enylpyrazolo[3,4-d]pyrimidin-3-one), a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof.

Clause 56. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 54, wherein the WEE1 inhibitor is PD0166285:



(6-(2,6-dichlorophenyl)-2-[4-[2-(diethylamino)ethoxy]anilino]-8-methylpyrido[2,3-d]pyrimidin-7-one), a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof.

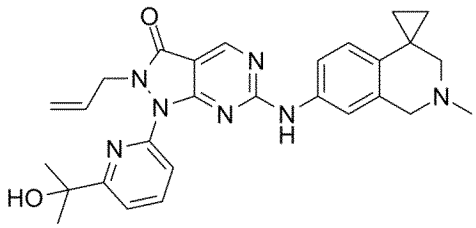
Clause 57. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 54, wherein the WEE1 inhibitor is ZN-c3:



,

a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof.

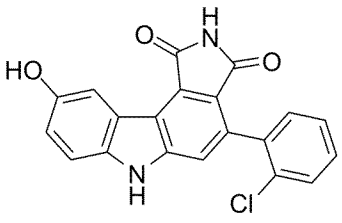
Clause 58. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 54, wherein the WEE1 inhibitor is WEE1-IN-3:



,

a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof.

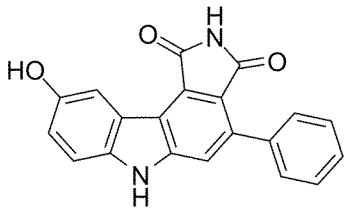
Clause 59. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 54, wherein the WEE1 inhibitor is WEE1-IN-4:



,

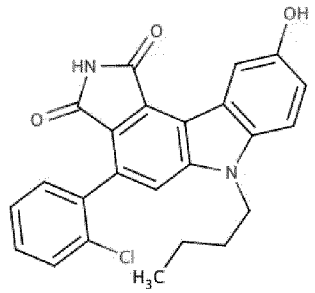
a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof.

Clause 60. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 54, wherein the WEE1 inhibitor is PD 407824:



(9-hydroxy-4-phenyl-6H-pyrrolo[3,4-c]carbazole-1,3-dione), a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof.

Clause 61. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 54, wherein the WEE1 inhibitor is WEE1 Inhibitor II:



(6-butyl-4-(2-chlorophenyl)-9-hydroxypyrrolo[3,4-c]carbazole-1,3-dione), a pharmaceutically acceptable salt and/or a pharmaceutically acceptable solvate thereof.

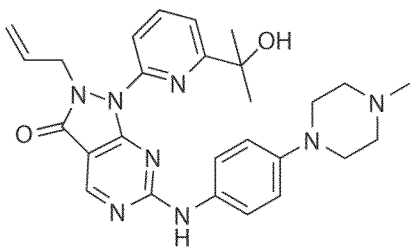
Clause 62. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 61, wherein the WEE1 inhibitor is in its free form.

Clause 63. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 61, wherein the WEE1 inhibitor is a pharmaceutically acceptable salt.

Clause 64. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 61, wherein the WEE1 inhibitor is a pharmaceutically acceptable solvate.

Clause 65. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 61, wherein the WEE1 inhibitor is a pharmaceutically acceptable salt and pharmaceutically acceptable solvate.

Clause 66. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 55, wherein the WEE1 inhibitor is adavosertib:



(1-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]-6-[4-(4-methylpiperazin-1-yl)anilino]-2-prop-2-enylpyrazolo[3,4-d]pyrimidin-3-one).

Clause 67. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 66, wherein the CTPS1 inhibitor is CTPS-IA or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof and the WEE1 inhibitor is adavosertib.

Clause 68. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 67, wherein the CTPS1 inhibitor is CTPS-IA or a pharmaceutically acceptable salt thereof and the WEE1 inhibitor is adavosertib.

Clause 69. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 68, wherein the WEE1 inhibitor is provided in a natural isotopic form.

Clause 70. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 69 wherein the CTPS1 inhibitor and the WEE1 inhibitor act synergistically in treating the cancer.

Clause 71. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according clause 70 wherein the combined administration of the CTPS1 inhibitor and the WEE1 inhibitor results in a beneficial effect greater than the sum of the beneficial effects of each agent administered alone.

Clause 72. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to either clause 70 or 71 wherein the CTPS1 inhibitor and the WEE1 inhibitor achieve a Bliss score (Bliss 1939; Zheng 2021) of ≥10 when applied to a cancer cell line as set out in Example 6.

Clause 73. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 72, wherein the WEE1 inhibitor and the CTPS1 inhibitor are administered to a mammal.

Clause 74. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 73, wherein the WEE1 inhibitor and the CTPS1 inhibitor are administered to a human.

Clause 75. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 74, wherein the CTPS1 inhibitor and the WEE1 inhibitor are separately formulated.

Clause 76. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 75, wherein the CTPS1 inhibitor and the WEE1 inhibitor are administered separately.

Clause 77. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 75, wherein the CTPS1 inhibitor and the WEE1 inhibitor are administered simultaneously.

Clause 78. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 77, wherein the CTPS1 inhibitor and the WEE1 inhibitor are co-formulated.

Clause 79. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 78, wherein the CTPS1 inhibitor is administered by oral, parenteral, buccal, sublingual, nasal or rectal administration.

Clause 80. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 79, wherein the CTPS1 inhibitor is administered orally.

Clause 81. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 80, wherein the WEE1 inhibitor is administered by oral, parenteral, buccal, sublingual, nasal or rectal administration.

Clause 82. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 81, wherein the WEE1 inhibitor is administered orally.

Clause 83. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 82, wherein the CTPS1 inhibitor and WEE1 inhibitor are administered separately, sequentially or simultaneously with one or more further pharmaceutically acceptable active ingredients.

Clause 84. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 83, wherein the one or more further pharmaceutically acceptable active ingredients are selected from tyrosine kinase inhibitors such as, for example, axitinib, dasatinib, erlotinib, imatinib, nilotinib, pazopanib and sunitinib.

Clause 85. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 83, wherein the one or more further pharmaceutically acceptable active ingredients are selected from zacitidine, decitabine, or cytarabine.

Clause 86. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 83, wherein the one or more further pharmaceutically acceptable active ingredients are selected from anticancer antibodies, such as those selected from the group consisting of anti-CD20 antibodies (such as obinutuzumab, ofatumumab, tositumomab or rituximab) or other antibodies such as olaratumab, daratumumab, necitumumab, dinutuximab, traztuzumab emtansine, pertuzumab, brentuximab, panitumumab, catumaxomab, bevacizumab, cetuximab, traztuzumab and gentuzumab ozogamycin.

Clause 87. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 86, administered in combination with radiotherapy.

Clause 88. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 87, administered in combination with surgery.

Clause 89. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 88, administered in combination with hyperthermia therapy.

Clause 90. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 89, administered in combination with cryotherapy.

Clause 91. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 90, wherein the cancer is a cancer displaying high replicative stress.

Clause 92. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 91, wherein the cancer constitutively expresses c-myc.

Clause 93. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 92, wherein the cancer is a non-haematological cancer.

Clause 94. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 93, wherein the cancer is selected from the group consisting of colorectal cancer, bile duct cancer, endometrial cancer, hepatic cancer, gastric cancer, oesophageal cancer, sarcoma, bladder cancer, pancreatic cancer, ovarian cancer, lung cancer, mesothelioma, melanoma, bone cancer, head and neck cancer, breast cancer, brain cancers, prostate cancer, renal cancer, thyroid cancer and neuroblastoma.

Clause 95. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 94, wherein the cancer is selected from the group consisting of colorectal cancer, bile duct cancer, endometrial cancer, hepatic cancer, gastric cancer, oesophageal cancer, sarcoma, bladder cancer, pancreatic cancer, ovarian cancer, lung cancer, mesothelioma and melanoma.

Clause 96. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 95, wherein the cancer is selected from the group consisting of colorectal cancer, bile duct cancer, endometrial cancer, hepatic cancer, gastric cancer and oesophageal cancer.

Clause 97. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 96, wherein the cancer is a solid tumour.

Clause 98. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 93 or 97, wherein the cancer is a non-haematological cancer is selected from prostate cancer, pancreatic cancer, ovarian cancer, lung cancer, renal cancer, colorectal cancer or breast cancer, especially prostate cancer, pancreatic cancer, ovarian cancer, renal cancer, colorectal cancer or breast cancer.

Clause 99. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 92, wherein the cancer is a haematological cancer.

Clause 100. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 99, wherein the haematological cancer is selected from the list consisting of acute myeloid leukemia, angioimmunoblastic T-cell lymphoma, B-cell acute lymphoblastic leukemia, Sweet syndrome, T-cell non-Hodgkin lymphoma (including natural killer/T-cell lymphoma, adult T-cell leukaemia/lymphoma, enteropathy type T-cell lymphoma, hepatosplenic T-cell lymphoma and cutaneous T-cell lymphoma), T-cell acute lymphoblastic leukemia, B-cell non-Hodgkin lymphoma (including Burkitt lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma), hairy cell leukemia, Hodgkin lymphoma, lymphoblastic lymphoma, lymphoplasmacytic lymphoma, mucosa-associated lymphoid tissue lymphoma, multiple myeloma, myelodysplastic syndrome, plasma cell myeloma, primary mediastinal large B-cell lymphoma, chronic myeloproliferative disorders (such as chronic myeloid leukemia, primary myelofibrosis, essential thrombocythemia, polycythemia vera) or chronic lymphocytic leukemia.

Clause 101. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 100, wherein the haematological cancer is selected from the list consisting of B-cell non-Hodgkin lymphoma (including Burkitt lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma), multiple myeloma and plasma cell leukaemia.

Clause 102. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 101, wherein the haematological cancer is selected from the list consisting of T cell lymphoma, diffuse large B cell lymphoma, plasma cell myeloma, acute myeloid leukaemia, chronic lymphocytic leukaemia or peripheral T cell lymphoma

Clause 103. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 102, wherein the haematological cancer is T cell lymphoma.

Clause 104. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 102, wherein the haematological cancer is diffuse large B cell lymphoma.

Clause 105. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 102, wherein the haematological cancer is plasma cell myeloma.

Clause 106. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 102, wherein the haematological cancer is acute myeloid leukaemia.

Clause 107. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 102, wherein the haematological cancer is chronic lymphocytic leukaemia.

Clause 108. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 102, wherein the haematological cancer is peripheral T cell lymphoma.

Clause 109. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 99, wherein the haematological cancer is T-cell prolymphocytic leukemia.

Clause 110. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 109, for administration to a subject identified as having a cancer expected to be susceptible to treatment by a CTPS1 inhibitor and a WEE1 inhibitor.

Clause 111. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 109, for administration to a subject from whom a sample of cancer cells has been shown to be susceptible to treatment by a CTPS1 inhibitor and a WEE1 inhibitor.

Clause 112. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 111, wherein the CTPS1 inhibitor and WEE1 inhibitor are administered orally.

Clause 113. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 112, wherein the CTPS1 inhibitor is in a solid pharmaceutical composition.

Clause 114. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 113, wherein the WEE1 inhibitor is in a solid pharmaceutical composition.

Clause 115. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 114, wherein the CTPS1 inhibitor is in a solid pharmaceutical composition and the WEE1 inhibitor is in a solid pharmaceutical composition.

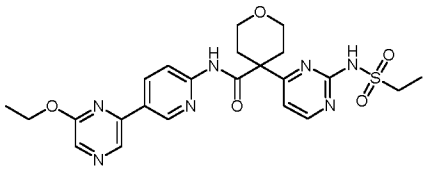
Clause 116. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 115, wherein the CTPS1 inhibitor is administered orally in a solid pharmaceutical composition.

Clause 117. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 116, wherein the WEE1 inhibitor is administered orally in a solid pharmaceutical composition.

Clause 118. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 117, wherein the CTPS1 inhibitor is administered orally in a solid pharmaceutical composition and the WEE1 inhibitor is administered orally in a solid pharmaceutical composition.

Clause 119. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 118, wherein the WEE1 inhibitor is administered at a daily dose of up to 300 mg, suitably once daily on days 1 to 5 and days 8 to 12 of a 21-day treatment cycle.

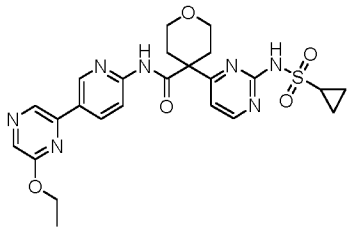
Clause 120. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 119, wherein the CTPS1 inhibitor is:
N-(5-(6-ethoxypyrazin-2-yl)pyridine-2-yl)-4-(2-(ethylsulfonamido)pyrimidin-4-yl)tetrahydro-2*H*-pyran-4-carboxamide:



,

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof; and the WEE1 inhibitor is adavosertib, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 121. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 119, wherein the CTPS1 inhibitor is:
4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide:



,

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof; and the WEE1 inhibitor is adavosertib, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 122. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 121, wherein the WEE1 inhibitor is not adavosertib.

Clause 123. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to clause 122, wherein the WEE1 inhibitor is not adavosertib, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 124. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 123, wherein the CTPS1 inhibitor is not a CTPS1 inhibitor as defined in claim 1 of WO2022/087634.

Clause 125. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 124, wherein the CTPS1 inhibitor is not a CTPS1 inhibitor as defined in WO2022/087634.

Clause 126. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 123, wherein the CTPS1 inhibitor is a CTPS1 inhibitor disclosed in PCT publication number WO2022087634.

Clause 127. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 123, wherein the CTPS1 inhibitor is (i) a compound described in any one of claims 1 to 31 of WO2022087634 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof, (ii) a compound selected from compounds I-1 to I-286 of WO2022087634, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof, or (iii) a compound selected from compounds Z-1 to Z-10 of WO2022087634, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

Clause 128. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 123, wherein the CTPS1 inhibitor is not a CTPS1 inhibitor disclosed in PCT publication number WO2022087634.

Clause 129. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of clauses 1 to 123, wherein the CTPS1 inhibitor is not (i) a compound described in any one of claims 1 to 31 of WO2022087634 or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof, (ii) a compound selected from compounds I-1 to I-

286 of WO2022087634, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof, or (iii) a compound selected from compounds Z-1 to Z-10 of WO2022087634, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

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Claims

1. A CTPS1 inhibitor for use in the treatment of cancer with a WEE1 inhibitor.

2. A WEE1 inhibitor for use in the treatment of cancer with a CTPS1 inhibitor.

3. A pharmaceutical composition comprising a CTPS1 inhibitor and a WEE1 inhibitor.

4. Use of a CTPS1 inhibitor in the manufacture of a medicament for the treatment of cancer with a WEE1 inhibitor.

5. Use of a WEE1 inhibitor in the manufacture of a medicament for the treatment of cancer with a CTPS1 inhibitor.

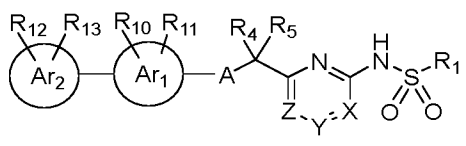
6. A method of treating cancer in a subject which method comprises administering to the subject a CTPS1 inhibitor and a WEE1 inhibitor.

7. A kit of parts comprising:
   a) a first container comprising a CTPS1 inhibitor; and
   b) a second container comprising a WEE1 inhibitor.

8. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to any one of claims 1 to 7, wherein the CTPS1 inhibitor has an IC_{50} of 10uM or lower, established using the assay procedure set out in Example 1.

9. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to any one of claims 1 to 8, wherein the CTPS1 inhibitor has a selectivity for CTPS1 over CTPS2 of at least 2-fold, established using the assay procedure set out in Example 2.

10. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to any one of claims 1 to 9, wherein the CTPS1 inhibitor is a compound of formula (III):



(III)

wherein

A is an amide linker having the following structure: -C(=O)NH- or -NHC(=O)-;

X is N or CH;

Y is N or CR_2;

Z is N or CR_3;

with the proviso that when at least one of X or Z is N, Y cannot be N;

R_1 is C_{1-5}alkyl, C_{0-2}alkyleneC_{3-5}cycloalkyl which cycloalkyl is optionally substituted by CH_3, or CF_3;

R_2 is H, halo, C_{1-2}alkyl, OC_{1-2}alkyl, C_{1-2}haloalkyl or OC_{1-2}haloalkyl;

R_3 is H, halo, CH_3, OCH_3, CF_3 or OCF_3;

wherein at least one of R_2 and R_3 is H;

R_4 and R_5 are each independently H, C_{1-6}alkyl, C_{1-6}alkylOH, C_{1-6}haloalkyl, C_{0-2}alkyleneC_{3-6}cycloalkyl, C_{0-2}alkyleneC_{3-6}heterocycloalkyl, C_{1-3}alkyleneOC_{1-3}alkyl, or R_4 and R_5 together with the carbon atom to which they are attached form a C_{3-6}cycloalkyl or C_{3-6}heterocycloalkyl; and

when A is -NHC(=O)-:

R_4 and R_5 may additionally be selected from halo, OC_{1-6}haloalkyl, OC_{0-2}alkyleneC_{3-6}cycloalkyl, OC_{0-2}alkyleneC_{3-6}heterocycloalkyl, OC_{1-6}alkyl and $NR_{21}R_{22}$;

Ar1 is a 6-membered aryl or heteroaryl;

Ar2 is a 6-membered aryl or heteroaryl and is attached to Ar1 in the para position relative to the amide;

R_{10} is H, halo, C_{1-3}alkyl, C_{1-2}haloalkyl, OC_{1-2}alkyl, OC_{1-2}haloalkyl or CN;

R_{11} is H, F, Cl, C_{1-2}alkyl, CF_3, OCH_3 or CN;

R_{12} is attached to Ar2 in the ortho or meta position relative to Ar1 and R_{12} is H, halo, C_{1-4}alkyl, C_{2-4}alkenyl, C_{0-2}alkyleneC_{3-5}cycloalkyl, OC_{1-4}alkyl, OC_{0-2}alkyleneC_{3-5}cycloalkyl, C_{1-4}haloalkyl, OC_{1-4}haloalkyl, hydroxy, C_{1-4}alkylOH, SO_2C_{1-2}alkyl, $C(O)N(C_{1-2}alkyl)_2$, $NHC(O)C_{1-3}$alkyl or $NR_{23}R_{24}$; and

when A is -NHC(=O)-:

R_{12} may additionally be selected from CN, $OCH_2CH_2N(CH_3)_2$ and a C_{3-6}heterocycloalkyl comprising one nitrogen located at the point of attachment to Ar2, or R_{12} together with a nitrogen atom to which it is attached forms an N-oxide (N^+-O^-);

R_{13} is H or halo;

R_{21} is H, C_{1-5}alkyl, $C(O)C_{1-5}$alkyl, $C(O)OC_{1-5}$alkyl;

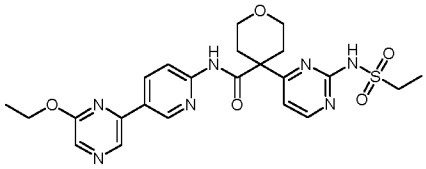
R_{22} is H or CH_3;

R_{23} is H or C_{1-2}alkyl; and

R_{24} is H or C_{1-2}alkyl;

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

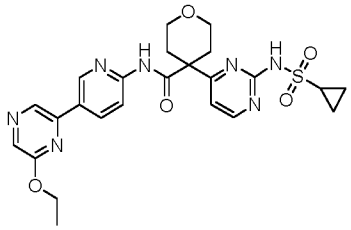
11. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to any one of claims 1 to 10, wherein the CTPS1 inhibitor is *N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)-4-(2-(ethylsulfonamido)pyrimidin-4-yl)tetrahydro-2*H*-pyran-4-carboxamide:



,

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

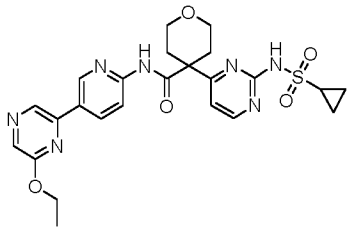
12. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to claim 10, wherein the CTPS1 inhibitor is 4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide:



,

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

13. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to claim 1, wherein the CTPS1 inhibitor is 4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide:



,

or a pharmaceutically acceptable salt thereof.

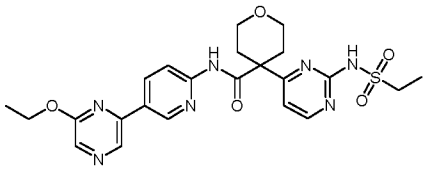
14. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to any one of claims 1 to 9, wherein the CTPS1 inhibitor is selected from the compounds disclosed in any one of Lists A to H or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

15. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to any one of claims 1 to 14, wherein the WEE1 inhibitor has a Ki value for binding to WEE1 of 50 nM or lower established using the WEE 1 kinase assay procedure or the WEE1 CDC2 phosphorylation assay procedure set out in Example 3.

16. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to any one of claims 1 to 15, wherein the WEE1 inhibitor is selected from adavosertib, PD0166285, ZN-c3, WEE1-IN-3, WEE1-IN-4, PD 407824 and WEE1 Inhibitor II, pharmaceutically acceptable salts thereof and/or pharmaceutically acceptable solvates thereof.

17. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to claim 16, wherein the WEE1 inhibitor is adavosertib, pharmaceutically acceptable salts thereof and/or pharmaceutically acceptable solvates thereof.

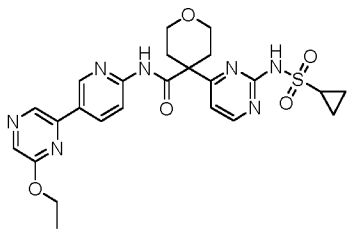
18. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to any one of claims 1 to 17 wherein the CTPS1 inhibitor is: *N*-(5-(6-ethoxypyrazin-2-yl)pyridine-2-yl)-4-(2-(ethylsulfonamido)pyrimidin-4-yl)tetrahydro-2*H*-pyran-4-carboxamide:



,

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof; and the WEE1 inhibitor is adavosertib, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

19. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to any one of claims 1 to 17, wherein the CTPS1 inhibitor is: 4-(2-(cyclopropanesulfonamido)pyrimidin-4-yl)-*N*-(5-(6-ethoxypyrazin-2-yl)pyridin-2-yl)tetrahydro-2H-pyran-4-carboxamide:



,

or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof; and the WEE1 inhibitor is adavosertib, or a pharmaceutically acceptable salt and/or pharmaceutically acceptable solvate thereof.

20. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to any one of claims 1 to 19, wherein the cancer is a haematological cancer.

21. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to claim 20, wherein the haematological cancer is T cell lymphoma.

22. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to claim 20, wherein the haematological cancer is diffuse large B cell lymphoma.

23. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to claim 20, wherein the haematological cancer is plasma cell myeloma.

24. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to claim 20, wherein the haematological cancer is acute myeloid leukaemia.

25. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to claim 20, wherein the haematological cancer is chronic lymphocytic leukaemia.

26. The CTPS1 inhibitor, WEE1 inhibitor, composition, method, use or kit according to claim 20, wherein the haematological cancer is peripheral T cell lymphoma.

27. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to claim 20, wherein the haematological cancer is a myelodysplastic syndrome (MDS), such as MDS with single lineage dysplasia, MDS with multilineage dysplasia or MDS with excess blasts.

28. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to claim 20, wherein the haematological cancer is cutaneous T-cell lymphoma.

29. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to claim 20, wherein the haematological cancer is follicular lymphoma.

30. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to claim 20, wherein the haematological cancer is mantle cell lymphoma.

31. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to claim 20, wherein the haematological cancer is marginal zone lymphoma.

32. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to any one of claims 1 to 19, wherein the cancer is a non-haematological cancer.

33. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to claim 32, wherein the cancer is a non-haematological cancer selected from prostate cancer, pancreatic cancer, ovarian cancer, lung cancer, renal cancer, colorectal cancer or breast cancer.

34. The CTPS1 inhibitor, WEE1 inhibitor, use, method, composition or kit according to claim 33, wherein the cancer is a non-haematological cancer selected from prostate cancer, pancreatic cancer, ovarian cancer, renal cancer, colorectal cancer or breast cancer.

Fig. 1

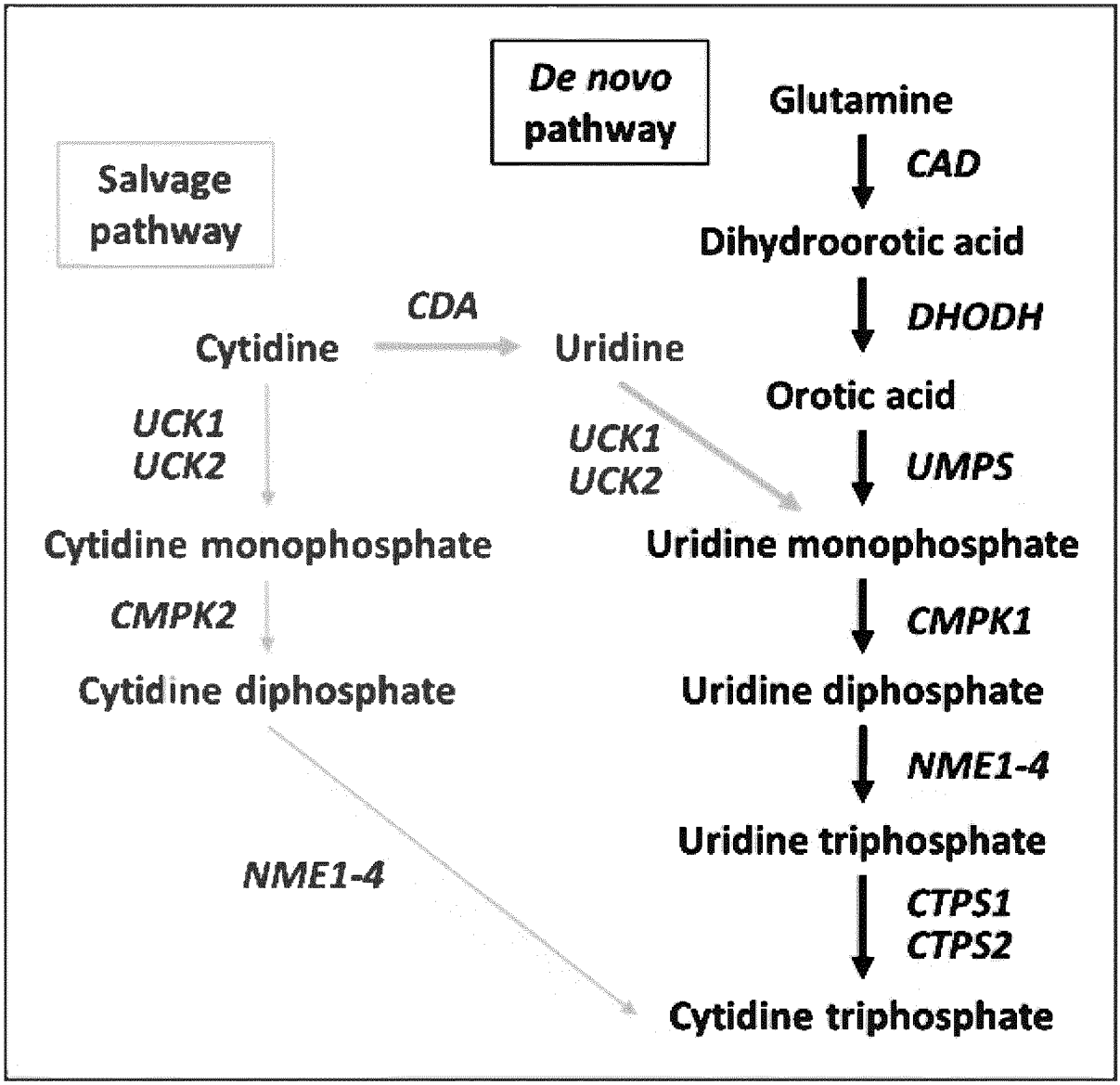
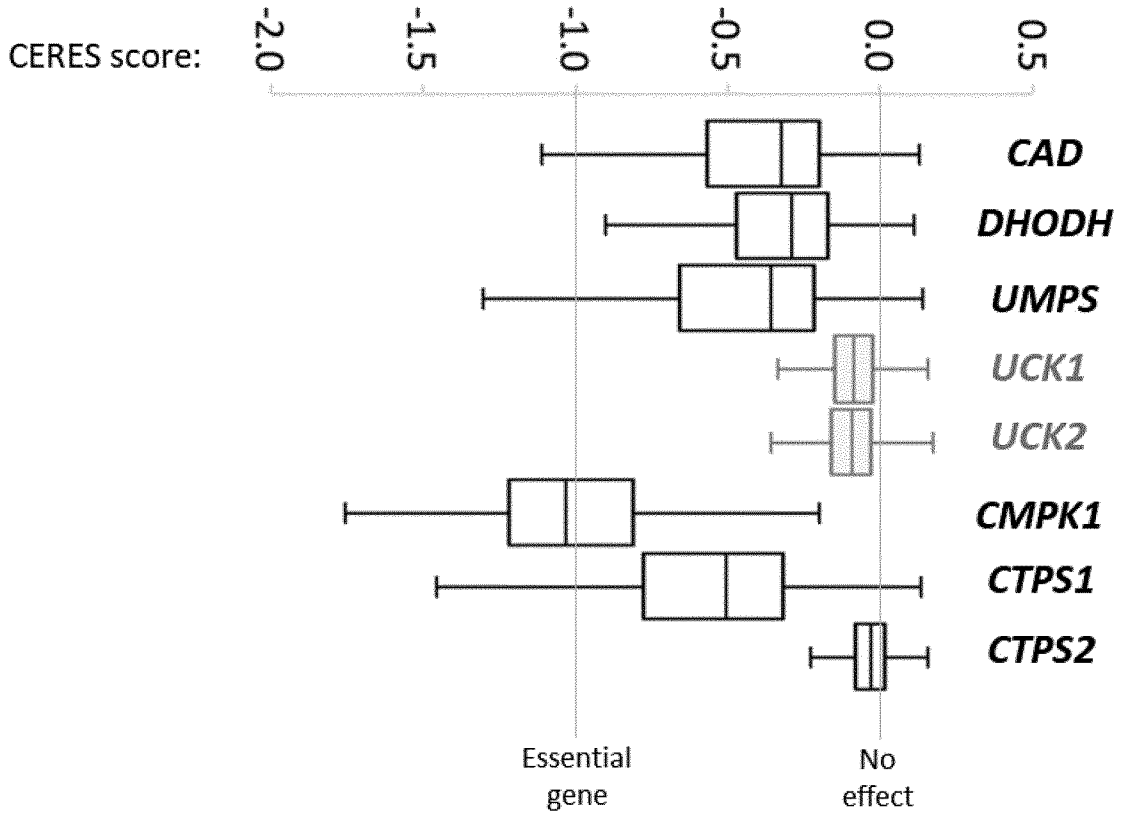

De novo pathway
Glutamine
CAD
Dihydroorotic acid
DHODH
Orotic acid
UMPS
Uridine monophosphate
CMPK1
Uridine diphosphate
NME1-4
Uridine triphosphate
CTPS1
CTPS2
Cytidine triphosphate
Salvage pathway
CDA
Cytidine
Uridine
UCK1
UCK2
UCK1
UCK2
Cytidine monophosphate
CMPK2
Cytidine diphosphate
NME1-4

Fig. 2



Achilles CRISPR screen comprising 1032 cancer cell lines; graph shows box and whisker plots representing number of cell lines by median, interquartile range and overall range; x-axis shows CERES score: 0=no effect, <0=reduced proliferation, -1=median of all common essential genes.

Fig. 3

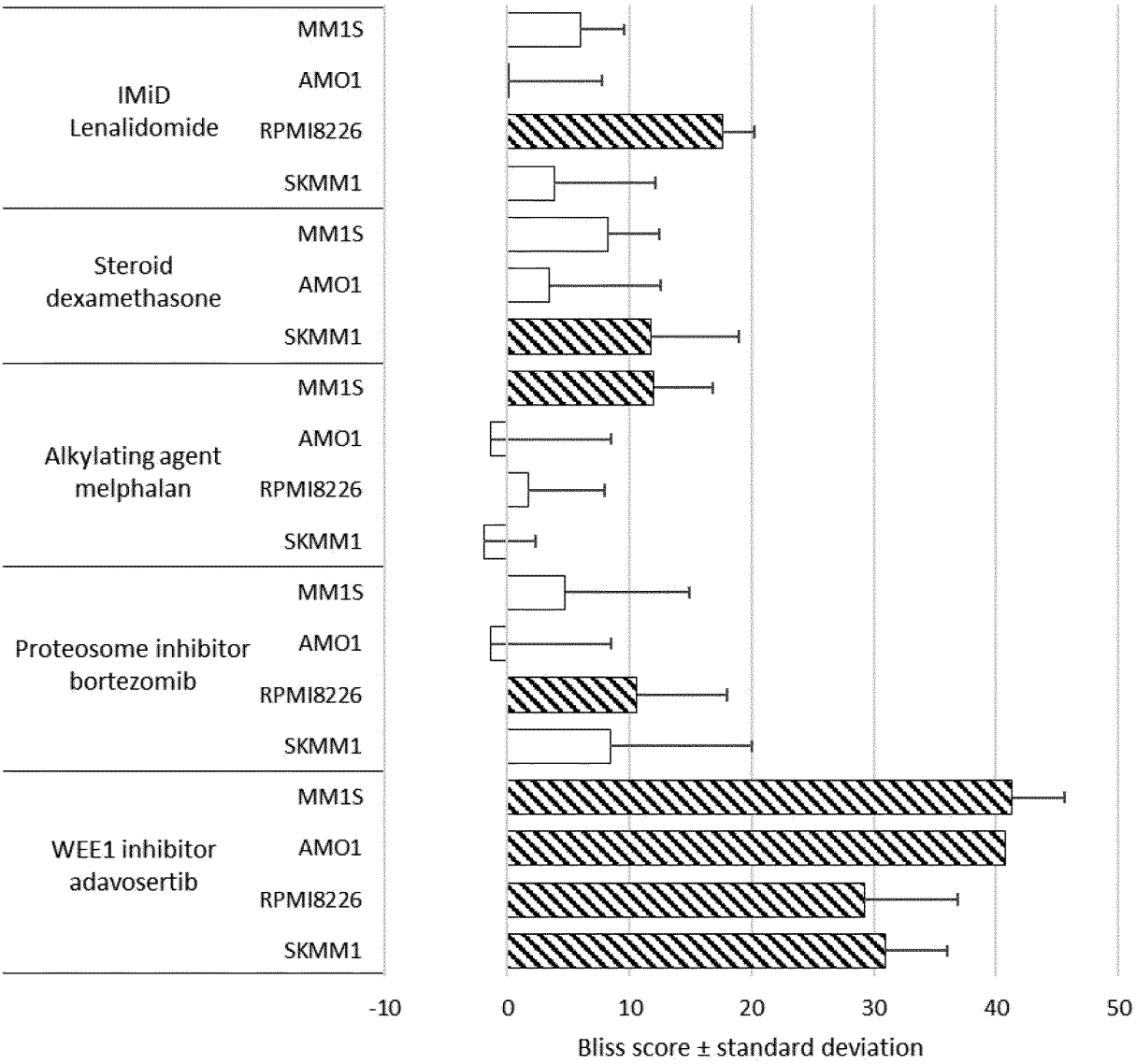

IMiD Lenalidomide
MM1S
AMO1
RPMI8226
SKMM1
Steroid dexamethasone
MM1S
AMO1
SKMM1
Alkylating agent melphalan
MM1S
AMO1
RPMI8226
SKMM1
Proteosome inhibitor bortezomib
MM1S
AMO1
RPMI8226
SKMM1
WEE1 inhibitor adavosertib
MM1S
AMO1
RPMI8226
SKMM1
-10
0
10
20
30
40
50
Bliss score ± standard deviation

Fig. 4

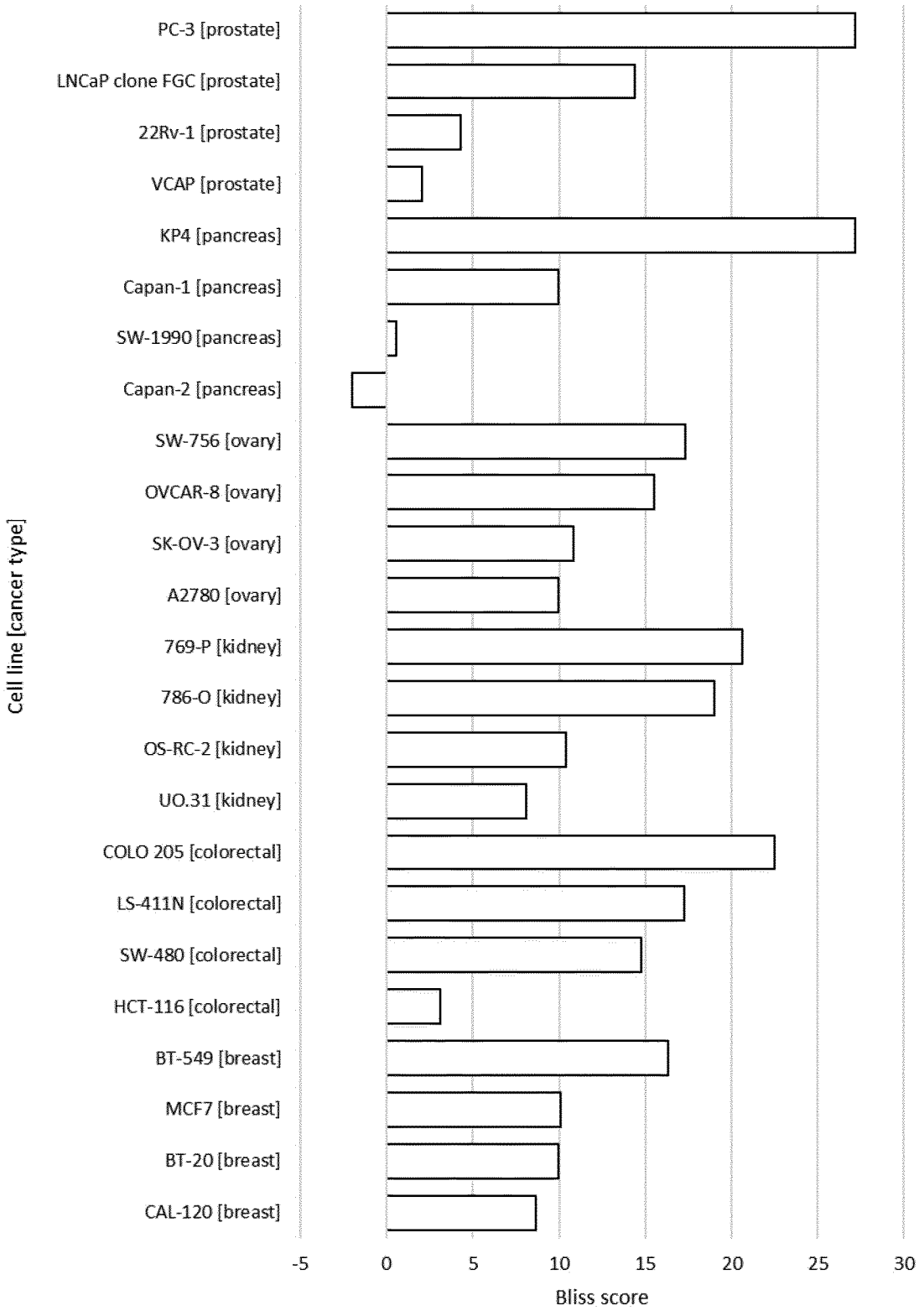
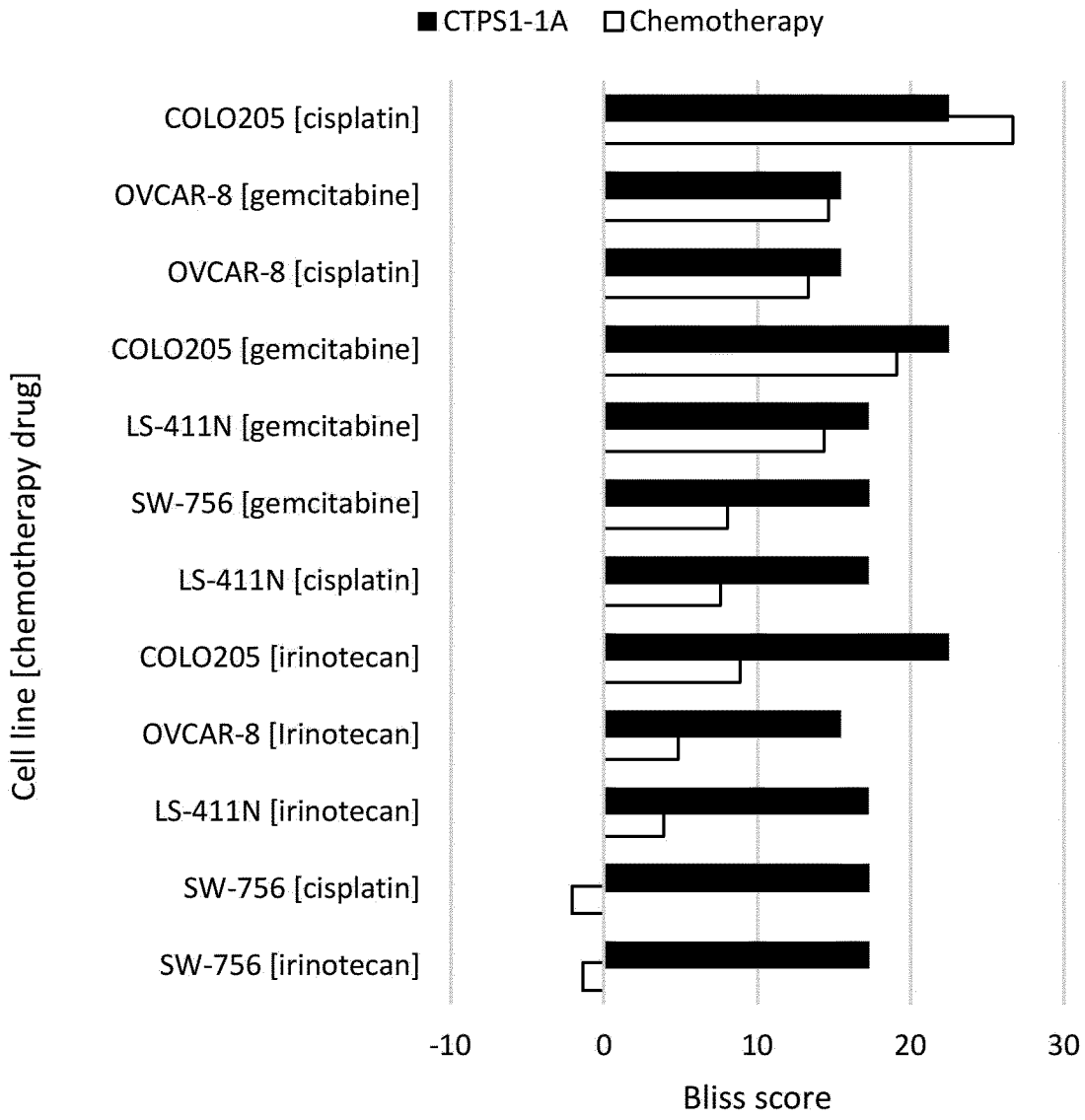

PC-3 [prostate]
LNCaP clone FGC [prostate]
22Rv-1 [prostate]
VCAP [prostate]
KP4 [pancreas]
Capan-1 [pancreas]
SW-1990 [pancreas]
Capan-2 [pancreas]
SW-756 [ovary]
OVCAR-8 [ovary]
SK-OV-3 [ovary]
A2780 [ovary]
769-P [kidney]
786-O [kidney]
OS-RC-2 [kidney]
UO.31 [kidney]
COLO 205 [colorectal]
LS-411N [colorectal]
SW-480 [colorectal]
HCT-116 [colorectal]
BT-549 [breast]
MCF7 [breast]
BT-20 [breast]
CAL-120 [breast]
Cell line [cancer type]
-5
0
5
10
15
20
25
30
Bliss score

Fig. 5


CTPS1-1A
Chemotherapy
COLO205 [cisplatin]
OVCAR-8 [gemcitabine]
OVCAR-8 [cisplatin]
COLO205 [gemcitabine]
LS-411N [gemcitabine]
SW-756 [gemcitabine]
LS-411N [cisplatin]
COLO205 [irinotecan]
OVCAR-8 [Irinotecan]
LS-411N [irinotecan]
SW-756 [cisplatin]
SW-756 [irinotecan]
Cell line [chemotherapy drug]
-10
0
10
20
30
Bliss score

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/055222

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/506 A61K31/519 A61K45/06 A61P35/02
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LHEUREUX STEPHANIE ET AL: "Adavosertib plus gemcitabine for platinum-resistant or platinum-refractory recurrent ovarian cancer: a double-blind, randomised, placebo-controlled, phase 2 trial", THE LANCET, ELSEVIER, AMSTERDAM, NL, vol. 397, no. 10271, 21 January 2021 (2021-01-21), pages 281-292, XP086465624, ISSN: 0140-6736, DOI: 10.1016/S0140-6736(20)32554-X [retrieved on 2021-01-21]	1-7, 15-17, 32-34
Y	abstract; p. 282, last par.	1-17, 20-34
A		18,19

-/--

[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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 April 2023	10/05/2023

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

1

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/055222

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	WO 2014/170435 A2 (INSERM INST NAT DE LA SANTÉ ET DE LA RECH MÉDICALE [FR] ET AL.) 23 October 2014 (2014-10-23) claim 18	
Y	WO 2020/245664 A1 (STEP PHARMA S A S [FR]) 10 December 2020 (2020-12-10) claims 23, 28-31	1-17, 20-34
Y	WO 2019/179652 A1 (STEP PHARMA S A S [FR]) 26 September 2019 (2019-09-26) p. 171, claims 24-26	1-17, 20-34

1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2023/055222

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

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

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

   b. [ ] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      [ ] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2023/055222

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014170435 A2	23-10-2014	CA 2909434 A1	23-10-2014
		CN 105473136 A	06-04-2016
		EP 2986287 A2	24-02-2016
		JP 2016523818 A	12-08-2016
		US 2016051674 A1	25-02-2016
		US 2018185476 A1	05-07-2018
		WO 2014170435 A2	23-10-2014
WO 2020245664 A1	10-12-2020	CN 114008039 A	01-02-2022
		EP 3980411 A1	13-04-2022
		IL 288508 A	01-01-2022
		JP 2022536092 A	12-08-2022
		US 2022324837 A1	13-10-2022
		WO 2020245664 A1	10-12-2020
WO 2019179652 A1	26-09-2019	AU 2018413791 A1	17-09-2020
		BR 112020018701 A2	29-12-2020
		CA 3093050 A1	26-09-2019
		CN 111868051 A	30-10-2020
		EA 202092263 A1	15-01-2021
		EP 3768674 A1	27-01-2021
		IL 277455 A	30-11-2020
		JP 2021518436 A	02-08-2021
		KR 20200135463 A	02-12-2020
		PH 12020500655 A1	21-06-2021
		SG 11202103238X A	29-04-2021
		US 2021024507 A1	28-01-2021
		WO 2019179652 A1	26-09-2019